Movement Disorders
Vol. 24, Suppl. 1, 2009, pp. S1–S6

Guided Poster Tour I
Hall Bordeaux
13:00 – 14:30

Monday, June 8, 2009

Ataxia
(For complete abstracts please see page S7)

Mo-3 **Presymptomatic markers of neurodegeneration in SCA17. A multimodal imaging approach by transcranial sonography, MRI and PET**
K. Brockmann, M. Reimold, C. Globas, T.K. Hauser, J.H. Machulla, U. Walter, A. Rolfs, L. Schoels (Tuebingen, Germany)

Mo-9 **The cerebellar phenotype of adult-onset Sandhoff disease: Three new cases**
C.C.S. Delnooz, D.J. Lefeber, S. Hoffjan, J. Schelhaas, B.P.C. van de Warrenburg (Nijmegen, Netherlands)

Tu-3 **A new phenotype (SAP) for the spinocerebellar ataxias resulting from senataxin, aprataxin, and protein kinase C gamma gene mutations**
M. Feldman, J.J. Esper, A. Ahmed (Cleveland, Ohio)

Tu-8 **Restless Legs syndrome and sleep disturbance in Friedreich ataxia**
B. Högl, S. Hering, B. Frauscher, V. Gschliesser, W. Poewe, S.M. Boesch (Innsbruck, Austria)

Tu-11 **Spinocerebellar ataxia 14: Study of a Norwegian family with a novel mutation in exon 5 in the PRKCG gene**
J. Koht, G. Stevanin, E. Mundwiller, A. Durr, A. Brice, C.M.E. Tallaksen (Paris, France)

We-9 **Genetic heterogeneity of SCA linked to chromosome 15?**
I.N. Petrovic, A. Weissbach, A. Djarmati, K. Lohmann, N. Dragasevic, C. Zuhlke, M. Svetel, C. Klein, V.S. Kostic (Belgrade, Serbia)

We-12 **Ataxia with ophthalmoplegia and/or sensory neuropathy is frequently caused by POLG mutations**
C. Schulte, M. Synofzik, T. Gasser, L. Schöls (Tubingen, Germany)

Th-2 **Movement disorders in ataxia-telangiectasia**
A.G. Shaikh, T.O. Crawford, D.S. Zee, H.A. Jinnah (Baltimore, Maryland)

Th-4 **Genotype-Phenotype (G2P) correlations in SCA12**
A.K. Srivastava, F. Mohammed, I. Singh, M.V. Padma, M. Mukerji, M. Behari (New Delhi, Delhi, India)

Th-10 **Spinocerebellar ataxia type 2: A clinical, molecular, neurochemical and electrophysiological study of the mutation in 106 Cuban families**
L. Velazquez-Perez, G. Sanchez-Cruz, L. Galicia-Polo, G. Auburger, J. Garcia-Rodriguez, R. Rodriguez-Labrada, L. Almaguer-Mederos, D. Coello-Almarales, J. Laffita-Mesa, R. Aguilera-Rodriguez, C. Gonzalez, N. Canales-Ochoa (Holguin, Cuba)

Drug-induced Movement Disorders

Mo-40 **Tardive chorea secondary to low dose quetiapine**
F. Amjad, S.E. Lo (Washington, District of Columbia)

Mo-41 **Could tardive dystonia be cured with botulinum toxin treatment?**
M. Anca-Herschkovitsch (Holon, Israel)

Tu-42 **Manganese-induced extrapyramidal symptoms: Methcathinone encephalopathy**
D. Ince Gunal, K. Agan, H. Horozoglu, P. Kahraman Koytak (Istanbul, Turkey)

Tu-43 **Levosulpiride-induced hemichorea**
S.Y. Kang, H.-I. Ma, Y.J. Kim, S. Jung, S.-B. Kwon, S.H. Hwang (Seoul, Republic of Korea)

Tu-44 **Clinical course of ephedronic encephalopathy**
M. Kapianidze, I. Khatiashvili, M. Megrelishvili, N. Kvirkvelia (Tbilisi, Georgia)

Tu-45 **Ephedrone encephalopathy: Treatment approaches**
I. Khatiashvili, M. Kapianidze, M. Megrelishvili, K. Akhvlediani (Tbilisi, Georgia)

Tu-46 **Akathisia and second-generation antipsychotic drugs**
R. Kumar, P. Sachdev (Woden, ACT, Australia)

We-43 **Effects of risperidone at "protective" doses on balance control in healthy individuals**
E. Pourcher, H. Cohen, P. Corbeil, M. Simoneau, J.-F. Rodrigue (Quebec, Quebec, Canada)

We-44 **Acute onset tremor associated with combination of chipmax and fluoxetine**
A.Q. Rana (Toronto, Canada)

Th-41 **Two year follow up in ephedrone induced parkinsonism with dystonia**
Y. Sanotsky, M. Selikhova, L. Fedoryshyn, Y. Matvienko, I. Komnatska, M. Kyrylchuk, A. Friedman, A.J. Lees (London, United Kingdom)

Huntington's disease and Choreas, Non-Huntington's

Mo-111 **Dopamine D2 receptors vulnerability in Huntington's disease: A role of the Rho/ROCK signaling pathway**
S. Betuing, C. Deyts, E. Martin, N. Bouveyron, B. Galan-Rodriguez, D. Charvin, E. Roze, J. Caboche (Paris, France)

Mo-112 **A phase 2 trial of minocycline in Huntington's disease**
M.E. Cudkowicz, M. McDermott, R. Doolan, F. Marshall, K. Kieburtz, HSG (Charlestown, Massachusetts)

Tu-107 **Acoustic analysis of voice in Huntington's disease patients**
M.J. Velasco, I. Cobeta, G. Martín, H. Alonso-Navarro, F.J. Jiménez-Jiménez (Madrid, Spain)

Tu-108 **Neuroprotective effects of kynurenic acid analog in a transgenic mouse model of Huntington's disease**
P. Klivenyi, D. Zadori, F. Fulop, J. Toldi, L. Vecsei (Szeged, Hungary)

Tu-110 **An ADORA2A polymorphism modifies age at onset in Huntington's disease**
S. Burnouf, C.-M. Dhaenens, C. Simonin, E. Vanbrussel, A. Duhamel, L. Defebvre, C. Duru, I. Vuillaume, C. Cazeneuve, P. Charles, P. Maison, S. Debruxelles, C. Verny, H. Gervais, J.-P. Azulay, C. Tranchant, A.-C. Bachoud-Levi, A. Dürr, L. Buée, B. Sablonnière, D. Blum, P. Krystkowiak, Huntington French Speaking Network (Amiens, France)

We-31 **Movement disorders associated with diabetes mellitus: A prospective case series**
M. Rodríguez-Violante, A. Cervantes-Arriaga, G. Arrambide-García, T. Corona (Mexico City, Mexico)

We-109 **Social intelligence in Huntington's disease**
S.L. Mason, M. Armstrong, A.A.O. Goodman, R.A. Barker (Cambridge, Cambrdigeshire, United Kingdom)

We-111 **Dysfunctional error monitoring in the anterior cingulate cortex in prediagnostic and manifest HD during an anti-saccade task**
J.D. Rupp, T. Blekher, M. Dzemidzic, V. Bragulat, J.D. West, J. Wojcieszek, A.J. Saykin, D.A. Kareken, T. Foroud (Indianapolis, Indiana)

We-114 **DNA instability in replicating Huntington's disease lymphoblasts**
M. Cannella, V. Maglione, T. Martino, G. Ragona, L. Frati, G.-M. Li, F. Squitieri (Pozzilli, IS, Italy)

Th-116 **The degree of atrophy of striatum and pallidum in preclinical Huntington's disease strongly predicts estimated years to clinical onset**
D. Stoffers, J. Kuperman, S. Sheldon, D.J. Hagler, J. Goldstein, A.M. Dale, J. Corey-Bloom, A.R. Aron (San Diego, California)

Neuroimaging

Mo-148 **FMRI correlates of ideomotor apraxia in Parkinson's disease**
T. Foki, N. Klinger, A. Geissler, J. Rath, T. Steinkellner, I. Hoellinger, S. Gruber, D. Haubenberger, J. Lehrner, G. Pusswald, G. Grabner, S. Trattnig, W. Pirker, E. Auff, R. Beisteiner (Vienna, Austria)

Tu-133 **Cortico-striatal activation during implicit sequence learning in Parkinson's disease with deep brain stimulation of the subthalamic nucleus**
M. Jahanshahi, L. Wilkinson, G. Hotton, Y. Tai, N. Pavese, D.J. Brooks (London, United Kingdom)

Tu-146 **A systematic, comprehensive, blinded radiological study of MR findings in pathologically confirmed PSP, MSA and PD**
L. Massey, D. Paviour, S. O'Sullivan, D. Burn, J. Holton, T. Revesz, A. Lees, R. Jager, C. Micallef (London, United Kingdom)

We-124 **Usefulness of cardiac ^{123}-MIBG scintigraphy in the differential diagnosis of parkinsonism**
R. Miyamoto, H. Shibayama, F. Katada, S. Sato, T. Fukutake (Kamogawa City, Chiba, Japan)

We-129 **Diffusion weighted imaging of the olfactory tract and its association with hyposmia in PD**
M. Nocker, K. Seppi, M. Schocke, R. Esterhammer, I. Virgolini, S. Boesch, W. Poewe, C. Scherfler (Innsbruck, Austria)

We-146 **Metabolic-morphometric correlates of preclinical compensation in asymptomatic heterozygous PINK1 mutation carriers**
K. Reetz, C. Eggers, J. Hagenah, C. Gaser, H.R. Siebner, Y. von Cramon, G.R. Fink, C. Klein, R. Hilker, F. Binkofski (Lubeck, Germany)

Th-134 **Changes in brain metabolism and dysphagia in Parkinson's disease**
A. Kikuchi, A. Takeda, T. Baba, N. Sugeno, M. Kobayashi, T. Hasegawa, E. Mori, Y. Itoyama (Sendai, Japan)

Th-141 **Equally normalized motor activation in medicated Parkin-associated and sporadic PD**
T. van Eimeren, C. Buhmann, J. Hagenah, P.P. Pramstaller, H.R. Siebner, C. Klein (Toronto, Canada)

Th-140 **Tonic stimulation of the orbitofrontal cortex by dopamine agonists in PD wipes out reward processing and increases risk taking behaviour: Are they at risk of gambling?**
T. van Eimeren, B. Ballanger, G. Pellecchia, J. Miyasaki, R. Chuang, T. Steeves, A.E. Lang, A.P. Strafella (Toronto, Canada)

Th-142 **Genotype-related changes in brain activity are influenced by the speed of task performance in non-manifesting carriers of a single mutant *Parkin* or *PINK1* allele**
B.F.L. van Nuenen, B.R. Bloem, J.P.M. van der Vegt, M.M. Weiss, F. Binkofski, C. Klein, H.R. Siebner (Nijmegen, Netherlands)

Guided Poster Tour II
Hall Bordeaux
13:00 – 14:30

Tuesday, June 9, 2009

Dementia in movement disorders

(For complete abstracts please see page S171)

Mo-118 **Mesencephalic ^{123}I-FP-CIT uptake differentiates Lewy body dementia from other parkinsonisms**
F. Roselli, N.M. Pisciotta, L. Catalano, D. Martino, P. Livrea, G. Rubini, G. Defazio (Bari, Italy)

Mo-117 **Association of neuropsychiatric symptoms and dopamine transporter levels in dementia with Lewy bodies: A 123I-FP-CIT SPECT study**
F. Roselli, N.M. Pisciotta, M. Pennelli, M.S. Aniello, M.F. De Caro, E. Ferrannini, D. Liuzzi, B. Tartaglione, G. Defazio, G. Rubini, P. Livrea (Bari, Italy)

Mo-119 **Prevalence of parkinsonism and other movement disorders in outpatients with Alzheimer's disease using cholinesterase inhibitors and/or memantine**
G. Fabiani, H. Teive, R.P. Munhoz, N. Becker (Curitiba, Parana, Brazil)

Tu-113 **Rapidly progressive diffuse Lewy body disease**
C. Gaig, F. Valldeoriola, S. Llufriu, M.J. Rey, E. Tolosa (Barcelona, Spain)

Tu-115 **Computerized tracing in Huntington patients: A standard measure for hyperkinetic activity**
S. Thanendrarajan, A. Hoffmann, B. Landwehrmeyer, J. Andrich, P.H. Kraus (Bochum, Germany)

We-115 **Quantitative map of hypoperfusion in 62 stereotactic cerebral cortical segments by IMP-SPECT reveals a specific pattern of Lewy body dementia**
K. Ohta, M. Seki, Y. Shinohara (Tachikawa, Tokyo, Japan)

We-116 **Whole brain diffusion tensor imaging in Parkinson's disease, Parkinson's disease with dementia and dementia with Lewy bodies**
B. Park, J.-H. Seo, H.-J. Park, S.K. Song, Y.H. Sohn, P.H. Lee (Seoul, Korea)

We-117 **The CERAD-(plus) neuropsychological battery does not clearly differentiate Parkinson's disease dementia from Alzheimer's disease and mixed dementia**
G. Ransmayr, G. Baumgartner, A. Fuchs, V. Bayr, M. Steffelbauer, H. Traegner, C. Dorninger (Linz, Austria)

We-118 **Olfactory dysfunction in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17)**
P. Robowski, J. Slawek, E. Narozanska, M. Schinwelski, E.J. Sitek, W. Kucharska, B. Brockhuis, P. Lass, D. Wieczorek, M. Dubaniewicz, B. Jasinska-Myga, M.C. Baker, R. Rademakers, Z.K. Wszolek (Gdansk, Pomorskie, Poland)

Th-117 **Visual hallucinations are related to gray matter volume in the dorsal visual pathway in Dementia with Lewy bodies and in the orbitofrontal cortex in Parkinson's disease with dementia**
C. Sanchez-Castaneda, B. Ramirez-Ruiz, R. Rene, J. Campdelacreu, J. Gascon, C. Falcon, M. Calopa, S. Jauma, M. Juncadella, C. Junque (Barcelona, Spain)

Neuropharmacology

Mo-151 **A pharmacoeconomic evaluation of botulinum toxin A therapy in the Philippines**
J.T. Colacion, L.G. Fugoso, Jr., R.D.G. Jamora (Manila, Philippines)

Mo-153 **"Espresso coffee" for the treatment of excessive daytime sleepiness in Parkinson's disease: Results of four pilot n-of-one clinical trials**
J.J. Ferreira, L. Correia-Guedes, R.A. Freire, M. Coelho, M.M. Rosa, O. Rascol, C. Sampaio (Lisbon, Portugal)

Mo-154 **A systematic review of the incidence of fatigue as an adverse event in placebo-controlled trials for Parkinson's disease**
J.J. Ferreira, T. Teodoro, D. Pires, T. Mestre, M. Coelho, M.M. Rosa, C. Sampaio (Lisbon, Portugal)

Tu-152 **Valvular heart regurgitation and pergolide in Parkinson's disease: Follow-up of an observational study**
C. Jean-Christophe, B. Anne-Marie, L. Lucette, I. Richard (Paris, France)

Tu-154 **Pore-forming iron-induced alpha-synuclein oligomers – A target for developing compounds against pathological protein aggregation**
J. Levin, K. Boetzel, T. Hoegen, M. Kostka, H. Kretzschmar, A. Giese (Munich, Germany)

We-153 **Overexpression of cannabinoid CB2 reecptors results in decreased behavioral and neurochemical vulnerability to intracaudate administration of 6-hydroxydopamine**
A. Ternianov, M.S. Garcia-Gutierrez, M.J. Cano, F. Navarrete, J.M. Perez-Ortiz, C. de Cabo, C. Leiva, M.F. Galindo, J. Manzanares (Alicante, Spain)

We-155 **An environmental xenobiotic compound realise an neuroprotective effect against neurodegeneration of dopaminergic neurons from striatum nigra**
A.G. Mititelu (London, United Kingdom)

We-156 **A metanalysis of neutralizing antibody conversion following a specific formulation of botulinum toxin type A (BoNTA, Allergan, Inc): An analysis of large clinical trials across five indications**
M. Naumann, S. Abu-Shakra, T. Boodhoo, M.A. Miller-Messana, G. Demos, M.F. Brin (Augsburg, Germany)

Th-153 **The use of dopamine agonists (DAGs) in "de novo" Parkinson's disease patients (PDpts) first diagnosed after 70years old**
J.M. Rabey, E. Dubronevsky, A. Miniovich, T. Prokhovic (Beer Yakov, Israel)

Th-156 **Botulinum toxin type A injection as a novel treatment for kinetic tremors associated with FXTAS**
L. Zhang, L.L. Lua, P. Adams, R.J. Hagerman (Sacramento, California)

Non-Motor Manifestations of Parkinsonism

Mo-156 **Sexual Health in Parkinson's disease**
J. Azevedo, A. Palha, M.J. Rosas, M. Esteves, M.A. Vieira-Coelho, C. Sousa, R. Fonseca, P. Linhares, C. Garrett, R. Vaz (Porto, Portugal)

Mo-158 **Effects of continuos application of L-dopa/carbidopa gel on psychiatric symptoms in advanced Parkinson's disease (PD)**
K. Fox, T. Fox, K. Dietrich, A. Gies, H. Honig, R. Chaudhuri, A. Antonini, P. Martinez-Martin, A. Rüssmann, P. Odin (Bremerhaven, Bremen, Germany)

Tu-157 **Regulation of movement energetic costs is impaired in pre-symptomatic Huntington's disease (pHD) and in the early stages Parkinson's disease (PD)**
D. Crupi, C. Moisello, A. Di Rocco, B. Perfetti, A. Feigin, D. Eidelberg, M.F. Ghilardi (New York, New York)

Tu-158 **Progressive supranuclear palsy impairs emotion recognition**
B.C.P. Ghosh, A.J. Calder, P. Peers, A.D. Lawrence, J. Hodges, J.M. Rowe (Cambridge, United Kingdom)

We-158 **Limitations of traditional screening tools to detect depression in Parkinson's disease**
J.E. Howard, S. Varanese, D. Penesetti, C. Morrison, S. Hirsch, R. Brown, A. DiRocco (New York, New York)

We-159 **Cognitive impairment in essential tremor without dementia**
J.-S. Kim, I.-U. Song, Y.-S. Shim, K.-S. Lee, Y.-D. Kim, H.-T. Kim (Seoul, Korea)

Th-158 **Prevalence of pseudobulbar affect in movement disorders and its relationship with mood symptoms**
R.E. Strowd, M.S. Cartwright, M.S. Okun, M.S. Siddiqui (Winston-Salem, North Carolina)

Th-159 **Mood differences between women diagnosed with psychogenic movement disorders and psychogenic seizures**
A.M. Strutt, J. Ferrera, S. Hill, M.K. York, L. Uber-Zak, T. Fogel, J. Jankovic (Houston, Texas)

Th-160 **Hemichorea-hemiballism caused by hyperglycemia associated with hypomania in acute stage: A brief report**
C.-S. Su, J.-S. Liu, M.-Y. Lan, Y.-Y. Chang (Kaohsiung, Taiwan)

We-157 **Autonomic and sensory symptoms are frequent and of mild severity in patients with incident, untreated PD**
B. Muller, K. Haugarvoll, G.O. Skeie, J.P. Larsen, O.-B. Tysnes (Bergen, Norway)

Parkinson's disease: Clinical Trials

Mo-177 **Observer bias in biological/surgical trials of novel Parkinson's disease therapies**
R.L. Alterman, M. Tagliati, W. Olanow (New York, New York)

Mo-193 **Cholinergic augmentation in frequently falling subjects with Parkinson's disease**
K.A. Chung, B.M. Lobb, J.G. Nutt, F. Horak (Portland, Oregon)

Tu-185 **Efficacy of preladenant, a novel A2A antagonist, as an adjunct to levodopa for the treatment of Parkinson's disease**
R.A. Hauser, E. Pourcher, F. Micheli, V. Mok, M. Onofrj, S.B. Huyck, K. Wolski, M. Cantillon (Tampa, Florida)

Tu-202 **Evaluation of a computerized telephone system to monitor falls**
M.A. van der Marck, M.Ph.C. Klok, S. Overeem, B.R. Bloem, M. Munneke (Nijmegen, Netherlands)

We-182 **Amantadine given as adjuvant to levodopa in the treatment of levodopa induced dyskinesias and motor fluctuations in Parkinson's disease**
N. Oztekin, F. Oztekin, H. Okkan, S. Bilen, F. Ak (Ankara, Turkey)

We-184 **Rasagiline 1 mg/day provides benefits in the progression of non-motor symptoms in patients with early Parkinson's disease: Assessment with the revised MDS-UPDRS**
W. Poewe, R. Hauser, A.E. Lang, ADAGIO Investigators (Innsbruck, Austria)

We-192 **A longitudinal program for biomarker development in Parkinson's disease**
B. Ravina, C. Tanner, D. DiEuliis, E. Flagg, I. Shoulson, Parkinson Study Group, LABS-PD Investigators (Rochester, New York)

We-199 **Efficacy and safety of pramipexole extended-release for advanced Parkinson's disease**
A. Schapira, P. Barone, R.A. Hauser, Y. Mizuno, W. Poewe, O. Rascol, M. Busse, N. Juhel, Pramipexole ER Studies Group (London, United Kingdom)

Th-182 **Ropinirole prolonged release is effective in reducing "off" time in patients with advanced Parkinson's disease even at low doses**
F. Stocchi, L. Giorgi, N. Earl, R. Pahwa (Rome, Italy)

Th-192 **Motivations and concerns of Parkinson's disease patients to participate in clinical trials**
A. Valadas, M. Coelho, M. Finisterra, A. Noronha, M. Rosa, C. Sampaio, J. Ferreira (Lisbon, Portugal)

Guided Poster Tour III
Hall Bordeaux
13:00 – 14:30

Wednesday, June 10, 2009

Basic Science
(For complete abstracts please see page S25)

Mo-15 **The role of muscarinic transmission in the substantia nigra reticulata of normal and 6-OHDA hemilesioned rats**
D.R. Andersson, E. Björnsson, F. Bergquist, H. Nissbrandt (Goteborg, Sweden)

Mo-17 **Identification and functional characterization of a novel mutation in the mortalin/GRP75 gene in German Parkinson's disease patients**
L.F. Burbulla, C. Schelling, B. Maurer, L. Schöls, O. Riess, R. Krüger (Tubingen, Germany)

Mo-20 **Aging and Parkinson's disease: A stochastic acceleration hypothesis**
T.J. Collier, N.M. Kanaan, J.H. Kordower (Cincinnati, Ohio)

Mo-30 **Comparative analyses of Purkinje cell gene expression profiles reveal common molecular abnormalities in different polyglutamine diseases**
B. Friedrich, P. Euler, R. Ziegler, A. Kuhn, B. Landwehrmeyer, C. Weiller, B. Zucker (Freiburg, Baden-Wuerttemberg, Germany)

Tu-16 **SNARE protein accumulation in a model of early Parkinson's disease**
P. Garcia Reitbock, O. Anitchtchik, G.K. Tofaris, M. Goedert, M.G. Spillantini (Cambridge, United Kingdom)

Tu-30 **Modulation of mitochondrial morphology and function by interaction of Omi/HtrA2 with the fusion protein OPA1 – Implications for neurodegeneration**
N. Kieper, K. Holmström, D. Ciceri, L.M. Martins, P.J. Kahle, R. Krüger (Tuebingen, Germany)

Tu-32 **Mitochondrial dysfunction and impaired lysosomal degradation due to loss of Parkinson's disease associated protein DJ-1**
G. Krebiehl, S. Ruckerbauer, J. Waak, H. Wolburg, Z. Gizatullina, F.N. Gellerich, O. Riess, P.J. Kahle, T. Proikas-Cezanne, R. Krüger (Tubingen, Germany)

We-13 **Proteomic analysis of the substantia nigra in patients with Parkinson's disease**
V. Licker, L. Dayon, N. Turck, M. Côte, N. Rodrigo, D.F. Hochstrasser, J.-C. Sanchez, P.R. Burkhard (Geneva, Switzerland)

We-17 **Detection of elevated levels of alpha-synuclein oligomers in cerebrospinal fluid from patients with Parkinson's disease and dementia with Lewy bodies**
W. Maetzler, M.M. Qureshi, D. Berg, M. Synofzik, T. Gasser, O.M.A. El-Agnaf (Tuebingen, Germany)

Th-27 **Isolation and characterization of genetically modified neural stem cells by fluorescence-activated cell sorting (FACS) analysis**
M. Tani, T. Nihira, H. Hayakawa, N. Hattori, Y. Mizuno, H. Mochizuki (Tokyo, Japan)

Electrophysiology

Mo-38 **Integrative function of single neurons in the human subthalamic nucleus during checking behavior**
P. Burbaud, M.-L. Welter, M. Goillandeau, A.-L. Clair, P. Sauleau, M. Simonetta-Moreau, S. Chabardes, S. Besnard, H. Magnie-Mauro, J. Coste, L. Mallet (Bordeaux, Paris, France)

Tu-37 **Increased excitability induced by tDCS can unmask mirror movements**
J.E. Dundas, G.W. Thickbroom, A. Fox, F.L. Mastaglia (Perth, Western Australia, Australia)

Th-35 **Real-time analysis of EEG in the elucidation of volition**
L. Schneider, E. Houdayer, O. Bai, A. Ellenstein, M. Hallett (Bethesda, Maryland)

Th-36 **Neuronal mechanisms of motor signals transmission in nonspecific (CM-Pf) and motor (Voi) human brain thalamic nuclei in spasmodic torticollis patients**
A.S. Sedov, S.N. Raeva (Moscow, Russian Federation)

Mo-234 **Pedunculopontine and subthalamic deep brain stimulation affects motor cortex network function**
B.R. Aravamuthan, C.E. Hatch, R.A. French, N.I. Novikov, D.A. Bergstrom, J.R. Walters (Bethesda, Maryland)

Mo-235 **Lack of efficiency of levodopa treatment on motor cortex excitability in dyskinetic patients with Parkinson's disease**
L. Barbin, C. Leux, C. Meyniel, P. Sauleau, J.M. N'Guyen, Y. Pereon, P. Damier (Nantes, France)

Mo-241 **Cortical plasticity in Parkinson's disease (PD) with levodopa-on**
W.-L. Chuang, R.-S. Chen, Y.-Z. Huang, S.-C. Lai, C.-S. Lu (Taoyuan, Taiwan)

Mo-243 **Modulation of sensorimotor integration by intermittent theta-burst stimulation in Parkinson's disease**
A. Degardin, F. Cassim, D. Devos, L. Defebvre, P. Derambure, H. Devanne (Lille, France)

Tu-236 **Resonance in subthalamo-cortical circuits in Parkinson's disease**
A. Eusebio, A. Pogosyan, S. Wang, B. Averbeck, L. Doyle Gaynor, S. Cantiniaux, T. Witjas, P. Limousin, J.-P. Azulay, P. Brown (London, United Kingdom)

Tu-245 **Lack of plasticity in the motor cortex (M1) is a primary marker of Parkinson's disease (PD) and is L-dopa sensitive only when motor dysfunction sets in: A TMS study**
T. Joseph, S. Meunier, A. Kishore (Thiruvananthapuram, Kerala, India)

Genetics and Epidemiology

Mo-78 **Prevalence and incidence study of Parkinson's disease in the metropolitan city of Kolkata, India – A community based study**
S.K. Das, A. Hazra, B.K. Ray, A. Misra, M. Ghosal, T.K. Banerjee, T. Roy, D.K. Raut, A. Chaudhuri (Kolkata, West-Bengal, India)

Tu-75 **Study of the prevalence of Parkinson's disease using dopamine transporter imaging**
J.S. Kim, J.M. Kim, K.W. Kim, Y.K. Kim, S.E. Kim, B.S. Jeon (Seong nam-si, Kyeong ki -do, Korea)

Tu-79 **NSAID use and the risk of Parkinson's disease: The influence of comorbidity**
J.A. Driver, G. Logroscino, J.M. Gaziano, T. Kurth (Paris, France)

Tu-80 **Co-occurrence of substantia nigra hyperechogenicity and putative premotor signs as well as risk factors of PD in a large cohort older than 50 years**
I. Liepelt, S. Behnke, K.J. Schweitzer, B. Wolf, U. Dillmann, A. Gaenslen, A. Di Santo, J. Godau, D. Berg (Tuebingen, Germany)

Th-81 **A 15-year population-based longitudinal study of incidence of Parkinson's disease (PD) and parkinsonian syndromes (PS) in an elderly French population (PAQUID)**
F. Perez, C. Helmer, S. Auriacombe, J.-F. Dartigues, F. Tison (Pessac, France)

Mo-91 **CTCF depletion in the FXN gene constitutes an epigenetic switch in Friedreich ataxia**
S.I. Bidichandani, Y. Chutake, I. De Biase (Oklahoma City, Oklahoma)

Tu-89 **The phenotype of the 202A deletion in the *Parkin* gene in two large Muslim Israeli-Arab kindreds**
S. Hassin-Baer, N. Hattori, C. Cohen, M. Massarwa, S.D. Israeli-Korn, R. Inzelberg (Tel Hashomer, Israel)

Tu-98 **Comprehensive molecular genetic analysis of the *LRRK2* gene in a UK familial Parkinson's disease cohort**
A.J. Lewthwaite, T.D. Lambert, F.E. Marely, N.W. Wood, D.J. Nicholl, K.E. Morrison (Birmingham, West Midlands, United Kingdom)

We-99 **Parkinsonism and early cortical involvement in a Swedish family with alpha-synuclein Ala53Thr mutation**
A.J. Puschmann, O.A. Ross, C. Vilarino-Guell, S.J. Lincoln, Z.K. Wszolek, M.J. Farrer, H. Widner, C. Nilsson (Lund, Sweden)

Th-99 **Genome-wide association study for sporadic Parkinson's disease**
T. Toda, W. Satake, Y. Nakabayashi, I. Mizuta, T. Yoshikawa, M. Yamamoto, N. Hattori, M. Murata, Y. Nakamura, Japan PD Gene Consortium (Suita, Osaka, Japan)

Surgical Therapies

Mo-348 **Combined neurostimulation therapy (DBS and SCS) for orthostatic tremor: A case report**
S. Biguzzi, M. Haefele, C. Lettieri, C. Mantovan, G. Devigili, C. Conti, M. Brollo, G. Trincia, E. Cagliari, M. Bevilacqua, M. Barca, P. Fontana, G. Pinato, R. Eleopra (Mestre-Venice, Italy)

Tu-352 **Long-term follow-up of pallidal deep brain stimulation for secondary dystonias**
I.U. Isaias, J. Volkmann, R.L. Alterman, M.H. Mehdorn, M. Pinsker, R. Reese, G. Deuschl, M. Tagliati (Monza, Italy)

Mo-328 **Motor and cognitive effects of subthalamic nucleotomy in one hundred patients with Parkinson's disease**
L. Alvarez, R. Macias, N. Pavon, M.C.O. Rodriguez, J.A. Obeso (Havana City, Cuba)

Mo-339 **Localization and anatomo-clinical correlation of DBS electrodes contacts in the MLR in Parkinson's disease**
S. Chabardès, L. Goetz, N. Torres, M. Ferraye, E. Seigneuret, B. Debu, B. Piallat, V. Fraix, C. Maineri, E. Bardinet, J. Yelnik, J.F. Lebas, P. Pollak, A.L. Benabid (Grenoble, France)

Mo-341 **Subthalamic nucleus-deep brain stimulation modulates thermal sensation and pain thresholds in Parkinson's disease**
D. Ciampi de Andrade, Y. Beaugendre, J.-M. Gurruchaga, D. Boërio, C. Goujon, H. Lepetit, S. Palfi, J.-P. Lefaucheur (Creteil, France)

Tu-330 **Effects of PPN area stimulation on gait disorders in PD**
M.U. Ferraye, B. Debû, V. Fraix, L. Goetz, S. Chabardès, E. Lhommée, C. Ardouin, C. Lagrange, P. Krack, E. Seigneuret, A.L. Benabid, P. Pollak (Grenoble, France)

Tu-331 **Effects of unilateral pedunculopontine nucleus deep brain stimulation (PPN-DBS) in parkinsonian patients with prominent freezing of gait (FOG)**
N.B. Galifianakis, P.A. Starr, P.S. Larson, G.A. Glass, M.M. Volz, S.L. Heath, J.L. Ostrem (San Francisco, California)

We-324 **Pallidotomy abolishes STN lesion induced dyskinesias in Parkinson's disease without further deterioration**
R. Macias, N. Pavon, G. Lopez, M.C.R. Oroz, J.A. Obeso (Havana City, Cuba)

We-328 **Brain tissue changes following deep brain stimulation**
K. Nolte, M. Kronenbuerger, J. Burgunder, V. Coenen, J. Weis, J. Krauss (Aachen, Germany)

Th-340 **Gamma knife subthalamotomy in Parkinson's disease: Long-term follow-up**
T. Witjas, J.P. Azulay, A. Eusebio, J.C. Peragut, J. Régis (Marseille, France)

Movement Disorders
Vol. 24, Suppl. 1, 2009, pp. S7–S542

ATAXIA

Mo-1

Epidemiological, clinical, paraclinical and molecular study of a cohort of 102 patients affected with autosomal recessive progressive cerebellar ataxia from Alsace, Eastern France

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Objective: To report the clinical, molecular and epidemiological data of a large series of patients from Eastern France affected with autosomal recessive cerebellar ataxia (ARCA).

Background: While Friedreich's ataxia (FRDA) and ataxia telangiectasia (AT) are known to be the two most frequent forms of ARCA, knowledge on the other forms of ARCA has been obtained only recently and they appear to be rarer. Little is known about the epidemiological features and the relative frequency of the ARCAs and few data are available about the comparative features of ARCAs.

Methods: We prospectively studied between 2002 and 2008, 102 suspected ARCA cases from Eastern France (including 95 from the Alsace region) in order to examine the clinical, paraclinical and molecular features of a large cohort of patients and to compare features and epidemiology according to molecular diagnosis (MD).

Results: A MD could be established in 57 patients: 36 FRDA, 7 ataxia with oculomotor apraxia type 2 (AOA2), 4 AT, 3 ataxia with oculomotor apraxia type 1 (AOA1), 3 Marinesco-Sjögren syndrome (MSS), 2 autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), 1 ataxia with vitamine E deficiency (AVED) and 1 ARCA2. Patients without MD had less severe disease and later onset of symptoms. Babinski sign and the lack of cerebellar atrophy were rarer in non-FRDA patients with a MD. The prevalence of ARCA and FRDA in Alsace, France were 1/19000 and 1/50000, respectively and the prevalence of AT is about 8 time less frequent than FRDA.

Conclusions: ARCAs are rare, early-disabling and genetically heterogeneous diseases dominated by FRDA. ARCA cases can be divided into two major groups of different prognosis, an early onset group with a highly probable genetic cause and an adult onset group with better prognosis for which a genetic cause is more difficult to prove but not excluded. Several of the recently identified ARCAs, such as AVED, ARSACS, AOA1, AOA2 and MSS, have a prevalence close to AT and should be searched for extensively, irrespective of ethnic origins.

Mo-2

Comparative study of prevalence of depression between autosomal dominant ataxia and sequel of cerebrovascular accident – Organic component (cerebellar) of depression

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Objective: To evaluate the impact of morbidity in genesis of depressive symptomatology in patients with autosomal dominant cerebellar ataxia and the possible implication in cerebellar lesions themselves to play a role at the beggining and severity of those symptoms.

Background: On our clinic of ataxia, there was a high frequence of depressive complaints. We have designed a study to define whether depression has organic basis or if it has another cause that justifies such finding.

Methods: It is a descriptive longitudinal study comparing the prevalence of depression through Hamilton's Scale (HAM-D21) in two groups, one with 42 patients with autosomal dominant cerebellar ataxia, and the other with 50 patients with sequels of CVA, selected after inclusion and exclusion criteria.

Results: All patients from both groups presented grade 03 in Modified Rankin Scale. Average age in ataxia was 43,4762 and in CVA, 54,04, with confidence interval (CI)-95% = 4.832-16.295 p = 0.1134; the average score in HAM-D21 in ataxia was 21,0476 and in CVA, 12,48, with CI-95% = 11.743-5.392 p<0.0001.

Conclusions: There was a difference statistically significant between the two groups, with higher prevalence of depression in patients with autosomal dominant cerebellar ataxia.

Mo-3

Presymptomatic markers of neurodegeneration in SCA17. A multimodal imaging approach by transcranial sonography, MRI and PET

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Objective: Analysis of the structural and functional processes underlying ataxia and extrapyramidal symptoms in SCA17.

Background: Spinocerebellar ataxia type 17 (SCA17) is an autosomal dominantly inherited ataxia caused by the expansion of a CAG trinucleotide repeat in the TBP gene coding for the general transcription initiation factor TATA binding protein (Nakamura et al., 2001). Clinically SCA17 is characterized by the affection of cerebellar, extrapyramidal and cognitive systems with huge phenotypic variability (Rolfs et al., 2003; Stevanin et al., 2003; Zuhlke and Burk, 2007). Whereas in some patients the disease starts with gait difficulties due to ataxia, dementia or psychosis marks the onset of disease in others (Rolfs et al., 2003). Extrapyramdial signs include dystonia, chorea but rarely parkinsonism (Hernandez et al., 2003).

Methods: To analyse the structural and functional processes underlying ataxia and extrapyramidal symptoms in SCA17 we used a combined approach including 3D magnetic resonance sequences (MPRAGE), positron emission tomography (PET) imaging of the pre- and postsynaptic dopaminergic system, and transcranial sonography (TCS). To establish the onset of neurodegeneration asymptomatic mutation carriers (n=4) were included besides patients (n=5) with manifest signs and symptoms of SCA17.

Results: Analysis showed that D2 receptor binding is severely reduced in SCA17 even in presymptomatic stages of disease ($P < 0.01$). Analogue in MRI atrophy of the putamen and of the caudate nucleus was evident in symptomatic patients as well as asymptomatic carriers ($P < 0.01$) resulting in a close correlation between D2 receptor density in RAC-PET and putaminal volumes in MRI (r2=0.78; p = 0.02).

Table 1 (Mo-3). Pre- and postsynaptic dopaminergic PET imaging in SCA17

	SCA17 (total group)	SCA17 (manifest group)	SCA17 (presymptomatic group)	Controls
RAC binding putamen (average)	1,36 ± 0,24***	1,30 ± 0,27*	1,44 ± 0,21**	1,71 ± 0,192
RAC binding caudate nucleus (average)	0,89 ± 0,31***	0,82 ± 0,33**	0,98 ± 0,30**	1,36 ± 0,19
MPD binding putamen (average)	1,14 ± 0,53	1,02 ± 0,69*	1,30 ± 0,27	1,37 ± 0,27
MPD binding caudate nucleus (average)	0,93 ± 0,46*	0,79 ± 0,55*	1,11 ± 0,278	1,22 ± 0,26

Mean values ± standard deviation are given. Values were compared to matched controls by one sided t-test. P values are indicated as: *P < 0.05; **P < 0.01; ***P < 0.001

Table 2 (Mo-3). MR volumetry in SCA17

	SCA17 (total group)	SCA17 (manifest disease)	Presymptomatic SCA17	Controls
Total intracranial volume (TICS)	1458848 ± 170687	1548277 ± 187646	1369420 ± 116756	1441588 ± 116711
Frontal lobe (average)	158765 ± 20482	166362 ± 25139	151168 ± 15610	159145 ± 16801
Temporal lobe (average)	130282 ± 25923	142900 ± 30714	117665 ± 16095	139377 ± 13123
Parietal lobe (average)	152734 ± 22731	151390 ± 32843	154078 ± 14414	162710 ± 17274
Occipital lobe (average)	32751 ± 5722	33231 ± 7227	32272 ± 5380	36967 ± 4330
Putamen (average)	2900 ± 945**	2595 ± 1311**	3205 ± 483*	3633 ± 309
Caudate nucleus (average)	2693 ± 1028**	2616 ± 1510**	2771 ± 585**	3872 ± 603
Brainstem	28742 ± 4572**	28726 ± 6384*	28759 ± 3391*	32237 ± 2090
Pons	19035 ± 3712	18650 ± 5262	19419 ± 2511	20783 ± 1721
Medulla	6110 ± 881*	6173 ± 434*	6046 ± 1320*	7360 ± 1150
Cerebellum	104729 ± 23870**	91760 ± 28054***	117698 ± 11525	123121 ± 7169
Cerebellar vermis	11472 ± 3305**	9780 ± 3157**	13164 ± 2959	15932 ± 2987

Mean values ± standard deviation are given. Values were compared to matched controls by one sided t-test. P values are indicated as: *P < 0.05; ** P < 0.01; ***P < 0.001

Conclusions: Since D2 receptor binding correlates with disease duration (r2= -0,956; p= 0,006) it is likely that raclopride binding is a biomarker indicating neuronal degeneration even before clinical symptoms become manifest.

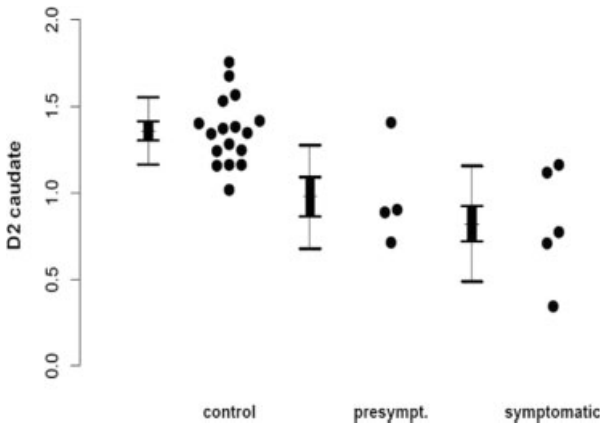

FIG. 1 (Mo-3).

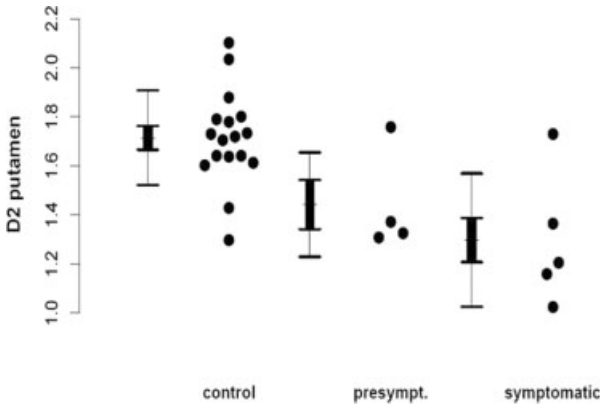

FIG. 2 (Mo-3).

Mo-4

Autossomal dominant cerebellar ataxia- frequency analysis and clinical characterization of 45 families from Portugal

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Objective: To report the relative frequency and clinical features of a series of 45 Portuguese families with autosomal dominant cerebellar ataxia (ADCA).

Background: The ADCAs, also know as spinocerebellar atrophies (SCAs), represent a clinically heterogeneus groups of genetic disorders. The relative frequency of the different ADCA types varies widely among different geographic locations.

Methods: Cerebellar ataxia patients were referred to our department by clinicians working in Lisbon and in the South region of Portugal. Inclusion criteria for ADCA were progressive cerebellar ataxia and evidence of autosomal dominant transmission. Patients underwent a clinical examination protocol and genetic testing for SCA1 to MJD/SCA3, SCA6, SCA7, SCA10, SCA12, SCA17 and dentatorubro-pallido-luysian atrophy (DRPLA). We registered the different clinical characteristics and the frequency of each type of ataxia.

Results: Machado-Jopseph Disease(MJD)/SCA3 was the most frequent ADCA (26 families, 57.8% of all families), followed by DRPLA (5 families, 11.1%), SCA 7 (2 families, 4.4%), SCA2 and SCA1 (1 family each, 2.2% each); only about a quarter of our families had no molecular diagnosis (10 families, 22.2%). All the SCA 1 and SCA 7 patients had an African ancestry. Ophtalmoparesis was the most distinctive feature in MJD/SCA 3, whereas DRPLA was characterized by prominent anticipation and a variable combination of epilepsy, extra-pyramidal symptoms and dementia. In SCA2, slow saccades was the most characteristic feature, while retinopathy was only seen in SCA 7.

Conclusions: MJD/SCA 3 was the most common ADCA, as reported in previous portuguese series. There was an unexpected high frequency of DRPLA, even higher than in some Japanese series. SCA 1 and SCA 7 are also seldomly reported in European series. The presence of these rarer ADCA could reflect migration phenomena specifically related to Portugal, and poses a specific challenge for ADCA differential diagnosis. The clinical features agreed with those already described.

Mo-5

The pattern of instability and its dependence on posture in spino-cerebellar ataxia type 6 (SCA6)

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Objective: To investigate whether the pattern of whole-body instability in SCA6 1) has a directional preponderance, 2) is localised to specific joints of the body, 3) is influenced by posture, and 4) correlates with clinical scales of disease severity.

Background: SCA6 has a relatively 'pure' pathology localised to the cerebellum. It is clinically characterised by impaired balance and ataxia of movement, frequently causing falls. The characteristics and patterns of instability and their dependence on posture and disease severity are poorly understood.

Methods: Seventeen subjects with SCA6 were recruited together with a group of matched healthy controls. Whole-body measures of posture and balance were collected using 3D-motion capture (Coda) over 40s trial durations, whilst subjects stood quietly on a force plate (Kistler) with their eyes open and with a variable stance-width posture. Infrared-emitting diodes were fixed to each of the body segments. Anatomical landmarks were referred to these clusters for off-line analysis of joint angles (C-Motion). Clinical assessment of disease severity was measured using the Scale for Assessment and Rating of Ataxia (SARA).

Results: Global measures of instability, from motion at the level of C7 and centre of pressure of ground reaction forces, revealed that

SCA6 subjects were more unstable than control subjects in both AP and ML directions at all stance widths. For both groups, standing with the feet closer together caused greater instability in both cardinal directions. However, this stance-width effect was disproportionally large in the SCA6 group in the ML direction (group x stance width interaction; $p<0.001$). Analysis of joint angle motion showed that the excessive instability of the SCA6 subjects with feet together occurred at all joints but with most angular motion taking place at the ankle joint. A number of measures of whole-body instability were found to correlate with disease severity.

Conclusions: The stance-width posture of SCA6 subjects is an important determinant of their pattern of standing instability and helps to explain why many subjects spontaneously adopt a wide-based posture. Correlations between quantitative stability measures and the SARA indicate that this score could be used not only to monitor overall disease severity but also as a balance impairment predictor.

Mo-6

Vestibular processing for balance control in spino-cerebellar ataxia type 6 (SCA6)

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(London, United Kingdom)

Objective: To investigate whether SCA6 subjects can process vestibular information appropriately to control balance.

Background: SCA6 is characterised by impaired balance and ataxia of movement, and is one of the SCAs in which pathology is limited to the cerebellum. The disordered control processes responsible for the balance impairment remain undetermined. Animal experimentation has suggested that the cerebellum has roles in processing of vestibular information. We hypothesise that poor balance in SCA6 results from impaired vestibular processing.

Methods: Seventeen subjects with SCA6 were recruited together with a group of matched healthy controls. Subjects stood quietly on force plates (Kistler) with their feet 8cm apart and with different head yaw directions (head forward or right/left 90 degrees). Infrared-emitting diodes were fixed to each of the body segments and motion was recorded in 3D (Coda). Galvanic vestibular stimulation (GVS, 1mA bipolar R+L-/R-L+) was used to provide a standardised and repeatable vestibular balance perturbation and visual conditions (vision intact/obscured) were varied using liquid crystal spectacles (Plato).

Results: In both groups, average responses to GVS were normally timed and normally directed (along the intra-aural line, towards the anodal ear). Furthermore, average response magnitudes typically increased with removal of vision. However, despite these many similarities to healthy controls, in all conditions SCA6 response magnitudes were consistently larger than those of the healthy control group.

Conclusions: Our data suggest that many aspects of vestibular processing are normal in SCA6. However, SCA6 subjects' abnormal 'over-response' to GVS could contribute to instability. This may be due to abnormal gain control of the vestibular channel of balance control.

Mo-7

Phenotype-genotype correlation in autosomal dominant cerebellar ataxias (SCA): MRI findings distinguish between forms with point mutations and polyglutamine expansions

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Objective: The aim of the study was to compare cerebral MRI in SCAs according to the underlying mutational mechanisms.

Background: SCAs are clinically and genetically heterogeneous group of autosomal dominantly inherited progressive neurodegenerative diseases with the implication of more than 30 loci/genes. They are often caused by the expansion of (CAG)n repeats encoding polyglutamine (polyQ) tracts as in SCA1, 2, 3, 6, 7 and 17 accounting for >50% of the ADCAs. Interestingly, expanded repeats are no longer the only type of mutation responsible; point mutations have been identified in several genes including SCA5, 13, 14 and 28, at least. Cerebral MRI shows variable degrees of cerebellar and pontine atrophy.

Methods: We reviewed cerebral MRI of 41 patients (21 men and 20 women) with SCAs caused by known mutations either polyglutamine expansions or point mutations. Severity of ataxia was quantified with SARA (Scale for the Assessment and Rating of Ataxia). MRIs were performed for all patients with a variable delay from onset of the disease and were analysed blinded for the genetic cause by two clinicians. Cerebellum, pons and corpus callosum atrophy were rated as mild, moderate or severe. White matter abnormalities, molar tooth and cross sign were also identified.

Results: 33 Patients had polyglutamine (Q) expansions, 10 patients point mutations (M). Cerebellar atrophy was significantly milder in Q than in M ($p<0.003$). Interestingly, cerebellar ataxia measured by SARA was more severe in Q than in M (17.3 versus 9.94, $p<0.02$). Disease duration was longer in M (18.15 versus 10.78, $p=0.026$) despite the milder phenotype.

Conclusions: Patients with M have significantly more cerebellar atrophy that those with Q despite longer diseases duration and lesser severity. Therefore, the evaluation of clinical severity and of the degree of cerebellar atrophy could guide genetic analyses. A prospective cerebral MRI study is necessary to confirm that these MRI differences are also present at the onset of symptoms in SCAs.

Mo-8

Abetalipoprotenemia – Long term observation

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Objective: To present 2 cases of ABL treated with high doses of vitamin A and vitamin E in long term observation.

Background: Abetalipoproteinemia (Bassen-Kornzweig disease, ABL) is a rare autosomal recessive disorder, clinically characterized by hipolipidemia, acanthocytosis, retinitis pigmentosa, cerebellar ataxia and fat malabsorption. Early combined treatment of ABL with high doses of vitamin A and E can influence on the disease course.

Methods: We present 2 cases of siblings: 33-year-old female and 29-year-old male who were diagnosed with ABL in childhood and have been treated with massive oral doses of vitamin A (50000 IU per day) and vitamin E (500 mg per day). They had a history of fat malabsorption in infancy, vibration sense disturbances and ataxic gait in adolescence. To assess progression of ABL EMG, neuroimaging, neuropsychological tests and ophthalmological examination were made twice within 3 years of time.

Results: The first neurological examination of female had revealed weak tendon reflexes in upper and areflexia in lower limbs, ataxia in heel-to-knee test, positive Romberg test, during the second one impairment of proprioception and vibration sense in gloves-stocking distribution were noted additionally. Comparing to the first neurological examination of male, in which weak tendon reflexes in 4 limbs, ataxia in heel-to-knee test and distal sensory deficiency had been found, only 2 former have worsen. Furthermore unsteadiness of gait was seen in both. In the last few months disturbances in walking have deteriorated in both. EMG tests were consistent and confirmed sensorimotor polineuropathy in female and sensitive polineuropathy in male. Neuroimaging demonstrated slightly extended ventricular system and subarachnoidal space without progression in female and was normal in male. Neuropsychological assessment revealed no deterioration in cognitive processes in female and mild cognitive decline in male. The pigmentary retinopathy, without progression, was seen during fundoscopic examination in male, whereas female ophthalmological examination was unremarkable. Laboratory test revealed undetectable plasma cholesterol, triglyceride and almost complete acanthocytosis of erythrocytes.

Conclusions: Although early treatment commence, the progression of the disease is still noted.

Mo-9

The cerebellar phenotype of adult-onset Sandhoff disease: Three new cases

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Objective: To report three patients with late-onset Sandhoff disease.

Background: Sandhoff disease is a lipid storage disorder caused by a defect in ganglioside metabolism. It is caused by a lack of functional N-acetyl-β-D-glucosaminidase A and B due to mutations in the *HEXB* gene. Typical, early-onset Sandhoff disease presents before nine months of age with progressive psychomotor retardation and early death. A late-onset form is rare and its symptoms are heterogeneous. This late-onset form thus poses a challenge to the clinician and there is often a significant diagnostic delay. As drug trials that aim to intervene in the disease mechanism are emerging, the recognition and identification of Sandhoff disease patients is becoming more and more important.

Methods: Clinical report and auxiliary examinations.

Results: We describe three patients presenting with walking difficulties and balance problems at a variable adult age. The first patient presented with slurred speech as well. Two of the patients were brothers of Dutch descent, while the third patient was of Turkish descent and had consanguineous parents. Neurological examination showed cerebellar limb ataxia, spastic ataxic gait and sensory disturbances. Neuroimaging reported marked atrophy of the cerebellum in the brothers; some white matter lesions, a hyperintense lesion in the right thalamus, and subtle cerebellar atrophy in were seen in the third patient. Nerve conduction studies and electromyography were in all three patients indicative for predominantly sensory, peripheral neuropathy. Laboratory studies showed a profound decrease in *N*-acetyl-β-D-glucosaminidase activities in plasma and leucocytes samples, compatible with a diagnosis of M. Sandhoff. Mutation analysis showed two mutations: IVS12-26 G/A and c.1514G>A; p.Arg505Gln.

Conclusions: Our patients presented with a cerebellar syndrome combined with sensory neuropathy. We identified two known mutations: IVS12-26 G/A and c.1514G>A, with a suggestion of a possible correlation between the c.1514G>A mutation and this phenotype. In a setting that suggests a possibly recessive disease, Sandhoff disease should be considered in patients with a cerebellar syndrome, even if age at onset is above 45 years. Assessment of total N-acetyl-β-D-glucosaminidase and N-acetyl-β-D-glucosaminidase A activities should be requested.

Mo-391

Idiopathic ataxia responsive to a gluten-free diet

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Objective: To report a case of ataxia which improved after introduction of a gluten-free diet.

Background: Sensitivity to Gluten is an immunomediated disorder caused by intake of this substance in genetically susceptible people. According to Hadjivassiliou, Gluten Ataxia is located in this spectrum of Sensitivity to Gluten, as well as Celiac disease and Dermatitis Herpetiformis. It may be defined as sporadic cerebellar form, with presence of antigliadine antibodies, with no other diagnostic alternatives for the ataxia.

Methods: Case report.

Results: Patient, female, born and resident in Aracaju – SE, 18 years, had begun, at the age of 16, to present a gait disturb, balance disorder, even when standing up, with changes on calligraphy and voice. Those symptoms progressed slowly and insidiously, with a later involvement of the extremity of the limbs. No family history for any neurological disease. The patient presented, at neurological examination, bilateral dysmetria in finger-to-finger and finger-to-nose tests and bilateral disdiadocokinesis; no nystagmus; dysarthria with occasional incomprehensible words; dysgraphy; dysbasia with ebrius gait. Magnetic Resonance Imaging revealed no alterations. Frataxine screening test negative; ADCA's screening test negative. With no previous use of any drug or chemical substance that can induce ataxia. Dosage of antigliadine antibodies IgG: 16.9 U/ml (reference – lower than 10 U/ml). After 90 days of a gluten-free diet, the patient has presented a prominent improve on gait, calligraphy, dysartria and no dysmetria. New dosage of antigliadine antibodies IgG: lower than 02 U/ml. New reassessments after 06 and 09 months of introduction of the gluten-free diet have shown maintenance of benefits and improvements mainly of balance and gait.

Conclusions: In what concerns the effectiveness of a gluten-free diet, literature is controversial. Nevertheless, as it is a pathology with few therapeutic options, it is necessary to evaluate properly the possibility of the sensitivity to gluten be involved in such movement disorder.

Mo-392

Frontal ataxia as a late sequel of severe traumatic brain injury

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Objective: To report a case of a man, 42 years, victim of severe traumatic brain injury, who developed gait disturb and appendicular motor coordination, with a pseudocerebellar pattern, eight years after trauma.

Background: Ataxia originated from lesions in frontal cortex has not its pathophysiology completely clarified yet, being important the study of patients with sequels of traumatic brain injury in frontal lobe, which have developed some disturb of motor coordination, for a more comprehensible understanding of this issue.

Methods: Case report.

Results: In 1999, the patient (male, 34 years, right-handed, born and resident in Salvador – BA), a truck driver, has suffered a severe brain injury, attending an accident and emergency hospital, where he has undergone neurosurgical procedure due to extensive sinking of bilateral frontal skull, associated to hemorrhagic contusions, pneumoencephalus and traumatic subarachnoid haemorrhage, being in coma for one week. He was discharged twenty days later with no motor impairment. In 2006, patient went to our service with a complaint of frequent falls, changes in voice, insidiously progressing in six months. With no previous use of neuroconvulsants, neuroleptics or other drugs that can cause ataxia, without family history of neurological diseases. Neurological examination revealed dysarthria, dysmetria at the finger-to-nose, finger-to-finger and ankle-over-tibia tests, more accentuated on the left, dystasia, dysbasia with ebrius gait. Magnetic Resonance Imaging of brain revealed left frontal lobe destruction, extending up to the ipsilateral orbitofrontal area; cerebellum in proper dimension and trophism, within the parameters for his age. Genetic screening for genetic types of ataxia all negative. Patient referred to physiotherapy and speech treatment.

Conclusions: The clinical features of this patient, associated with imaging findings and after exclusion of other causes of ataxia, have led to this diagnose, which agrees with the few similar cases in literature, where such movement disorder appears as a late manifestation.

Tu-1

Gait and limb ataxia in posterior circulation stroke: Clinical-MRI correlations

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Objective: To study correlations betweeen gait and limb ataxia and lesions in the cerebellar systems, including both its hemispheres and peduncles, in posterior circulation (PC) strokes.

Background: Ataxia consists in a lack of coordination in the gait or in the limbs. Ataxia is classically attributed to cerebellar hemispheric lesions, although cerebellar peduncles lesions in the brainstem may also cause this sign. The differential role of the cerebellar cortex and nuclei in causing ataxia has been examined through the International Cooperative Ataxia Rating Scale (ICARS) in hemispheric cerebellar strokes, showing that damage in cerebellar nuclei has a more lasting effect than cerebellar cortical lesions. However ataxia related to cerebellar peduncles damage has not yet been evaluated by ICARS.

Methods: Seventy patients with an acute PC stroke were consecutively recruited in a multicentre setting at North Eastern Italian centres over a 10 month period. Axial T2 MRI and ICARS evaluation were performed.

Results: According to the clinical and MRI data, five patterns were identified. P. 1 (16 pts). Inferior hemispheric cerebellar infarct: no limb ataxia; gait ataxia was present. P. 2 (9 pts). Superior hemispheric cerebellar infarct: both limb and gait ataxia were present. P. 3 (9 pts). Hemispheric cerebellar infarct and brainstem infarct involving the cerebellar peduncles: both limb and gait ataxia were present. P. 4 (29 pts). Brainstem infarct involving the cerebellar peduncle: both limb and gait ataxia were present. P. 5 (7 pts). PC infarct sparing cerebellar pathways: neither limb nor gait ataxia were present.

Conclusions: These cases indicate that gait ataxia is always present when the cerebellar system is damaged, regardless the site of the lesion (cerebellar hemispheres or peduncles). Instead, it appears that limb ataxia is more often associated with a damage in cerebellar peduncles rather than in cerebellar hemispheres. Moreover the severity of both limb and gait ataxia was higher when the cerebellar peduncles were damaged than when the lesion involved the cerebellar cortex.

Tu-2

Ataxia with oculomotor apraxia type 2: Two Spanish families and three novel mutations in the senataxin gene

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Objective: To describe the clinical and molecular findings in two spanish families with ataxia with oculomotor apraxia type 2 (AOA2). They are the first and second families reported in Spain with this disease.

Background: AOA2 is a neurodegenerative disorder characterized by onset between age 3 and 30 years, gait ataxia, cerebellar atrophy, axonal sensorimotor neuropathy, oculomotor apraxia and elevated serum alpha-fetoprotein (AFP). It is an autosomal recessive disease, caused by mutations in the *SETX* gene that encodes the protein senataxin. It is a rare disease and, to date, only 35 mutations have been found in 40 families.

Methods: Four patients from two unrelated families (two siblings each), were studied. All of them were born to non-consanguineous parents. Every patient underwent a clinical examination, a detailed biochemical screening, MRI scans, electrophysiological studies, and molecular testing of the *SETX* gene by direct sequencing of exons and flanking sequences.

Results: All the patients had a fairly homogeneous clinical picture in accordance with the reported AOA2 presentation (table 1).

The *SETX* analysis resulted in the finding of two variations with three novel mutations: A compound heterozygous variation in kindred A, and a homozygous one in kindred B. The compound heterozygous mutation was composed by a 5825T>C substitution, corresponding with a I1942T missense mutation in the protein sequence, and a 7082_7083delAA mutation, corresponding with a nonsense mutation causing a frameshift in Lys2361, followed by a stop codon at position 2364 (K2361fsX2364). The other variation was a 2755_2756delGT mutation, which caused a frameshift in Val919, followed by a stop codon at position 920 (V919fsX920). The proteins resulting from these variations have altered the helicase domain of senataxin, and therefore, its activity. In this regard, these novel mutations are similar to others reported in AOA2 patients.

Table 1 (Tu-2). Clinical features of the patients, and serum level of AFP

Gender, age (years)	Age onset (years)	Gait ataxia	Oculomotor apraxia	Cerebellar atrophy	Peripheral neuropathy	Alpha-fetoprotein (normal : ≤15ng/mL)
Family A						
Male, 27	12	Yes	Yes	Yes	Yes	93.6
Female, 25	23	Yes	Yes	Yes	No	26.7
Family B						
Male, 44	26	Yes	Yes	Yes	Yes	37.7
Female, 37	25	Yes	Yes	Yes	Yes	52.1

Conclusions: We have found three novel mutations in the *SETX* gene in two Spanish families. We have not observed phenotypical differences with regard to the classic AOA2 phenotype.

Tu-3

A new phenotype (SAP) for the spinocerebellar ataxias resulting from senataxin, aprataxin, and protein kinase C gamma gene mutations

M. Feldman, J.J. Esper, A. Ahmed (Cleveland, Ohio)

Objective: To report a novel phenotype of Spinocerebellar ataxia resulting from the overlap of 3 co-existing genetic mutations never before found concurrently in one individual.

Background: The spinocerebellar ataxias (SCA) encompass a complex group of inherited neurological disorders, the genetics of which are not completely understood. A total of 28 gene loci have been identified thus far, and in 14 of these, the underlying mutations are known. Each mutation is associated with a specific phenotype and disease entity. We report a patient with a new phenotype of SCA based on the overlap of 3 co-existing genetic mutations that have never been found concurrently in an individual.

Methods: We evaluated a 65 year old Caucasion male with a 30 year history of progressive tremor and ataxia with a comprehensive neurological examination, neuroimaging, genetic testing, and laboratory work-up. A complete review of the English literature was also conducted.

Results: On physical exam, the patient was found to have dysarthria, severe action tremor, cerebellar ataxia, decreased deep tendon reflexes, axial myoclonus, and evidence of a peripheral neuropathy. An MRI of the brain demonstrated atrophy of the cerebellum. Laboratory testing was normal. Genetic analysis performed by Athena diagnostics revealed mutations of the Aprataxin (APTX), Senataxin (SETX), and Protein Kinase C gamma (PKCγ) genes on chromosomes 9p13.3, 9q34, and 19q13.4 respectively. Out of 7,000 individuals analyzed in the Athena database, only 8 had co-occurence of an APTX mutation with PKCγ mutation, but none had co-occurance of mutations on genes APTX, SETX, and PKCγ.

Conclusions: APTX, SETX, and PKCγ mutations are individually associated with distinct diseases: AOA1, AOA2, and SCA14 respectively. However, no individual or family has ever been reported as possessing all three mutations concurrently. The phenotype that we have described appars to be an overlap of these three individual genetic conditions which we have coined as "SAP". In this particular family, this SAP phenotype appears to be an autosomal dominant inheritance pattern. We plan to proceed with genetic testing on the rest of the family. Differential also includes fragile X tremor ataxia syndrome, though this is less likely as female members of the family have the same phenotype.

Tu-4

Spinocerebellar ataxia type 7 in four Venezuelan families: Clinical caracterization and genetic features

M. Gallardo, A. Soto (Caracas, Venezuela)

Objective: To present the clinical and genetic features of 4 patients from 4 different Venezuelan families with SCA type 7.

Background: Spinocerebellar ataxia 7 is a progressive autosomal dominant neurodegenerative disorder characterized clinically by cerebellar ataxia with progressive macular dystrophy.

Methods: Cases reports.

Results: Patient 1: A 33 years-old Venezuelan man reported a progressive gait disorder and decreased visual acuity of 3 years of evolution. The patient had several familiy members with the same clinical description. Neurological examination showed increased reflexes, lower limbs spasticity and sphincter disturbances. Absence of optocinetic nistagmus and bilateral macula degeneration was observed. MRI was normal. Genetic study revealed a 49 CAG repeats **Patient 2**: A 43 years-old Venezuelan woman with a 8- year history of visual impairment followed of progressive gait disorder and dysartrhia 5 years ago. Her mother, two brothers and one sister had the same condition. Neurological examination showed bilateral horizontal nystagmus, slow saccades, macular atrophy, dysartrhia, dysphagia and severe gait impairment with brisk reflexes. MRI showed moderate cerebellar atrophy. Genetic analysis reported 42 CAG repeats. **Patients 3**: A 17 years-old-venezuelan man presented at age of 15 loss of balance and gait disorder associated with dysartria and decreased visual acuity with progressive worsening of symptoms. His father and his grandmother had the same symptons. Neurological examination showed dysarthria, severe slow saccades, bilateral horizontal nystagmus with macular atrophy, Brisk reflexes and moderate gait ataxia. MRI imaging showed cerebellar atrophy. Genetic analysis showed 59 CAG repeats. EMG demostrated axonal neuropathy. **Patients 4**: A 30 years-old- Venezuelan man who presented at age 25 progressive loss of balance and gait disorders and decreased visual acuity in the following 2 years. Family history was positive. Neurological examination showed dysarthria, severe gait ataxia, brisk reflexes and macular degeneration. Brain MRI revelead moderate cerebellar atrophy. Genetic analysis showed 64 CAG repeats.

Conclusions: We report 4 Venezuelan patients with the SCA 7 mutation belong to 4 different families. All patients showed variable neurological signs with progressive macular degeneration wich is the clinical characteristic of SCA type 7.

Tu-5

Clinical characterization of a Venezuelan family with spinocerebellar ataxia type 10

M. Gallardo, A. Soto (Caracas, Venezuela)

Objective: To describe the clinical characteristic of a Venezuelan Family with Spinocerebellar Ataxia Type 10.

Background: Spinocerebellar ataxia type 10 (SCA 10) is an autosomal dominant neurodegenerative disease characterized by ataxia and epilepsy caused by an unstable ATTCT pentanucleotide repeat in intron 9 of the SCA 10 gene on chromosome 22.

Methods: We studied a patient with SCA10 and his family, which included five affected members of a 3 generation Venezuelan kindred. Detailed clinical history was taken. Physical examination and routine laboratory test were performed. Magnetic resonance imaging of the brain, electroencephalography, nerve conduction studies, genetics study and neuropsychological test were also performed on the affected patient.

Results: The patient is a 30 years old Venezuelan man who developed epilepsy at age 14 years, presenting complex partial seizures and secondary generalized tonic-clonic seizures. When the patient was 20 years old, he complained of walking problems with unbalanced gait that increased progressively. He later complained of dysarthia. On clinical examination, dysmetria was present in the upper limbs. He had severe difficulty for walking. Cognitive dysfunction was observed and Minimental test was 19/30. Cranial nerves examination was normal except for pathological nistagmus and decreased saccadic velocity. The MRI showed brain stem atrophy and cerebellar atrophy. Molecular testing on this patient showed an expansion of 4400 ATTCT repeats at the *SCA10* locus. Family members affected included the father, grandmother, uncle with progressive ataxia and epilepsy and a female cousin which first clinical manifestation was head tremor followed 5 years later by ataxia and no history of epilepsy.

Conclusions: We report the first Venezuelan family with Spinocerebellar Ataxia type 10 with large expansion ATTCT repeats at the *SCA10* locus. SCA Type 10 has been described previously only in Mexican and Brazilian families. The clinical characterization of the Venezuelan family here described presents similarities to the Mexican Families regarding the present of epilepsy and ataxia and is different of the Brazilian Families where ataxia is more frequent and epilepsy is less frequently observed.

Tu-6

A clinico-pathological report of SCA17 associated with a heterozygote small trinucleotide expansion

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Objective: We report the clinical and neuropathological features of a patient with spinocerebellar ataxia type 17.

Background: SCA17 is caused by the expansion of a CAG/CAA repeat within the TATA-box binding protein (TBP) gene on chromosome 6. Although it is still debated, results from several studies suggest that the threshold for pathological expansions varies from 43 to 45 repeats. To our knowledge, neuropathological features of SCA17 have been described in only six patients so far.

Results: The patient's neurological history started at age 32 by an unsteady, broad-based, ataxic gait. Neurological impairment gradually worsened over years and she later developed chorea, dementia and generalized tonico-clonic epileptic seizures. Family history revealed ataxia and cognitive deterioration in her mother and one of her sister but detailed clinical features are lacking. On admission at our clinic, the patient was bedridden and showed signs of chorea and severe dementia. Brain atrophy was diffuse and severe on MRI. Cerebral glucose metabolism measured using positron emission tomography was markedly decreased in all areas including the basal ganglia, cerebral cortex and cerebellum. After ruling out Huntington's disease by genetic testing, the patient was found to carry a heterozygote expansion of CAG/CAA repeats (45/38) in the TBP gene, leading to a diagnosis of SCA17. The patient died several months later from a bronchopneumonia at age 57. Neuropathological features were in keeping with those previously described. We observed diffuse brain atrophy, which was particularly severe in the cerebellum. In cerebral cortex, microscopic changes were most severe in the motor cortex and primary and secondary visual areas. Hippocampus and entorhinal cortex appeared normal. In the striatum, vacuolar changes, neuronal loss and gliosis were severe and predominated in the caudate nucleus and the posterior putamen. The cerebellar cortex showed a profound depletion of Purkinje cells with prominent Bergman glia and severe astrocytosis of the white matter. Immunohistochemistry demonstrated the characteristic neuronal nuclear inclusions positive for ubiquitine, polyglutamine and TBP.

Conclusions: This clinico-pathological report adds to the existing literature suggesting that the size of the pathological repeats has a limited influence on the course of SCA17.

Tu-7

Inter-disciplinary therapy assessment and intervention in ataxia: Current clinical model and case study

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Objective: 1) To describe the model of inter-disciplinary therapy (IDT) clinic currently provided at the Ataxia Centre at NHNN and 2) to provide an illustration of intervention through a case-study of an individual with SCA6.

Background: Research has shown that disease management through an integrated IDT model has positive outcomes for individuals with long term conditions (NSF for LTC Dept of Health 2005). A specialist ataxia IDT clinic was established in 2007, comprising an occupational therapist (OT), physiotherapist (PT) and speech and language therapist (SLT), as well as the Consultant neurologist. This is the first ataxia IDT model in the UK.

Methods: The clinic process was systematically described and a 6 month audit extracted data on the following: number of referrals into the clinic; the subsequent interventions recommended; location of direct therapy delivered i.e. tertiary or community services. An in-depth case study is used to illustrate the clinic process, using retrospective baseline and outcome measures, and feedback from the patient collected through structured interview and questionnaire.

Results: Audit of referrals will show: the proportion of the consultant caseload referred to the IDT clinic; numbers of patients assessed at the tertiary level IDT; percentage of cases in which IDT intervention (PT, OT and/or SLT) was recommended and proportion of therapy delivered through local services or by IDT members as part of their therapy caseload. The case example will demonstrate the outcomes of the service model and of the specific interventions and the effect on quality of life for the individual.

Conclusions: The review of the IDT clinic will demonstrate how a specialist therapy service for patients with ataxia operates within a tertiary centre and supports on-going care through a combination of specialist and community intervention. The holistic nature of the clinic enables core signs and symptoms, such as fatigue, to be managed consistently, and so more effectively, across therapy disciplines. More data on patient experience is needed to investigate further the added-value of the IDT clinic.

Tu-8

restless legs syndrome and sleep disturbance in Friedreich ataxia

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Objective: Friedreich Ataxia (FA) is the most common type of hereditary ataxia. Based on patients complaints about sleep disturbance and pathophysiological considerations we systematically assessed sleep history and polysomnography in FA.

Background: Frataxin deficiency due to a GAA expansion in the first intron of chromosome 9 results in intra-mitochondrial iron accumulation. Its main features include progressive spinocerebellar ataxia, peripheral neuropathy, diabetes mellitus and hypertrophic cardiomyopathy.

Methods: Sixteen consecutive FA patients (10 men, 6 women; mean age, 35.4±11.1 years) with a mean FA duration of 16.5±7.0 years were included and underwent a standardized protocol including a detailed sleep history and polysomnographic recordings.

Results: Eight out of 16 patients were diagnosed with restless legs syndrome (RLS). In 7 patients, RLS onset was after the onset of FA. FA patients with RLS had significant lower ferritin levels than FA patients without RLS (76.3±56.0 vs. 176.3±100.7; $P=0.039$). In polysomnography, all patients had a period leg movement (PLM) index > 15/h during wakefulness, 7 of them also during sleep. An inverse correlation between ferritin levels and PLMW indices was found (rho 0.538, $P=0.039$).

Conclusions: RLS and PLM are common in FA. Their frequency in this primarily spinal ataxia may strengthen the view of a substantial role of spinal sensorimotor integration in the pathophysiology of RLS and PLM. Moreover, ferritin levels appear to correlate with both RLS and PLM during wakefulness in FA, pointing to an additional supraspinal trigger in both conditions.

Tu-9

Transcranial sonography in Friedreich's ataxia reveals hypoechogenicity of the substantia nigra

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Objective: Given the possibility of a systemic mitochondrial defect in Friedreich's Ataxia (FRDA), the present pilot study was performed to determine whether transcranial sonography (TCD) detects altered echogenicity in the substantia nigra (SN).

Background: FRDA is a recessive neurodegenerative disorder which is caused by a loss of function mutation in the X25 gene leading to a reduced expression of the gene product Frataxin. Loss of Frataxin results in mitochondrial dysfunction and cellular iron accumulation. Autopsy studies in FRDA have revealed iron accumulation in the heart and brain. TCS studies have shown altered echogenicity in SN in several neurological disease.

Methods: TCS of the SN of 12 clinical and genetic definite FRDA patients were compared to 25 age and sex-matched controls. FRDA patients (5 female, 7 male) had a mean onset of disease at the age of 20 years (20–54). Their mean disease duration was 15.5 years. All FDRA patients showed triplet repeat extension on chromosome 9 (range 250-1000, mean 422 ± 199). Ataxia scores ranged from 12 to 34 (mean 20.75 ± 6.0). TCS was performed from both sides using the temporal approach. Hyperechogenic areas of both sides were analyzed separately, and a sum-area for both sides was calculated.

Results: Areas of echogenicity in the SN did show significant differences between FRDA patients and controls ($P = 0.03$). The prevalence of SN hypoechogenicity in FRDA patients was 33.3% compared to 8% in healthy control subjects ($P = 0.02$). There was no significant sex difference in echogenicity in any group. Neither did repeat length, age at onset nor disease duration correlate with the extension of SN echogenicity.

Conclusions: We found echogenicity in the SN of patients to be significantly lower compared to age-matched normal control subjects. Although the reason for altered ultrasound echogenicity in the area of SN in FRDA remains elusive, a distinct subcellular iron compartmentalization due to dysfunctional intracellular iron transport may be discussed.

Tu-10

The wide clinical spectrum and nigrostriatal dopaminergic damage in spinocerebellar ataxia type 6

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Objective: To examine the presence of nigrostriatal dopaminergic system derangement in spinocerebellar ataxia type 6 (SCA6).

Background: SCA6 manifests a wide-spectrum of non-cerebellar system involvements, including parkinsonism. However, the cause of parkinsonism is unknown.

Methods: Eight patients with SCA6 who underwent a regular follow-up for at least 2 years participated in this study. A detailed neurological examination was performed and striatal dopamine transporter (DAT) was evaluated using [^{99m}Tc]–TRODAT-1 SPECT.

Results: The main clinical feature of SCA6 was cerebellar ataxia with impaired eye movements. However, a wide-spectrum of non-cerebellar system involvements, such as dysfunctions of the autonomic nervous system, pyramidal and extrapyramidal signs, was also observed. In two patients, mild bradykinesia was noted, and one of these patients was administered $_{L}$-dopa without benefit. [^{99m}Tc]–

TRODAT-1 SPECT showed that in a patient manifesting mild bradykinesia (CAG repeats 13/22), DAT density was reduced to the Parkinson's disease (PD) range with a rostrocaudal gradient typical of PD. The other patient with bradykinesia (12/25) had mildly decreased [^{99m}Tc]–TRODAT-1 uptake. Of the four patients without extrapyramidal signs, three (12/22, 11/25, 17/22) showed mild to severe reduction of DAT density, and one (13/22) had a normal binding.

Conclusions: This study shows that SCA6 has a heterogeneous degree of the nigrostriatal dopaminergic system derangement. Two patients manifested mild bradykinesia, emphasizing the need to screen SCA6 even in patients with progressive ataxia and parkinsonism. Further histopathological studies would be helpful to determine the degree and pathogenesis of nigrostriatal dopaminergic damage in SCA6.

Tu-11

Spinocerebellar ataxia 14: Study of a Norwegian family with a novel mutation in exon 5 in the PRKCG gene

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Objective: To find the genotype in a Norwegian family with dominant ataxia.

Background: Spinocerebellar ataxia type 14 is an autosomal dominant neurodegenerative disorder characterized by a mild and slowly progressive form of cerebellar ataxia. Additional symptoms and signs such as myoclonus, spasticity, hyperreflexia, dystonia, tremor and cognitive decline are reported. The disorder is described as rare, representing 1.5% of the French dominant ataxia families and 4% of the Dutch dominant ataxia families. Age of onset is reported highly variable from early childhood to the sixth decade of life. SCA14 is caused by mutations in the PRKCG gene on chromosome 19q13.4, which is composed of 18 exons and encodes protein kinase C gamma, a protein expressed in the brain and particularly in the Purkinje cells.

Methods: We studied a five-generation family of Norwegian ancestry with ten affected family members. All affected and 17 healthy members were examined. Pathological expansions in the SCA 1, 2,3,6,7 and 8 genes were excluded. Haplotyping using microsatellite markers on chromosome 19q was used to test linkage to the SCA13 and SCA14 loci. The PRKCG gene (exons 1,2,3,4,5 and 10) were then sequenced.

Results: After a mean disease duration of 18.5 years +/- 12 years (range: 4 to 35 years) all 10 affected subjects displayed a slowly progressive cerebellar syndrome that included gait and limb ataxia, slight dysarthria and saccade slowing. Age at onset ranged from 10 to 45 years with a mean of 22.4 years +/- 12 years. All, but the oldest one, aged 70, walked unaided. Genetic studies revealed a C to A missense mutation altering Histidine to a Glutamine at codon 139. The mutation is located in the cystein rich cys2 C1 regulatory domain, a highly conserved region in the gene. The mutation completely co-segregated with the affected family members, and was neither seen in other healthy family members nor in 288 control chromosomes.

Conclusions: We here report a new mutation in the PRKCG gene and the first Scandinavian family with SCA14. This new mutation causes a mild ataxia with pyramidal signs in our family.

Tu-12

The Cuban pathological CAG mutation causing SCA2 was introduced by Hispanics and probably originated between 1408CE and 1733CE in the Cuban population

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Objective: 1) To determine genetic similarity around of CAG repeat in Cuban SCA2 pedigrees. 2) To gain insights in the mutational history of SCA2 in Cuba by using chronologic and molecular approaches.

Background: Till date several hypotheses have been proposed to trace the origin of SCA2 in Cuba. *De novo* mutation (Cuban origin) and the founder effect (Hispanic origin) are the more alluded explanations to explain the origin of SCA2 in Cuba.

Methods: We performed CAG repeat size determination by gene sequencing and haplotype analysis by using microsatellites markers in families with SCA2 from the homogeneous Cuban population. Availability of sequence and haplotypic data in this sample enable us to determine the probably Age when SCA2 mutation arose in Cuba.

Results: STR haplotypes from SCA2 famillies are very homogeneous, with sparse famillies and individuals showing rare haplotypes. Our calculations based on DMLE+2.3, using 6 STR spanning a region of 3 cM with growth rate 0.45-fold per generation, estimated that this mutation originated around 392 years ago, showing a clear picture of a recent mutation origin at about 15.68 generations ago (95% Confidence Interval, 10.23 to 24.56 generations). This 392 year range places the arrivement of SCA2 mutation at 1615CE in the period (1408CE-1733CE) with the foundation important villes by Hispanics at western region of Cuba and out of the slavery introduction.

Conclusions: The importance of estimating age of mutation revolves around the conditions and life style by which SCA2 was fixed and reached the tremendous prevalence in our region.

Tu-13

Loss of CAA interruption in large normal alleles ATX2 is a risk factor to SCA2 gene instability: A haplotype and sequence based study in large Cuban kindreds

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Objective: 1) To decipher the mechanism predisposing to SCA2 locus instability. 2) To identify other factor than CAG predisposing to SCA2.

Background: In Holguín, Cuba, SCA2 reach the highest concentration (43/100,000 people) at worldwide scale. CAA loss linked to certain haplotypes in large alleles can be a predisposing factor for expanded alleles in Cuba.

Methods: We carried out haplotypes and CAG sequence studies in 13 SCA2 pedigrees and 89 controls (n=132 chromosomes) using 6 microsatellite markers –STR- surrounding the mutant CAG.

Results: Strong linkage disequilibrium (LD) between SCA2 mutation and some STR alleles were found. CAG sequence analysis revealed new large alleles 30-31 CAG. These alleles were either pure or lacked the most proximal 5′ CAA interruption and were overrepresented respecting other alleles. We found strong association (p=0.0070) between allele 4 at D12S1672 marker and 22 CAG allele lacking 5′CAA (configuration 13+8). Alleles with CAG different of 22 repeat, and lacked of CAA interspersion were strongly associated (p=0.0000) with allele 4 of STR and the haplotype (3-3-4) (p=0.0013). Further tests narrowed this group to the 29-31 CAG range, showing association (p=0.0063) only with the haplotype 3-3-4 at *D12S1332-D121672-D12S1333*. Alleles with 29-31 CAG were unstable at somatic level (No. peaks = 3±0.18SEM, range 3-8 peaks) contrasting to stable chromosomes (No. peaks = 1±0.18 SEM, range 1-2 peaks) in our kindreds.

Conclusions: Large alleles are the principal source of SCA2 expansion. Somatic mosaicism in normal alleles is a valuable predictor to determine predisposition to genetic instabilities.

Tu-392

Fahr's syndrome as a late manifestation of hypoparathyroidism secondary to subtotal thyroidectomy

N.F. Bernardo, R.A. Kruschewsky, M.N.C. Pereira, I.B.M. Barreto, A.S. Andrade-Filho (Salvador, Bahia, Brazil)

Objective: To report a case of a patient who underwent subtotal thyroidectomy 13 years ago, presenting, about a year ago, compatible

symptoms of Fahr's Syndrome secondary to hypoparathyroidism after subtotal thyroidectomy.

Background: Fahr's Syndrome is clinically translated into calcium deposit in brain parenchyma, particularly in basal nuclei, dentate nucleus and cerebellar cortex, leading to clinical manifestations such as seizures, muscular stiffness and dementia. Endocrine alterations may be involved in its genesis, mainly metabolic disturbs of calcium.

Methods: Case report.

Results: Patient, female, 67 years, with a complaint of difficulty to walk for about one year and seizures – generalized tonic-clonic seizures, and the last episode, two months before the assessment on our service. Concomitantly, she presented joint stiffness and slowed movements. Medical history of subtotal thyroidectomy 13 years ago, in use of levothyroxine 200 mcg/day. General physical examination revealed bradikinesia, muscular stiffness, predominantly distal, symmetric, low to moderate intensity; mini mental state examination 28/30, lost points in attention and calculation. Complementary tests: normal haemogram; Albumin: 3.7g/dl; Urea: 37 mg/dl; Creatinine: 1.1 mg/dl; AST: 76 U/l, ALT: 68 U/l; Fasting plasma glucose: 91 mg/dl; Sodium: 139 mEq/l; Potassium: 3.8 mEq/l; Calcium: 7.4 mg/dl; Magnesium: 1.2 mg/dl; Phosphorus: 8.5 mg/dl; PTH: 3.0 pg/ml; euthyroidic at the moment; EEG: diffuse paroxysmal activity; CT scan: symmetric diffuse calcifications, predominance in dentate nuclei, basal nuclei, occipital lobe and corona radiata. We have started calcium and vitamin D3, and anticonvulsant therapy. After six months, she remained with no seizures and normalized EEG.

Conclusions: Isolate cases of hypoparathyroidism after surgery are considered rare, particularly when compared to idiopathic ones, since the assessment of patient in postoperative period allows recognizing hypocalcaemia and its correction appears to prevent calcification.

Tu-393

Cerebrovascular accident in parietal lobe leading to voluntary movement disorders – Parietal ataxia

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Objective: To describe a case of acute sensitive hemiataxia after ischemic CVA involving parietal lobe and stress the importance of the knowledge of those motor presentations in lesions of this region.

Background: Critchley, in 1953, and Denny-Brown and Chambers, in 1958, have already listed ataxia as a motor manifestation in parietal lobe injuries, sub-dividing it in two groups: sensitive and pseudocerebellar. Ghika and cols., in a prospective study of 32 patients in acute stage of cerebrovascular accident located only in parietal lobe, have found 75% of incidence of ataxia (70% sensitive and 5% pseudocerebellar), being the groups dependant on the areas primarily damaged for ischemia, stressing correlation between chronic lesions and the sensitive pattern.

Methods: Case report.

Results: Patient, female, 55 years, hypertensive, dyslipidemic, tabagist, presented, in 2005, an episode of right faciobrachiocrural hemiparesis, associated to ipsilateral disproportionate hemiparesis, with regression of motor impairment until its complete restitution in a few days, as well as the paresthesic complaints. Since then, she has presented frequent falls, mainly at the twilight, referring balance disturb when she closed her eyes; gait disorder, with preponderant support in heels. Neurological examination revealed preserved superior mental functions, clock test normal, right kinetic-postural sensitivity impairment, right vibration sensitivity deficit, dysmetria on the right side, with visual correction in finger-to-nose test; anomalies at localization and direct tactile discrimination; astereognosis in right hand; no protopathic sensitivity impairment; preserved diadochokinesis. Axial Computed Scan (CT) of the brain revealed hypodensity in left parietal area, compatible with post-central gyrus. Syndromic diagnosis of right sensitive hemiataxia. Laboratory tests to other causes of sensitive ataxia all negative (VDRL, polyneuropathies, diabetes, vitamin B12 dosage, etc).

Conclusions: This case is important to highlight an unusual presentation of a common neurovascular pathology and bring to discussion the motor impairment of parietal lobe.

We-1

Spinocerebellar variant of adrenoleukodystrophy with a novel ABCD1 gene mutation

J.-Y. Li, C.-C. Hsu, C.-R. Tsai (Kaohsiung, Taiwan)

Objective: To describe a novel ABCD1 gene mutation in a patient with X-linked adrenoleukodystrophy (ALD) presenting as adult-onset spinocerebellar ataxia.

Background: X-linked ALD is a genetic disorder caused by a defect in the gene ABCD1, which mapped to Xq28 and codes for a peroxisomal membrane protein that is a member of the ATP-binding cassette transporter superfamily. The genetic defect results in defective peroxisomal β-oxidation and the accumulation in all tissues of saturated very long chain fatty acids (VLCFAs). Childhood cerebral ALD and adrenomyeloneuropathy, the two most common phenotypes, accounts for 70-80% of patients. Clinical presentation as spinocerebellar ataxia has been reported rarely.

Methods: A 37-year-old man has been suffered from progressive gait unsteadiness since age 28. On neurological examination, there was a mild dysarthria, and limb and gait ataxia. He also revealed generalized hyperreflexia, extensor plantar responses, and spastic paraparesis. There was no somatic or cortical sensory loss.

Results: His brain T2-weighted magnetic resonance imaging showed hypersignal lesions in the bilateral areas extending from the

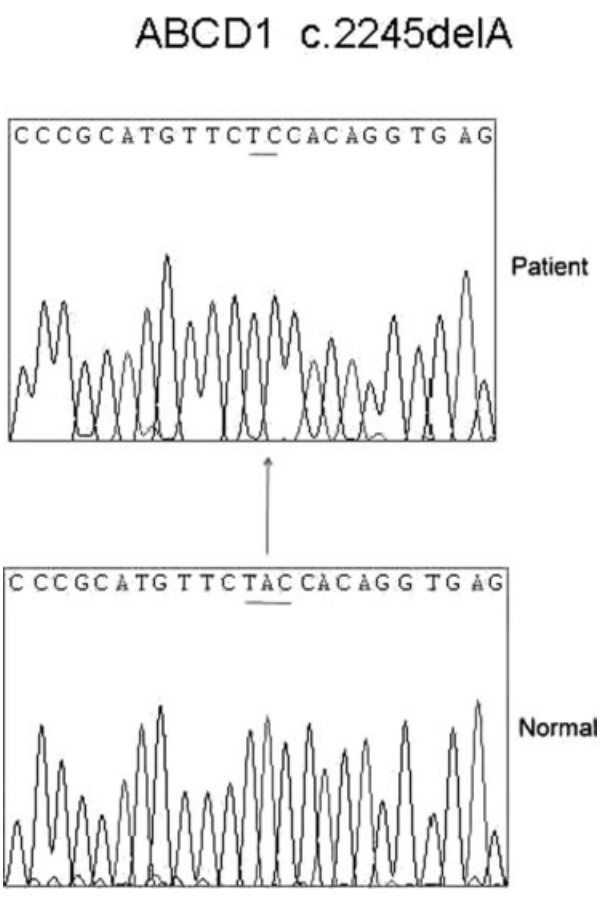

FIG. 1 (We-1).

posterior limbs of internal capsule to the cerebral peduncles, and mild cerebellar atrophy. MRI of spine revealed mild atrophy of upper cervical cord. Laboratory examinations showed normal plasma concentrations of cortisol and ACTH. Biochemical studies revealed elevated plasma VLCFA (C24/C22= 0.9469, C26/C22= 0.0425). His mother does not have any clinical abnormalities or elevated VLCFA. Direct sequencing for the ABCD1 gene of the patient and his mother revealed a deletion of 1 base pair in exon 8 at nucleotide position 2245 (2245delA) in the ABCD1 gene.

Conclusions: Spinocerebellar ataxia is an unusual manifestation in an adult with X-linked ALD. It is important to consider X-ALD as a differential diagnosis in patients with spinocerebellar ataxia. The 2245delA mutation is first reported in patients with spinocerebellar variant of X-ALD.

We-2

Safety and tolerability study of lithium carbonate in spinocerebellar ataxia type 1 (SCA1) patients

G.J. Lopez, E. Considine, B. McElroy, D. Haubenberger, A. Razzook, H. Zoghbi, M. Hallett (Bethesda, Maryland)

Objective: Ongoing pilot study to determine lithium carbonate safety, tolerability and side effect profile in patients with SCA1.

Background: SCA1 is an autosomal dominant neurological disorder caused by a trinucleotide repeat expansion encoding glutamine in the ataxin-1 gene. The neurological disorder results from degeneration of neurons in the cerebellum, spinal cord and brainstem resulting in progressive ataxia and loss of muscle coordination and strength. Lithium carbonate is a mood stabilizer that has been reported to show neuroprotective effects in a variety of disease models, including the SCA1 knock-in mouse model.

Methods: Currently, 7 patients with molecularly diagnosed SCA1 have been enrolled and evaluated at the National Institutes of Health Clinical Center during lithium carbonate titration, while on lithium therapy for 3 months, and one month after discontinuation of lithium. Safety measures have included laboratory parameters, EKG, balance/ataxia rating scales, tremor evaluation and cognitive measures.

Results: Of the 7 subjects enrolled, 3 have completed the study, while the remaining 4 are at different phases of the protocol. Our end-point for the study will be the completion of 10 subjects. All subjects thus far have tolerated lithium carbonate without significant systemic side effects or worsening of symptoms.

Conclusions: Our preliminary experience suggests that lithium carbonate appears to be tolerated safely in this patient population. Further studies are necessary to evaluate efficacy.

We-3

Sleep pathology characterization in presymptomatic relatives of the SCA2

V.-P. Luis, R.-L. Roberto, C.-O. Nalia, G. Sanchez-Cruz, G.-P. Lourdes, G.-Z. Yanetza, H.-V. Reyes, A.-R. Raul, T.-P. Cira (Holguin, Cuba)

Objective: To characterize the sleep pathology in SCA2 presymptomatic relatives by polysomnographic recording and to evaluate its relation with the molecular features of the disease.

Background: The SCA2 has a prevalence of 42 per 100,000 inhabitants in Holguin province, which is the highest one reported worldwide. The sleep disorders are common complaints of SCA2 patients and their relatives, fundamentally towards the final stages of the disease.

Methods: Thirty six genetically confirmed SCA2 presymptomatics relatives and sex-and age-matched healthy controls were studied by two all-night video polysomnographies, Multiple Sleep Latency Test (MSLT) and sleep interviews. The polyglutamine expansion size were obtained in all subjects.

Results: Almost all presymptomatics reported good subjective sleep quality and negated incidents of REM behavior disorders (RBD). Nevertheless, REM sleep was abnormal in 60% of the presymptomatics relatives. The most striking and consistent pathology of REM sleep was its significant reduction in relation to the control group. The mean Epworth scores was not significantly different from healthy controls, which were supported by the results of MSLT. Other PSG abnormalities were decrease of REM density, increase of arousal index and significant reduction of sleep efficiency. Regression analysis showed a significant influences of time to manifestation on sleep efficiency ($r=0.53$, $p=0.001$). There was not correlation between CAG repeat and any sleep parameter. The mean Epworth scores of presymptomatics were not significantly different from healthy controls, which were supported by the results of MSLT.

Conclusions: The early and progressive REM sleep reduction can be associated with the pons, nigrostriatal and thalamic degeneration. This is the first clinical and polysomnographic characterization of

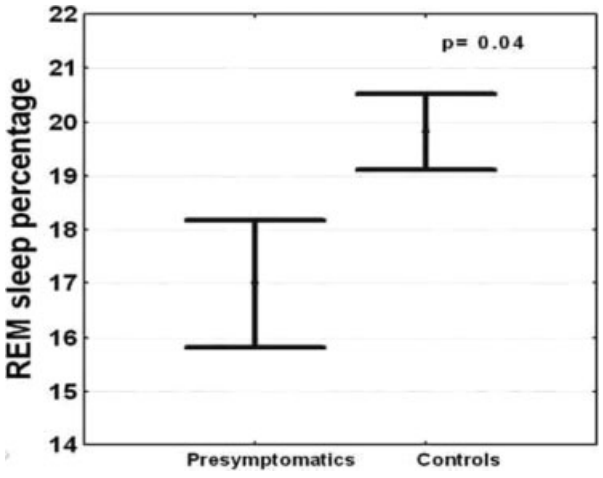

FIG. 1 (We-3).

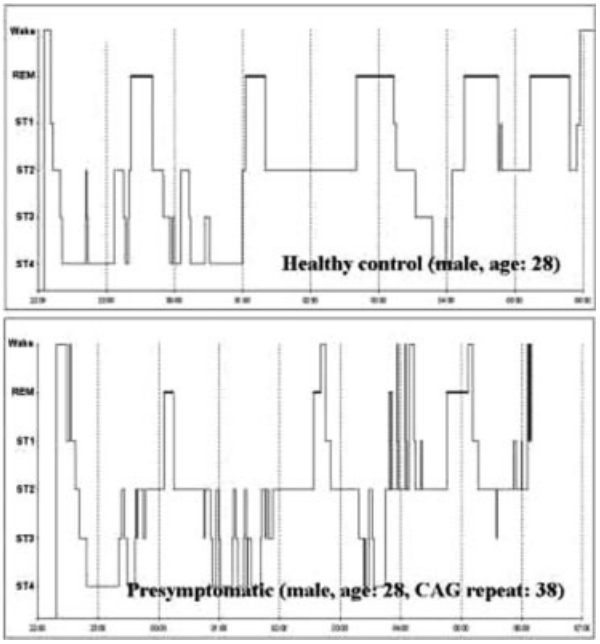

FIG. 2 (We-3).

sleep disorders in a large population of SCA2 presymptomatics. Thus, REM pathology is a sensitive SCA2 endophenotype, reflecting early brainstem degeneration and preceding ataxia manifestation. Velazquez-Perez Luis. Spinocerebellar Ataxia Type 2. Neurophysiological Features for the diagnoses, prognoses and evolution of the disease. Ed. Holguin. 2008. 2nd Edition, (Printed in Colombia).

We-4

A need for global networking to clarify phenotypic dilemma in hereditary ataxias: An overview from clinicogenetic analysis of SCA families of Indian origin

F. Mohammed, V. Scaria, I. Singh, B. Natt, A. Srivastava, M. Mukerji (New Delhi, India)

Objective: 1) Creation of locus specific disease database of SCAs for G2P 2) Study of prevailing clinical and genetic variations in different SCAs in India for accurate clinical characterization.

Background: Spinocerebellar ataxias constitute a group of disorders majority of which are dominantly or recessively inherited e.g. SCA (1-29), DRPLA and FRDA. The remaining SCAs are linked to mitochondrial mutations or sporadic group (MSA). Molecular analysis has allowed diagnosis and classification of SCAs but their growing number and widely prevalent phenotypic heterogeneity have rendered confusion in genetic investigations. Identification of new loci would facilitate elucidation of the pathological events behind these incurable disorders.

Methods: We looked for genetic and symptomatic variability in 530 families of SCAs (familial and sporadic cases). Genetic screening was carried out for SCA1-3, SCA6-8, SCA11-12, SCA17, FRDA and DRPLA. Molecular analysis for other known disease is underway i.e. SCA5, SCA14, FXTAS etc.

Results: 43% of the total no. of patients was characterized to 6 known SCA types. SCA2 has the highest prevalence followed by SCA12 in India. Among 300 uncharacterized cases 20% were familial and rest were sporadic manifesting the phenotype of ADCA category, multiple system atrophy etc. SCA6, SCA8, DRPLA&SCA11 were not observed in any of the families. Clinically we observed wide amount of heterogeneity w.r.t. each subtype which often misleads in diagnosing and patient management. In order to facilitate, reporting & awareness of observed phenotypic variability we have created one of the largest LSDB (SCA-LSVD) which houses clinical and genotypic information pertaining to the various SCA loci of patients from more than 500 families across India.

Conclusions: Research in SCAs requires systematic multinational reporting of new variants and clinical abnormalities observed across the world at single platform. SCA-LSVD would be a very useful starting point for understanding the molecular correlates of phenotypes in ataxia.

We-5

Molecular analysis of Friedreich's ataxia (FRDA) mutation in Indian families: Evidence for common founder

I.S. Mudila, F. Mohammed, A.K. Srivastava, M. Mukerji, M.V. Padma, S. Jain, M. Bihari (New Delhi, Delhi, India)

Objective: To trace founder chromosome of expanded GAA allele at Friedreich's Ataxia locus in Indian population.

Background: FRDA is a progressive recessive ataxia caused by expansion of GAA repeats in the range of 600 to 1200 in the intron 1 of frataxin gene, while normal individuals are restricted to a threshold which varies in length from 7-16.

Methods: For haplotype we studied 23 patients of north Indian and 8 patients of south Indian origin. 250 unrelated ethnically matched controls from both the population were also recruited for the study. The families though inhabitants of diverse geographical regions were of Indo-European (IE)and Dravidian origin (Indian Genome Variation Consortium). For analysis 5 tag SNPs were derived from CEU population spanning the region 165 kb around GAA repeats, which also include three SNPs (CS2- rs2871223; ITR3-rs3829062; FAD1 – rs11145465) which have earlier been reported to be associated with GAA expanded alleles in the French population as well as few East Indian families.

Results: Haplotype analysis using 5 SNPs revealed that haplotype AGCCC is associated with 50% and 62.5% of expanded GAA allele in north and south Indian population respectively, similar haplotype is observed with majority of large normal alleles (LN) allele in both the populations. We observed 4 SNPs rs11145465, rs7861997, rs11145326 and rs3829062 significantly associated ($p<10^{-6}$) with expanded as well as LN allele in both north and south Indian population, whereas rs2871223 (CS2) is found to be significantly associated with FRDA families of north Indian origin only. The SNPs rs11145465, rs3829062 and rs2871223 have been significantly associated with expanded alleles in French population. The frequency of LNs is 17% in French population and we observed frequency of LNs to be 6.6% in the north Indian and 9.8% in the south Indian population.

Conclusions: This suggests that majority of the expanded alleles have similar haplotype background suggesting the presence of common founder. FRDA mutation predates divergence of European and Indian populations of Indo-European origin and comparatively lower frequency of LNs in Indian population suggest the differences in prevalence of FRDA between two populations.

We-6

Dysarthria in Friedreich's ataxia

J.E. Folker, B.E. Murdoch, L.M. Cahill, A.P. Vogel, M.B. Delatycki, L.A. Corben (Brisbane, QLD, Australia)

Objective: To provide a comprehensive description of the perceptual speech dimensions, speech intelligibility and dysarthria severity of a group of 38 individuals diagnosed with Friedreich's ataxia (FRDA).

Background: FRDA, a neurodegenerative spinocerebellar disorder, is the most common hereditary ataxia. Its major clinical features are progressive ataxia, dysarthria, scoliosis and cardiomyopathy. The dysarthria associated with FRDA has been described as prominently ataxic in nature with mixed spastic components also commonly presenting.

Methods: The study included 38 individuals (21 female, 17 male) with a confirmed diagnosis of FRDA. A group of 20 non-neurologically impaired individuals, matched for age and gender, served as controls. A speech sample was obtained from each participant and the Assessment of Intelligibility of Dysarthria Speech was administered. Two qualified speech-language pathologists perceptually analysed each speech sample, rating 30 different dimensions of speech and classifying the dysarthria type and severity.

Results: All FRDA participants presented with dysarthria with severities ranging from mild to moderate. Correlation analysis indicated a relationship between dysarthria severity and disease duration. Disturbances were evident across all subsystems of speech with prosody the most prominently affected. A range of pure and mixed dysarthria was described with a mixed spastic-ataxic type the most frequently occurring.

Conclusions: The findings are indicative of the extensive and variable neuropathologies that can be involved in the disease of FRDA. A relationship between dysarthria severity and disease duration was revealed, proposing that an investigation of speech over time may provide an avenue to assist in the prediction of disease progression.

We-7

Articulatory disturbance in Friedreich's ataxia: An electropalatographic study

J.E. Folker, B.E. Murdoch, L.M. Cahill, M.B. Delatycki, L.A. Corben, A.P. Vogel (Brisbane, QLD, Australia)

Objective: To use the instrumentation of electropalatography (EPG) to investigate the spatial and temporal aspects of linguopalatal

contact during consonant production in a group of individuals with Friedreich's Ataxia (FRDA).

Background: FRDA is an autosomal neurodegenerative disease primarily affecting the spinocerebellar tracts, the corticospinal pathways and the dorsal columns. Clinical manifestation generally begins in childhood, with the individual becoming wheelchair bound in early adulthood and life expectancy being markedly reduced. Dysarthria constitutes a core symptom of FRDA, presenting between 5 and 19 years post onset of disease. Perceptual and acoustic studies have revealed an articulatory disturbance to be prominent in the dysarthria associated with FRDA.

Methods: The subject group consisted of seven individuals, four females and three males, with confirmation of FRDA. The mean age of the group was 41.71 years (SD = 8.3) with an age range of 35 to 56 years. A group of 14 non-neurologically impaired adults served as controls. The Reading EPG3 system was used to measure the amount and pattern of linguopalatal contact at the point of maximum contact and the consonant phase durations for an array of consonants, /t/, /l/, /s/, /k/. All consonants were word initial position, within words of CV and CVC construction, embedded into short sentences and repeated aloud five times by each subjects while wearing an EPG palate.

Results: The FRDA group exhibited normal spatial configurations of linguopalatal contact. Temporal measures revealed significantly prolonged closure phase durations for each consonant singleton, contributing to longer consonant phase durations compared to the control group.

Conclusions: The FRDA group demonstrated disturbances in articulatory timing while maintaining normal linguopalatal contact patterns. The results are discussed in relation to the neuropathophysiological effects of spinocerebellar degeneration on speech motor control systems.

We-8

Autosomal dominant ophthalmoplegia and ataxia in an Austrian family carrying the SCA28 mutation

W. Nachbauer, S. Hering, D. Di Bella, F. Taroni, M. Schocke, W. Poewe, S. Boesch (Innsbruck, Tirol, Austria)

Objective: We here report the first multigenerational Austrian family carrying the spinocerebellar ataxia type 28 (SCA28) mutation.

Background: SCA28 is a novel form of autosomal dominant cerebellar ataxia and has recently been linked to chromosome 18p11.22-q11.2 in 2 Italian families.

Methods: The family consists of 8 subjects out of 3 generations. Four affected family members were detected. Neurological work-up was extensive in 2 affected sisters, especially in the index patient who has been followed-up for more than 10 years. Clinical assessment consisted of repeated evaluation including ataxia rating scales such as the Scale for the Assessment and Rating of Ataxia (SARA), magnetic resonance imaging (MRI), as well as neurophysiological and neuropsychological testing. Genetic confirmation was obtained as described by Cagnoli and co-workers (2006).

Results: In generation I family history revealed an affected male person with predominant ophthalmoplegia and only mild cerebellar ataxia. Ophthalmoplegia occurred in his forties while he was still able to walk with a walking aid when he died at the age of sixty. Two of his children, including the index patient, developed double vision due to ophthalmoplegia and the need of surgical neuro-ophthalmologic intervention in their twenties. Gait ataxia remained mild, but was more severe in the second affected generation. Dysarthria and upper limb ataxia was slowly progressive reflected by SARA score points of 14/40 after a disease duration of 25 years. Repeated MRI revealed minimal progression of cerebellar atrophy. Neurophysiology and neuropsychological assessments remained unremarkable. Generation III consists of 4 young subjects in their twenties, one of whom showed signs of oculomotor disturbance, but no ataxia and was tested positive for SCA28.

Conclusions: Clinically SCA28 is defined by predominant ophthalmoplegia and slowly progressive cerebellar ataxia. In contrast to recently reported Italian SCA28 families, we found earlier onset and more severe course of the disease in generation II and III. Given the clinical presentation of this SCA mutation, genetic testing for SCA28 in the case of the above described combination of symptoms may be useful. Video of the index patient will be presented.

We-9

Genetic heterogeneity of SCA linked to chromosome 15?

I.N. Petrovic, A. Weissbach, A. Djarmati, K. Lohmann, N. Dragasevic, C. Zuhlke, M. Svetel, C. Klein, V.S. Kostic (Belgrade, Serbia)

Objective: Clinical and genetical description of new form of autosomal dominant spinocerebellar ataxia.

Background: Autosomal dominant spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of neurodegenerative disorders, characterized by degeneration of the cerebellum and spinocerebellar tracts, variably combined with involvement of the other neuronal systems. Hallmark features of all SCAs are a progressive impairmant of muscular coordination of the extremities, dysarthria and unsteadiness of gait, wich may be combined with additional neurological signs.

Methods: We clinically and genetically investigated a Serbia family (Family DII), four members of whom are affected with a novel form of SCA. All affected and ten unaffected individual underwent a standardized clinical interview and detailed neurlogical examination. Repeat expansions were excluded in the genes causing SCAs 1-3, 6, 7, 10, 12, and 17. A genome-wide linkage analysis was performed using more than 400 microsatellite markers, followed by sequence analysis of two candidate genes in the linked region including the recently identified SCA 11 gene (TTBK2) and SEMA6D.

Results: All four affected family members had truncal and limb ataxia combined with gaze-evoked nystagmus, dysarthria, tremor, pyramidal signs, a polyneuropathy, and urinary incontinence. In addition one affected member showed marked cognitive and psychiatric signs, and two others showed depression. The mean age at onset was 20.3 (range 18-23 years). The mode of the inheritance was compatible with autosomal dominant transmission with high penetrance. The putative disease gene in this family was most likely mapped to a region telomeric of D15S994 on chromosome 15q with a maximum model-based multipoint LOD score of 1.80. This region also included the TTBK2 gene that is associated with SCA 11. However, mutations in this gene, as well as in another candidate gene on chromosome 15q, SEMA6D, were exculuded.

Conclusions: Our findings suggest the presence of a second SCA gene on chromosome 15q.

We-10

Using a simplified trail making test B to assess visuo-spatial and sequencing abilities in hereditary spinocerebellar ataxias (SCA)

E. Pretegiani, G. Veneri, P. Federighi, N.R. Polizzotto, G. Cevenini, F. Rosini, M.T. Dotti, A. Federico, A. Rufa (Siena, SI, Italy)

Objective: To assess visuo-spatial and sequencing abilities using a simplified visual trial making test B (sTMTB) in patients with SCA2 compared to other hereditary cerebellar ataxias (hSCA) and controls.

Background: While it is convincing that the cerebellum plays a crucial role in the control of space-related behavior not only regulating the motor system but, also, participating in higher order cognitive functions such as visuo-spatial processing, the modality of this contribution has not yet been clearly established. SCA are a group of inherited rare disorders due to cerebellar degeneration. In SCA2 basal ganglia, cerebral cortex, white matter and brainstem are also involved determining impairment of eye movement control. The sequence of fixations and saccades during visual exploration, as recorded by an

eye tracking system, is an useful and reproducible method to study cognitive behavioral pattern.

Methods: Subjects were asked, in an eye tracking setting, to complete a visual sequence of numbers and letters (sTMTB) and to perform a pro-saccade and anti-saccade test. Patients also underwent a neuropsychological evaluation. A quantitative analysis of saccadic and common gaze quantification parameters was performed. Sequencing ability on sTMTB was evaluated by respecting the sequence and by analysis of fixations in each region of interest (ROI) and from a ROI to another.

Results: On sTMTB number of explored ROI was significantly higher in SCA2 and hSCA in respect to controls and correlated to the correctness in sequencing ($p<0.01$). The number of fixations out of ROI and their mean distance from ROI was higher in patients than in normal subjects. No significant differences were found between SCA2 and hSCA. The peak saccade velocity was reduced, while the saccade duration was increased in pro and anti-saccade test in SCA2 compared to hSCA or controls, no significant differences were found between hSCA and controls.

Conclusions: Our findings show that SCA patients present a common visuo-spatial pattern of exploration and sequencing, which may reflect a difficulty in building a visual map, confirming the crucial role played by cerebellum in cognitive functions as visuo-spatial and sequencing ability.

We-11

Saccadic movements in SCA2. From disorders to electrophysiological biomarkers for genetic and clinical researchs

R.-L. Roberto, V.-P. Luis, C.-O. Nalia, S. Carola, A. Georg, M.-M. Jacqueline, T.-P. Cira, G.-Z. Yanetza (Holguin, Cuba)

Objective: To characterize the saccadic abnormalities related to SCA2 by electronystagmography; evaluate their correlation with disease duration, ataxia score and polyglutamine expansion.

Background: Saccadic eye movement is a rapid shift of eye position to capture an object in the environment. Saccade pathology is a common symptom of SCA2.

Methods: 107 SCA2 patients, 53 presymptomatics and 110 controls were studied by electronystagmography to evaluate the maximal saccade velocity (MSV), latency and deviation. For a longitudinal study, 50 SCA2 patients and controls were followed during six years.

Results: SCA2 patients showed significant reduction of maximal saccade velocity (MSV), prolonged latencies and hypometric saccades to 600 predictable amplitude. Significant saccadic slowing, but less severe than patients, was observed in presymptomatics. MSV was negatively correlated with the polyglutamine expansion in both groups. In SCA2 patients, all saccadic abnormalities were significantly accented along time. Compared with controls, the saccadic slowing and hypometria showed a larger magnitude of progression than latency prolongation.

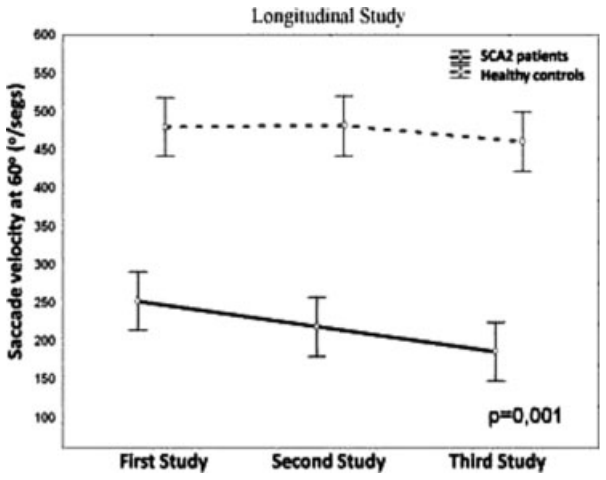

FIG. 1 (We-11).

Conclusions: Saccade velocity is the most important electrophysiological research tool for the study of genetic determinants of SCA2. The progression patterns of saccade slowing and hypometria appear to be objective biomarkers that reflect the severity of neurodegenerative process in the brainstem and cerebellum along time in SCA2 patients. This is the first electronystagmographical study carried out in a large population of SCA2 patients and presymptomatic carriers. Also it includes the first longitudinal study of saccadic abnormalities in SCA2 patients. Those findings identify MSV as the most important endophenotype for the estimation of SCA2 mutation size. Rodriguez-Labrada R, Velazquez-Perez L, Siegfried C, et al. Saccadic movements in SCA2: From disorders to electrophysiological biomarkers for genetic and clinical research. Clin Neurophy 2008; 119(2):143–177. Velazquez-Perez Luis, Sanchez-Cruz G, Canales Ochoa N, et. Al. Electrophysiological Features in Patients and Presymptomatic Relatives with Spinocerebellar Ataxia type 2. J Neurol Sci 2007, 263:158-164.

We-12

Ataxia with ophthalmoplegia and/or sensory neuropathy is frequently caused by POLG mutations

C. Schulte, M. Synofzik, T. Gasser, L. Schöls (Tubingen, Germany)

Objective: To analyse the indicative value of ophthalmoplegia and sensory neuropathy for mutations in DNA polymerase gamma (POLG).

Background: Genetic heterogeneity of ataxias is immense and phenotypic characteristics indicating the responsible gene are highly warranted to guide genetic analyses. Patients with sensory ataxic neuropathy, dysarthria and/or dysphagia and ophthalmoparesis (SANDO) have been reported to carry mutations in DNA polymerase gamma (POLG).

Methods: A continuous series of 26 ataxia patients from 23 families with either external ophthalmoplegia or sensory neuropathy were screened for POLG mutations by direct sequencing. Patients with common repeat expansion disorders (Friedreich ataxia, SCA1-3, SCA6+7, SCA17) were excluded.

Results: Well-established POLG mutations were found in 11 of 23 index patients. All but two patients presented with recessive mutations with A467T (5x) and W748S (5x) being most frequent. Two novel POLG mutations were identified: An insertion leading to a premature stop-codon (insA c.3594; p.T1199fs1215X) and a homozygous -10c>t mutation in intron 16 which was not found in 212 control chromosomes. One patient carried a heterozygous N468D mutation which was only described as recessive mutation in earlier studies but cosegregated in our family in a dominant pattern over two generations. POLG patients varied in age of onset from 12 to 44 years. Patients with the full SANDO phenotype were positive for POLG mutations in 78%. Of the 13 patients with ataxia plus sensory neuropathy 3 (23%) had POLG mutations. The single patient presenting with ataxia plus ophthalmoplegia without neuropathy was carrying an established autosomal dominant POLG mutation (G517V). Affective disorder, in particular depression, was frequent in POLG mutation carriers (6 of 11 patients; 55%), but not in non-POLG patients (1 of 12 patients, 8%). Sensory neuropathy was of axonal type in all POLG mutation carriers whereas 6 of 12 patients without POLG mutations revealed a demyelinating component of sensory neuropathy.

Conclusions: Ophthalmoplegia had a predictive value of 8/10 (80%) and neuropathy of 10/22 (45%) for POLG associated ataxia. Our results strongly suggest sequencing of the POLG gene as first line analysis in ataxia patients with ophthalmoplegia and recessive or sporadic disease when Friedreich's ataxia is excluded.

We-387

SCA-2 and periodic limbs movements during sleep with anticipation phenomenon

H. Orrego-Castellanos, M. Rodriguez, V. Alatriste, M. Merlos
(Mexico City, Mexico)

Objective: To report an SCA-2 case with periodic limb movements.

Background: Spinocerebellar ataxia (SCA) case series have already been described elsewhere, some of them with anticipation phenomenon. Either REM or some No-REM sleep disorders have been reported in neurodegenerative diseases included SCA, but the finding of periodic limb movements during sleep is not coined at all.

Methods: 44 year old women with 3 year onset hypertension. She had no toxic or drugs exposure. She presented with a 3 year history of loss of balance, gait instability, indistinct lateropulsión with frequent falls, head and intention tremor. Progressive dysartia began two years ago. She had no weight loss nor other systemic symptoms. Her offspring (13 year old boy and 18 year old girl) has similar symptoms. Neurological examination showed ocular dysmetria, slow saccades and abolishment of optokinetic ocular movements as well as hypotonia, bilateral dysmetria, dysdiadochocinesia and ataxic gait. Head and intention tremor was also seen.

Results: Diagnostic work-up ruled out tumors, ELISA HIV was negative, cerebrospinal fluid was normal. Hormonal profile, vitamins E and B complex were in range. Given the family history, spinocerebellar ataxia was intentionally investigated. MRI (figure 1)showed prominent atrophy of all structures of brainstem and cerebellum. Ataxin-2 (CAG expansion) was positive with 198 and 214 alleles for the patient and her daughter respectively (figure 2). Ophtalmologic examination revealed no other findings. No electrophysiological evidence of neuropathy was found. The polysomnography met diagnostic criteria for periodic limb movements during sleep. Video will be available.

Conclusions: This case highlights not only by the presence of the anticipation phenomenon, but also for the documentation of periodic limb movements, which has not been strongly associated with SCAs.

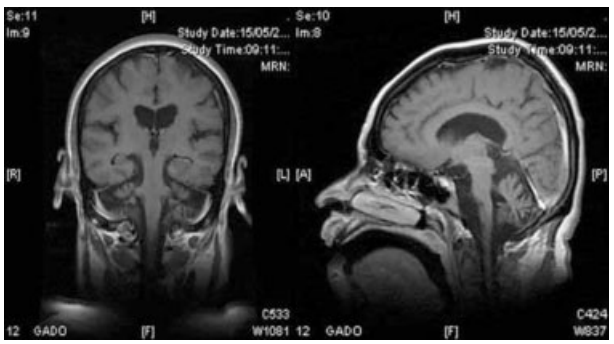

FIG. 1 (We-387).

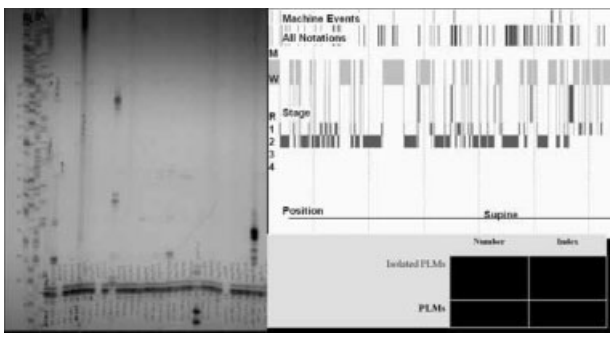

FIG. 2 (We-387).

We-388

Objectification of spinocerebellar syndrome in hereditary ataxias by combined dynamic and kinematics motion analysis

J. Schwabova, F. Zahalka, Z. Musova, M. Kopeckova, A. Zumrova
(Prague, Czech Republic)

Objective: The term "ataxia" is typical clinical neurological symptom for affection of cerebellum or its centripetal and centrifugal tracts. Goal of the study is to upgrade ataxic neurological testing by implement of combined dynamic and kinematics motion analysis in diagnostic process and test of physiotherapy effect routine practice.

Background: We register 1120 ataxic patients of Czech origin from unrelated families attending genetic testing because of idiopathic, progressive ataxia and inheritance compatible with autosomal dominant, recessive or sporadic disease. 42 patients from the examined group were homozygous for a GAA triplet-repeat expansion in intron 1 of the FRDA gene; in 10 patients from 5 families have been found mutation in gene that causes spinocerebellar ataxia type 1 (SCA1), in 36 patients from 21 families SCA2 verified, and 1 SCA7 patient.

Methods: We examined the effect of degenerative cerebellar and dorsal columns lesions on postural control in 3 groups of adult subjects: 5 patients with autosomal dominant spinocerebellar ataxia (ADSCA), 3 patients with Friedreich ataxia (FRDA)–both groups are confirmed by DNA analysis, and 5 matched healthy controls. The subjects were first tested on a force platform (Kistler) that measures ground reaction forces in three axes (X,Y,Z), providing information about oscillations of the projection of the centre of gravity on the ground. Two conditions were performed with eyes open–quiet stance with feet at a comfortable distance and with feet joint together. A third condition consisted in standing with joint feet and eyes closed. Later, the subjects were tested for movement coordination using a 3D motion analysis (CODA Motion) combined with footpads containing electronic pressure sensors (Footscan). An off-line analysis of the data was performed.

Results: Preliminary results showed specific differences in movement coordination between each patient group and the healthy control group. The most revealing test condition in this respect was the combination of tiptoe standing and arms raising. The difference between AD SCA and FRDA patients was statistically insignificant.

Conclusions: This examination is a good neurological tool for all ataxic patients and improve the quality of diagnostic methods.

Th-1

Postural sways in ataxia-telangiectasia

A.G. Shaikh, T.O. Crawford, D.S. Zee, D. Solomon
(Baltimore, Maryland)

Objective: Characterizing postural sways in ataxia-telangiectasia (A-T).

Background: Pathological body sways have localizing diagnostic significance in cerebellar disease. Antero-posterior, 3 Hz body sways suggest lesions of anterior vermis. Omnidirectional sways with a frequency less than 1 Hz often reveal lesions in the posterior vermis. Here we show a combination of high and low frequency body sways in 5 A-T patients. Superimposed upon these oscillations are high frequency isolated jerks; a myoclonic versus a dystonic etiology of these jerks is investigated.

Methods: Five A-T patients were seated in an arm-less chair placed on the surface of a force plate that measured angular and shearing body forces along antero-posterior, lateral, and up-down

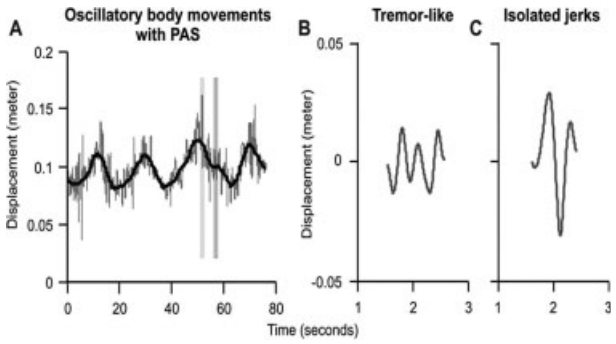

FIG. 1 (Th-1).

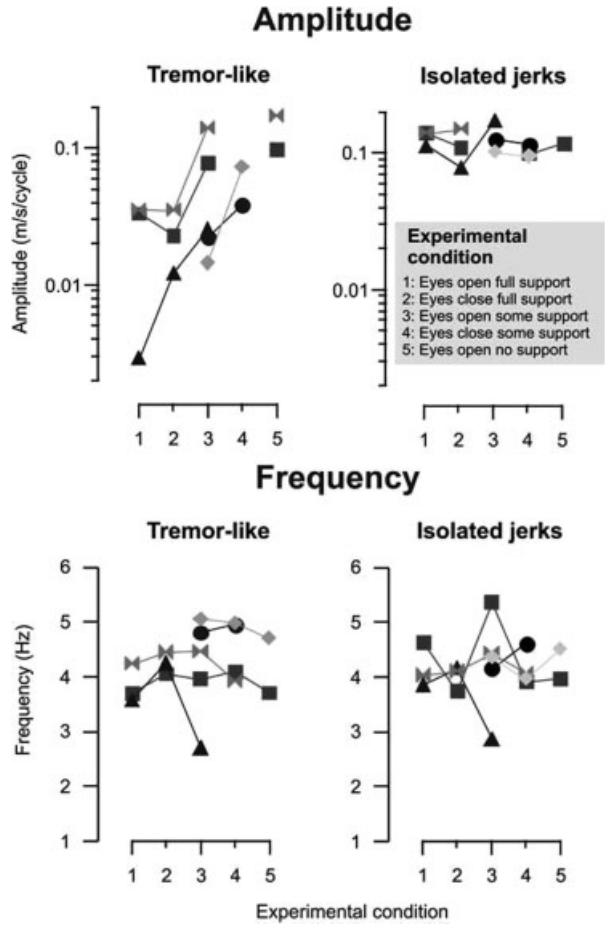

FIG. 2 (Th-1).

axes. These forces were then converted to the linear displacement of the body's center of gravity.

Results: Figure 1A illustrates an example of oscillatory body movements in an A-T patient. These movements were decomposed into three subgroups. (1) Periodic alternating sways (PAS): These are low frequency (0.1 Hz or less) periodic oscillations (Figure 1A: black line). Superimposed on PAS were two types of relatively small amplitude and high frequency oscillations. First, tremor-like oscillations: 3 Hz, rhythmic, high-frequency oscillatory body movements (Figure 1B – grey highlighted portion of Figure 1A), and second, Isolated-jerks: omnidirectional, non-rhythmic, and relatively large amplitude movements (Figure 1C – yellow highlighted portion of Figure 1A). The cycle duration of the typical isolated jerk was more than 300 ms. The displacement trajectories of the oscillatory movements were multi-directional and multi-planar in all patients. The amplitudes of tremor-like oscillations increased as the body support and/or visual feedback were removed. The amplitude of isolated jerks did not change with decreasing body support (Figure 2B). Figure 2A illustrates this phenomenon in 5 A-T patients. The frequency of either type of oscillations did not change with decreasing body support (Figure 2C,D).

Conclusions: These characteristics of postural sways in A-T reflect mixed etiology – lesions of anterior and posterior vermis. Quantitative characteristics of the isolated jerks favor a dystonic etiology.

Th-2

Movement disorders in ataxia-telangiectasia

A.G. Shaikh, T.O. Crawford, D.S. Zee, H.A. Jinnah
(Baltimore, Maryland)

Objective: Delineating movement disorders in Ataxia-telangiectasia (A-T).

Background: A-T is an autosomal recessive disorder characterized by early onset, progressive cerebellar ataxia, oculomotor apraxia, chorea, and athetosis. Dystonia and hypokinetic movement disorders are rarely described. Here we report the study of movement disorders in 24 patients with A-T.

Methods: Videos of neurological examination from 24 A-T patients (11 males and 13 females; age range: 2-35 years) were rated for the severity of ataxia, dystonia, chorea, athetosis, bradykinesia, tremor, and hypomimia. Patients who manifested dystonia were further evaluated with a Global Dystonia Rating Scale (GDS) to assess the severity and segmental distribution of dystonia. Ataxia was generalized, and traditional ataxia rating scales were not suitable to assess A-T patients. Ataxia was only rated on the scale of mild, moderate, severe.

Results: Mixture of hyper- and hypokinetic movement disorders were noticed. Ataxia, dystonia, chorea, and athetosis were prominant amongst hyperkinetic disorders. Bradykinesia and hypomimia were common hypokinetic disorders. Figure 1 illustrates the incidence of various movement disorders in the cohort of our patients. Typically ataxia was generalized. In younger patients (early in the disease

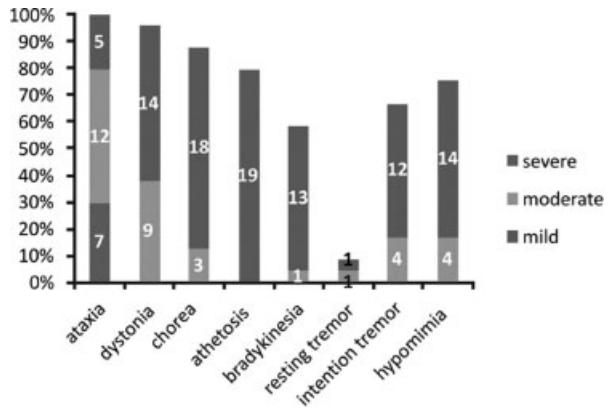

FIG. 1 (Th-2). Percent distribution of movement disorders in 24 patients with ataxia-telangiectasia. Given disorder is scaled by severity. The number of patients in the given group are indicated in white color in the bar diagram.

course) trunk ataxia and postural instability were relatively remarkable. Multi-focal dystonia was present in 23 patients. Severity and segmental distribution of dystonia varied amongst patients. Dystonic posturing of feet in varus position, hand dystonia, and cervical dystonia were common. The abnormal movements, but chorea, athetosis, and dystonic posturing, were relatively minor at rest and became most obvious with anticipation or voluntary movements. Postural and gait instability was seen in all patients. Combination of ataxia and dystonia in a given patient seemed to affect posture and gait. Bradykinesia seemed to associate with the degree of dystonia. Deep tendon reflex was absent in 10 patients. Dysarthria was clearly present in 20 (85%) patients. Amongst remaining, three patients were relatively young to assess the quality of speech (2-3 years).

Conclusions: These results suggest mixed, cerebellar and extra-pyramidal, origin of movement disorders in A-T. These results also underscore the high incidence of dystonia, bradykinesia, and hypomimia – rarely reported movement disorders in A-T.

Th-3

SUMO-1 modification modulates transrepression activity but not ubiquitination or subcellular localization of ataxin-3

L. Shen, Y.-F. Zhou, S.-S. Liao, J. Du, J.-G. Tang, B.-S. Tang (Changsha, Hunan, China)

Objective: To identity the action of sumoylation of ataxin-3 in the pathogenesis of SCA3/MJD.

Background: Spinocerebellar ataxia type 3 (SCA3) is an autosomal dominant neurodegenerative disease caused by polyglutamine-expanded ataxin-3 (AT3). We have previously shown that SUMO-1 was a novel AT3 interacting protein by yeast two hybrid technologies. Subsequently, By co-immunoprecipitation we showed that both the wild-type AT3 and polyQ expanded AT3 were covalently modified by SUMO-1 in mammalian cell, and by immunofluorescence we detected that the intranuclear aggregates formatted by polyQ expanded AT3 co-localized with SUMO-1.

Methods: Immune coprecipitation, immunofluorescence colocalization, RNA interference, flow cytometry and other techniques were used in this research.

Results: We demonstrate for the first time that AT3 is modified by SUMO-1 on lysine 166. SUMO-1 modification inhibits the degradation of pathological (68Q) AT3 and represses the transrepression activity of wild-type (20Q) and pathological (68Q) AT3, but has no affection on the ubiquitination and subcellular localization.

Conclusions: Taken together, our data suggest that the biological function of AT3 should be regulated by SUMO-1, and SUMO-l might participate in the pathogenesis of SCA3/MJD.

Th-4

Genotype-Phenotype (G2P) correlations in SCA12

A.K. Srivastava, F. Mohammed, I. Singh, M.V. Padma, M. Mukerji, M. Behari (New Delhi, Delhi, India)

Objective: We aimed at clinical profiling of SCA12 patients to understand the genetic correlates of phenotypes.

Background: SCA12 is an inherited neurodegenerative disorder caused by abnormal expansions of CAG repeats in 5' upstream non-coding sequence of PPP2R2B gene. SCA12 is unique to Indian population and in single American family of German descent. It has not been found from large scale screening in European, US population and other populations.

Methods: We evaluated 74 affected individuals from 67 genetically established families of SCA12. All the patients were neurologically evaluated and disability was scored using various scales i.e. ICARS, tremor rating scale and MMSE. Repeat lengths were estimated by standard PCR using fluorescently labeled primers followed by sizing analysis on ABI automated sequencer.

Results: Clinical evaluation of 74 affected individuals (49 males 25 females) revealed that majority of SCA12 patients (68%) presented with the hand tremor as symptom at onset, whereas gait ataxia was the first symptom in 15% of patients. Gait ataxia, head tremor, extrapyramidal features, hyper-reflexia developed later in the disease course. There is one group of patients in whom gait ataxia was the major disability than hand tremor throughout their disease period while most of the patients remained disabled with progressively deteriorating action tremor in hands, head tremor and voice tremulousness. Extrapyramidal features (21%), electrophysiological evidence of peripheral neuropathy (25%), autonomic dysfunction (34%) and non motor symptoms (15%) were observed. Radiological investigations show variable degree of cerebral, cerebellar atrophy, gliotic changes and white matter hyper-intensities. Expanded CAG repeat lengths were found in the range of 45-68 where two individuals were homozygous for the expanded allele. Homozygosity does not confer disease severity. The length of CAG repeat track explains 46% variability observed in age of onset (anticipation is observed in SCA12). All expanded alleles share common haplotype background.

Conclusions: Though SCA12 presents with unique phenotype, symptoms overlaps with other SCAs. However young adults presenting with prominent tremor with mild ataxia may be subjected to DNA testing for SCA 12. Probably there are two subtypes one with tremor predominance and other with tremor and ataxia both.

Th-5

Degeneration of synapses in spinocerebellar ataxia 6 may depend on disease duration: Neuropathological study of two autopsy cases from a family

X.-J. Wang, H. Wang, Y.-J. Xia, B.-S. Tang (Changsha, Hunan, China)

Objective: We describe a family with SCA6, characterized by an earlier onset and a more rapid course. Neuropathological changes were detected at autopsy in two patients.

Background: Neural degeneration is one of the neuropathological characters of spinocerebellar ataxia 6 (SCA6). However, synaptic degeneration was not detected in previous studies.

Methods: The number of CAG repeat in the CACNLIA4 gene was detected by DNA sequence. Immunohistochemistry and electron microscopy were used to study routine neuropathology, Golgi and synaptic in patients with SCA6.

Results: We show both light and electron microscopic evidence of synaptic degeneration of Purkinje cells in the cerebellar cortex, which is accompanied by deterioration of Purkinje cells, and both inferior olivary complex and the dentate nucleus. Synaptic loss in the cerebellar cortex may be the impetus for SCA6 of earlier onset, and correlated with the disease duration.

Conclusions: Morphologically, these findings confirm the mechanisms underlying neurodegeneration in the inferior olivary complex and dentate nucleus, which can be interpreted as the retrograde transsynaptic degeneration and the anterograde transsynaptic degeneration to be secondary to the cerebellar cortical lesion.

Th-6

Spinocerebellar ataxia types 3 and 10. Progression rate of gait ataxia in a group of 40 patients

H.A.G. Teive, R.P. Munhoz, A.C. Dariva, L.C. Werneck, T. Ashizawa (Curitiba, Parana, Brazil)

Objective: To evaluate the comparative progression rate of gait ataxia in 40 patients with genetically proved spinocerebellar ataxia (SCA) types 3 and 10.

Background: Spinocerebellar ataxia comprehends an extensive group of neurodegenerative disease affecting the cerebellum and its afferents and efferents conexions. To date there are 30 types of SCA and in a brazilian series of 180 families with SCA we found that SCA type 3 is the most frequent and SCA 10 is the second most common.

Methods: We selected 40 patients with genetically proved SCA type 3 (20 patients) and SCA type 10 (20 patients). These patients were followed in a Neurology outpatient clinic of Hospital de Clínicas of Federal University of Paraná, since 1989. To evaluate the progression rate of gait ataxia we used the new scale for the assessment and rating of ataxia (SARA), using only the score 1 (gait). This score varies from grade 0 (normal, no difficulties in walking, turning and walking tandem) to 8 (unable to walk, even supported). Several clinical data were analyzed including, age, gender, age of onset, age of examination, time of evolution and SARA scale (Gait score 1).

Results: In the group of SCA 3 patients, the mean age of onset was 38.55 years and the mean time of evolution was 12.66 years. The SARA scale (Score 1= Gait) varies from 3.95 to 6.45. In the group of SCA 10 patients, the mean age of onset was 35.55 years and the mean time of evolution was 14.1 years. The SARA scale (Score 1= Gait) varies from 2.2 to 4.3. There was no correlation between the progression rate of gait ataxia and the expansion repeats of CAG triplets (in SCA 3) and of ATTCT pentanucleotide (in SCA 10).

Conclusions: Our data demonstrate that patients with SCA type 3 have a progression rate of gait ataxia faster than patients with SCA 10.

Th-7

Postural cerebellar axial tremor after Malaria

J.T. Teo, O. Swayne, E. Silber (London, United Kingdom)

Objective: To study the abnormal tremors in the post-malaria delayed cerebellar syndrome.

Background: Malaria caused by Plasmodium falciprum can be associated with a delayed onset cerebellar ataxia (Senanyake *et al*., 1994). This ataxia syndrome can develop in the absence of cerebral malaria and develops a 3-5 days after the initial malaria presentation. The appearances on MRI and the nature of the ataxia during the subacute phase is not well-described in the literature.

Methods: We present a case report of a gentleman who developed a severe limb action tremor and an axial tremor 1 week after mild falciprum malaria that was treated. Investigations including neuroimmunological investigations, MRI, CSF examination, and tremor analysis were performed. The clinical examination was also recorded on video.

Results: Routine investigations including MRI and CSF examination did not show any other CNS pathology and serology confirmed recent malaria infection. Tremor analysis showed an enhanced physiological tremor (9-12 Hz) related to peripheral mechanical factors. In addition, there was a 5Hz tremor which did not change frequency in different arm postures. While standing, there was marked coherent 3Hz tremor in both gastrocnemii. This is consistent with a cerebellar axial tremor.

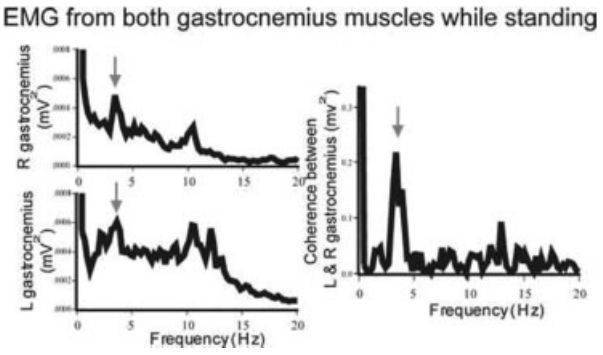

FIG. 1 (Th-7).

Conclusions: In this patient with post-malaria cerebellar syndrome, a postural axial tremor is found in the lower limbs on standing similar to cerebellar postural tremors described in the literature (especially those associated with vermis pathology).

Reference: *Senanayake N, de Silva HJ. Delayed cerebellar ataxia complicating falciparum malaria: a clinical study of 74 patients. J Neurol. 1994 Jun;241(7):456-9.*

Th-8

A novel mitochondrial ATPase mutation in adult-onset Leigh syndrome presenting with ataxia

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Objective: To describe a novel mitochondrial ATPase 6 mutation in adult-onset Leigh syndrome presenting with ataxia.

Background: A 52 year old woman presented with progressive cerebellar ataxia commencing in her second decade. Who developed unsteadiness in her late 20's. Physical examination revealed mild parkinsonism and brisk reflexes accompanying the cerebellar syndrome. Pyruvate and lactic acid were elevated more than two fold in the blood. A muscle biopsy was normal. Brain MRI of the brain revealed diffuse white matter changes in the cerebral hemispheres and atrophy of the basal ganglia only. Two daughters had died of pathologically verified Leigh Syndrome, both at about the age of 20.

Methods: A novel mitochondrial ATPase 6 mutation, T9035C, was found by direct sequencing. PCR-RFLP analysis with a mismatched primer creating a diagnostic restriction enzyme site was carried out in the proband and in pedigree members to quantify the degree of heteroplasmy. From a lymphoblastoid cell line derived from the proband, transmitochondrial cybrids were generated using a 143B derived rho zero cell line. In these cybrid lines and in control cybrid lines, the activities were measured of the respiratory chain enzyme activities by standard spectrophotometric techniques and ATP synthase by a luciferase based assay.

Results: The mutation, which alters the highly conserved Leu170 to Pro, was heteroplasmic in various tissues from the pedigree members in our PCR-RFLP assay. The main finding in the enzyme assays was a severe decline in ATP synthase activity in homoplasmic cybrid lines bearing the mutation.

Conclusions: We conclude that this mutation in the carboxyl terminal end of the ATPase 6 subunit is pathogenic and causes a severe ATP synthase defect. Leu>Pro mutations elsewhere in the carboxyl terminal end of the same subnit have been described in Leigh syndrome and familial bilateral striatal necrosis. This may be a pattern and the pedigree draws attention to mitochondrial ATPase mutations presenting like spinocerebellar ataxia.

Th-9

Novel compound heterozygous mutations in a family with Sacsin-related ataxia (ARSACS)

J. Tsugawa, Y. Tsuboi, Y. Naitoh, H. Inoue, S. Ohma, H. Shimazaki, Y. Takiyama, T. Yamada (Fukuoka, Japan)

Objective: To describe newly identified Japanese family with autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) associated with novel compound heterozygous mutations in SACS gene.

Background: ARSACS is an early-onset spastic ataxia associated with axonal neuropathy, hypermyelination of retinal nerve fibers. Mutations in SACS gene have been identified to be causative with ARSACS.

Methods: Case reports.

Results: The proband is a 27-year-old man complained slowly progressive gait disturbance. His mother noticed the unsteady gait since the period of a elementary school. Neurologic examination at age 27 showed a severe spastic-ataxic gait, mild ataxic dysarthria, and pes cavus. Ocular movements were full, but saccadic with nys-

tagmus in lateral gaze. Cognitive function was normal. There was bilateral distal muscle weakness, and hands and feet were mildly amyotrophic. Pyramidal involvement was revealed by brisk upper and lower limb tendon reflexes, spasticity, and bilateral Babinski sign. Neurophysiologic studies showed prevalently axonal distal sensory-motor neuropathy both in upper and lower limbs, and severe denervation in distal muscles. Funduscopy reveal hypermyelinated retinal fibers. Brain MRI showed moderate atrophy of the upper cerebellar vermis. Two elder brothers, who are twin aged 30 years, are clinically healthy. The proband's younger sister is a 22-year-old woman is similar clinical presentation to proband. She had also spastic-ataxic gait, mild ataxic dysarthria, and saccadic eye movement with gaze evoked nystagmus. However, she had hypoplasia in her left upper and lower extremities without pes cavus. Both patients revealed markedly reduced bone mineral density. Genetic analysis of proband revealed novel heterozygous mutation c.3769>A/11362insT in the Sacsin gene.

Conclusions: Clinical phenotype in the family is similar to original description of Quebec cases. However, this family showed more prominent skeletal abnormalities and the phenotypes are different between brothers. The kindred were the 12th ARSACS family in Japan, indicating ARSACS may be more widely distributed than originally assumed.

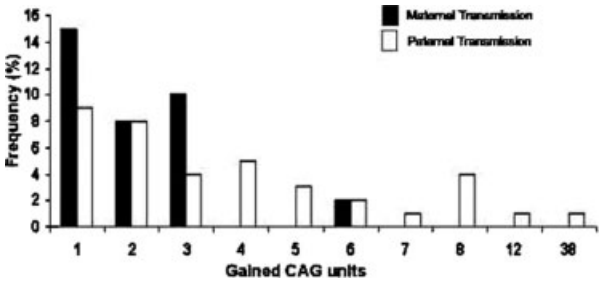

FIG. 1 (Th-10).

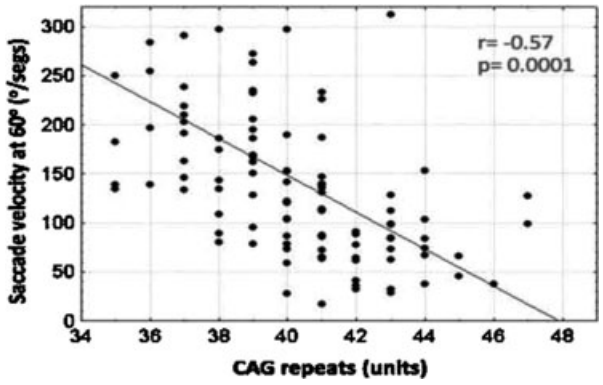

FIG. 2 (Th-10).

Th-10

Spinocerebellar ataxia type 2: A clinical, molecular, neurochemical and electrophysiological study of the mutation in 106 Cuban families

L. Velazquez-Perez, G. Sanchez-Cruz, L. Galicia-Polo, G. Auburger, J. Garcia-Rodriguez, R. Rodriguez-Labrada, L. Almaguer-Mederos, D. Coello-Almarales, J. Laffita-Mesa, R. Aguilera-Rodriguez, C. Gonzalez, N. Canales-Ochoa (Holguin, Cuba)

Objective: To evaluate the clinical epidemiology, electrophysiological, molecular and neurochemical biomarkers of SCA2.

Background: Cuban SCA2 patients derive from a founder population that migrated to Cuba during the last 500 years.

Methods: Clinical, molecular, neurochemical and neurophysiological studies were done in all Cuban SCA2 families.

Results: The highest frequency of SCA2 mutation was observed in Holguin province, the prevalence rate is 42 per 100 000 inhabitants, but there are regions where the prevalence reaches up to 503 per 100 000 inhabitants. The genetic anticipation was observed in the 80% of transmissions and the expansions were presented in 89%.

Table (Th-10). Genetic Anticipation of Age at Onset in SCA2 Patients

Generation	Age at onset	N
III	40.93	104
IV	34.40	205
V	29.29	147
VI	27.23	73
VII	16.20	10
Total	32.96	578

The neurochemical analyses demonstrated a significant decrease of serum and CSF levels of Zn, Cu and Fe in patients. The neurophysiological studies showed the involvement of nervous structures since presymptomatic stages, specially the sensitive amplitudes and P40 components of SSEPs. The progression of these abormalities was correlated with disease duration, polyglutamine expansion size and ataxia score. The polysomnography showed the severe REM pathology with insufficient muscle atonia and periodic legs movements (PLMs) occurs in several cases. The electronystagmographical studies showed a significant reduction of maximal saccade velocity (MSV) in patients and presimptomatic. MSV was negatively correlated with the CAG repeats in both groups.

Conclusions: Hereditary ataxias in Cuba represents the highest prevalence in the world. Electrophysiological abnormalities reflect an early and progressive axonal damage. REM pathology can be associated with the pons, nigrostriatal and thalamic degeneration and PLMs may be related with a dysfunction of dopaminergic pathways. MSV is the most important electrophysiological biomarker for genetic researches of SCA2. Neurochemical results indicate an homeostasis impairment. Velazquez-Perez L, Seifried C, Santos-Falcon N, et al. Saccade velocity is controlled by polyglutamine size in Spinocerebellar Ataxia type 2 (SCA2) Ann Neurol. 2004; 56(3):444-447.

Th-393

Detection of cerebellar dysfunction clinically masked by severe sensory ataxia in a patient with Paraneoplastic syndrome

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Objective: To identify cerebellar degeneration masked by sensory ataxia in a patient with paraneoplastic syndrome associated with anti-Hu antibody.

Background: Cerebellar degeneration often coexists with subacute sensory neuropathy in patients with paraneoplastic syndrome associated with anti-Hu antibody. In such patients, it is often difficult to detect cerebellar dysfunction clinically because of severe sensory neuropathy. We performed magnetic cerebellar stimulation to detect

masked cerebellar dysfunction in a patient with paraneoplastic syndrome associated with anti-Hu antibody.

Methods: A 74-year-old man with small cell lung cancer developed subacute sensory ataxia. The positive anti-Hu antibody suggested that he had anti-Hu-associated paraneoplastic subacute sensory neuronopathy. Magnetic cerebellar stimulation using paired-pulse technique was carried out in addition to conventional nerve conduction studies (NCSs) and somatosensory evoked potentials (SEPs). The test magnetic stimulus over the left primary motor cortex (M1) was preceded by the conditioning stimulus over the right cerebellum. Motor evoked potential (MEP) was recorded from the right first dorsal interosseous muscle.

Results: Conventional NCSs and SEPs were compatible with severe pure sensory neuropathy. Suppressive effects of magnetic cerebellar stimulation on the contralateral M1 were abnormally reduced in this patient.

Conclusions: Although cerebellar signs could not be evaluated clinically due to severe sensory ataxia, the magnetic cerebellar stimulation indicated that cerebellar efferent pathway or dentatothalamocortical pathway was involved in this patient. The magnetic cerebellar stimulation might be useful to reveal cerebellar degeneration masked by co-existing sensory ataxia in patients with paraneoplastic sensory neuropathy.

BASIC SCIENCE

Mo-10

Expression of GDNF receptors of nigral dopaminergic neurons is preserved during normal aging in humans

P.A. Alladi, A. Mahadevan, T.R. Raju, S.K. Shankar, U.B. Muthane (Bangalore, Karnataka, India)

Objective: To investigate quantitative and qualitative changes in levels of GFRα1 and RET expression with age in humans.

Background: Glial derived neurotrophic factor (GDNF) protects dopaminergic nigral neurons and may slow down the progression of Parkinson's disease (PD). The multi-component receptor complex which mediates the neuroprotective action of GDNF comprises of GDNF receptor alpha1 (GFRα1), a ligand binding cell surface component and RET receptor tyrosine kinase (RET), the signaling component. These receptors are expressed in nigral dopaminergic neurons of mice and rats. RET expression is preserved thru aging in substantia nigra pars compacta of primates and of post mortem brains of human PD patients. However, expression pattern of both these receptors in normal adult and during aging in human substantia nigra pars compacta is not known.

Methods: Coronal cryosections of autopsied midbrains were processed for immunohistochemistry (n=31, 28GW-88yrs). *1)* We counted numbers of GFRα1 and RET labeled neurons using stereology. *2)* We performed optical densitometric quantification of immunofluorescence by confocal microscopy to measure changes in level of receptor expression.

Results: 1) Both GFRα1 and RET are expressed in the nigral dopaminergic neurons in the human substantia nigra pars compacta at all ages. 2) The number of GFRα1 (r^2 linear= 0.199; p value = 0.282) or RET labeled neurons (r^2 linear=0.249; p value = 0.177) did not decline with age. *3)* Immunostaining intensity levels of GFRα1 (r^2 linear = 0.080; p value = 0.669) or RET (r^2 linear = 0.087; p value = 0.641) did not correlate with age, suggesting absence of age-related reduction.

Conclusions: There was no reduction in the number of neurons expressing these receptors as a function of age. Moreover, there was no age-related decline in immunostaining intensity of both these receptors either. This suggests that the nigral dopaminergic neurons are GDNF responsive thru life. It is likely that preservation of GDNF receptors is because these receptors are constitutively expressed in the human substantia nigra through aging. It is equally possible that their preserved expression is another marker of conserved nigrostriatal function in Asian Indians. This may explain a lower incidence of PD in Asian Indians compared to Caucasians.

Mo-11

Extracellular proteases in experimental parkinsonism: mRNA expression and protein synthesis of MMP-9, plasminogen and tissue-type activator

V. Annese, C. Barcia, F. Ros Bernal, A. Gomez, P. Paggi, M.T. Herrero, M.E. De Stefano (Rome, Italy)

Objective: We investigate changes in mRNA and protein levels of metalloproteinase-9 (MMP-9), plasminogen (plgn) and its tissue-type activator (tPA), components of extracellular MMPs and plasminogen activators (Pas)/plasmin enzymatic systems, respectively,in the striatum and substantia nigra (SN) of MPTP-injected mice.

Background: Autoptic brains from Parkinson's disease (PD) patients and MPTP animal models undergo a microglia-mediated inflammatory reaction in the SN. MMPs and Pas/plasmin systems play a role in several neurodegenerative diseases, also characterized by neuroinflammation, but their involvement in the molecular pathways leading to nigrostriatal neuron degeneration in PD is still unknown.

Methods: C57/Bl6 mice received acute administration of MPTP (80 mg/Kg b.w.) and were killed 1,24,48 and 72h,1 and 2 wk after the last MPTP injection. Control mice received saline. Changes in mRNA and protein levels of MMP-9, tPA and plgn have been investigated by real-time RT-PCR and Western blot, respectively.

Results: *SN:* compared with control,MMP-9 mRNA levels decrease significantly 1h after the last MPTP injection, increase at 24h and remain higher than control in the following dates. Differently, protein levels of both pro- and active MMP-9 increase after 24h, decrease near control at 72h and further increase at 1-2wk.mRNA and protein levels of both tPA and plgn increase after 1h and then decrease to control levels,or significantly lower, at 24-48h. *Striatum*: modulation of MMP9- mRNA and protein levels is different from what observed in SN*pc*, as they both decrease after 1h and 48h, remaining significantly lower than control.

Conclusions: *SN*: MMP-9 may be involved in both early neuronal degeneration, which associates with an inflammatory response, and late axonal regeneration of survived neurons. Differently, the rapid decline in both mRNA and protein levels of tPA and plgn suggests they are not primarily involved in these processes. *Striatum*: Although early increase in MMP-9 mRNA would suggests proliferation of inflammatory cells, its subsequent drastic decrease,as well as that of its active protein, suggests it may not be related to the progression of inflammation.

Mo-12

Increased expression of a T-helper-cell transcriptional factor t-bet in Parkinson's disease

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Objective: To examine the T-helper-cell differentiation in Parkinson's disease (PD) and assess the influence of neuroinflammation on development of disease mechanism.

Methods: Five consecutive sporadic PD patients (2 males) were enrolled in this study. The mean ± SD age was 68.2 ± 10.1 years, and the mean ± SD disease duration was 7.5 ± 3.4 years. All patients were treated with levodopa/DCI in combination with dopamine agonist therapy. None received immunosuppressive therapy. Age- and sex-matched healthy controls (n = 5) and disease controls (Alzheimer's disease, n = 5) were recruited. Expression of transcriptional factors associated with T-helper-cell differentiation, including t-bet, GATA3, ROR-γ, and Foxp3, in peripheral lymphocyte cells were evaluated by using western blotting. Observed results were compared among 3 groups.

Results: PD groups had a significantly increased expression of t-bet compared to healthy controls and disease controls ($p < 0.05$ for both groups, Kruskal-Wallis test).

Conclusions: T-bet that induces the differentiation of naïve T-helper-cell to type 1 T-helper-cell significantly expressed in PD, suggesting the possibility that protective function to intracellular pathogens and induction of excessive immune reaction based on autoimmunity exist in the disease mechanism.

Mo-13

Release your horses: Deep brain stimulation of the subthalamic nucleus improves motor functions at the expense of response inhibition. A $H_2{}^{15}O$ PET study

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Objective: The aim of the present study was twofold: (i) to extend previous observations by providing evidence that the subthalamic nucleus (STN) may influence and prevent the execution of any response even during low-conflict decisions, and (ii) to identify the neural correlates of this effect.

Background: In Parkinson's disease (PD) patients, deep brain stimulation (DBS) of the STN may contribute to certain impulsive behavior during high-conflict decisions. A neurocomputational model of the basal ganglia elaborated on the basis of behavioral data from decision making tasks has recently proposed that this behavioral aspect may be related to the role played by the STN in relaying a "hold your horses" signal intended to allow more time to settle on the best option.

Methods: We measured regional cerebral blood flow (rCBF) during a Go/NoGo (GNG) and a control (Go) task to study the motor improvement and response-inhibition deficits associated with STN-DBS in 7 PD patients.

Results: While improving UPDRS motor ratings and inducing a global decrease in reaction time during task performance, STN-DBS impaired response-inhibition as revealed by an increase in commission errors in NoGo trials. These behavioral effects were accompanied by changes in synaptic activity including a reduced activation in the cortical network responsible for inhibition and error-related processing (e.g., DLPFC, precuneus, PCC, ACC, pre-SMA) and an increase of activation in a network of structures associated with impulsivity in GNG task (e.g. inferior frontal and orbitofrontal cortex).

Conclusions: The present results suggest that modulation of STN hyperactivity with DBS by acting on the gating mechanism involved in response initiation, while improving motor functions in PD patients may tend at the same time to favor the appearance of impulsive behavior. Accordingly, we propose that impairment of the response inhibition network plays an important role in both akinesia and impulsivity. In other words, akinesia and impulsivity could represent opposite sides of the same coin.

Mo-14

Increase of glial IFN-γ and TNF-α in the substantia nigra pars compacta of parkinsonian macaques years after MPTP intoxication

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Objective: To elucidate whether IFN-γ and TNF-α may play a role in a chronic model of experimental parkinsonism in non human primates.

Background: Patients with Parkinson's disease (PD) show an increase of certain pro-inflammatory cytokines in the CNS and in the blood serum such as IFN-γ and TNF-α. The role of this cytokines in parkinsonism is not fully elucidated. Previous experimental studies, performed with different knock out mice, have shown that both cytokines may play a crucial role in dopaminergic neurodegeneration involving glial cells. Activated astroglial and microglial cells are thought to be decisive mediators of this local inflammation but their role, protective or deleterious on dopaminergic neurons, remains controversial. Both, PD patients and parkinsonian animals, show activation of glial cells in the Substantia Nigra pars compacta (SNpc) which may be sustained over the years. This fact has lead many researchers to speculate that local inflammation may be a possible cause of the perpetuation of dopaminergic neuronal loss.

Methods: In the present work, we have analyzed different inflammatory markers in a group of chronic parkinsonian macaques (n=14) and compared with control animals (n=6). We first measured the levels of cytokines in blood serum using ELISA, and after the sacrifice, we analyzed inflammatory markers in fixed brain tissue sections by immunohistochemistry and studied the sections with stereological methods and confocal imaging.

Results: Immunohistochemistry of the SNpc revealed that activated microglial cells and astrocytes persist locally, years after MPTP exposure. We also observe that higher levels of IFN-γ and TNF-α are also maintained in blood serum of parkinsonian animals. Most importantly, glial cells in the SNpc of parkinsonian animals showed significant higher expression of IFN-γ and TNF-α than the control monkeys.

Conclusions: These results indicate that IFN-γ and TNF-α could have a crucial role in the persistency of glial-mediated inflammation after dopaminergic neurodegeneration and suggests new pharmacological approaches for PD therapy.

Mo-15

The role of muscarinic transmission in the substantia nigra reticulata of normal and 6-OHDA hemilesioned rats

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Objective: To investigate if endogenous acetylcholine release in the substantia nigra modulates locomotor-induced nigral dopamine release and motor performance in normal and 6-OHDA hemilesioned rats.

Background: Dopamine released from cell bodies and dendrites in the substantia nigra can facilitate motor function by mechanisms that may act independently of axon terminal dopamine release in the striatum. The dopamine neurons in the substantia nigra receive a cholinergic input from the pedunculopontine nucleus. This nucleus was recently introduced as a potential target for deep brain stimulation to treat motor symptoms in Parkinson's disease, but its cholinergic influence on somatodendritic dopamine release, and potentially also nigral modulation of motor functions, is not well understood.

Methods: Simultaneous measurements of motor performance and monoamine neurotransmitter release in the substantia nigra and the striatum were obtained by testing rats in a rotarod protocol during continuous microdialysis.

Results: In intact and 6-OHDA-hemilesioned animals alike, the muscarinic antagonist scopolamine, when perfused in the substantia nigra, amplified the locomotor-induced somatodendritic dopamine release to approximately 200% of baseline, compared to 120-130% of baseline in vehicle-treated animals. A functional importance of nigral muscarinic receptor activation for motor control was demonstrated in hemilesioned animals, where motor performance was significantly improved by scopolamine from 51% to 82% of pre-lesion performance, whereas it remained unchanged in lesioned animals perfused with vehicle. In normal rats, however, scopolamine perfusion did not affect motor performance on the rotarod.

Conclusions: The results indicate that muscarinic receptor activation in the substantia nigra is increased during locomotor activity in normal and 6-OHDA hemilesioned rats, and that the increased nigral muscarinic activity influences motor performance in lesioned, but not normal, rats. This corroborates previous observations of increased activity of the pedunculopontine nucleus in 6-OHDA lesioned rats, and suggests that such activation can alter motor functions by modulating nigral neurotransmission.

Mo-16

Chronic L-dopa treatment modifies serotonin function in depression-related structures of the hemiparkinsonian rat brain

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Objective: To examine the effects of short- and long-term L-DOPA administration on serotonin (5-HT) function in the hemiparkinsonian rat brain.

Background: Co-morbid depression affects approximately 50% of Parkinson's disease (PD) patients, an incidence almost twice that seen in similarly disabled patients, suggesting that disease-specific processes contribute. Risk factors that positively correlate with PD-related depression include disease severity and L-DOPA dose. While 5-HT neurons of the raphe nuclei appear integral for the conversion and release of L-DOPA-derived dopamine (DA) in later stages of PD, this compensatory adaptation may adversely diminish 5-HT catabolism and release leading to depressive symptoms.

Methods: In order to examine this possibility, adult male hemiparkinsonian rats received daily L-DOPA (12 mg/kg, s.c.) for 1 week. A subset of rats received intermittent L-DOPA (12 mg/kg, s.c., 2-3 times/week) for an additional 5 weeks. On the final day of testing, rats received either Vehicle or L-DOPA (12 mg/kg, s.c.). One hour later, rats were decapitated and multiple structures including the dorsal raphe, striatum, hippocampus, prefrontal cortex and amygdala were dissected for analyses by real-time reverse transcription polymerase chain reaction (RT-PCR) to examine mRNA expression and/or high performance liquid chromatography (HPLC) for the measurement of monoamine levels.

Results: Real-time RT-PCR demonstrated that duration of L-DOPA treatment differentially increased dorsal raphe tyrosine hydroxylase while tryptophan hydroxylase levels were consistently squelched by L-DOPA. Furthermore, HPLC analyses of brain monoamines following long-term L-DOPA treatment revealed increased DA and reduced 5-HT levels ipsilateral to lesion in multiple structures.

Conclusions: Collectively, these findings indicate that chronic L-DOPA treatment may induce a shift within the dorsal raphe nuclei towards DA catabolism and release at the expense of 5-HT, elevating the potential risk for depression-like symptoms in PD.

Mo-17

Identification and functional characterization of a novel mutation in the mortalin/GRP75 gene in German Parkinson's disease patients

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Objective: We identified mortalin/GRP75 as a mitochondrial DJ-1-interacting protein that shows significantly reduced levels in affected brain regions of Parkinson's disease (PD) patients. To define the relevance of mortalin/GRP75 in DJ-1-mediated mitochondrial protection, we performed a detailed mutation analysis and subsequent functional studies in PD.

Background: Genes idendified in PD encode proteins that are involved in the maintenance of mitochondrial homeostasis and oxidative stress response and lead, if mutated, to an increased sensitivity for the onset of neurodegeneration. Loss of DJ-1 function causes reduced mitochondrial membrane potential, suggesting a potential relevance of its interaction with the intramitochondrial stress response protein mortalin/GRP75 for mitochondrial homeostasis.

Methods: To determine whether mutations in mortalin/GRP75 gene may contribute to PD we performed a detailed mutation analysis in a large sample of 286 German sporadic and familial PD patients. Using DHPLC analyses for high throughput mutation screening, we defined sequence variations that were compared to a group of 290 healthy controls. Identified sequence variations were analyzed concerning differential interaction, mitochondrial morphology and mitochondrial function, reactive oxygen species production and cell death in different cellular models.

Results: We identified 8 sequence variations, including 4 silent base substitutions in the coding region and 4 intronic polymorphisms. One mutation in exon 12 of the mortalin/GRP75 gene lead to an amino acid exchange in a highly conserved region of the peptide sequence. This variant was not present in more than 500 control chromosomes. Using immunoprecipitation we found no evidence for differential interaction of the mutant protein with DJ-1. However first functional studies argue in favour of subcellular mislocalization caused by mutant mortalin/GRP75 in stably transfected HEK293 cells.

Conclusions: Mutations in the mortalin/GRP75 gene in PD are a rare event. We identified for the first time a mutation in the human mortalin/GRP75 gene that links this DJ-1-interacting protein with PD. Future studies focus on functional effects of the identified novel variant in neurons to determine the relevance of mortalin/GRP75 in neurodegeneration.

Mo-18

MPP+ impairs autophagic clearance of α-synuclein by interfering the activity of dynein

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Objective: To determine whether MPP+ may interfere with the activity of dynein leading to impaired autophagic clearance of α-synuclein.

Background: Increasing evidence suggests that α-synuclein (aggregate-prone protein) is one of the major components of Lewy Bodies. Degradation and/or removal of misfolded or aggregated protein is thus a key issue in neurodegenerative disorders such as Parkinson's disease. MPP+ has been shown to induce symptoms similar to those of Parkinson's disease in experimental animals and humans. More recently, a role has been proposed for dynein in the clearance of misfolded proteins by autophagy.

Methods: After PC12 and A30P cells were treated with MPP+ (0.5mMol/L) and staurosporine (1μM, 12-h exposure), we use Western blotting, (RT)-PCR, Immunofluorescence microscopy, monodansylcadaverine-stain to study the changs of dynein, lamp1 and LC3-II, and their co-localization in cells.

Results: After being treated with MPP+, dynein was mainly aggregated at the periphery of cytoplasma and lost its co-localization with α-synuclein and lamp1, which indicates that dynein lost its function in the aggresome formation and failed to return autophagosome and lysosomes to the cell center for degradation. Though the number of autophagic vacuoles and expression level of LC3-II were increased, it wasn't really a sense of autophagy up-regulation (autophagosomes couldn't effectively fuse with lysosomes), and couldn't degrade abnormally aggregated proteins.

Conclusions: We consider that dynein has an important role in the autophagic clearance of aggregate-prone proteins and its significance needs further study.

Mo-19

Analysis of aggregates dynamics and mitochondrial function in synphilin-1 overexpressing cells

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Objective: To study the role of protein aggregates in Parkinson's disease (PD) and the mechanisms for their clearance from affected cells. In particular, we want to evaluate if the activation of autophagy could remove synphilin-1 (SYPH1) aggregates and to study the effects of wild-type and mutant R621C SYPH1 overexpression on mitochondria.

Background: Protein aggregation in affected brain regions plays an important role in the pathogenesis of PD, but it's still debated

whether aggregates are linked to cell death or if they represent an active protective mechanism. Recent evidences suggested that protein inclusions could be degraded by lysosomes via autophagy. SYPH1 is a protein that is present in Lewy bodies, it interacts with key elements of PD pathogenesis and it shows tendency to aggregate. Our group recently reported the R621C amino acid substitution in SYPH1 in two PD patients.

Methods: Aggregates in GFP-SYPH1 overexpressing HEK cells were evaluated by fluorescence microscopy. ROS levels in the mitochondria were measured by FACS, lysosomes were stained with Lysotracker. Autophagosome were visualized by immunofluorescence in FLAG-SYPH1 overexpressing HEK cells transiently transfected with GFP-LC3 DNA.

Results: The activation of autophagy by both rapamycin and trehalose was able to reduce significantly the number of cells bearing SYPH1 aggregates; this effect was completely abolished by the autophagy inhibitor wortmannin. Moreover, we observed co-localization of SYPH1 inclusions with lysosomal structures and the formation of autophagosomes in cells with aggregates. Preliminary data suggested that SYPH1 overexpression may interfere with mitochondrial homeostasis.

Conclusions: We showed that SYPH1 aggregates may have a protective role in previous studies; however, the way such inclusions mediate protection is not clear. Here we showed that inclusions bodies formed by SYPH1 are a target for lysosomal degradation via autophagy. On the other hand, we observed a negative effect of overexpressed SYPH1 on mitochondria. We hypothesize that aggregates represent temporary structures that help to remove noxious proteins and that autophagy can participate in their clearance.

Mo-20

Aging and Parkinson's disease: A stochastic acceleration hypothesis

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Objective: To test the hypothesis that markers for factors implicated in cell death in Parkinson's disease (PD) accumulate in midbrain dopamine (DA) neurons with advancing age in a regional pattern consistent with vulnerability or resistance to degeneration based upon the concept that aging and PD are related processes.

Background: Aging is acknowledged to be a primary risk factor for PD, but previous studies have led to the conclusion that the cellular processes underlying aging and PD are distinct. This relationship has not been examined in the context of likely contributors to DA neuron degeneration in PD and stereological microscopic techniques.

Methods: We utilized tissue derived from rhesus monkeys ranging in age from 9-29 years for our analysis. Three sets of markers were analyzed: 1) autophagy: ubiquitin-positive inclusions and lipofuscin, 2) oxidative/nitrative stress and DA uptake: 3-nitrotyrosine (3-NT), DA transporter (DAT) and vesicular monoamine transporter-2 (VMAT-2), 3) glia: GFAP (astrocytes) and LN-3 (microglia). Our analysis utilized stereological cell counting and fluorescence intensity measurements to characterize the distribution of markers within midbrain subregions that are known to be more vulnerable (ventral tier substantia nigra (vtSN)) or less vulnerable (ventral tegmental area (VTA), dorsal tier substantia nigra (dtSN)) to degeneration in PD.

Results: 1) intranuclear ubiquitin-positive inclusions accumulated with advancing age specifically in the vulnerable neurons of vtSN. Lipofuscin localized to the resistant neurons of dtSN and VTA. 2) 3-NT accumulated with aging and was correlated with higher levels of DAT and VMAT-2. All three markers were highest in the vulnerable vtSN. 3) all regions exhibited comparable staining for astrocytes, while vtSN of aged subjects exhibited increased activation of microglia.

Conclusions: Our findings suggest that at least some cellular mechanisms associated with aging of DA neurons and their degeneration in PD are fundamentally the same and exist along a continuum. Normal aging actively produces a vulnerable pre-parkinsonian state that when accelerated by a variable combination of genetic and/or environmental factors results in PD.

Mo-21

Impact of substantia nigra pars compacta lesion on the spontaneous discharge and the electrophysiological properties of identified pyramidal neurons in the rat motor cortex: An in vivo study

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Objective: The aim of the present study was to characterize, at the cellular level, the electrophysiological changes induced in the motor cortex by the dopaminergic (DA) transmission interruption.

Background: In the current pathophysiological model of Parkinson's disease (PD), the degeneration of DA neurons of the substantia nigra *pars compacta* (SNc) is expected to induce a hyperactivity of the GABAergic output structures of the basal ganglia (BG) leading to an inhibition of the related thalamo-cortical circuits. At odds with this hypothesis, transcranial magnetic stimulation studies in PD patients suggested that excitability of neurons in primary motor cortex is majored and imaging studies revealed an increased metabolism in the primary motor cortex. These results were obtained using global approaches.

Methods: Spontaneous activity and electrical membrane properties of pyramidal cells from the motor cortex were investigated by performing *in vivo* extra- and intracellular recordings in both intact and unilaterally SNc-lesioned rats. Cortico-subthalamic and cortico-striatal neurons were identified by the antidromic activation method.

Results: Our results indicate that following SNc lesion, the frequency of the cortical cells was significantly increased. In addition, the firing pattern of the cells was modified, with a marked increase of both the burst occurrence and the intra burst frequency. *In vivo* intracellular recordings revealed that, in SNc-lesioned rats, the membrane potential of the neurons was significantly more depolarized than in control situation and their input resistance was increased. Interestingly, changes in frequency and in electrical membrane properties were more pronounced in the cortico-striatal than in the cortico-subthalamic cells.

Conclusions: These results stress the major impact of DA neurons degeneration on the functional properties of the motor cortex and call for a reappraisal of the mechanisms underlying motor impairments in PD. (Supported by ANR-05-JCJC-0076-01 and ANR-05-NEUR-013)

Mo-22

Dopamine turnover decrease accompanies 7-nitroindazole reduction of L-dopa induced dyskinesia

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Objective: Comparisons between 6-OHDA lesioned (dyskinetic) and sham (non-dyskinetic) L-DOPA-treated cases, receiving either saline or 7-nitroindazole were then carried out with regard to striatal levels of dopamine (DA), DA metabolite DOPAC, serotonin (5-HTA) and 5-HTA metabolite 5-hydroxyindoleacetic acid (5-HIAA) as assessed by HPLC-striatum analyses. As it has been shown that the nigrostriatal DA system has functional and neurochemical asymmetry it was investigate if the left and right striatum responded similarly to lesion.

Background: Neuronal nitric oxide sinthase selective inhibitor 7-nitroindazole is able to reduce L-DOPA-induced dyskinesias in experimental Parkinson.

Methods: Unilaterally, 6-hydroxydopamine (6-OHDA, medial forebrain bundle) lesioned or sham Wistar male rats were treated

chronically (21 days) with L-DOPA (30mg/kg) for an induction and monitoring of abnormal involuntary movements (AIMs).

Results: Reduction of the endogenous nitrergic tone by 7-nitroindazole treatment per se increased DA level in sham-L-DOPA treated rats. L-DOPA induced AIMs in all 6-OHDA lesioned rats attenuated by 7-nitroindazole. 6-OHDA lesion induced a decrease of DA system components in the striatum ipsilateral to lesion. The content of 5-HT increased in the left striatum, the level of 5-HIAA decreased in both striatum and 5HIAA/5HT-ratio decreased in the left one. In the dyskinetic and 7-nitroindazole treated animals levels of DA in striatal tissue did not differ. Level of DA metabolite was larger in the striatum of dyskinetic (right, 25 times and left, 3 times), compared to 7-nitroindazole-treated animals. The DOPAC/DA ratio, regarded as a measure of DA turnover, was 2.5 times larger in the ipsilateral striatum of dyskinetic rats. In this group the content of 5-HT system did not differ.

Conclusions: This study evidenciates that rats dyskinesia was associated with DA dysregulation in striatum. In the denervated striatum there was an increase in the DA turnover reduced by 7-nitroindazole all together with attenuation of dyskinesia. These results indicate the interdependent regulation of the two nigrostriatal systems maybe providing compensatory support for the function and behavioral performance.

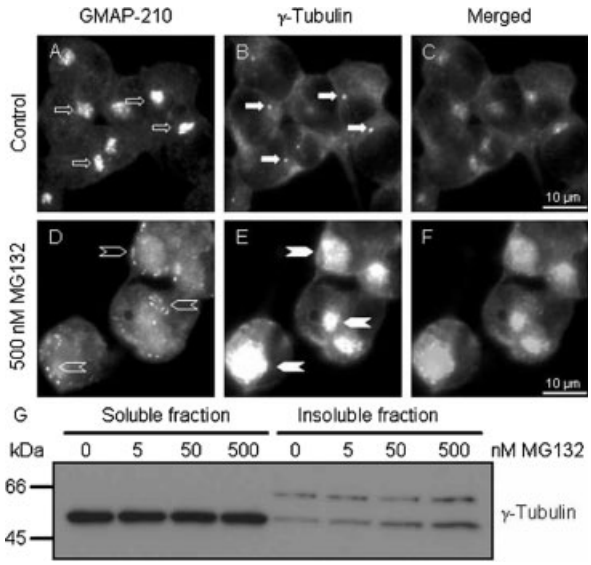

FIG. 1 (Mo-23). Proteasome inhibition induces GA fragmentation and γ-tubulin aggregates.

Mo-23

Proteasome inhibition induces protein aggregation at the centrosome and disrupts golgi apparatus transport; relevance in the pathogenesis of Parkinson's disease

F.J. Diaz-Corrales, R.M. Rios-Sanchez (Seville, Spain)

Objective: To induce Golgi apparatus (GA) fragmentation using an experimental model of Parkinson's disease (PD) in order to evaluate dysfunction in GA transport and its relationship with protein aggregation.

Background: The GA is a cytoplasmic organelle composed of flattened-parallel cisternae stacked and connected by tubular bridges forming a reticular network closely associated with the centrosome. Proteins newly synthesized in the rough endoplasmic reticulum are transported through GA where are processed, sorted and dispatched to the cell surface packed into transport vesicles. Growing evidences have shown that GA fragmentation is a morphological change frequently observed in neurodegenerative diseases including PD. However, whether GA fragmentation has some remarkable influence on protein aggregation in neurodegenerative diseases is still poorly understood.

Methods: SH-SY5Y cells were treated with the proteasome inhibitor MG132 (5, 50 or 500 nM) for 24 or 48 h. Several constitutive proteins of GA (GMAP-210) and cytoskeleton including the centrosomal protein γ-tubulin were tested by immunofluorescence (IF) and Western blotting. In order to analyze GA transport, cells were transfected with the vesicular stomatitis virus glycoprotein (VSVG) fused with green fluorescent protein (GFP).

Results: IF-microscopy images of non-treated cells (Fig. 1; A-C) showed an intact GA ribbon (A; empty arrows) clustered near to the centrosome (B; filled arrows). On the contrary, MG132-treated cells (Fig. 1; D-F) displayed a dramatic fragmentation of GA (D; empty arrowheads) and large aggregates of γ-tubulin (E; filled arrowhead). Aggregation of γ-tubulin was corroborated by the increment on protein concentration at the insoluble fraction in a dose dependent manner (Fig. 1; G). On the other hand, control VSVG-GFP-transfected cells (Fig. 2; A-D) delivered the VSVG-GFP to the cell surface after low-temperature incubation (C; arrows). In treated cells (Fig. 2; E-H) VSVG-GFP signal did no reach the plasma membrane, and it was accumulated (G; arrowhead) in cells that had both GA fragmentation (E; empty arrowheads) and γ-tubulin aggregates (F).

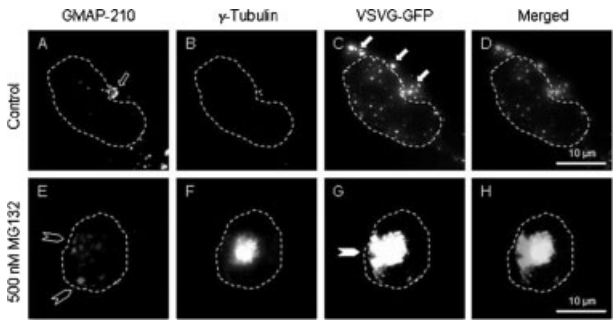

FIG. 2 (Mo-23). Vesicular transport was disrupted in cells with GA fragmentation and γ-tubulin aggregates induced after proteasome-inhibition treatment.

Conclusions: Our results suggest that protein aggregates at the centrosome as well as disruption of GA transport are related processes that might play a role in the pathogenesis of PD.

Mo-24

Identification of kinases and phosphatases involved in a-synuclein phosphorylation

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Objective: To identify novel kinases and phosphatases involved in the pathological phosphorylation of a-synuclein protein on serine 129.

Background: Lewy Bodies are composed of a-synuclein and other proteins. Although whether LBs are toxic or neuroprotective remains a point of contention, it is clear that the post-translational hyperphosphorylation of a-synuclein protein on serine 129 is an important neurotoxic event. The mechanisms whereby a-synuclein is phosphorylated on serine 129 remain very poorly defined, despite the potential therapeutic relevance of this phosphorylation in mitigating neurodegeneration in PD and PDD.

Methods: We have developed a high-throughput, cell-based assay for the rapid quantitation of total a-synuclein and serine 129 phosphorylated a-synuclein levels. Using this assay, we screened a library

of siRNAs targeting known and predicted kinases throughout the genome.

Results: Several novel candidate a-synuclein kinases, in addition to a known a-synuclein kinase (casein kinase 2), emerged from this screen.

Conclusions: Our assay is a useful tool for identifying kinases that phosphorylate a-synuclein *in vitro* and has generated a list of kinases for further investigation *in vivo*. In addition, our results show that this approach will be useful for identification of phosphatases involved in a-synuclein metabolism, which may serve as better potential targets for modification of serine 129 phosphorylation in PD.

Mo-25

An improved sham stimulation protocol for transcranial direct current stimulation (tDCS)

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(Perth, Western Australia, Australia)

Objective: To develop a protocol which eliminates perceptual differences between real tDCS and sham stimulation, by employing a preceding desensitizing period.

Background: Transcranial direct current stimulation (tDCS) is a promising clinical intervention for neurological disorders such as Parkinson's disease, however, evaluating its effectiveness depends on a comparison with a suitable form of sham stimulation. With tDCS, current is applied for several minutes, whereas, sham stimulation typically uses just a brief application of current (5–20 sec). Applying current to the skin evokes a range of itching sensations, and it is important to determine whether there are perceptual differences between the two forms of stimulation that might compromise the effectiveness of the sham. In addition, habituation to the sensation of itch raises the possibility of using preconditioning to modify itch sensation.

Methods: Using a repeated measures protocol we compared participants' ($n=11$) perception of comfort, rated according to an 11–point visual analogue scale (0–very uncomfortable, to 10–very comfortable), during 2 min of tDCS; 2 min of tDCS preconditioned with 20 sec of DCS followed by a 100 sec desensitization period, and sham stimulation (20 sec DCS with no further stimulation).

Results: Sham was significantly more comfortable than tDCS 1 min after stimulus onset (8 ± 0.78, 5 ± 0.73; $p<0.05$), however, when tDCS was preceded by a desensitizing period there was no difference compared to sham (7 ± 0.90, 8 ± 0.78; $p>0.05$).

Conclusions: A perceptual difference exists between sensations evoked during tDCS and sham stimulation, however, by applying a desensitizing DCS period prior to stimulation the difference between current-evoked sensations is eliminated. This suggests that short-stimulation sham is not an adequate control for tDCS, but that the addition of a desensitizing DCS period to both sham and tDCS can eliminate perceptual differences between real and sham stimulation.

Mo-26

Anodal tDCS over left M1 produces simultaneous bidirectional effects on bilateral M1 excitability

J.E. Dundas, G.W. Thickbroom, F.L. Mastaglia
(Perth, Western Australia, Australia)

Objective: To determine whether tDCS applied to one motor cortex produces effects on excitability in the homologous region of the unstimulated, contralateral motor cortex.

Background: Transcranial direct current stimulation (tDCS) modulates excitability in the cortical area directly beneath the stimulating electrode, but recent studies suggest it might also induce effects in distant brain regions by modulating the activity of interconnected motor areas. As prolonged tDCS-effects on motor cortex (M1) excitability have been well established and anatomical connections are known to exist between both motor cortices, we aimed to study whether anodal tDCS over left M1 modulates corticomotor excitability bilaterally.

Methods: Eight participants received 10 min anodal tDCS (1mA) with the cathode positioned over the contralateral supraorbita. Motor evoked potentials (MEPs) from single pulse transcranial magnetic stimulation (TMS) were used to assess cortical excitability in left and right motor cortices every 5 mins for 30 min following stimulation.

Results: During this period left motor cortex excitability increased (av. change in MEP amplitude: 120.6% ±8.2; $p<0.05$) and right motor cortex excitability decreased (av. change in MEP amplitude: 82.2% ±6.4; $p<0.05$).

Conclusions: Our results demonstrate that anodal stimulation of the left M1 can modulate corticomotor excitability levels bilaterally–enhancing left M1 and suppressing right M1 excitability–presumably by modulating the activity in transcallosal and subcortical pathways interconnecting both motor cortices. These findings have implications for the potential use of this intervention in clinical populations with asymmetric motor disturbances.

Mo-27

Parkin dysfunction results in defective depolarization-induced exocytosis of large dense core vesicles

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Objective: To evaluate whether parkin plays a role in exocytosis such as neurotransmitter release from dopaminergic cell or insulin release from pancreatic β cell.

Background: Parkin is the causative gene for an autosomal recessive form of Parkinson's disease. Parkin is expressed ubiquitously, and part of it associate with synaptic vesicles. Presynaptic proteins such as Septin 5 (CDCrel-1), synphilin-1, and synaptotagminXI are identified as substrates for parkin E3 ligase, which may be involved in depolarization-induced exocytosis. Also, Parkin-deficient models have shown impaired neurotransmission in glutamatergic neurons and altered expression of proteins involved in the regulation of cytoskeleton and vesicular transport. Thus, we hypothesize that parkin plays a role in exocytosis of large dense core vesicle(LDCV).

Methods: We accessed effects of knocking-down and overexpression of parkin on high K+-evoked exocytosis in HIT-T15 and PC12 co-transfected with a reporter human growth hormone (hGH). We used total internal reflection fluorescence (TIRF) imaging analysis to reveal the process of first- and second-phase LDCV exocytosis.

Results: PC12 cells in which parkin is knocked down show a reduced exocytosis, which is restored by re-expression of exogenous parkin. Overexpression of parkin mutants but not wild-type parkin inhibit exocytosis in the HIT-T15 cells and PC12 cells. In parkin-knockout mouse β-cell, the number of fusion events from previously docked granules were markedly reduced; second-phase fusion from newcomers was preserved.

Conclusions: Our data suggests that parkin functions physiologically as a regulator of large dense core vesicle fusion not only in dopaminergic cell but also in pancreatic β cell.

Mo-28

Regulatory role of short interval intracortical inhibition during paired associative stimulation

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Objective: To Investigate the role of short interval intracortical inhibition during paired associative stimulation induced plasticity.

Background: Repetitive median nerve stimulation followed by single pulse transcranial magnetic stimulation (TMS) can increase the amplitude of motor-evoked potentials (MEP) in the median nerve innervated small hand muscles. This phenomenon is termed paired associative stimulation (PAS), and shares a number of physiological

aspects with long term potentiation (LTP) in motor cortex. This LTP-like plasticity is disturbed in dystonia and Parkinson's disease.

Methods: In 4 healthy subjects, we test a novel paradigm to induce cortical plasticity by engaging short interval intra-cortical inhibition (SICI) (mainly mediated by GABAergic cortical circuit) during PAS to assess the role of inhibitory intra-cortical circuits in motor cortex plasticity. The first protocol involved median nerve stimulation combined with paired pulse TMS, with a subthreshold conditioning stimulus 2 ms before a test stimulus that produced 1 mV MEPs. The second protocol was the same as the first but the test stimuli were adjusted to produce 1 mV MEPs in the presence of the conditioning stimuli. The third protocol is a traditional PAS paradigm using single pulse TMS. Each subject went through the three protocols in random order with at least one week between sessions. We measured how these stimulation protocols changed MEP amplitudes, cortical excitability and different cortical inhibitory circuits such as SICI, short-interval afferent inhibition (SAI) and cortical silent period and intra-cortical facilitation (ICF). This allowed us to explore the effect of intra-cortical inhibitory circuits on measures of cortical excitability and PAS induced plasticity.

Results: We found increased SICI and reduced MEP amplitude compared to baseline after the first protocol (repetitive median nerve and paired pulse stimulation). The second (adjusted the paired pulse stimulation intensity to produce 1mV MEP) and third (traditional PAS 25ms) protocols both induced higher MEP amplitude especially in the second protocol which higher test stimuli intensity was used.

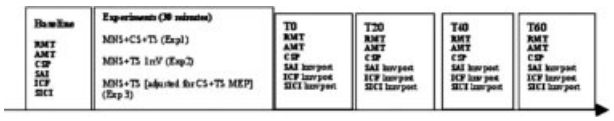

FIG. 1 (Mo-28).

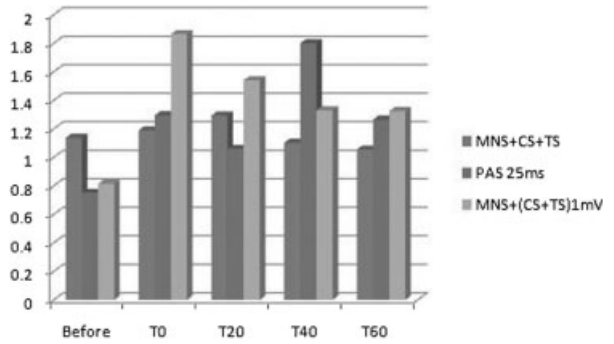

FIG. 2 (Mo-28).

Conclusions: Our results suggest SICI may have a homeostatic and regulatory role during plasticity protocols

Mo-29

Metabolic activity of the subthalamic nucleus in a primate model of L-dopa unresponsive parkinsonism

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Objective: We investigate the differential pathophysiology of multiple system atrophy versus Parkinson s disease.

Background: Increased activity of the subthalamic nucleus (STN) is critical in mediating motor symptoms of Parkinson s disease.

Methods: To determine if altered STN functioning also occurs in levodopa-unresponsive parkinsonism in multiple system atrophy (MSA-P), metabolic activity of the STN was assessed using cytochrome oxidase (CO) histochemistry in monkeys with nigral, striatal or nigral + striatal degeneration induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and/or 3-nitropropionic acid (3NP).

Results: MPTP and MPTP + 3-NP treated monkeys had a similar parkinsonian score and were clinically indistinguishable. However, CO activity in the STN was significantly increased in MPTP-induced parkinsonism but not in MPTP + 3-NP-induced striatonigral degeneration.

Conclusions: These results indicate that metabolic activity of the STN is normal in levodopa-unresponsive parkinsonism and provide a pathophysiological mechanism for the lack of effect of STN stimulation in MSA.

Mo-30

Comparative analyses of Purkinje cell gene expression profiles reveal common molecular abnormalities in different polyglutamine diseases

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Objective: To determine whether Spinocerebellar ataxia type 7 (SCA 7) and Huntington's disease (HD) share pathogenic events, we performed a molecular screen in Purkinje cells (PC) of two transgenic mouse models.

Background: Polyglutamine diseases have a number of common features including progressive neuronal degeneration and formation of protein aggregates. There is growing evidence for critical nuclear events leading to transcriptional alterations in SCA 7 as well as in HD and both share a cerebellar degenerative phenotype.

Methods: Taking advantage of the use of laser capture microdissection, we compared PC gene expression profiles of two transgenic mouse models by using microarrays. Validation was performed by quantitative PCR. As PC are affected late in HD we examined animals showing already severe symptoms (R 6/2, 12 weeks). SCA 7 animals were analyzed at an earlier stage (P7E, 15 weeks).

Results: The majority of transcriptional alterations were detected in the transgenic model of HD, e.g. parvalbumin (downregulated to 48% of wildtype), diacylglycerol lipase α (11%) and IP_3-gated receptor 1 (Itpr1, 31%). Almost all the changes identified in the SCA 7 model were found in the HD model as well, such as phospholipase C ß3 (SCA 7: 58%; HD: 5%), purkinje cell specific protein 2 (SCA 7: 54%; HD: 31%) and aldolase C (SCA 7: 43%; HD: 50%). The comparison of laser-dissected neurons with cerebellar homogenates of the SCA 7 model (comprising all cell types) revealed Itpr1 downregulation in homogenates (59%), not in laser-dissected PC.

Conclusions: These findings suggest disturbances in calcium signaling making PC more susceptible to excitotoxicity. This may be exacerbated by the loss of the neuroprotective aldolase C. Downregulation of Itpr1 in homogenates of the SCA 7 model may be an indicator for pathogenic mechanisms outside the PC. Thus, our data reveal common and distinct molecular events in different polyglutamine disorders.

Mo-31

Only the labile iron pool is increased in parkinsonian substantia nigra

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Objective: Assessment of the labile iron pool in parkinsonian substantia nigra (SN).

Background: Parkinson's disease (PD) is a progressive neurodegeneration involving mostly the substantia nigra (SN). The pathomechanism of the neurodegeneration includes oxidative stress. Iron is believed to be the trigger of oxidative stress in PD. Although several

studies have shown an increase of the concentration of total iron in PD SN, others did not. As the stress may be triggered only by labile iron pool we decided to assess the concentration of this iron.

Methods: 29 control and 17 parkinsonian were used for Mössbauer spectroscopy for determination the concentration of total iron in SN, identification of iron binding compound and evaluation of the ratio Fe2+/Fe3+. As Mössbauer spectroscopy does not need any pretreatment of the samples and does not destroy them during the procedure, out of these samples 8 control SN and 6 PD were assessed for the concentration of iron and copper in supernatants by atomic absorption. The samples were homogenized, centrifugated and filtrated through filters blocking all substances bigger than 10 kDa. Therefore all ferritin-bound iron was blocked by filters and only "free" iron could be found in supernatants. As copper does not have a similar binding substance, one could admit that virtually all copper will be found in supernatants.

Results: The concentration of total iron was similar in PD and control SN (177±18 vs. 177±14 ng/mg, the ratio PD/control being 1.00±0.13). Mössbauer spectra of control and PD SN obtained at 90 K have shown only ferritin-like iron with no detectable divalent iron. The concentration of labile iron in PD was significantly higher vs. control (135±10 and 76±5 ng/g). The difference is significant at $p<0.01$. No difference was found in the concentration of copper between PD and control 115±17 vs. 122±19 ng/g.

Conclusions: Our results show that in PD SN the increase of the concentration of iron concerns only the labile iron, whose amounts are more than 1000 times smaller than the concentration of the total iron. These results correspond to our previous finding of a decreased concentration of L-ferritin in PD SN. The loss of L-ferritin may cause an easier efflux of small amounts of labile, non-ferritin bound iron. These tiny amounts may trigger the oxidative stress.

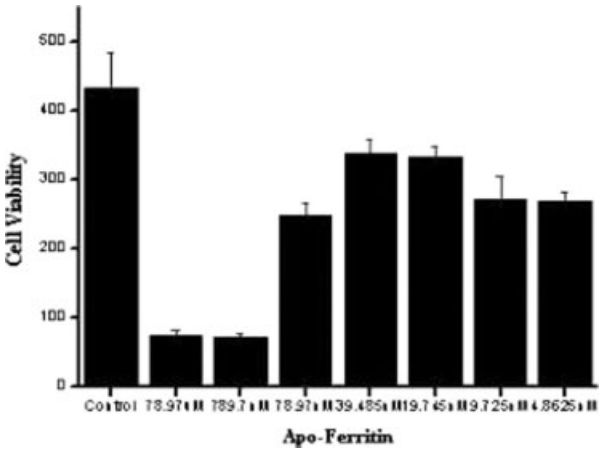

FIG. 1 (Mo-393).

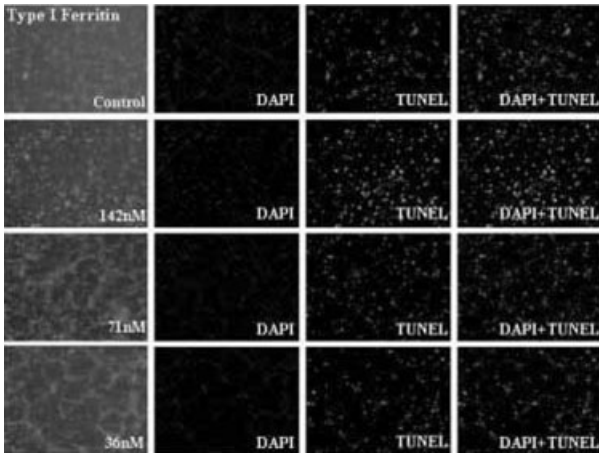

FIG. 2 (Mo-393).

Mo-393

The study on safety of quantum materials for the diagnosis and treatment of Parkinson's disease

U. Lee, Y.-M. Yoo, Y.-J. Kim, H.-T. Yoo (Incheon, Republic of Korea)

Objective: Advances in nanomedicine have led to the development of nanoparticles, such as quantum dots, carbon nanotubes, and metallic nanostructures, for many innovative applications in diagnostics, gene delivery, and cancer therapy.

Background: Nanoparticles(NPs) have a proportionately very large surface area and this surface can have a high affinity for metals (e.g., iron) and organic chemical combustion products such as polycyclic aromatic hydrocarbons; PAHs. In medical therapeutics, many drug candidates fail to reach their targets at appropriate concentrations, which can severely limit their effectiveness. However, when drugs are encapsulated into nanoscale particles and treated to prevent clumping, the result is often a stable and water-soluble material, due to the very large surface to volume ratio. New drugs based on nanoparticle-mediated delivery systems are being developed for preventive treatment of the oxidative damage occurring in neurodegenerative diseases like Alzheimer's, Wilson's and Parkinson's.

Methods: In this study, we have attempted to assess the impact of many of these variables utilized for in vitro toxicity studies with the stated goal of developing an in vitro culture system that could provide a reasonably accurate, predictive early screen for assessing the pulmonary toxicity of particulate materials. We used a wide range of concentrations of NPs, including some that are much higher than those published for commercial product using spectroscopy.

Results: Using the MTT assay the viability of cultured cells was measured at various concentrations of NPs. The figure clearly illustrates that the neural cells showed a rapid decrease of viability in the NP high concentration.

Conclusions: Further studies are needed to examine the nestin-expressing glial cells in response to NPs when NPs are injected into the cortex.

Tu-14

Effect of Parkinson's disease on medio-lateral motion of the centre of mass when walking over a ground-based obstacle

B. Galna, A.T. Murphy, M.E. Morris (Melbourne, Victoria, Australia)

Objective: To examine whether the medio-lateral motion of the centre of mass (CoM) is greater in people with mild to moderately-severe Parkinson's disease (PD) compared to age-gender matched control participants when walking over a ground-based obstacle.

Background: Impaired dynamic postural control during gait contributes to the high incidence of trips and falls observed in PD. Balance in standing is impaired by PD yet has not been examined during functional gait tasks such as obstacle crossing.

Methods: 19 people with mild to moderate PD (4 females; mean age 65.8yr, SD 7.8; Unified Parkinson's Disease Rating Scale (Motor) Mean: 12.5, SD: 5.2; Hoehn and Yahr stage range 1-3) and 19 age-gender matched control participants (Mean age: 64.8yr SD: 8.1) were included. Participants walked at their self-preferred pace over a ground-based obstacle (height 10% of leg length x 600mm x

10m) 16 times. People with PD were tested at the peak dose of their levodopa medication. Thirty-four retroreflective markers taped onto the head, arms, trunk, pelvis and lower limbs were recorded using a Vicon 3D motion analysis system (100Hz). Whole-body centre of mass (CoM) was calculated using the plug-in-gait model. Centre of pressure (CoP) was measured using two floor-embedded Kistler force plates (1000Hz). Dependant variables included medio-lateral range of motion, peak velocity and CoM-CoP inclination angles for both lead and trail limb crossing steps.

Results: Despite walking at a slower pace, people with PD demonstrated greater medio-lateral excursion than control participants during the lead limb step ($p=.025$) but not during the trail limb step ($p=.157$). People with PD had faster peak medial velocities (Lead: $p=.044$; Trail: $p=.004$) and greater CoM-CoP separation angles (Lead: $p=.010$; Trail: $p=.024$) during both lead and trail limb crossing steps.

Conclusions: Although it is well established that movement is slow and underscaled in PD, this study found larger and faster medio-lateral sway of the CoM during obstacle crossing. Impaired postural control during functional gait tasks may predispose those with PD to falls. Medio-lateral sway of the CoM during obstacle crossing has been shown to identify elderly fallers and so it is warranted to assess if it can also identify potential fallers in people with PD.

Tu-15

PINK1 associated Parkinson's disease is caused by neuronal vulnerability to calcium induced cell death

S. Gandhi, A. Wood-Kaczmar, N.W. Wood, M.R. Duchen, A.Y. Abramov (London, United Kingdom)

Objective: To determine the mitochondrial pathophysiology caused by loss of PINK1 function in mammalian neurons in vitro.

Background: Mutations in the PINK1 gene cause an autosomal recessive form of Parkinson's disease. The PINK1 protein is a mitochondrial kinase and thus mitochondrial dysfunction may be central to the pathogenesis of PINK1 associated Parkinson's disease.

Methods: We performed dynamic imaging of calcium handling, oxidative stress, and respiration in neuronal models of PINK1 deficiency. We employed three cell models: (1) stable PINK1 knockdown in neuroblastoma cells, (2) stable PINK1 knockdown in human neurons derived from mesencephalic stem cells and (3) transgenic PINK1 knockout mouse cortical and midbrain neurons.

Results: PINK1 deficiency results in dysfunction of the mitochondrial sodium/calcium exchanger, causing reduced mitochondrial calcium efflux, and mitochondrial calcium overload. This reduces the mitochondrial calcium capacity of the cell in response to cytosolic calcium stimuli. Furthermore, calcium overload stimulates reactive oxygen species (ROS) production via NADPH oxidase. ROS production inhibits the glucose transporter, reducing substrate delivery, and causing impaired respiration. The impaired respiration may be restored by provision of mitochondrial complex I and II substrates.

Conclusions: There is significant cross talk between the bioenergetic function and the calcium homeostasis function of mitochondria. Taken together, reduced mitochondrial calcium capacity and increased ROS lower the threshold of opening of the mitochondrial permeability transition pore (mPTP) such that physiological calcium stimuli become sufficient to induce mPTP opening in PINK1 deficient cells. As dopaminergic neurons are exposed to significant calcium fluxes and oxidative stress, these findings suggest a mechanism by which PINK1 dysfunction renders such neurons vulnerable to cell death.

Tu-16

SNARE protein accumulation in a model of early Parkinson's disease

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Objective: To investigate possible causes of the recently observed dopaminergic dysfunction in a transgenic mouse model of Parkinson's disease.

Background: The presynaptic protein α-synuclein plays a major role in the development of Parkinson's disease, where it is the major component of the Lewy body. We recently reported a transgenic mouse model expressing truncated (1-120) human α-synuclein in dopaminergic cells in a mouse α-synuclein null background. These mice develop α-synuclein aggregates, striatal dopamine deficiency, reduced locomotion but no nigral dopaminergic cell loss.

Methods: Syn (1-120) transgenic mice express human (1-120) truncated α-synuclein under the TH-promoter and in a mouse α-synuclein null background and were previously described (J Neurosci. 2006, 26(15):3942-50) In vitro enzymatic assays to measure proteasome and aconitase activities, western blotting, immunohistochemistry and immunofluorescent confocal imaging were used to study the pathology in syn (1-120) mice.

Results: Neither changes in the proteasomal or lysosomal system nor an increase in oxidative stress account for the dopaminergic dysfunction in syn (1-120) mice. Instead we found that in the striatum of these transgenic mice, synaptic accumulation of truncated (1-120) α-synuclein was associated with specific, age-dependant redistribution of SNARE-proteins. Truncated (1-120) α-synuclein and SNARE proteins were found to colocalize in the same striatal terminals. SNARE protein accumulation was not limited to the over-expression of truncated (1-120) α-synuclein, as this was also observed in transgenic mice over-expressing human A30P or A53T mutated full-length α-synuclein. Lack of SNARE redistribution in the R6/2 transgenic mice (a model of Huntington's disease) and P301S mice (a model of tau aggregation) indicated that the effects on SNARE proteins were specific to α-synuclein.

Conclusions: Our observations indicate a novel neurotoxic mechanism of action of α-synuclein at the synapse and suggest that synaptic pathology caused by α-synuclein is an early event in Parkinson's disease that precedes the occurrence of dopaminergic cell death.

Tu-17

Pole test and dopaminergic cell loss correspondence in two different MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) mouse models

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Objective: To determine whether a widely used clinical tool such as the pole test may appoint the underlying dopaminergic cell loss in acute and chronic MPTP regiments.

Background: MPTP administration in C57/bl mice results in loss of dopaminergic (DA) neurons in the substantia nigra (SN) and a depletion of dopamine in the striatum. However, there is a discrepancy between the neurochemical (massive DA damage) and the behavioral (recovery of motor performance) changes in this animal model. Although pole test is a useful method to evaluate movement disorder caused by striatal DA depletion, there is no study specifying it's accuracy in various time points following MPTP administration.

Methods: The acute (4 IP injections of 20mg/kg MPTP every 2 hours) and chronic (1 IP injection of 4mg/kg MPTP daily, for 20 days) MPTP models were induced in 25 and 26 C57/bl mice, respectively. Nineteen mice, served as overall vehicle controls for both models. Pole tests for acute and chronic models were performed at 1-3-7-14-21 and 1-7-21-42-63 days post-last-injection (PLI), respectively. The Tyrosine-hydroxylase positive (TH+) neurons per mm2 of the substantia nigra were studied in the pre-determined time points ($n=5$-6 animals per time point) and were correlated to the pole test parameters.

Results: There was a significant reduction in the mean number of TH+ neurons in SN of both acute and chronic model ($P<0.001$). The reduction was greater at days 1 and 3 PLI (45 and 39%, $P<0.001$) in the acute model, stabilizing thereafter, while it was greater at days 7 to 21 (plateau) in the chronic model, upturning only at day 63 ($P<0.05$). Pole test performance was significantly worse only at days 1 ($P<0.05$) and 7 ($P<0.01$) PLI in acute and chronic

models, respectively, recovering to control levels thereafter. The number of TH+ neurons was correlated to pole test only at days 1 (Spearman's rho = -0.891, $P<0.05$) in the acute, and 7 (-0.845 $P\leq0.01$) PLI in the chronic model, but not at the rest time points.

Conclusions: Our results indicate that pole test may be a reliable clinical tool, with a value limited to the early, pick dopaminergic destruction.

Tu-18

Increased cytosolic calcium levels and oxidative stress promote alpha-synuclein aggregation in vivo

J.J. Goodwin, D.L. Pountney (Gold Coast, Queensland, Australia)

Objective: To investigate (1) the role that calcium plays in the aggregation dynamics of alpha-synuclein both in vitro and in vivo and (2) to determine whether oxidative stress acts additively or synergistically with calcium in alpha-synuclein aggregate formation.

Background: Neuronal cell loss in Parkinson's disease (PD) and Parkinson's-plus diseases is associated with abnormal, aggregated forms of the cytoplasmic protein, alpha-synuclein (α-syn). The causes of α-syn aggregation are unclear, however the breakdown of tightly regulated cellular processes, such as calcium signalling, and the increased level of oxidative stress in the ageing brain may interact with α-syn, leading to the formation of cytotoxic α-syn species and the neurodegeneration associated with PD. In this study, we investigate the affects of calcium and oxidative stress on the production of aggregated α-syn species both in vitro using recombinant α-syn protein and in vivo using cell culture models.

Methods: We have treated highly purified recombinant monomeric α-syn with calcium and/or hydrogen peroxide in vitro, and used scanning electron microscopy to investigate protein conformation. In cell culture experiments, we used thapsigargin to induce transient increases of icytosolic calcium in human cell lines expressing an α-syn-GFP construct. Fluorescence microscopy techniques, including live-cell imaging and confocal microscopy, allow the observation of calcium flux, α-syn aggregation and cytotoxicity.

Results: Incubation (24 hrs; 4 degrees C) of monomeric α-syn (10 μM) with calcium (100μM) or hydrogen peroxide (1mM) resulted in the generation of large (50-150 nm) globular or annular structures, whilst control incubations showed no large protein aggregates. Our current cell culture data shows that a transient increase in intracellular free calcium induced by thapsigargin (1μM) or oxidative stress caused by hydrogen peroxide (0.5mM) was able to induce frequent microscopically-visible, perinuclear or cytoplasmic α-syn aggregates after 24 hrs in human 1321N1 cells expressing α-syn-GFP.

Conclusions: Our data indicates that calcium or hydrogen peroxide can promote the formation of annular α-syn oligomeric species similar to those observed in pathological tissue in vitro, as well as promote in vivo aggregate formation in cell culture.

Tu-19

Motor dysfunction is more severe in predominantly right- than left-hemispheric Parkinson's disease

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Objective: To test the hypothesis that a physiological left-hemispheric dopaminergic predominance leads to a relatively greater right-hemispheric vulnerability to dopamine depletion, such as occurring in Parkinson's disease (PD).

Background: Some but not all studies of the healthy human brain have suggested that dopaminergic processes may be lateralized towards the left hemisphere. We addressed this issue in a clinical approach of PD, which is characterized by asymmetric dopaminergic degeneration of either predominantly the left (PD-L) or the right (PD-R) nigrostriatal system. Following the above-mentioned hypothesis, we predicted greater motor dysfunction in PD-R than in PD-L patients.

Methods: Motor function was assessed separately for the left and right hand in 155 early, dopa-naïve PD patients with clear symptom asymmetry (PD-R: n=86, PD-L: n=69) and 48 healthy age-matched controls. PD-L and PD-R groups were matched for age, gender and disease duration. All subjects were right-handed. Motor assessments consisted of the UPDRS-III and the pegboard dexterity test, a timed motor test that proved highly sensitive to subtle motor dysfunction in PD. Based on the healthy control data, PD results were corrected for physiological motor asymmetries due to right-handedness.

Results: PD-R patients exhibited a markedly larger difference between right and left dexterity scores than PD-L patients ($p<0.001$). This could be attributed to greater motor dysfunction of the more-affected left hand in PD-R patients compared to the more-affected right hand in PD-L patients. The less-affected hand performed similarly in both groups. This effect was not found in the UPDRS-III scores, possibly due to the higher sensitivity of the pegboard dexterity test compared to the UPDRS-III.

Conclusions: The results fit the hypothesis that the right hemisphere might be more susceptible to dopaminergic denervation than the left hemisphere.

Tu-20

Rotigotine protects dopaminergic neurons against glutamate excitotoxicity via dopamine receptor activation and PI3-Akt signalling

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Objective: To investigate the neuroprotective potential of the non-ergot dopamine (DA) agonist rotigotine towards DAergic neurons exposed to glutamate excitotoxicity.

Background: Previously found neuroprotective effects of rotigotine to DAergic neurons were further explored with respect to the mechanism of action.

Methods: Cultures of primary DAergic neurons from embryonic mouse mesencephalon were pre-treated with rotigotine (0.1, 1μM) on the 8^{th} or 10^{th} day in vitro (DIV) with or without DA receptor antagonists (10nM GR103691, 20μM sulpiride). Glutamate (0.5mM) was added 24h later for 9min. Two days later, DAergic neurons and total neurons were identified immunocytochemically by tyrosine hydroxylase (TH) and NeuN staining, respectively. LDH release was determined spectrophotometrically. Superoxide radicals were detected by a fluorescent indicator (MitoSOX Red reagent) 24h after glutamate treatment. The role of the PI3-kinase pathway was tested adding Wortmannin (100nM) or LY294002 (10μM) 1h prior to rotigotine.

Results: Glutamate decreased TH positive neurons by 60%. The total number of neurones decreased only by 23% suggesting a higher sensitivity of DA neurons. Pre-incubation with rotigotine (1μM) on 10 DIV increased the survival rate of TH positive neurons significantly by 22% against glutamate intoxication. The receptor antagonists GR103691 or sulpiride blocked the protective effect of rotigotine. No protective effect on the total number of neurones was observed as LDH release did not change. Inhibition of the PI3-kinase pathway with PI3-kinase inhibitors Wortmannin or LY29400 completely abolished protection suggesting involvement of that pathway. Rotigotine treatment (1 μM) on 10 DIV also caused a marked reduction of superoxide radicals in the culture measured 24h after glutamate administration.

Conclusions: Rotigotine exerts significant protection to DAergic neurons in primary culture against glutamate toxicity. Protection depends on stimulation of DA receptors and is mediated via the PI3-kinase pathway.

Tu-21

The role of α-synuclein in neural stem cells in vivo

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Objective: In this study, we examined that the role of α–synuclein in neural stem cells in vivo.

Background: The physiological role of α -synuclein is poorly defined. Recently, Crews et al. reported that α–synuclein regulated the proliferation in ES cells.

Methods: We injected the retroviral vector encoding human α –synuclein gene into the subventricular zone(SVZ) of mice. We examined the kinetics of the neural stem cells in the rostral migratory stream (RMS) by the immunohistochemistry.

Results: After injection with retro–α–synuclein vector, the number of migration cells from SVZ to OB was decreased compared to the number of these cells after injection with control vector.

Conclusions: Our results indicate that overexpression of α –synuclein might regulate the migarating neural stem cells from SVZ to OB, or the induction of the differentiation of these cells in SVZ.

Tu-22

Kinetics of microglial activation and degeneration of dopamine-containing neurons induced by 6-OHDA in a rat model of Parkinson's disease

V. Henry, V. Paille, F. Lelan, P. Brachet, P. Damier (Nantes, France)

Objective: To analyze the kinetics of the microglial activation and the dopaminergic cell death induced by the neurotoxin 6-hydroxydopamine (6-OHDA) in a rat model of Parkinson's disease (PD).

Background: Aside from the loss of dopaminergic neurons, the ventral midbrain is also the site of a microglial reaction in both PD and animal models of PD. Many questions on the role of activated microglia remain unanswered.

Methods: Twenty-one rats received an injection of 6-OHDA in the right MFB and were compared to 7 sham-lesioned rats and 3 controls. The motor behavior was assessed by the stepping test. Groups of 3 lesioned-rats and 1 sham-lesioned rat were sacrificed 1, 5, 7, 14, 21, 28 and 35 days after surgery. Series of section were processed for tyrosine hydroxylase (TH), OX42 immunohistochemistry and fluorojade B (FJB) staining. Number of TH-, FJB- positive cells and OX42-positive cell densities were measured using an image analysis system (Explora Nova). We differentiated two types of OX42-positive cells: 'ramified slightly stained' (i.e. quiescent microglia cells) and 'amoeboid and intensely stained' (i.e. activated microglia cells).

Results: As early as the first day after the injection, the motor performance of the 6-OHDA-lesioned rats decreased, with this decline in performance being correlated with the reduction of the dopaminergic innervation (TH optical density) of the contralateral striatum. In the ventral midbrain, the loss of dopaminergic neurons was observed a few days later and appeared to follow a specific temporo-spatial pattern. The highest number of FJB-positive neurons and the highest activated OX42-positive cell density were observed in the ventral midbrain 7 days after the 6-OHDA injection. Neurons in degeneration and activated microglia were observed solely in the dopaminergic areas where dopaminergic cells were no longer observed, suggesting that the loss of dopaminergic phenotype preceded the degenerative process *per se*. In the sham-lesioned rats a transient activation of the microglia was observed in the vicinity of the needle trajectory without any cell degeneration.

Conclusions: The chronology of the events supports the hypothesis that microglia activation is a secondary rather than a primary phenomenon in dopaminergic cell degeneration induced by 6-OHDA.

Tu-23

Characterization and regulation of the promoter region of human neuronal uncoupling protein-4 (UCP4) and its neuroprotective role in Parkinson's disease

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Objective: We aimed to identify the promoter region and potential essential response elements (EREs) in regulating UCP4 gene expression, and its role in neuroprotection against mitochondrial dysfunction and oxidative stress.

Background: Parkinson's disease (PD) is characterized by degeneration of dopaminergic neurons in substantia nigra. Decreased activity of mitochondrial Complex I in PD causes oxidative stress, and neuronal cell death. UCP4 is expressed in brain. We have previously shown that overexpressing UCP4 is protective against MPP+ and dopamine-induced neuronal cell death, by suppressing ROS and maintaining ATP levels. Neuroprotection mechanisms and regulation of UCP4 gene expression are unclear.

Methods: A 3k-bp DNA fragment upstream of the transcription start site (TIS) of human UCP4, and a series of 5'-deleted fragments were cloned into luciferase reporter vector. Luciferase activity was measured to determine critical promoter region of UCP4. Potential EREs were identified by computer analyses and site-directed mutagenesis. NFκB inhibitor, HNE, was used to study the effects of NFκB in UCP4 expression against MPP+ toxicity. Electrophoretic-mobility-shift-assay (EMSA) was performed to study DNA-protein binding interaction of NFκB on UCP4 promoter region.

Results: Promoter activity was observed within 100bp upstream of TIS, which involves Sp1 and CAAT-box. Either mutated Sp1 or CAAT-box significantly decreased UCP4 promoter activity. Putative NFκB binding site was identified, which mediated UCP4 expression under MPP+ toxicity. Specific binding of NFκB was observed by EMSA. Treatment of HNE significantly decreased UCP4 mRNA expression. This induction was abolished after mutagenesis of this putative NFκB binding site.

Conclusions: We have identified the critical promoter region of human UCP4. Identification of NFκB response element in the promoter region and its significant modulation of UCP4 expression indicate molecular linkages between NFκB signalling and the neuroprotective role of UCP4 against mitochondrial dysfunction induced by MPP+.

Tu-24

Synergistic role of neuronal uncoupling protein homologues, UCP2, 4 and 5, in neuroprotection against mitochondrial dysfunction in Parkinson's disease

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Objective: The aim of this study was to determine the inter-relationship and synergistic role of UCP2, 4 and 5 against mitochondrial dysfunction in neurons.

Background: Parkinson's disease (PD) is characterized by loss of dopaminergic neurons in substantia nigra. Neuroprotective strategies involve alleviating deleterious effects of mitochondrial dysfunction in PD. Mitochondria provide ATP but inherently generates oxidative stress. Uncoupling occurs via neuronal uncoupling proteins (UCPs) when ATP production is delinked from oxidative phosphorylation resulting in less ATP but also less oxidative stress. UCP2 is expressed ubiquitously. UCP4 and 5 are specifically expressed in brain. The physiological function of these neuronal UCP homologues is unclear.

Methods: Neuroprotective effects of neuronal UCP4 and 5 were studied by stably overexpressing UCP4 and 5 in SH-SY5Y cells. Uncoupling activity was monitored from ADP/ATP ratio in cells after ADP supplement; the neuroprotective effects of overexpressing UCP4/5 were monitored by cell proliferation under MPP+ toxicity; changes in mitochondrial membrane potential (MMP) and oxidative stress were determined by flow cytometry. Respiratory rate after UCP4 and 5 overexpression was determined by measuring oxygen consumption in purified mitochondria.

Results: UCP4 or 5 overexpression attenuated MPP+-induced cell death, preserved MMP and ATP levels; ROS levels were reduced. Induction of UCP2 expression by MPP+ toxicity was significantly suppressed by overexpression of UCP4, but conversely, knockdown of UCP2 increased UCP4 expression. Surprisingly, overexpressing

UCP4 increased ATP production but in case of UCP5 ATP level was decreased. The respiratory rate was increased in overexpression of UCP4, but not in UCP5.

Conclusions: Our findings indicate that neuronal UCP2, 4 and 5 act differently in terms of their uncoupling activities, and hence their protective mechanisms against MPP+ toxicity. We suggest that these neuronal UCP homologues might function synergistically to attain homeostasis between ATP production and oxidative stress in neurons under mitochondrial dysfunction.

Tu-25

Rotenone reduces magnesium-dependent block of NMDA currents in substantia nigra dopamine neurons

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Objective: To investigate the mechanism by which the pesticide rotenone augments NMDA-gated currents in rat substantia nigra pars compacta (SNC) dopamine neurons.

Background: Rotenone is a pesticide that has been used to produce a rodent model of Parkinson's disease. We reported previously that rotenone potently augmented NMDA-evoked currents in rat SNC dopamine neurons via a tyrosine kinase-dependent mechanism. We now report on the voltage-dependent effect of this rotenone/NMDA interaction.

Methods: Currents from single SNC neurons were recorded under voltage-clamp with whole-cell patch pipettes in slices of rat midbrain. Currents were measured during continuous voltage ramps from -120 to -30 mV (4 s duration).

Results: In a physiologic concentration of extracellular Mg^{2+} (1.2 mM), a 30 min perfusion with rotenone (100 nM) produced marked increases in NMDA currents especially when measured at relatively hyperpolarized currents. At -100mV, for example, NMDA (20 μM) evoked 819 ± 50 pA of inward current in the presence of rotenone compared to 288 ± 39 pA in control conditions. In the presence of rotenone, NMDA currents lost the characteristic region of negative slope conductance that is normally produced by voltage-dependent block by Mg^{2+}. In the presence of 0.2 mM Mg^{2+}, NMDA produced 1338 ± 125 pA of inward current at -110 mV, and this current was not significantly increased after 30 min perfusion with rotenone (1638 ± 134 pA). Furthermore, an elevated concentration of Mg^{2+} (6 mM) nearly completely blocked the ability of rotenone to potentiate NMDA-induced inward currents. Voltage-dependent augmentation of NMDA currents by rotenone was blocked by the tyrosine kinase inhibitor genistein (100 μM).

Conclusions: Rotenone potentiates NMDA currents by a tyrosine kinase-dependent process that attenuates voltage-dependent Mg^{2+} block of NMDA-gated channels. These data support the hypothesis that an excitotoxic mechanism might participate in rotenone toxicity of SNC dopamine neurons. We speculate that elevated levels of Mg^{2+} might be neuroprotective in animal models of Parkinson's disease.

Tu-26

Progression of MPTP induced parkinsonism in monkeys. A multiligand PET study

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Objective: To describe changes in dopaminergic radioligand and 18F- Fluorodeoxyglucose (FDG) uptake by positron emission tomography (PET) in a progressive model of MPTP induced parkinsonism in monkeys.

Background: Parkinson s disease (PD) is characterised by dopaminergic depletion associated with metabolic and monoaminergic compensatory changes during disease evolution There is a lack of in vivo information about such mechanisms in a progressive MPTP monkey model.

Methods: MPTP was chronically (every 2 weeks over 6 months) administered to 20 monkeys (maccaca fascicularis). PET studies using monoaminergic (6-fluoro-(18F)-L-3,4-dihydroxyphenylalanine (FDOPA) and (11C) Dihydrotetrabenazine (DTBZ)) and metabolic (FDG) radiotracers were conducted in different stages of evolution (basal, asymptomatic, recovered, mild and severe). The analysis based on Regions of interest was done over normalized parametric images in FDOPA and DTBZ PET and SPM2 analysis was also conducted for three radiotracers.

Results: The evolution of MPTP induced parkinsonism was associated with a progressive dopaminergic striatal depletion from 30% in the asymptomatic stage to 80%-90% depletion observed in the severe stage. DTBZ radiotracer was more sensitive to detect the degree of dopaminergic depletion as compared to FDOPA PET. The metabolic pattern in each state showed a progressive cortical hypometabolism in the different stages evaluated, more intense in the severely affected group. Contrary to PET findings in PD patients, no striatal hyper-metabolism was evident in any MPTP group.

Conclusions: MPTP induced progressive dopaminergic depletion when administered slowly and chronically. The dopaminergic and metabolic changes observed were distinctive for each motor stage. These findings validate the usefulness of in vivo PET imaging in MPTP induced parkinsonism for monitoring disease progression and putative neuroprotective therapies.

Tu-27

Effect of minocycline on dopamine neurons and microglia in the nigra of zitter mutant rats

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Objective: To investigate the effect of minocycline on tyrosine hydroxylase (TH) cells and microglial cells of zitter mutant rat.

Background: The homozygous zitter rat is an autosomal recessive mutant derived form the Sprague-Dawley (SD) rat, and is characterized by curled body hair, bent whiskers, fine tremor and flaccid paresis. The mutant rat has abnormalmetabolism of oxygen species. In this mutant rat, there is also a loss of dopamine (DA) neurons with age and there is a corresponding loss of DA fibers and presence of abnormal DA fibers similar to Parkinson's disease. Minocycline has been shown to block microglial activation of parkinsonism animal models and protect against nigrostriatal dopaminergic neurodegeneration in previous studies. However, the efficacy of minocycline in the mutant rat is unknown.

Methods: One-, 2-, 4- and 6-month-old zitter rats and age-matched SD rats were used. Zitter rats from 10 days after birth until one month received intraperitoneal (i.p.) injections of minocycline (45mg/kg). Then, we gave perorally minocycline to zitter rats from one month to six months. Animals were perfused and free-floating frozen sections were stained using TH and ionized calcium binding adapter molecule 1(Iba1) antibody.

Results: TH cells decreased in 6-month-old (6M) zitter rats, as compared to 6M SD rats. TH cells of minocycline administrated 6M zitter rats maintained, as compared to 6M zitter rat. On the other hand, microglia forms and numbers in the nigra of minocycline administrated 6M zitter rats did not change, as compared to 6M zitter rats.

Conclusions: These results suggest that minocycline has nothing to do with micloglial activation in the nigra of zitter rats, although minocycline has neuroprotective properties. We consider that microglial cytokines or other glial cells such as astorocyto may play a role of the neuroprotection, because microglia does not change the form.

Tu-28

Simple magnetic swallowing detection system

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Objective: The purpose of this study is to develop a simple swallowing detection tool for the movement disorder using the magnetic sensor and microphone.

Background: The swallowing test (ST) using Videofluorography (VF) has been widely used to evaluate swallowing disorders due to various neurological disorders such as Parkinson's disease. However the large VF system has a problem of radiation exposure because of X ray detection. Therefore, simple ST system for point of care test is needed to evaluate the swallowing disorder in clinical situation.

Methods: We have developed the simple detection method for ST using the magnetic detection technique. The system consists of two coils (oscillation and pickup coils) to detect the thyroid cartilage and the condenser microphone to detect the swallowing sound. The two coils and the microphone are installed in one neck holder. The induction magnetic field (20 kHz) detected by the pickup coil is used to calculate the distance between two coils, which are put on the thyroid cartilage. Using the magnetic detection system, we measured the changes of distance and the sound envelope in nine normal male controls (mean age: 28.8) when the subjects drunk 20 ml water. Moreover, we measured peak time of swallowing sound and second peak time of the distance waveform.

Results: We observed bimodal peaks in the distance wave and normally one peak in the swallowing sound. The average peak time of swallowing sound, which indicates the time interval of oral stage, was 1.64 s. The average time intervals between peak time of swallowing sound and second peak time of the length waveform was 71 ms, which is suggested the time interval of pharyngeal stage.

Conclusions: We developed a simple magnetic swallowing detection system using the magnetic sensor and microphone. The system could detect the time interval of oral stage and the time interval of pharyngeal stage. Consequently, we consider that the simple magnetic system for ST can evaluate the swallowing movement.

Tu-29

Animal model of endotoxin induced neurodegeneration in Parkinson's disease

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Objective: To characterize the distributions and densities of (1) specific cytokines involved in inflammation-induced neurodegeneration (2) localize and quantify these cytokines with abnormal increases of PD associated proteins tau, ubiquitin and α-synuclein in vulnerable areas of the rat brain.

Background: In animal and human models of sporadic PD, a neuroinflammatory process mediated by microglial activation from exposure to toxic substances, i.e., bacterial endotoxin lipopolysaccharide (LPS), has been implicated in nigral cell loss and the degenerative process. We hypothesized that exposure of adult rats to high dose LPS would initiate increased expresssion of IL-1β, IFNγ, IL-4, Il-10, Il-6,TNFα, tau, ubiquitin, and α-synuclein in the olfactory bulb (Olf) and midbrain substantia nigra (SN).

Methods: Adult rat brains from untreated saline injected and 35 mg/kg LPS IV treated animals were removed 3 hours post injection and fixed; sections probed with primary and tagged secondary antibodies. Deconvolution fluorescent microscopy images were acquired in stepwise thickness (0.1-0.25 μm) in the Olf and SN. Image emission patterns created 3D models; fluorescence intensity measured labeled proteins and cytokines.

Results: LPS treated rats showed significantly increased levels of tau, ubiquitin,α-synuclein in midbrain SN and Olf compared to controls ($p<.05$). TNFα, Il-6, IFNγ, Il-4 were significantly elevated in midbrain SN after LPS compared to controls ($p<.05$). TNFα, Il-4,Il-10,Il-1β, IFNγ levels (not Il-6) were significantly elevated after LPS in Olf compared to controls ($p<.05$). Patterns of co-localization emerged with increased levels of Il-6, TNFα, and IFNγ occurring with increased levels of α-synuclein, tau, and ubiquitin in the midbrain SN. Increased levels of TNFα, Il-4, and Il-10 co-localized with increased levels of ubiquitin in the Olf.

Conclusions: Our current theory suggests that administration of LPS in high doses leads to an endotoxin induced expression of proinflammatory cytokines. We postulate that chronically elevated proinflammatory cytokines, while essential to defend against infection, eventually cause damage to surrounding neurons via a cytotoxic effect. Our study demonstrates that increased expression of specific cytokines is associated with specific increases in tau, ubiquitin and α-synuclein in the olfactory bulb and midbrain SN areas.

Tu-30

Modulation of mitochondrial morphology and function by interaction of Omi/HtrA2 with the fusion protein OPA1 – Implications for neurodegeneration

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Objective: To characterize the effects of the knockout of Omi/HtrA2 in mouse embryonic fibroblasts concerning mitochondrial potential, ROS production and mitochondrial morphology.

Background: Loss of Omi/HtrA2 function leads to nerve cell loss in different mouse models and has been linked to neurodegeneration in Parkinson's disease and Huntington's disesase. Omi/HtrA2 is a nuclear encoded mitochondrial protein involved in stress response and a key mediator of apoptosis.

Methods: For ROS measurement and analysing the mitochondrial potential we used FACS analysis and immunofluorescent methods to dissect mitochondrial morphology. To detect protein-protein interaction between Omi and OPA1 Immunoprecipitation was performed. Differences in the protein levels of OPA1 were analysed by semi-quantitative PCR. Cellular viability was assessed by Caspase 3/Parp cleavage.

Results: Loss of Omi/HtrA2 caused an accumulation of reactive oxygen species (ROS) and reduced mitochondrial membrane potential. We found increased mitochondrial fusion and increased levels of the mitochondrial fusion protein OPA1. Co-immunoprecipitation demonstrates direct interaction of Omi/HtrA2 with endogenous OPA1. Complementation with wild-type Omi/HtrA2 protein rescued the observed increased mitochondrial fusion in knockout cells and restored increased levels of OPA1 to normal. Finally, Omi/HtrA2 knockout mouse embryonic fibroblasts were sensitized to proteotoxic stress by proteasome inhibition.

Conclusions: We show for the first time a direct involvement of Omi/HtrA2 in the modulation of mitochondrial dynamics and demonstrate a novel role of this mitochondrial serine protease in the regulation of OPA1 steady state levels. Our results underscore a critical role of impaired mitochondrial dynamics in neurodegenerative disorders.

Tu-31

Motor behavioral and oxidative stress alterations in nigrostriatal system of mice treated with mitochondrial inhibitor rotenone

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Objective: to evaluate (1) the motor behavior and (2) the oxidative stress in brain regions of mice inoculated with rotenone.

Background: Rotenone has been one of the most investigated pesticides that can act as neurotoxin. It is a natural pesticide extracted from a root known in Brazil as timbó. Beyond its use in agriculture as pesticide, rotenone is also used in pisciculture and in fishing activities by some Amazonian populations. One of the deleterious action of rotenone is complex I inhibition on the transporting electron chain. This inhibition can generate free radicals that can damage proteins, DNA and lipids, which could cause cell death. The action on lipids initiates a chain reaction known as lipid peroxidation. Complex I inhibition associated with oxidative stress has been one of the most significant events related with Parkinson's disease (PD) pathogenesis.

Methods: we inoculated acutely and subcutaneously 5 mg/kg or 10 mg/kg of rotenone in mice and evaluated lipid peroxidation products as thiobarbituric acid reactive substances (TBARs) in brain regions directly involved in the PD as the substantia nigra and the

striatum, as well as other regions as cortex, cerebellum, hippocampus and hypothalamus. The amount of antioxidant enzymes catalase and glutathione peroxidase was also evaluated as index of oxidative stress. The number of dopaminergic neurons in the substantia nigra was evaluated to investigate cell death. Besides the biochemistry analysis, behavioral tests were performed to assess motor behavior.

Results: We have found increased TBARS levels in all the studied brain regions of mice following acute rotenone administration. GSH-Px and CAT activities are reduced in most of the brain regions evaluated. The experimental animals presented motor alterations, including reduction in the locomotor activity and rearing, but no difference in the number of dopaminergic neurons in the substantia nigra was observed.

Conclusions: The detected lipid peroxidation associated with the lower antioxidant enzymes activity characterizes the oxidative stress. Therefore, it is not possible to discard the possibility that the motor changes observed were consequence of multiple function disruption occurring in several brain regions, including or not the nigrostriatal system.

Tu-32

Mitochondrial dysfunction and impaired lysosomal degradation due to loss of Parkinson's disease associated protein DJ-1

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Objective: To analyse the role of DJ-1 in the regulation of mitochondrial and lysosomal function.

Background: Loss of DJ-1 function is a rare cause of autosomal recessively inherited Parkinson's disease. Regarding the physiological role of the protein, the targeting of DJ-1 to mitochondria seems to be critical to mediate its known cytoprotective role. Impaired mitochondrial function is critically linked to imbalanced dynamic fusion and fission events of mitochondria, to energetic depression and may subsequently result in the activation of programmed cell death mechanisms. Hence, selective removal of dysfunctional mitochondria by lysosomal degradation pathways is critical for the maintainance of cellular integrity. Here we provide evidence that loss of DJ-1 function in mouse embryonic fibroblasts (MEF) causes a prominent disturbance of both, mitochondrial function and morphology, that is linked to impaired lysosomal degradation.

Methods: To determine the role of DJ-1 in PD we used immortalized MEF from a DJ-1 KO mouse model and wild-type littermates. Mitochondrial and lysosomal function was studied using FACS-analysis, Western-blotting, fluorescence microscopy, and electron microscopy.

Results: Loss of DJ-1 was linked to an accumulation of intramitochondrial reactive oxygen species, decreased rates of mitochondrial respiration, a decreased mitochondrial membrane potential, and decrease of mitochondrial branching. Importantly, ultrastructural analyses and lysosomal activity assays revealed disturbed lysosomal degradation pathways, including macroautophagy, in DJ-1 KO cells.

Conclusions: Based on our study of impaired DJ-1 protein function that leads to prominent changes in mitochondrial dynamics and lysosomal degradation, we provide evidence for a novel link between mitochondrial and lysosomal dysfunction in neurodegeneration in PD.

Tu-33

Early diagnosis of Parkinson's disease from plasma fluid by Fourier-Transform infrared spectroscopy (FTIR)

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Objective: Pattern discrimination of different spectral variables may serve as biomarkers in diagnosis of early PD as well as monitor progress of PD.

Background: FTIR spectroscopy is a powerful technique in the field of biology for studying the secondary structure of protein molecules and other substrates.

Methods: 13 patients with Idiopathic Parkinson's disease{(Age 45–70yrs) H &Y(Hohn & Yahr)Stage 1-4 patients, stage 2-4 patients and Stage 3-5 patient) respectively attending the movement disorder outpatient clinic at the SRM medical College hospital were recruited for the study. 11 age matched controls were taken. 5 ml of blood was obtained from each patient and centrifuged for 5 mins at14000 rpm in Eppendorf centrifuge and the plasma was collected and stored. High IR radiation transparent bromide iodide crystals were used as the slide material. Five experimental replicates of each sample were subjected to FTIR micro spectroscopy to standardize spectral data. Statistical cluster analysiis was performed.

Results: Peak variation were noted between patient and healthy subjects. The peak at 1147 cm-1 assigned to C–O bending modes of variation in glucose, lactose and glycerol level increases in intensity level in PD patients. The peak intensity at 3050 cm-1 region is significantly lower in all PD patients when compared to the normal controls. Peaks at 2905cm-1, 1519 cm-1 increase in intensity of absorption compared to the normal control. Peaks at 3206 cm-1 and 3371cm-1 increase in absorption level compared to the normal and are relatively important for staging of the disease and show an increase as the disease progresses from stage1 to stage3. The intensity of the peak at 3047 cm-1 decrease compared to normal. This peak clearly classifies the difference between all three stages compared to normal controls.

Conclusions: Cluster of spectra at these specific regions provide correlation with clinical data. However the influence of various medication effects on the spectra need to be analyzed. The spectral parameters may prove to be useful in evaluating suspected cases of PD as well as preclinical detection in the family members of those suffering from PD. Further studies in PD patients and normals keeping in mind the role of drugs and the stages of disease would be worthwhile.

Tu-34

Hepatic de novo lipogenesis in the different types of Wilson's disease

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Objective: To evaluate de novo lipogenesis (DNL) in patients with Wilson's disease in order to get insights into some aspects of metabolic changes of lipids and carbohydrates metabolism in this disease.

Background: Wilson's disease (WD), or hepatolenticular degeneration, is an autosomal recessive genetic disorder in which copper accumulates in tissues; this manifests as neurological or psychiatric symptoms and liver disease. As already known and well documented, liver is a key organ in the supply, storage and excretion of copper. On the other hand, we have very few sources describing the lipid metabolism and particularly de novo lipogenesis in Wlison's disease.

Methods: Triacylglycerod concentrations were measured with a colorimetric assay. Insulin and cortisol were analysed with commercial radioimmunoassay. Gas chromatography-mass spectroscopy was used for isotopic enrichments of pamitate-methyl esters from VLDL. The ratio of double-labeled to single-labeled excesses in VLDL-palmitate reveals the isotopic enrichments of the true precursor for lipogenesis (hepatic cytosolic acetyl-CoA).

Results: A total of 28 Wilson's disease patients with two forms: rigid-arythmohyperkinetic (RA-13) and shaking (S-15) participated in the high-fat, low-carbohydrate diet protocol. In patients with rigid-arythmohyperkinetic form decreased level of DNL and hypolipidemia in shaking form were revealed. Fasting plasma glucose concentrations didn't differ significantly between groups. For a triacylglycerol concentrations, there was a significant group-by-time interaction. Consumption of a high-fat, low-carbohydrate diet for 5 days signifi-

cantly affected plasma triacylglycerol concentration in the patients with S form, but not in RA group.

Conclusions: This research elucidates the role of DNL pathway in carbohydrate and lipid metabolism in one of very specific hereditary hepatic and CNS disease. We found that different forms of Wilson's disease have various types of metabolic presentation, which could be caused be as different genes pathogenic regulation. We can consider this issues in terms of the new classification of Wilson's disease.

Tu-394

Neurotropic autoantibodies in the blood serum of children first 2 years old with perinatal CNS pathology different severity

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Objective: Under supervision there were 131 children first 2 years old: 55 children with delay of motor development; 46 children with cerebral palsy, hydrocephaly and 30 health children for control. Auto-antibodies (A1) to brain proteins (GFAP- glial fibrillary acidic protein, S100, MBP- myelin basic protein, NGF–nerve growth factor.) and antiidiotypic antibodies (A2) level were analyzed.

Background: The neural system dysfunctions are usually accompanied by the immune changes; in particular, changes in the serum contents of natural auto-antibodies against nervous cells proteins (Poletaev). It is proved newborns after perinatal CNS damage had increased level of auto-antibodies against nervous cells proteins and such level depend on severity of CNS pathology. Some scientists thought that temporary elevation of neurotropic level auto-antibodies are compensatory mechanisms after acute pathology process (dysfunction of blood-brain barrier after hypoxia-ischemia). But well known that proof increasing of auto-antibodies level can cause and support autoimmune diseases.

Methods: We used ELISA method for determination autoantibodies to brain proteins.

Results: The obtained data indicates that the generalized and balanced increased production of neurotropic A1 and A2 is typical for children with cerebral palsy, hydrocephaly. Children with delay of motor development had neurotropic A1 and A2 level not differ from health children. Children with cerebral palsy, hydrocephaly had statistically significant increasing level of neurotropic A1 and A2 compare with children with delay of motor development: S 100 A1 (78,9 ± 28,36 and 111,6 ± 43,18, p<0,001), A2 (78,3 ± 29,09 and 110,8 ± 45,41, p=0,027); GFAP A1 (77,2 ± 31,48 and 105,5 ± 42,03, p<0,001), A2 (84,1 ± 44,50 and 110,8 ± 46,99, p=0,016); MBP A1 (76,5 ± 34,92 and 117,5 ± 50,32, p<0,001), A2 (83,8 ± 40,33 and 118,4 ± 55,88, p=0,001); NGF A1 (95,3 ± 38,74 and 146,1 ± 60,04, p<0,001), A2 (94,4 ± 36,22 and 141,2 ± 59,15,p<0,001).

Conclusions: Children with cerebral palsy and hydrocephaly had increasing level of neurotropic autoantibodies and antiidiotypic antibodies. It talks that pathological process caused by perinatal hypoxia-ischemia proceeds, with engaging in it of the immune system.

We-13

Proteomic analysis of the substantia nigra in patients with Parkinson's disease

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Objective: The present study aimed to gain new insights in the pathogenesis of Parkinson's disease (PD) by providing an extensive survey of the substantia nigra (SN) proteome in patients with PD compared to aged-matched controls.

Background: Neuropathological hallmarks of PD involve the selective loss of dopaminergic neurons in the SN coupled with the occurrence of Lewy bodies and neurites in surviving neurons. These inclusion bodies, composed of a large variety of aggregated proteins, are thought to play a key role in neurodegeneration. Recently, the extended armamentarium of proteomics has allowed the systematic characterisation of thousands of proteins in complex samples. Application of this technology to human brain tissues enables the detection of alterations in protein expression levels and post-translational modifications resulting from physiological or pathological processes. Few data are currently available about the SN proteome.

Methods: Human SN tissue samples were obtained at autopsy (*post mortem delay*<24h) from PD patients (n=5) and age-matched controls (n=5). To compare the protein profile of the two groups, we employed several proteomic approaches including two-dimensional gel electrophoresis and a novel tandem mass spectrometry (MS/MS)-based quantitative proteomic technique termed tandem mass tags (TMT) followed by MS/MS analysis.

Results: About 250 proteins were identified and quantified. The functional classification of all proteins reveals that 25% are involved in cellular processes thought to be critical to PD pathogenesis (intracellular signaling, protein folding, protein degradation and oxidative stress) and at least 15% take part in neuronal activities (synaptic transmission, vesicular transport). Interestingly, more than 20 exhibited significant expression level changes (Mann-Whitney U test, $p<0.05$) in PD cases compared to controls.

Conclusions: This work represents one of the most extensive proteomic assessments of human SN tissue. Further confirmation of selected candidate proteins and elucidation of their biological function should provide new insights on the molecular mechanisms at the basis of neurodegeneration in PD.

We-14

The crosstalk between autophagy or proteasome degradation pathways and apoptosis in PC12 with overexpression of human α-synuclein

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Objective: To study the different roles of the proteasome and autophagy pathways in the degradation of α-synuclein, and the crosstalk between these proteasome and autophagy pathways.

Background: Parkinson's disease (PD) is a common degenerative disorder of the central nervous system; the pathology includes the loss and degeneration of dopaminergic neurons and the formation of Lewy bodies in neurons. Recent studies found that α-synuclein is the main component of Lewy bodies. Ubiquitin-proteasome and autophagy pathways play important roles in the degradation of α-synuclein.

Methods: In this study, PC12 cells, in which exogenous human wild-type or A30P α-synuclein were overexpressed, were treated with a proteasome inhibitor and/or an autophagy inhibitor or a stimulator. Cell apoptosis ratio was detected by flow cytometry. LC3, Heat shock protein 70 (hsp70) and caspase3 expression were determined in cell culture by Western Blot. The hallmarks of apoptosis and autophagy were displayed by using transmission electron microscopy (TEM).

Results: Compared to the control group or autophagy stimulator rapamycin group, apoptosis ratio of A30P and WT cells was significantly higher after the cells were treated with proteasome and macroautophagy inhibitor as shown in flow cytometry data. Western blot study also suggested that the results of caspase3 expressed was similar to that of flow cytometry; the protein HSP70 was significantly higher in proteasome inhibitor group than in control group, but in autophagy inhibitors and stimulators group, HSP70 was similar to the control group.

Conclusions: The inhibition of proteasome and autophagy can promote apoptosis and macroautophagy stimulator rapammycin may reduce apoptosis ratio. And inhibiting or stimulating autophagy has less impact on HSP70 than proteasome pathway.

We-15

Rab11a and HSP90 regulate recycling of extracellular α-synuclein

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Objective: Growing evidence suggests that extracellular a-synuclein (eSNCA) may play an important role in the pathogenesis of

Parkinson's disease (PD) and related synucleinopathies by producing neurotoxicity directly or via activation of glia. However, the mechanisms involved in the trafficking of eSNCA in neurons and/or glia remain unclear.

Background: Extracellular a-synuclein (eSNCA), both monomeric and oligomeric forms, have been proposed as biomarkers of Parkinson's disease (PD). Given the essential roles of eSNCA in PD related mechanisms, there is an urgent need to define the mechanisms by which eSNCA is able to traverse through different cellular compartments.

Methods: We conducted quantitative proteomic techniques and siRNA experiments. Some biochemistry techniques were also used to evaluate the conditions.

Results: We demonstrated that eSNCA could be re-secreted out of neurons via a process modulated by a recycling endosome regulator rab11a in addition to being degraded by an endosome-lysosome system. A quantitative proteomic analysis also revealed numerous proteins through which rab11a might execute its function. One of the candidate proteins, heat shock protein 90 (HSP90), was validated to be interacting with rab11a. Furthermore, geldanamycin, an HSP90 inhibitor, not only prevented re-secretion of eSNCA but also attenuated neurotoxicity induced by eSNCA.

Conclusions: HSP90 mediates the trafficking of eSNCA will likely provide novel insight into neurodegenerative diseases with synucleinopathies, including PD.

We-16

Bilateral stereotactic lesions of the rat entopeduncular nucleus prevent apomorphine-induced deficient sensorimotor gating and motor activity

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Objective: We here investigated whether excitotoxic lesions of the rat entopeduncular nucleus (EPN), the equivalent to the human globus pallidus internus (GPi), would improve deficient sensorimotor gating and hyperactivity induced by the dopamine receptor agonist apomorphine or the NMDA receptor antagonist dizocilpine (MK801). Additionally, we investigated whether the EPN lesions would affect cognition, motivation and motor skills.

Background: Sensorimotor gating is impaired in movement disorders, such as Tourette syndrome and Huntington's disease. Pharmacologically induced locomotor hyperactivity and deficient sensorimotor gating, measured as deficient prepulse inhibition (PPI) of the acoustic startle response (ASR), are used as animal models for these disorders.

Methods: For bilateral lesion of the EPN male Wistar rats were stereotactically injected with the excitotoxin ibotenate (4 μg in 0.4 μl phosphate buffered saline (PBS)) or for sham lesions with vehicle. After one week of recovery rats were first tested for learning and memory in the spatial continuous alternation T-maze, for motivation in the progressive ratio test (breakpoint of 3 min inactivity in the Skinner box), and for motor skills on the Roto Rod. Thereafter, rats were tested for PPI of ASR in the Startle response system and for locomotor activity in the open field after subcutaneous injection of apomorphine (0.5, and 1.0 mg/kg) or MK801 (0.07 and 0.15 mg/kg). Rats injected with vehicle (saline) were used as controls.

Results: Bilateral EPN lesions did not disturb learning and memory, motivation or motor skills. Moreover, basal locomotor activity and PPI was not affected by the lesion. However, EPN lesions prevented the apomorphine-induced locomotor hyperactivity and PPI-deficit, while MK801-induced deficits were not affected.

Conclusions: This work indicates an important role of the EPN in the modulation of dopamine agonist-induced deficient sensorimotor gating and locomotor hyperactivity, without affecting normal behavioral function. Targeting the EPN in this model may therefore be useful to test novel neurosurgical strategies for the treatment of movement disorders.

We-17

Detection of elevated levels of alpha-synuclein oligomers in cerebrospinal fluid from patients with Parkinson's disease and dementia with Lewy bodies

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Objective: This study aimed to investigate the presence of a-syn oligomers (o-a-syn) in CSF collected from Lewy body disease patients and controls, and to investigate the association between the levels of CSF o-a-syn and disease severity.

Background: Misfolding, oligomerization, and fibrillization of alpha-synuclein (a-syn) are considered central events in the onset and progression of Lewy body diseases, i.e. Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Recent data implicated that not the fibrillar a-syn, a major component of the Lewy bodies (LBs), is responsible for neurodegeneration, but rather the prefibrillar, oligomeric intermediate forms. As neuronal cells normally release a-syn, an association between Lewy body diseases and a-syn content in the cerebrospinal fluid (CSF) seems plausible and is underscored by recent data which showed that a-syn is detectable in human CSF, and its concentration is reduced within CSF from Lewy body diseases compared to healthy individuals.

Methods: From a total of 215 participants, i.e. 104 with Lewy body diseases (84 PD, 20 DLB), and 111 non-Lewy body disease subjects (86 controls, 25 with tauopathies), o-a-syn CSF levels were investigated, using a novel specific ELISA method for detecting o-a-syn recently developed in our laboratory.

Results: We found that Lewy body disease patients had significantly higher CSF o-a-syn levels, compared to patients with a tauopathy and to controls. In Lewy body diseases the CSF o-a-syn levels correlated negatively with age at onset of parkinsonism and age at onset of dementia, and positively with parkinsonism duration and dementia duration. Logistic regression analysis revealed a significant predictive value of increased CSF o-a-syn levels in Lewy body disease compared to controls ($p<0.001$, area under ROC curve, $c = 0.67$), and Alzheimer's disease ($p<0.001$, $c = 0.74$).

Conclusions: These findings indicate that CSF o-a-syn levels are associated with Lewy body disease pathology. The potential use as a biomarker needs further evaluation.

We-18

Quantification of alpha-synuclein in venous blood from a newly established, longitudinal case-control study

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Objective: To conduct a longitudinal biomarker trial for PD at Harvard Medical School, Boston and to quantify alpha-Synuclein (aSyn) in venous blood of well characterized donors. We hypothesized that aSyn values are elevated in donors with typical PD when compared to healthy controls (HCO) and to neurological control subjects (NCO).

Background: ASyn is a neural and hematological protein genetically linked to Parkinson's disease (PD). Furthermore, accumulation of aggregated, insoluble aSyn is a hallmark of PD and of several other neurodegenerative disorders that are referred to as synucleinopathies.

Methods: We established a longitudinal, case-control study of PD subjects diagnosed according to the UKPDS Brain Bank criteria, age-matched HCO subjects and NCO donors (with mainly neurodegenerative disorders). We performed neurological exams on PD and NCO subjects (including UPDRS, HY and MMSE scores). We collected serum, plasma and whole EDTA blood specimen and also obtained complete blood counts and reticulocyte numbers from each donor; total and oligomeric aSyn values were quantified by two established sandwich ELISA

methods (El-Agnaf et al., 2006; Mollenhauer et al., 2008). Data points were compared in the context of clinical diagnosis scores and subjected to group comparisons by ANOVA and ANCOVA testing.

Results: We enrolled 319 age-matched donors diagnosed with PD (n = 160; 50%), NCO (n = 74; 23 %) and HCO subjects (n = 85; 27 %). In the HCO group of normal adult donors, aSyn concentrations measured 15.0 ± 0.9 pg/ul in fresh serum, 45.0 ± 1.4 pg/ul in fresh plasma, and 24.16 ± 1.7 ng/ul in whole blood lysates. Corresponding values were also determined for the NCO and PD groups and subjected to statistical analyses that are underway.

Conclusions: We present the first data set from a newly established, case-control study of PD, NCO and HCO designed to evaluate total and oligomeric aSyn in blood with respect to hematological values as a biomarker for PD. We conclude that a simple blood test will help to diagnose PD.

We-19

Rescue of DJ-1 null mice from hypersensitivity to MPTP by ASK1 deletion

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Objective: To test (1) the role of apoptosis signal regulating kinase 1 (ASK1) in oxidative stress-induced degeneration of nigral dopamine neurons, and (2) to confirm that the neuroprotective function of DJ-1 is through ASK1 inhibition in vivo.

Background: Loss of function mutations in DJ-1 cause recessively inherited Parkinson's disease (PD) suggesting that wild-type DJ-1 has a protective function in dopaminergic neurons. DJ-1 null mice are particularly susceptible to MPTP compared to wild-type mice. We reported previously that DJ-1 blocks the apoptotic pathway mediated through the death associated protein Daxx and its effector kinase ASK1 (Junn et al, PNAS 102:9691, 2005.) ASK1 is a member of the mitogen-activated protein kinase 3 family that activates JNK and p38 pathways upon stress signaling including oxidative stress. (Part of this study was presented at the Society for Neuroscience meeting 2008.)

Methods: Four groups of mice (wild-type, ASK1 null, DJ-1 null, and double ASK1/DJ-1 null) were challenged systemically with MPTP for 5 days and their striata analyzed 14 days later by HPLC for catecholamine levels and by ELISA for tyrosine hydroxylase (TH) content. In addition, mesencephalic sections were analyzed by unbiased stereology for the number of TH positive neurons.

Results: Compared to wild-type mice, ASK1-deficient mice were relatively resistant to MPTP, with striatal dopamine and TH content as well as nigral dopamine neuron counts all reduced to a lesser extent following MPTP exposure. On the other hand, DJ-1 null mice demonstrated the expected hypersensitivity to MPTP with all these indices reduced to a greater extent compared to wild-type animals. By contrast, double DJ-1 and ASK1 deleted mice were relatively protected against MPTP, with indices of dopaminergic neuron and terminal integrity significantly better preserved than single DJ-1 deleted animals.

Conclusions: These findings demonstrate that ASK1 is a key regulator in oxidative stress-induced degeneration of nigral dopaminergic neurons, and that the susceptibility of these neurons due to loss of function mutations in DJ-1 can be rescued by inhibiting the downstream kinase ASK1. These observations suggest that ASK1 can be a therapeutic target in certain types of PD.

We-20

Deregulation of immune system pathways in peripheral blood cells of parkinsonian patients

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Objective: To evaluate the potential deregulation of immune system pathways in parkinsonian patients using a transcriptome approach of peripheral blood mononuclear cells (PBMC).

Background: Immune factors have been proposed among possible mechanisms of cell death in Parkinson's disease (PD). Leukocytes may participate to the disease process since several data showed their infiltration within substantia nigra of post-mortem PD patients and in animal models of PD. Moreover, increased levels of cytokines have been evidenced in the brain of PD patients together with microglial activation.

Methods: We compared gene expression patterns of PBMC derived from both patients with PD and healthy subjects using Agilent whole human genome expression micro-arrays (44K). Analyses of differential expression were performed with GeneSpring GX software. Genes with significant differences were analyzed using Ingenuity Pathway Analysis which generated networks and identified significantly deregulated canonical pathways. Several genes significantly deregulated were selected for further validation of expression by real-time quantitative PCR.

Results: Genes differentially expressed between patients and controls allowed us to highlight networks such as cell signaling, immune function and cell death. Moreover, canonical pathways corresponding to TGF-β signaling, interleukin signaling (IL-10, IL-4 and IL-6), leukocyte extravasation signaling and Toll-like receptor signaling were significantly deregulated.

Conclusions: Taken together, these data strengthen the hypothesis that PD is not only a neurodegenerative disorder but also a dysimmune condition involving neuroinflammatory processes and peripheral immune infiltration. Our work is the first to extend such observations to peripheral blood cells from parkinsonian patients.

We-21

Different effects of sensory afferent stimulation on subgroups of interneurons in human primary motor cortex

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Objective: To investigate whether sensory afferent stimulation has different effects on the various descending waves induced by transcranial magnetic stimulation (TMS).

Background: TMS to the primary motor cortex (M1) produces a series of descending waves, a direct (D) wave followed by several indirect (I) waves. TMS with lateral-medial (LM) directed current preferentially recruits D wave, whereas posterior-anterior (PA) current recruits I1 wave and anterior-posterior (AP) directed current recruits I3 wave. These waves generate motor evoked potentials (MEPs) with different latencies. Previous studies showed that stimulation of sensory afferents inhibit MEPs generated by PA stimulation at two distinct latencies, which were termed short (~20ms, SAI) and long latency (~200 ms, LAI) afferent inhibition. SAI and LAI were reduced in Parkinson's disease and were corrected with subthalamic nucleus deep brain stimulation.

Methods: We examined the effects of SAI and LAI on MEPs evoked by different current directions with a conditioning-test (CS-TS) TMS paradigm. The CS was electrical median nerve stimulation at the right wrist. The TS was TMS of the left M1 at different current directions. MEPs were recorded from the right first dorsal interosseous muscle. Four experiments were conducted in 11 normal subjects. In the first experiment, the time course of SAI and LAI was investigated using different interstimulus intervals (ISIs). The effects of different intensities of the CS and TS were investigated in the second and third experiments. The fourth experiment was performed to examine the effect of voluntary contraction on SAI and LAI.

Results: For the PA direction, SAI and LAI were present at ISI of ~20 ms and ~200 ms. Both SAI and LAI increased with increasing CS intensity and decreased with the increasing TS intensity. These results are consistent with previous studies. However, SAI and LAI were weaker when TS was applied with LM current direction and were weakest with AP current direction. Voluntary contraction reduced SAI and LAI with PA current direction but had less effect on SAI and LAI elicited by AP or LM current direction.

Conclusions: Sensory afferent stimulation produces greater inhibition of the I1 wave than the D and I3 waves. I1 and I3 waves may be mediated by different cortical circuits rather than a chain of cortical interneurons.

We-22

Factors influencing dopamine terminal replacement in Parkinson's disease: Perspective gained through grafting in the parkinsonian rat

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Objective: Identify factors underlying variations in efficacy and side-effects in Parkinson's disease (PD) patients grafted with embryonic dopamine (DA) neurons.

Background: We used the rat model of PD to examine whether three factors, identified from clinical trials, impact graft outcome. Host immune response, striatal target pathology, and host age were investigated for effects on graft efficacy and/or graft-induced dyskinesia (GID)-like behaviors.

Methods: 1] To examine immune response, we used a rat allograft model and varying degrees of immune activation. 2] To examine impact of target striatal medium spiny neuron dendrite spine loss secondary to severe DA depletion, half the rats received slow-release pellets containing the calcium channel blocker nimodipine to prevent spine loss; the other half received control pellets. 3] To examine whether compensating for reduced graft survival in aging hosts might allow for enhanced functional recovery, aged rats (22mo) received 5x the number of grafted cells as young rats (3mo).

Results: We found: 1] that an elevated, sub-lethal immune response correlated with elevation of aberrant synapse ultrastructure in grafted striatum and aberrant GIDs-like behaviors (Soderstrom et al., 2008); 2] DA grafts placed into parkinsonian rats with normal dendrite spine density show enhanced efficacy in a battery of motor tests and doubling of tyrosine hydroxylase (TH) fiber density with NO significant difference in number of TH cells or graft volume; 3] that even when DA grafts in aged rats contained 5-fold more TH neurons compared to young rats, the degree of TH neurite outgrowth was equal between aged and young graft recipients, and behavioral improvement was significantly delayed, requiring 10 wks to achieve that seen in younger rats with 5-fold fewer neurons.

Conclusions: Given that grafting paradigms in PD patients are: 1] allograft procedures, which result in mild-to-moderate immune activation, 2] carried out in patients with advanced disease and severe DA depletion, and 3] often involve patients of advanced years it is not surprising, based on the above preclinical data, that graft efficacy is often suboptimal. Identifying factors impeding the success of DA terminal replacement, whether through grafting or other means, will increase therapeutic options for PD.

We-23

Proapoptotic protein Bax expression and increased oxidative stress in fibroblasts from parkin mutation carriers

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Objective: The discovery of genes linked to rare familial forms of the Parkinson's disease (PD) has provided crucial insights into molecular mechanisms of disease pathogenesis. Recent findings implicate mitochondrial dysfunction, oxidative damage and apoptosis as key molecular mechanisms of both sporadic and familial PD.

Background: To characterize the possible role of these molecular mechanisms in samples originating from patients with monogenic PD, we employed human skin fibroblasts from 8 parkin mutation carriers (2 homozygous: delEx7, 1072Tdel and 1 compound heterozygous delEx7+c.1072Tdel; 5 heterozygous of either mutation) and 2 non-carriers from the same family.

Methods: After subcellular fractionation, protein lysates were analyzed using Western blotting and immunocytochemistry for the detection of apoptosis-related changes. Oxy Dot blot and dihydorethidium staining served to monitor the status of oxidative stress. In order to evaluate the role of mitochondrial function, we challenged fibroblasts with paraquat, an inhibitor of mitochondrial complex I.

Results: Western blotting revealed changes of Bax expression, with higher Bax levels in fibroblasts harbouring parkin mutations than in control cells. After paraquat treatment, the level of mitochondrial Bax was increased over that of cytosolic Bax. Compared to controls, the localization of cytochrome C was shifted from the mitochondrial towards the cytosolic fraction of mutant cells. This finding became more obvious after paraquat treatment. An almost two-fold higher level of protein oxidation was detected in mutant cells. Using immunostaining, we demonstrated an intensive localization of Bax in the mitochondrial network of mutant fibroblasts, whereas cytochrome C was diffusely localized throughout the cytosol. These changes were even more prominent after paraquat treatment.

Conclusions: First, our results strongly indicate an involvement of apoptotic processes and oxidative cell damage leading to cell death and support involvement of mitochondrial dysfunction in the pathogenesis of Parkin-related PD. Second, we here present a novel approach to study the pathogenesis of cellular damage underlying genetic PD, establishing human skin fibroblasts from parkin mutation carriers as a suitable model.

We-24

Aging effect on dopamine release in parkin knockout mice

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Objective: To evaluate (1) dopamine (DA) release in the striatum of *parkin* knock out (PKO) directly using *in vivo* voltammety, and (2) the aging effect.

Background: PKO have little sign of parkinsonism, there are a few reports suggesting physiological changes in dopaminergic neurotransmission. We reported reduced DA release at 6 month age in PKO before.

Methods: Three to twelve-month-old PKO were evaluated. The evoked DA overflow in the striatum was detected by a carbon fiber microelectrode following electrical stimulation of the medial forebrain bundle (MFB).

Results: The amplitude of evoked DA release was generally lower(two-way ANOVA, $F_{(1,62)} = 11.04$, $p = 0.0016$), and this difference was significant at 3 months(paired t test, 3.59 ± 0.62 μM, $p<0.01$). The difference was still significant after administration of DA transporter-blocker. Nine and Twelve-month-old PKO showed higher facilitation after repeated stimulation.

Conclusions: Our results are consistent with slice studies of PINK1 deficient mice, and different from *in vivo* studies of alpha-synuclein deficient mice. Marked changes in dopaminergic transmission at 3 months and no change of DA release with aging may implicate young onsets and slow progress in PARK2.

We-25

Progression of Parkinson's disease pathology is reproduced by intragastric administration of rotenone in mice

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Objective: Analyze the effect of intragastric administered rotenone on the ENS and its role in Parkinson's disease (PD) pathophysiology.

Background: PD pathology follows a characteristic pattern starting at the enteric nervous system (ENS) and the olfactory bulb (OB) and spreading to other nervous structures providing the basis for the neuropathological staging of the disease *(Braak et al. 2006)* . Interestingly both the ENS and the OB are the most exposed structures to

the environment and PD has been strongly related to the exposure to pesticides *(Gorell et al. 1998)* . To our knowledge, no animal models of the disease have been shown to reproduce the complete spectrum of PD pathological findings.

Methods: One year old C57BL/6J male mice were treated with 5 mg/kg of intragastric administered rotenone or vehicle for 1,5 and 3 months. Rotenone levels in blood and CNS tissue were detected using HPLC. Immunohistochemistry stainings were used to stain gut, spinal cord and brain frozen sections against different antigens. We also performed Thioflavine-S staining, that recognises filamentous aggregates. Quantification of TH+ neurons in the *substantia nigra* was performed using the Optical Fractionator principle. Immunofluorescence image analysis was made using ImageJ. Z-stacks from gut sections were used for quantifying the alpha-synuclein droplet size.

Results: Our results show that low doses of chronically and intragastrically administered rotenone induce PD pathology (i.e. alpha-synuclein phosphorilation, accumulation and aggregation or immflamation) in all the above-mentioned nervous system structures in wild-type mice without entering the systemic blood or the central nervous system. These alterations are sequential, treatment time-dependent and accompanied by inflammatory signs and motor dysfunctions.

Conclusions: These results strongly suggest that the local effect of pesticides on the ENS is sufficient to reproduce the neuroanatomical and neurochemical features of PD staging. Thus, providing new insight into how PD might propagate to and through the CNS indicating oxidative stress and a prion-disease-like mechanism as main underlying pathophysiological mechanisms.

We-26

Neural correlates of corticobulbar and corticospinal dysfunction in Parkinson's disease

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Objective: To examine behavioral and neurophysiological changes in corticobulbar versus corticospinal function in a rat model of Parkinson's disease (PD).

Background: Oral motor deficits occur in an estimated 90% of PD patients (Sapir et al., 2008), yet these impairments are largely resistant to standard pharmacological and surgical interventions necessitating the need for: a) an understanding of the neural mechanisms accounting for this lack of response and, b) the development of novel treatments targeting corticobulbar function. The present study examined potential differences in the fundamental neurophysiological processes governing corticobulbar and corticospinal functions in PD. The design provides an experimental model that may be used to test potential adjuvant therapies for treating oral motor versus corticospinal impairments in PD.

Methods: Adult male rats (n=12) received unilateral 6-hydroxydopamine injections into the striatum and were tested on a battery of behavioral tasks measuring corticospinal (forelimb) and corticobulbar (oral motor) function against aged-matched controls (n=12). Following behavioral testing, intracortical microstimulation was used to derive high resolution maps of forelimb and jaw movements within the motor cortex.

Results: Significant asymmetry of forepaw use was revealed in two different forelimb (corticospinal) motor tasks (cylinder test and vermicelli pasta handling) in the PD animals. In addition, this group demonstrated significant reductions in lick rhythm and rate (oral motor). The PD group showed a significant reduction in cortical forelimb movement representations but not jaw representations. Further, forelimb motor map area was significantly correlated with forelimb use asymmetry ratios.

Conclusions: These results confirm the presence of PD-like corticobulbar and corticospinal impairments in rats given intrastriatal 6-OHDA injections. Despite both oral motor and forelimb behavioral impairments, only forelimb cortical representations were significantly affected, suggesting differing neural mechanisms underlying corticospinal versus corticobulbar impairments in PD. The present animal model provides an experimental framework in which to investigate putative treatments and may guide the development of novel, more effective adjuvant therapies for oral motor impairments in PD.

We-27

Continuous delivery as a new strategy to test neuroprotection in a rotenone rat model of Parkinson's disease

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Objective: To test a new delivery modality of neuroprotective drugs in a PD model, by a continuous rate over a long interval of time, instead of the classical intermittent one.

Background: Parkinson's disease (PD) is a neurodegenerative disease characterized by progressive loss of specific neuronal populations, depletion of dopaminergic neurons of substantia nigra being responsible for motor signs of the disease. Rotenone (ROT) is an organic pesticide which inhibits mitochondrial complex I and trigger nigrostriatal damage, therefore being used to induce parkinsonian signs in animal models.

Methods: The model involved the implantation of each adult rat with two subcutaneous osmotic mini pumps, which are able to provide a relatively constant release rate. The first pump delivered ROT (2 mg/kg) or sham and the second pump delivered Cerebrolysin (CERE, 1.4g peptides/kg), a trophic factor based drug, or sham for 28 days. The animals were tested for catalepsy and locomotor activities in the open field box, at three time points. All animals were sacrificed at the end of treatments and the brains were prepared for histological examination.

Results: ROT treated animals showed significantly reduced activity, less lines crossed, rearing and head dipping, as compared to the sham group. CERE + ROT treatment significantly increased the total rearing number at 28 days, as compared to ROT only. Histological evaluation, based on counting of tyrosine hydroxylase positive neurons in substantia nigra in all animal groups, is under current investigation.

Conclusions: Our study proposes the delivery at a constant rate over a long period of time as a new method to test substances with neuroprotective potential in models of neurodegeneration. With recent medical technology achievements, the continuous delivery of neuroprotective drugs can reach applicability in humans with neurodegenerative diseases.

We-28

Interhemispheric conflicts and diagonistic apraxia after corpus callosum infarct: An oculomotor study

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Objective: To study eye movement impairments in a patient with diagonistic apraxia.

Background: Diagonistic apraxia consists of left-sided antagonistic movements, the left arm frequently counteracting the right arm. It is secondary to a callosal lesion and its pathophysiology is unknown.

Methods: A patient with a left-sided diagonistic apraxia (callosal infarct) underwent oculomotor and neuropsychological examinations. The oculomotor study consisted in the analysis of reflexive saccades (to visual or auditory targets), voluntary saccades (symbolic cues) and antisaccades (away from the target). Saccade latencies were analysed through a Linear Approach to Threshold with Ergodic Rate model in order to determine the underlying process most likely responsible for the observed impairments. Neuropsychological testing included an analysis of interhemispheric transfer and of visual awareness.

Results: All saccades performed in the left visual hemifield (irrespective of their direction), had markedly increased latencies with a

high variability. The model pointed to an increased threshold for saccade triggering. We propose that this elevation of threshold may reflect an interhemispheric conflict resulting from the callosal infarct. In our tasks, conflict could exist between gaze holding and gaze shifting processes, or between left and right hemi-visual fields. Normal influence of presence or absence of a fixation target on saccade latency ruled out the first hypothesis. In contrast, leftward antisaccades (i.e. in response to a right-sided target) with paradoxically shorter latencies than leftward prosaccades, favoured a conflict between both visual hemifields. Neuropsychological tests revealed a partial disconnection syndrome and elements of visual neglect.

Conclusions: This study investigates the underlying processes involved in motor execution by analysing an unusual pattern of partial disconnection syndrome (sparing of most posterior fibers). Our results support the idea that conflicting signals in the oculomotor system may arise after a callosal lesion. This conflict was not directional but between the two visual hemifields. At other levels of the nervous system these conflicting signals may induce a large spectrum of behavioural disorders such as left-sided antagonistic movements.

We-29

REM sleep primary deregulation following MPTP in the monkey model of Parkinsons disease

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Objective: To replicate the sleep-wake disorders of Parkinson's disease (PD) and to understand the temporal relationship between these sleep disturbances and the occurrence of parkinsonism.

Methods: We performed long-term continuous electroencephalographic monitoring of vigilance states in unrestrained rhesus monkeys using an implanted miniaturized telemetry device, and tested the effect of MPTP intoxication on their sleep-wake organization.

Results: Like humans, the animals displayed remarkable reproducibility and stability in their sleep-wake cycle organization. MPTP injection yielded a dramatic disruption of sleep-wake architecture that persisted years following MPTP administration with increased wake after sleep onset episodes and reduced sleep efficacy. Primary deregulation of REM sleep occurring before the emergence of motor symptoms was a striking feature of the MPTP acute effect. This was concomitant with a breakdown of dopaminergic homeostasis, as evidenced by decreased dopamine turnover measured after a single MPTP injection.

Conclusions: These findings are reminiscent of the REM sleep deregulation that sometimes predates motor symptoms in PD. This clinical feature of MPTP non-human primates may serve as an early premotor phase biomarker of PD and help to elucidate its pathophysiology.

We-389

Serum proteomic biomarkers correlate with disease status and severity in Parkinson's disease

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Objective: To validate sets of proteomic serum biomarkers in patients with Parkinson's disease (PD) and evaluate their relationship to disease status and severity.

Background: The diagnosis of PD is based on clinical criteria and is difficult in early disease stages. Though SPECT and PET imaging aid in diagnosis, availability and cost limit their use. Transcriptome analyses in sporadic PD patients identified a set of genes whose expression correlates with disease status. Its applicability in larger PD populations has not yet been confirmed. There remains a need for reliable, cost-effective methods to aid in disease diagnosis and monitor disease progression.

Methods: PD diagnosis was based on the Gelb criteria with the presence of at least two cardinal PD features, exclusion of secondary causes of PD, and good and lasting response to levodopa therapy. Disease severity was assessed using the UPDRS and Hoehn & Yahr scales. Serum from 60 PD patients and 40 age-matched controls obtained from the University of Thessaly movement disorders clinic was analyzed using a proteomic biomarker set developed by Power3, The Woodlands, Texas, USA. Statistical evaluation included linear discriminant analysis, unpaired t-test, and receiver operating characteristic curve analysis. Correlations of biomarkers with disease severity (UPDRS part III) were performed.

Results: A set of 57 proteomic biomarkers correlate highly with disease status (95% sensitivity). Biomarker subsets correlate with disease severity (UPDRS scores 1-15, 16-30, >31) and disease subtype (bradykinesia- vs. tremor-predominant). The biomarkers include proteins involved in inflammation and neurodegenerative pathways.

Conclusions: This validation study of the proteomic biomarker set in Greek PD patients confirms that it provides a set of proteomic serum biomarkers that can reliably identify disease status. Subsets of these biomarkers appear to correlate with disease subtype and with disease severity. These properties of the biomarker will contribute to accurate disease diagnosis and disease progression monitoring, and potentially help in assessing response to treatment. Further validation in larger patient cohorts is in progress.

We-390

Self-teaching and self-evaluation on movement disorders

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Objective: The goal of this educational multimedia CD-ROM is to facilitate the identification of the various movement disorders and simplify the understanding of their physiopathology. To assist in establishing the diagnosis and therapeutical protocol of movements disorder.

Background: The movement disorders are an important chapter of the neurology characterized by diverse aspects of the semiological, path physiological, etiological and therapeutical aspects.

Methods: The achieved multimedia CD-ROM consists of interactive self-teaching media, covering movement disorder pathology. The media uses commented video sequences assembled during our practice experience. Animated anatomical slices and diagrams are also presented aiming to facilitate the understanding of users especially internal trainees of neurology.

Results: Movement disorders represents is about 20% of the neurology, however underestimated large fraction neurologists. This is essentially due to the difficult pathophysiology associated to large etiological and semiological features. Hence, interactive self-teaching and self-education would be beneficial for enhancing the diagnostic and therapy while approaching movement disorder.

Conclusions: Our CD-ROM allows recognising movement disorders, to orient for complementary examinations and to treat some typical patients, however educated specialist in the field remains necessary.

Th-11

Pharmacologic effects of repeated administration of botulinum toxin type B on rat salivary glands

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Objective: To examine the local and systemic effects of multiple doses of Botulinum Toxin Type B (BoNT-B) on the rat salivary gland.

Background: Animal studies of BoNT injection into salivary glands demonstrate a reduction of saliva production and gland size. Thus far, there are no publications demonstrating the effects of repeat injections of BoNT into animal salivary glands. While BoNT-B may

be useful for treating excessive salivation or sialorrhea, the long term safety of repeat dosing in animals and humans is unknown.

Methods: During this 6 month study, the right submandibular gland of Sprague-Dawley rats (N=200) was injected with either 480, 720, 1000U of BoNT-B or vehicle controls at 6 week intervals. Half the animals received 2 repeat injections and the rest received 4 repeat injections. A satellite group examined the impact of a 6 versus 12 week recovery period. Gland weights, gross and histopathology and amylase staining were studied. This study was approved by an IACUC.

Results: All animals tolerated repeat injections well. There were no significant changes in body weight and food or water consumption. Aside from decreased gland weight and acinar cell shrinkage, gross and histopathologic findings were unremarkable at all doses. A dose response was observed with gland weights. Animals receiving the lowest dose (480U) had less gland shrinkage at the interim sacrifice, $p=0.2105$ than those receiving the higher two doses (720/1000U), $p=0.0323$, when compared to placebo treated animals. The 1000U dose provides exposure 80 times greater than dosing anticipated for humans when scaled by gland weight. A similar dose response trend was seen at the final sacrifice. As expected, gland weights were greater for animals in the 12 week recovery groups compared to those in the 6 week recovery groups.

Conclusions: No local or systemic toxicological findings other than reversible gland shrinkage were observed in the data. Gland function does not appear to be impaired from repeat treatment. The data suggests that repeat dosing in humans may proceed safely.

Th-12

Protein synthesis inhibition effects on dyskinesia induction

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Objective: As a first approach to understand some of the molecular factors and mechanisms involved in the development of Levodopa-induced dyskinesias (LID) we inhibited protein synthesis during sensitization to Apomorphine.

Background: Dyskinesias are one of the major limiting side effects encountered in the treatment of Parkinson's disease. Increasing data suggest that the development of LID involve profound and persistent molecular changes in the striatum, including abnormal activation of ERK (extracellular activated protein kinase) and upregulation of prodynorphin mRNA and fosB/ΔfosB related transcription factors. However the intimate mechanisms that underlie these abnormal movements are poorly understood.

Methods: 22-gauge stainless steel cannulae were implanted hemilaterally in the striatum of 6-OHDA lesioned rats. Anisomycin (160μg/1.6μl), a well characterized protein synthesis inhibitor, or vehicle were infused 15 min before Apomorphine (0.025mg/kg) once every 48 h for a total of three times (sensitization). Forty eight hours later, both groups received 0.05mg/kg Apomorphine. After Apomorphine administration contralateral rotations and dyskinesias were tested. Twenty minutes after Apomorphine, akinesia of the contralateral forepaw was also tested by means of the cylinder test.

Results: We found that Anisomycin-treated animals display less dyskinesias than vehicle-treated animals ($p<0.05$).

Conclusions: This preliminary data suggests that protein synthesis would be necessary for the induction of plastic changes that occur in response to dopamine agonists and lead to the development of dyskinesias in an animal model of parkinsonism. Strong evidence also suggests alterations in the induction phase of corticostriatal long term potentiation (LTP) and depotentiation in dyskinesias. It is known that LTP involves processes requiring protein synthesis. In view of this and based on our results it is tempting to speculate that molecular factors known to be involved in plastic changes such as LTP would also play a role in the development of dyskinesias. As a logical next step we will undertake the evaluation of these factors.

Th-13

Effects of G-CSF in the MPTP mouse model of PD

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Objective: The primary aim was to determine if granulocyte colony stimulating factor (G-CSF) administration would enhance recovery of locomotor function and restore striatal dopamine levels in the MPTP mouse model of PD.

Background: G-CSF is a multi-modal hematopoietic growth factor with therapeutic potential for neurodegenerative diseases and stroke. G-CSF increases the population of bone marrow derived cells (BMC) in the CNS and has direct anti-apoptotic and neurotrophic effects.

Methods: Chimeric C57BL6J mice with green fluorescent protein (GFP+) bone marrow cells were generated to follow the fate of BMC in brains of MPTP treated mice. Locomotor activity was measured on a rotometer at baseline when mice were 6-8M old before treatment with MPTP alone (30 mg/kg i.p. x 5d) or MPTP followed by 5 d of G-CSF (250 μg/kg s.c. x 5d). To prevent mobilization of BMC cells, a chemotactic receptor antagonist (CCR-ant) was given along with G-CSF x 5d. Behavior was measured again on day 6 and again on day 11 (5 days after completion of G-CSF or CCR2-ant treatment). After euthanasia, brains were divided along the midline; half brains were were dissected for determination of DA and metabolite levels and the other half brains were fixed for immunohistochemical analyses to determine the distribution, cellular fate and number of GFP+ cells in the nigro-striatal system.

Results: Control mice exhibited time dependent improvement in latency to fall from the rotometer. MPTP-treated mice had significant decrease in latency to fall from the rotometer on day 6 and on day 11 compared to baseline. MPTP-treated mice followed by G-CSF treatment, did not show improvement in rotometry performance compared to MPTP alone. MPTP-treated mice given CCR2-ant and G-CSF exhibited a significant improvement in locomotor function. CCR2-ant given alone after MPTP also showed a significant improvement in rotometry performance compared to MPTP alone.

Conclusions: Blocking mobilization and infiltration of BMC into brain with a CCR-2 antagonist had a positive impact on the rate of recovery, but the combination of G-CSF and CCR-2 antagonist had the greatest benefit. This dual treatment appears to have prevented the peripheral actions of G-CSF while allowing its direct neurotrophic actions to occur. Additional data on the rate of replenishment of striatal dopamine and the cellular fate of the BMC will be presented and discussed.

Th-14

Acoustic metrics of dysarthric vowel articulation: Comparison with vowel space area in Parkinson's disease and healthy aging

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Objective: To test new acoustic metrics of dysarthric speech secondary to Parkinson's disease.

Background: Acoustic metrics of speech can provide noninvasive, precise, sensitive, reliable and valid means to detect subtle signs of dysarthria and monitor its progression and its response to treatment. The *vowel space area [VSA, expressed as* $\mathrm{ABS}((F1i*(F2\alpha-F2u)+F1\alpha*(F2u-F2i)+F1u*(F2i-F2\alpha))/2)$, where F1 and F2 are first and second formants, ABS is absolute value] has been used as an acoustic metric of dysarthric speech, but with varying degrees of success. Here we tested new acoustic metrics, hypothesized to more effectively differentiate dysarthric from healthy speech and more robustly register treatment effects, as these metrics are designed to maximize sensitivity to vowel centralization (i.e., the acoustic manifestation of articulatory undershoot or hypokinetic articulation) and minimize sensitivity to interspeaker variability (due to gender and age differences).

Methods: Speech recordings of 38 individuals with idiopathic Parkinson's disease (IPD) and mild or moderate dysarthria (19 of whom received one month of intensive speech therapy (LSVT)) and 14

healthy controls were acoustically analyzed. Vowels were extracted from short phrases to construct and compare the VSA with other metrics of the forms *(F2i+F1α)/(F2u+F2α+F1i+F1u), (F2i+F1α +F1i)/(F2α +F2u+F1i), and sqrt((F2i-F2u)^2+(F1i-F1u)^2),* with and without logarithmic scaling of formant frequencies prior to the construction of these metrics.

Results: The new acoustic metrics outperformed the VSA, statistically and in terms of effect size. Logarithmic scaling of formant frequencies further improved performance. The correlations between the metrics were high. Unlike the VSA, the new metrics detected dysarthric vowel articulation in individuals with mild PD. These latter findings correlated highly with patients' self rating of "mumbled" speech.

Conclusions: Pending further research, the sensitivity and reliability of these new metrics suggest that they may help detect subtle signs of speech changes associated with PD, monitor the progression of the speech through the course of disease and its response to treatment, and possibly serve as acoustic biomarkers of the dysarthria associated with PD.

Th-15

Effect of deep brain stimulation of the pedunculopontine tegmental nucleus on c-fos expression in the rat 6-hydroxydopamine Parkinson model

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Objective: We here evaluated the expression of c-fos after 25 Hz and 130 Hz deep brain stimulation (DBS) of the pedunculopontine tegmental nucleus (PPTg) in the rat 6-hydroxydopamine (6-OHDA) Parkinson model.

Background: DBS is increasingly used to alleviate motor dysfunction in Parkinson's disease (PD). The PPTg may be a potential target for DBS in PD patients with severe postural instability with 25 Hz stimulation being considered more effective than 130 Hz stimulation.

Methods: Anaesthetized male Sprague Dawley rats with unilateral 6-OHDA induced nigrostrial lesions were stimulated with 25 Hz or 130 Hz for four hours by electrodes stereotaxically implanted into the ipsilateral PPTg. In sham-stimulated rats the electrode was placed in the PPTg for four hours without stimulation. Thereafter the distribution and number of neurons expressing the immediate early gene c-fos, a marker for acute neuronal activity, was assessed.

Results: DBS of the PPTg induced strong ipsilateral c-fos expression at the stimulation site, with 25 Hz having a more marked impact than 130 Hz. Additionally, c-fos was strongly expressed in the central gray. In the dorsal part expression was stronger after 25 Hz stimulation, while in the medial and ventral part there was no difference between 25 Hz and 130 Hz stimulation. Expression in the basal ganglia was negligible, but in the piriform cortex and motorcortex c-fos expression was reduced after 130 Hz or 25 Hz stimulation compared to sham-stimulation.

Conclusions: While in the rat 6-OHDA Parkinson model there was little change in c-fos expression in the basal ganglia after stimulation of the PPTg, c-fos was markedly altered in other functional circuitries. We conclude that PPTg stimulation might interfere also with other neuronal systems. Careful analysis of possible interferences with these systems in men would be warranted.

Th-16

CSF from Parkinson's disease patients affects α-synuclein density and cell growth in microglia and astrocytes

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Objective: To assess effects of CSF obtained from patients with sporadic PD 1) on functionally different glial cell lines, human derived microglia and astrocytes 2) compare cell growth, recovery, α-synuclein content and intracellular distribution between PD CSF treated, disease control CSF (dcCSF) treated and untreated microglia and astrocytes.

Background: Our preliminary studies suggest that cultured glial cells exposed to CSF from PD patients show loss of cellular adhesion and a necrotic death. We hypothesize that loss of cell adhesion is related to loss of function from excess or dysfunctional α-synuclein.

Methods: Microglia cells obtained from human brain glioblastoma cells and astrocytes from fetal brain tissue were cultured, grown to confluence, treated with PD CSF,or dcCSF at a ratio of 1ml CSF: 6 ml fresh media or media alone. Cell growth rates were monitored and manually counted; cell cultures were photographed, fluorescently probed for α-synuclein, actin, and nuclei over 0-9 days. Deconvolution fluorescence microscopy and 3D image reconstructions of α-synuclein, actin and nuclei were generated.

Results: **Day 4 Cell Growth**: **Microglia:** Untreated cells- confluent; PD CSF treated cells diffuse, blebbed morphology; dcCSF reduced growth rate, normal morphology. **Astrocytes:** Untreated cells- confluent; PD CSF teated cells- slower growth rate,no consisitent morphology change;dcCSF treated cells- slower growth rate than controls but greater than PD CSF, no morphological change. **Day 7 Cell Growth after replenished media without CSF: Microglia and Astrocytes**- all groups showed substantial cell growth. **Day 4 density and distribution of α-synuclein**: **Microglia**- three fold increase in PD CSF treated cells compared to control and dcCSF treated cells; change from cytoplasmic to peri-nuclear disctribution in PD CSF treated cells only. **Astrocytes-** no difference between groups; distribution pattern changed from concentrated cytoplasmic to diffuse in the treated PD CSF group.

Conclusions: Our hypothesis that excess α-synuclein leads to loss of cell adhesion is supported by the findings on day 4 when cell growth in the PD CSF incubated microglia reached its nadir with a dispersed non-adherent cell pattern correlated with markedly increased α-synuclein density. Constituent(s) in PD CSF cause this cell growth retardation.

Th-17

Are oxidative stress markers useful to predict clinical progression in Parkinson's disease? A case-control study

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Objective: To compare the levels of lipid peroxidation products between Parkinson's disease (PD) and study controls, and the relationship of these products in relation to clinical progression in PD.

Background: Oxidative stress may be important in the pathogenesis of Parkinson's disease (PD). The extent of oxidative stress damage was assessed using markers of lipid peroxidation in a cohort of PD patients and study controls.

Methods: A total of 62 PD patients and 86 age-gender matched study controls (25 ischemic stroke and 61 community-based healthy controls) participated in this study. Their demographic and clinical characteristics were obtained using a standardized questionnaire. In PD patients, the clinical severity of their disease was assessed using the Hoehn-Yahr scale and the Unified Parkinson's Disease Rating scales (UPDRS), and their cumulative exposure to levodopa calculated. Markers of lipid peroxidation (F_2-isoprostanes, F_2-IsoPs; hydroxyeicosatetraenoic acid, HETEs; and cholesterol oxidation products, COPs), were assessed in the plasma and urine samples using the gas chromatography-mass spectrometry method.

Results: The mean (standard deviation) age was 64 (8) years and there were no differences in the gender, ethnicity and medical history in the PD and study control groups ($p>0.05$). Higher levels of plasma esterified F_2-IsoPs, plasma free HETEs and COPs were observed in PD patients as compared to stroke and healthy controls ($p<0.05$, t-test). No significant correlation was observed between F_2-IsoPs, HETEs and COPs in relation to the cumulative dosage of levodopa ($r= -0.15$ to 0.21). A significant decrease in plasma free F_2-

IsoPs was observed with clinical progression of PD, according to the Hoehn-Yahr (p-trend<0.05) and UPDRS severity scales (r= -0.372, p=0.004). After adjusting for age, gender and cumulative levodopa dosage, lower plasma levels of free F_2-IsoPs independently predicted UPDRS scores (OR -292, 95% CI -527 to -56).

Conclusions: We identified certain markers of lipid peroxidation and COPs to be elevated in PD and suggested the use of plasma free F_2-IsoPs as a potential marker of clinical progression.

Th-18

Co-transplantation with olfactory ensheathing cells activate phosphatidylinositol 3-kinase/Akt signaling and protects neural progenitor cells in 6-OHDA lesioned rat model of Parkinson's disease

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Objective: In order to understand the basic mechanism of neuroregeneration and neuroprotection by neurotrophic factors, co-transplantation of Neural progenitor cells (NPCs) with olfactory ensheathing cells (OECs) was carried out in 6-Hydroxydopamine (6-OHDA) lesioned rats and attempts have been made to investigate the possible involvement of PI3K signaling pathway in neuroprotection.

Background: 6-OHDA degenerate dopaminergic neurons in nigrostriatal pathway of rat brain leading to abnormality in motor function resembling Parkinson's like symptoms. Specific neurotrophic factors such as GDNF, NGF and NT3 plays an important role in regeneration and neuroprotection against 6-OHDA induced neurotoxicity. OECs are endogenous neurotrophic factor secreting cells and may help in providing sustained neurotrophic support to transplanted cells in neural transplantation mediated therapeutic approach of PD.

Methods: NPCs and OECs were obtained from ED13 rat fetus and adult olfactory bulb respectively and were cultured and characterized using anti-nestin and anti-p75NTR (for OECs) antibody. The NPCs were transplanted in 6-OHDA lesioned rat model of PD with or without OECs. Functional restoration was assessed four week post transplantation by stereotypic behavior, gripstrength and locomotor activity and correlated with TH and GDNF expression. Possible involvement of PI3-K /Akt signaling in mechanism of neuroprotection of OEC was investigated *in-vitro* using OECs and NPCs co-cultures.

Results: Co-transplanted animals as compared to lesioned or NPC alone transplantion exhibited a significantly reduced rotational behavior, restored grip strength and locomotor activity along with restored TH/GDNF. Mechanism of neuroprotection of OEC investigated *in-vitro* indicates less loss of NPCs viability in presence of OECs on exposure to 6-OHDA (10^{-4} to10^{-9} M) as compared to NPC alone. The downstream events suggest induction of antiapoptotic pathways with restored BCl2:BAX and activation of p-BAD, p-AKT, reduction in p-GSK beta in presence of OECs which diminished on addition of L294002 (PI3K inhibitor).

Conclusions: The results suggest, possible involvement of PI3K pathway in neuroprotective action of OECs.

Th-19

Neuroprotective effects of deep brain stimulation of the rat STN: Advantages and limitations of the intrastriatal 6-OHDA model

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Objective: To evaluate the neuroprotective potential of deep brain stimulation of the subthalamic nucleus (STN DBS) in rats when stimulation is initiated after significant nigrostriatal dopaminergic neuronal loss.

Background: Preclinical studies demonstrate that STN DBS can provide neuroprotection of nigral dopamine (DA) neurons when initiated prior to or soon after experimental toxins. However, the ability of STN DBS to provide neuroprotection once progressive degeneration has been initiated has never been examined nor whether STN DBS can protect striatal DA terminals.

Methods: We lesioned rats with intrastriatal 6-hydroxydopamine (6-OHDA) and implanted stimulators in the ipsilateral STN. At the point at which animals had lost 50% of their nigral DA neurons, stimulation began and was administered continuously for 2 weeks. Functional neuroprotection of contralateral forepaw use and general motor activity was assessed using the cylinder task. Neuroprotection of the nigrostriatal system was evaluated via stereologic assessment of tyrosine hydroxylase immunoreactive (THir) nigral neurons, THir neurites in the striatum and measurements of striatal DA and DA metabolites.

Results: STN DBS halted ongoing nigral DA neuron loss. In contrast, rats implanted with inactive electrodes displayed significant DA neuron degeneration over the two-week stimulation interval. However, stereological analysis of striatal THir neurite density and DA levels revealed that the neuroprotective effects of HF STN DBS did not extend to the striatum. Behavioral analysis revealed that STN DBS provided functional improvements in generalized motor activity (rearing), improvements that were not observed when stimulation was turned off.

Conclusions: These studies demonstrate that STN DBS can halt ongoing, protracted nigral DA neuron degeneration but does not restore previously depleted dopaminergic terminals in the striatum. Further studies are warranted utilizing alternate models of PD in which protracted striatal terminal loss occurs in order to determine whether the neuroprotection of nigral cell bodies can be extended to neuroprotection of striatal dopaminergic terminals.

Th-20

Deep brain stimulation of the subthalamic nucleus in a rodent model: Effects on trophic factors

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Objective: To examine the effects of high-frequency deep brain stimulation of the subthalamic nucleus (STN DBS) on glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) in the STN and its target structures: substantia nigra (SN), Globus Palidus interna (GPi), Globus Palidus externa (GPe), Striatum (STR), and Frontal Cortex (FC).

Background: Preclinical studies in our laboratory and others have demonstrated STN DBS-mediated neuroprotection of SN dopamine neurons, but the mechanism of this neuroprotection is unknown.

Methods: Initial studies were done in unlesioned rats. Unilateral stimulation was initiated 2 weeks post-surgery for a period of 2 weeks (130 Hz, 60 μs, 30 μA). Enzyme-Linked ImmunoSorbent Assay (ELISA) was used to determine GDNF and BDNF protein levels and real-time reverse transcriptase polymerase chain reaction (qPCR) was used to determine mRNA levels. Currently we are repeating similar experiments in lesioned rats. Rats were assessed for forelimb akinesia via the cylinder task then given unilateral intrastriatal injections of 6-OHDA. Bipolar concentric electrodes were unilaterally implanted in the STN during the same surgical session. Two weeks post-surgery rats were reassessed for forelimb akinesia and then stimulation was initiated. After two weeks rats were reassessed for forelimb akinesia both "on" and "off" stimulation and then sacrificed. The STN and its target structures were microdissected and analyzed via fluorometric ELISA to determine BDNF protein levels.

Results: Results from unlesioned animals revealed no changes in GDNF protein associated with STN DBS. However, STN DBS showed a bilateral 3-fold increase of BDNF in the STR. Additionally, a unilateral 9-fold increase in BDNF mRNA was observed in the GPe. In the lesioned animals, behavioral analysis revealed that STN DBS provided functional improvements in lesion-induced contralateral forepaw akinesia, improvements that were not

observed when stimulation was turned off. Analysis of BDNF protein levels in the 6-OHDA lesioned rats is ongoing.

Conclusions: STN DBS upregulates BDNF protein in the striatum and mRNA in the GPe in unlesioned rats, suggesting a possible mechanism for neuroprotection.

Th-21

Effects of oligodendroglial α-synucleinopathy on striatal grafts in a transgenic mouse model of MSA

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Objective: To determine the effects of glial α-synucleinopathy on embryonic striatal grafts in a transgenic MSA mouse model.

Background: In contrast to Parkinson's disease parkinsonism in MSA is usually refractory to levodopa therapy reflecting loss of efferent striatopallidal circuitry. Experimental data suggest that striatal grafts may improve the response to exogenous levodopa in MSA-P, however, the impact of glial α-synucleinopathy on striatal graft survival has not been addressed so far.

Methods: Using standard protocols we implanted cell suspensions derived from E14 whole ganglionic eminence into the striata of transgenic mice featuring human oligodendroglial α-synuclein inclusions and MSA-like neurodegeneration augmented by 3-nitropropionic acid.

Results: Embryonic striatal allografts showed preserved survival but reduced P-zone volume and dopaminergic reinnervation 3 months post-transplantation. We consistently observed oligodendroglial cells expressing host-specific α-synuclein within the graft tissue indicating possible host-to-graft disease propagation.

Conclusions: Our findings indicate that embryonic striatal grafts survive in the presence of oligodendroglial α-synucleinopathy. Whether the reduced P-zone volume is associated with functional compromise is presently unclear. Further studies are warranted to clarify the role of α-synuclein positive cells within the grafts.

Th-22

Blood brain barrier integrity in a mouse model of MSA: towards mesenchymal stem cell therapy

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Objective: Determination of the blood brain barrier integrity in a mouse model of MSA, for possible mesenchymal stem cell transplantation as future therapeutic approach in MSA.

Background: Multiple system atrophy (MSA) is a fatal rapidly progressive neurodegenerative disorder associated with prominent alpha-synuclein oligodendroglial inclusions. Since symptomatic therapies are only partially effective there is a growing interest in disease modifying strategies. Within the last years, the therapeutic application of mesenchymal stem cells (MSCs) in animal models of stroke, amyotrophic lateral sclerosis, experimental autoimmune encephalomyelitis and Parkinson's disease appeared to be effective. MSCs are said to play a role in the modulation of deleterious immune responses, as well as neuronal survival by secretion of neurotrophic factors. Furthermore MSCs can be obtained from autologous tissue, thus providing an ethically justified source for transplantation. In 2007, Lee et al. reported preliminary efficacy and safety data in an open label trial of autologous MSCs delivered intravenously and intraarterially in 11 patients with MSA-C. However up to now, there is no pre-clinical experimental evidence supporting the use of MSCs as a cell therapeutic intervention in MSA. In this experimental study we therefore examine whether autologous MSCs induce functional improvement and modify neurodegeneration.

Methods: Our first step towards MSC transplantation was to analyze blood brain barrier integrity in a transgenic mouse overexpressing human alpha-synuclein in oligodendrocytes. Exposure to oxidative stress by 3-nitropropionic acid (3-NP) leads to MSA-like glial and neuronal pathology in this model (Stefanova 2005). Follwing intracardiac perfusion of Evans Blue and Hoechst, blood brain barrier integrity can be determined.

Results: Our results indicate that the blood brain barrier integrity is disrupted in the combined MSA mouse model allowing systemically infused MSCs to reach MSA-like glial and neuronal lesion sites.

Conclusions: Our findings imply that systemic MSC delivery is feasible to evaluate their therapeutic efficacy in MSA mice. Our present studies are aimed at determining MSC migration in affected brain areas and elucidating their functional role.

Th-23

Cytoprotective effects of extracellular dopamine under the dopamine overproduction

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Objective: To verify the potential cytoprotective effects of extracellular dopamine.

Background: In spite of much work and speculations, debates on the toxicity of dopamine have not been settled yet. Vulnerability of nigral neuron is pathological hallmark of PD and several lines of evidence have showed toxic effect of high dose dopamine *in vitro*. On the other hand, recent clinical papers showed that dopamine intake did not worsen the disease course of PD. Moreover, several papers suggested that dopamine stimulation on the D2 receptor family was neuroprotective.

Methods: We developed stable SH-SY5Y cell lines expressing human tyrosine hydroxylase under the transcriptional control of the Tet-On system. In this cellular model, expression of tyrosine hydroxylase was induced in the presence of tetracycline. After the induction of tyrosine hydroxylase, dopamine D2 receptor antagonist eticlopride (1-10mM) was added to the medium. Then, cell death and cell signaling markers were evaluated by western blots, immunocytochemistry and MTT assay. Extracellular dopamine concentrations were evaluated by HPLC.

Results: Following the induction of tyrosine hydroxylase, intra/extra-cellular dopamine was increased, although morphological features, growth rate and viability of cells were not changed. The extracellular dopamine concentration was elevated from undetectable levels to 5.8 nM. Eticlopride treatment per se did not change the cell viability. When tyrosine hydroxylase expression was combined with eticlopride treatment, increased cell death and cleaved PARP was observed.

Conclusions: This study suggested that the extracellular dopamine of appropriate concentrations might be cytoprotective. Without the blockade of D2 receptors cell death was not observed when intra/extra-dopamine was overproduced by tyrosine hydroxylase induction. Low concentration of extracellular dopamine, which was lower than one to ten thousand of the lower limit of toxic concentrations *in vitro*, might compensate the potential toxicity of intracellular dopamine. It was suggested that our cellular model is suitable to evaluate the putative interaction between intracellular and extracellular dopamines.

Th-24

The effects of chronic administration of ephedrone (methcathinone) and manganese in mice

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Objective: To evaluate the effects of ephedrone and manganese in mice.

Background: Parkinsonian syndrome related to intravenous use of a "designer" psychostimulant, derived from pseudoephedrine using

potassium permanganate as the oxidant, has been observed in drug addicts in several countries during the last decade.

Methods: The solution was prepared using saline, pseudoephedrine, vinegar and potassium permanganate. 4 groups (full dose, 50% dose, 20% dose, control group, 15 animals in each group) of C57B6 mice were injected with 0.3ml (contained 19.2 mg of manganese and estimated 0.15 mg of ephedrone) intraperitoneally once a day for a period of 7 months. At the beginning and at the end of the experiment behavioral testing (motility box) was done. The animals were weighed every week, their step length was measured every 4 weeks (ink test) to assess motor dysfunction. 11C-DTBZ ex vivo brain PET autoradiography was carried out after 3 and 6 months of injections to evaluate the integrity of the dopaminergic system. Whole brain radioactive tracer accumulation was measured at the same time intervals. In vivo whole body 11C-DTBZ PET-CT scans and ex vivo brain MRI scans were obtained after 7 months.

Results: Average distance in motility box was 343 m in full dose group and 215 m in control group ($p=0.041$). In full dose group 3.59% and in control group 3.06% of the injected dose of radioactivity per gram of brain tissue was detected, indicating possible decrease in the function of vmat2. PET autoradiography showed no significant increase of tracer uptake in striatum compared to cerebellum. There was no significant change in step length or weight during the experiment. MRI showed no significant structural change or manganese accumulation in the brain.

Conclusions: Behavioral testing showed a strong stimulating effect of the drug throughout the duration of the experiment. The mice expressed no signs of parkinsonism or dystonias in the ink-test. There was a markedly lower whole brain accumulation of the radioactive tracer labeling vmat2 in the treated animals. This finding indicates, that chronic treatment with methcathinone in combination with manganese can induce changes in vesicular dopamine transport and potentially induce nigrostriatal pathology.

Th-25

The research of the interaction between parkin and OGCP

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Objective: To confirm the interaction between parkin protein and 2-Oxoglutarate carrier protein (OGCP) and get insight of effects of parkin protein and OGCP on the apoptosis of HEK293 cells.

Background: Parkin gene is one of the virulence gene for Parkinson's disease. As one of the E3 enzymes of ubiquitin-proteasome pathway (UPP), parkin mediates many substrate proteins' ubiquitination which has close relationship with the nosogenesis of Parkinson's disease. OGCP is one of the proteins in mitochondrion. There was no report about the interaction of parkin proteins and OGCP previously.

Methods: Immunofluorescence, laser confocal microscope and Co-immunoprecipitation were used to confirm the interaction between parkin and OGCP. Subsequently, vitro and vivo Ubiquitination Assays were carried out to confirm that OGCP is one of the substrate proteins of parkin protein and parkin protein mediates OGCP's ubiquitination. Finaly, by Flow Cytometry Methods(FCM), we examined HEK293 cells apoptosis rate using fluorescence FITC as probe, tested the mitochondrion membrane potential ($\Delta\Psi_M$) using Rhodamine123 as probe and detected the cellular reactive oxygen species(ROS) level using DCFH-DA as probe.

Results: Parkin and OGCP could be co-localized in the HEK293 cells and the interaction between parkin and OGCP was confirmed by COIP. Parkin could promote the ubiquitination of OGCP. Parkin and OGCP could raise $\Delta\Psi_M$ of HEK293 cells treated by 100nmol/l rotenone and lowered the cellular ROS level and the cell apoptosis rate induced by 100nmol/l rotenone. Parkin mutant (R42P and T240R)lowered $\Delta\Psi_M$ of HEK293 cells especially the HEK293 cells induced by rotenone, raised the cellular ROS level and improved cell apoptosis. In addition, OGCP could inhibit the decrease of $\Delta\Psi_M$ and the increase of the cellular ROS level and the cell apoptosis rate resulting from parkin mutant(R42P and T240R).

Conclusions: Our data suggest OGCP is one of the substrate proteins of parkin and parkin mediates OGCP's ubiquitination. Both parkin protein and OGCP have positive effect on the function of mitochondrion, but the interaction between them doesn't increase the positive effect.

Th-26

Piclozotan (SUN N4057), a 5-HT_{1A} receptor agonist, improves motor complications induced by repeated administration of levodopa without reducing levodopa efficacy in parkinsonian rats

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Objective: To investigate the effects of piclozotan (SUN N4057), a serotonin 1A (5-HT_{1A}) receptor agonist, on motor complication induced by repeated administration of levodopa in parkinsonian rats.

Background: Levodopa has been considered the most effective remedy for Parkinson's disease (PD) but its long-term treatment induces motor complications such as dyskinesia and motor fluctuations. Recently, 5-HT_{1A} receptor agonists have attracted much interest as potential therapeutic agents, because dopamine (DA) released from 5-HT neurons is responsible for levodopa-induced dyskinesia in parkinsonian rats.

Methods: Male SD rats were used in this study. We employed unilaterally 6-hydroxydopamine (6-OHDA)-lesioned rats for an animal model of PD. Parkinsonian rats were administered levodopa (25 mg/kg i.p., twice daily) for 8 to 9 weeks. Based on the results of the rotational behavior and forelimb hyperkinesia in Week 5, the rats were allocated to three treatment groups. Piclozotan was administered via continuous subcutaneous infusion using an osmotic pump for about 3 to 4 weeks. At Week 7 of repeated levodopa dosing, we evaluated effects of drug on the levodopa-induced behaviors. In addition, the concentrations of levodopa-derived DA released from the striatum were measured by using microdialysis in Week 8-9 after completion of respective behavioral studies.

Results: Chronic treatment with levodopa induced forelimb hyperkinesia and shortening in duration of rotational behavior. Piclozotan low dose and high dose reduced levodopa-induced forelimb hyperkinesia by 55% ($P<0.05$) and 69% ($P<0.01$) respectively at 1 hour relative to control. Piclozotan high dose significantly lengthened the duration of rotational behavior vs control by 26% ($P<0.05$) and attenuated increase in striatal levodopa-derived extracellular DA levels.

Conclusions: These findings suggest the possibility that piclozotan (SUN N4057), a 5-HT_{1A} agonist with favorable dopamine receptor function profile, can improve motor complications without reducing the efficacy of levodopa in patients with advanced PD.

Th-27

Isolation and characterization of genetically modified neural stem cells by fluorescence-activated cell sorting (FACS) analysis

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Objective: Isolation and characterization of genetically modified neural stem cells, ES cells and iPS cells will be useful for the research of the future therapy for Parkinson's disease (PD) patients. We evaluated the direct method to identify the characterization of geneticlally modified stem cells by FACS analysis (BD FACSAria).

Background: We already established the genetically modified neural stem cells using the improved retrovirus vector for the transplantation (Hyakawa et al. 2007). However, it is not easy to identify the potential of the proliferation or the differentiation in theses cells. Most groups usually evaluated the proliferation or the differentiation by the immunohistochemistry and sometimes demonstrated the different results in each group. Therefore, we evaluated the direct method

to identify the characterization of geneticlally modified stem cells by FACS analysis.

Methods: We isolated the neurosphere forming cells from the striatum of embryonic mice and transduced the interest gene into these cells by the improved retrovirus vector. We stained them by using anti BrdU antibody and 7-amino-actinomycin D(BD BrdU Flow Kit), and analyzed by the FACS analysis.

Results: We clearly isolated and demonstrated the ratio of the differentiation and the proliferation of genetically modified neural stem cells by FACS analysis.

Conclusions: These techniques should be useful for directly evaluating the potential of the proliferation or the differentiation genetically modified stem cells.

Th-28

Allantoin, not uric acid, is the active neuroprotective metabolite of inosine in a rodent model of Parkinson's disease

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Objective: To determine the active metabolite involved in the neuroprotective effect of systemically administered inosine in the the 6-hydroxydopamine (6-OHDA) rodent model of Parkinson's disease (PD).

Background: Elevated serum urate has been associated with a slower rate of PD progression. While preclinical studies demonstrate that inosine/UA administration can provide neuroprotection in animal models of stroke and multiple sclerosis, this question has yet to be examined in parkinsonian models. In humans, UA is the end product of purine metabolism whereas in most other mammals, including rats, UA is further metabolized to allantoin via the enzyme urate oxidase.

Methods: Male Sprague-Dawley rats (200-225 grams) received subcutaneous matrix-driven pellets for compound delivery. Group 1 was administered the UA precursor inosine (9.52 mg/day), Group 2 received inosine plus the urate oxidase inhibitor potassium oxonate (9.52 mg/day each), Group 3 received allantoin (9.52 mg/day), and Group 4 received no pellets. Pellet implantation occurred prior to 6-OHDA infusion into the striatum with compound delivery continuing for six weeks during which animals were assessed for forelimb asymmetry. After six weeks brains were then removed with the striatum processed for dopamine (DA) biochemistry and the substantia nigra (SN) processed for tyrosine hydroxylase (TH) immunocytochemistry utilizing unbiased stereology.

Results: Both inosine and allantoin administration significantly ameliorated forepaw asymmetry ($p<0.001$); however, preventing the conversion of UA to allantoin completely eliminated this effect. Additionally, both inosine and allantoin treatment resulted in significant sparing of DA neurons in the SN ($p=0.02$) whereas inhibition of the metabolism of UA to allantoin abolished this nigral cell sparing. No significant differences in the levels of DA and its metabolites in the striatum were observed between groups.

Conclusions: These results are the first to indicate that the UA metabolite allantoin is a potent neuroprotective compound in a parkinsonian model and suggests that allantoin specifically, and not UA, is involved in the neuroprotective capacity of inosine.

Th-29

Substance P plays a deleterious role in early experimental Parkinson's disease

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Objective: To determine the role of substance P in 6-OHDA induced dopaminergic degeneration.

Background: Parkinson's disease (PD) is characterised by a loss of dopaminergic neurons within the substantia nigra (SN), which is an integral part of the basal ganglia (BG). As the BG is primarily involved with the execution of movement, the lack of dopamine input results in dysfunctional motor control. The neuropeptide substance P (SP) is also found in high concentration in the SN, and BG in general, where it is thought to be involved in dopamine release. In the late stages of PD, SP content within the SN and BG is decreased, thus implicating SP in the pathophysiology of PD. However, SP production has not been examined in the early stages of PD when dopaminergic degeneration is first initiated.

Methods: The current study therefore examined the role of SP in an early experimental model of Parkinson's disease. Male Sprague-Dawley rats were administered intrastriatal injections of 6-hydroxydopamine (6-OHDA; 2x2μL of 5μg/μL) to replicate the early stages of PD, and simultaneously treated with either SP (10μg/2μL) or the SP NK1 receptor antagonists, N-acetyl-L-tryptophan (NAT; 2μL at 50nM) or L-333,060 (2μL at 100nM), injected into the ipsilateral lateral ventricle. Motor function of all animals was assessed with the rotarod over a 3-week period, while SP production, inflammatory responses and dopaminergic degeneration in the BG was assessed using immunohistochemistry.

Results: In contrast to the prevailing dogma that a decline in SP is associated with neurodegeneration in PD, we observed that SP was actually increased within the striatum in early PD, particularly in perivascular tissue and within surviving dopaminergic neurons. Increasing exposure of the dopaminergic neurons to SP exacerbated the disease progression as indicated by more profound functional deficits, inflammatory responses and increased dopaminergic cell death. In contrast, when a SP NK1 receptor antagonist was simultaneously administered with 6-OHDA, dopaminergic neuronal cell death was attenuated, the inflammatory response was reduced and motor function was returned to near normal levels.

Conclusions: We conclude that SP is increased in early PD and that increased SP plays an important role in the degenerative process. Treatment with an NK1 antagonist may thus represent a novel therapeutic approach to early stage Parkinson's disease.

Th-30

LRRK2 processing revealed by new monoclonal antibody

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Objective: To investigate the processing of native LRRK2 protein in nervous system, we established new monoclonal antibodies LRRK2 protein.

Background: LRRK2 is a multifunctional and large protein, and its mutation is responsible for Park8 autosomal dominant parkinsonism which is a major cause of familial Parkinson's disease in European countries. We presented monoclonal antibodies (mAbs) reacting against LRRK2 in the histochemical examination in MDS meeting last year. However the sensitivity of mAbs was not enough to visualize of native LRRK2 on immunoblots.

Methods: We made 4 new mAbs against LRRK2. Antigens were obtained from E. coli protein expression system using vectors of histidine tag and GST tag with insertion of kinase domain of lrrk2. Polyhistidine fusion peptides were purified and injected into mice, and then GST fusion peptides were used for screening of antibodies. Antibodies were applied on immunoblots of brain homogenate and HEK293 cells highly expressed of full length of LRRK2. Fresh-frozen human and rabbit brains and praffin embedded human brain were also reacted.

Results: Four new mAbs were reacted against LRRK2 kinase portion on western blots. Two of them were IgG, one is IgM and one is IgA. All of them reacted LRRK2 in highly expressed HEK293 cells on immunoblots. Major band was 180 kDa and faint bands were also visible in the range over 250 kDa. The same band of 180kDa was also visualized in native HEK293 cells. Both water soluble and membrane bound fraction were reacted similar after subfractionation of cells. Only 180kDa band was reacted in the homogenate of human and rabbit brains. Immunohistochemical reactivity of LRRK2 was shown in perikarya of all types of neurons in the brain. Fresh-frozen samples showed ER distribution avoiding nuclei. Dendrites were

stained but not axons. On the other hands formalin fixed paraffin embedded sections stains nuclei.

Conclusions: LRRK2 immunoreactivity on immunoblots showed major 180kDa band instead of full length 270 kDa band. This indicates LRRK2 protein easily processed into smaller molecule holding kinase potion suggesting functional form in cells. Contribution of water soluble and membrane bound fractions is needed further investigation.

Th-31

Nonhomologous end joining: A novel deleterious pathogenic mechanism for parkinsonism?

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Objective: To investigate nonhomologous end joining (NHEJ) factors in peripheral blood mononuclear cells (PBMC) from parkinsonian patients and in the substantia nigra *pars compacta* (SNpc) in a rat model of low doses pesticide exposure.

Background: A link between defective DNA repair and neurodegeneration has been suggested. DNA double-strand breaks (DSB) are one of the most dangerous forms of DNA damage that, if left unrepaired, might cause genome instability and trigger cell death or tumorigenesis. DSB occurring in terminally differentiated non replicating cells like neurons can be repaired by NHEJ. Since associations between some cancers and Parkinson's disease (PD) have been demonstrated, we considered the hypothesis that defective NHEJ-mediated DSB repair is involved in PD.

Methods: We performed transcriptome analyses to investigate the expression of NHEJ factors in PBMC from patients with sporadic PD and in the SNpc in an animal model mimicking early parkinsonism. Laser capture microdissection was used to isolate SNpc from control (n=3) and rotenone (ROT)-intoxicated (n=3) animals. PBMC from control subjects (n=8) and sporadic PD cases (n=10) were isolated on a ficol gradient. Changes in transcript abundance were investigated on CodeLink rat whole genome microarrays (Amersham biosciences) and Agilent whole human genome expression microarrays (44K).

Results: We report a decreased expression of NHEJ factors in PBMC from PD patients. Likewise, other DNA repair mechanisms such as homologous recombination (the other DSB repair mechanism preferentially recruited in proliferating cells) or single strand break repair are also altered in PBMC from PD patients. Moreover, Nhej1 and Lig4 expression were similarly altered in the SNpc of ROT rats.

Conclusions: Altogether, these results in cellular and animal models of parkinsonism reveal a dysfunction of several DNA-repair pathways in PD, in particular in DSB repair, and provide novel insights into the pathogenesis of this neurodegenerative condition.

Th-32

Mitochondrial dysfunction in genetic parkinsonism: What muscles can tell us about the brain

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Objective: In this study we aim to clarify the possible role of mitochondrial dysfunction in Parkinsons disease (PD) and to define the molecular mechanisms underlying this mitochondrial dysfunction.

Background: Various studies have reported a possible correlation between PD and mitochondrial respiratory chain dysfunction. In the last two years, attention for the possible role of mitochondrial dysfunction has greatly increased because of fascinating observations on genetic variants of parkinsonism. At least two of the recessive forms, parkin and pink1, are associated with abnormal protein products that appear to kill neurons via mitochondrial dysfunction. This evidence thus far stems exclusively from preclinical studies. Especially, a Drosophila model of autosomal recessive juvenile PD showed that flies with both the parkin and pink1 mutant protein exhibit locomotor defects caused by apoptotic cell death.

Methods: In patients with a parkin mutation a needle-biopsy from the quadriceps muscle of the left leg is performed and processed for histopathological, electronmicroscopical and mitochondrial studies. Control values are obtained from previously obtained muscle tissue of 43 healthy individuals.

Results: Muscle biopsies from 5 PD patients (four patients with a proven parkin mutation and 1 patient with a positive family history) have been analysed and completed for 3 patients. All patients gave written informed consent and the study was approved by the local ethical committee. Results are presented in table 1. In summary, the muscle samples of two patients showed a reduced ATP + CrP production rate, related to a slight diminished mitochondrial energy-production capacity. Complex I activity, which has been reported to be reduced in patients with PD, was normal for all patients. Descriptive analyses of skeletal muscle by histology and electron microscopy showed no gross abnormalities, except for a minor increase in COX negative fibres. Electron microscopy showed normal mitochondria, except for one cristaline inclusion.

Table (Th-32). Mitochondrial activity

Substrate oxidation rates	Patient 1	Patient 2	Patient 3	Reference	Unit
[1-14C]pyruvate	5.6	3.72	4.17	3.61-7.48	nmol/CO2/ h.mUCS
[U-14]pyruvate + carnitine	6.13	4.54	5.04	2.84-8.24	nmol/CO2/ h.mUCS
[U-14C]malate + acetylcarnitine + malonate		5.44	4.89	3.43-7.3	nmol/CO2/ h.mUCS
[U-14C]malate + acetylcarnitine + arsenite		4.01		2.05-3.85	nmol/CO2/ h.mUCS
[1,4-14C]succinate + acetylcarnitine		3.17	2.78	2.54-6.39	nmol/CO2/ h.mUCS
ATP metabolism					
ATP + CrP production from pyruvate	59.1	37.6	40.5	42.1-81.2	nmol/ h.UCS
Enzyme activities					
Complex I	186	119	90	70-251	mU/UCS
Complex II	678	482	463	335-749	mU/UCS
Complex III	3608	3419	3826	2200-6610	mU/UCS
Complex II + III	727	473	457	300-970	mU/UCS
Complex IV	2211	2341	2790	810-3120	mU/UCS
Complex V		196	397	169-482	mU/UCOX
Citrate synthase	108	31	49	37.4-162	mU/mg
Pyruvate dehydrogenase		20.7			9.7-36

patient 2 and 3 = parkinmutation.

Conclusions: Only minor abnormalities were found in the mitochondrial energy generating system in two patients with a parkin mutation, with also slight abnormalities histologically, suggestive for mitochondrial dysfunction. For 2 additional patients analyses are almost completed and will be available in June.

Th-33

Effects of optic flow speed, gait asymmetry and egocentric reference point on navigation

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Objective: To investigate the influence of optic flow (OF) manipulations, gait asymmetries and egocentric reference point (ECRP) shifts on navigation in Parkinson's disease (PD).

Background: Our previous research demonstrates that a shifted ECRP influences heading direction during navigation. The present

study utilizes symmetric and asymmetric OF manipulations to assess the relative contributions of gait asymmetry, asymmetric OF perception and a shifted ECRP to heading direction.

Methods: PD patients with predominant right-hemisphere dysfunction (LPD, n=14), predominant left-hemisphere dysfunction (RPD, n=9) and age-matched adults (NC, N=17) wore a head mounted display and walked a virtual hallway at 0.8 m/s. During symmetric conditions, OF speeds of both walls were set at random to 0.0, 0.4, 0.8, 1.2 and 1.6 m/s. During asymmetric conditions, one wall, selected randomly, remained at 0.8 m/s, while the opposite wall was randomly manipulated through the above speeds. Walking speed, stride length, stride frequency, phase and frequency relations between arms and legs, and lateral drift were evaluated. An ANOVA with repeated measures and contrast analysis were applied.

Results: PD patients had a lower walking speed, higher stride frequency, and smaller stride length than NC adults, $F(1,37)>5.6$, $p<0.03$. Symmetric and asymmetric increases in OF speed resulted in a lower walking speed, smaller stride length and higher stride frequency, $F(1,37)>3$, $p<0.07$. Both LPDs and RPDs had a shorter stride length on the more affected body side than the less affected body side, $F(1,37)=4.2$, $p=0.049$. The phase relation between left and right arm was smaller than 180° in the LPDs and larger than 180° in RPDs ($p<0.001$), indicating that the less affected arm leads the more affected arm. During asymmetric OF manipulations, all groups veered away from the faster moving wall, ($F(1,38)=5.33$, $p<0.001$). However at the same time, LPD patients veered dominantly rightward and RPD patients leftward ($p<0.001$) as predicted by a shifted ECRP.

Conclusions: An asymmetric OF perception and asymmetry in gait may influence navigation. However, from the findings of the present study it can be concluded that in PD an altered ECRP dominantly influences heading direction during walking towards the side of the brain with basal ganglia deterioration.

Th-34

Behavioural disorders produced by electrical stimulation of the anterior striatum in monkeys

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Objective: Characterization of behavioural disorders induced from monkey's striatum and evaluation of effective stimulation parameters.

Background: The anterior striatum contrarily to the posterior part was considered as non responsive to the electrical stimulation (Alexander et al., 1985). Nevertheless, the human anterior striatum is considered for deep brain stimulation in various disorders. In a previous study (Worbe et al., 2008) we demonstrated that specific territories of the monkey's striatum are involved in different movement and behavioural disorders. Here we show that electrical stimulations perturb monkey's behaviour depending of localization and stimulation parameters.

Methods: Stimulation of the striatum was done on 4 monkeys, using a monopolar electrode moved by 1 mm steps. For each site the stimulation effects were video-recorded and evaluated for two intensities (200 μA and 400 μA) and 3 conditions (short-train of 100 μs, long-train of 700 μs and continuous stimulation at 200 Hz) and compared to control condition without stimulation. Post-mortem histological reconstruction of the stimulation sites were performed at the end of the experiments.

Results: Across the striatum, the stimulation induced an effect in 28 % (104/374) of the explored sites. Abnormal movements were observed after stimulation of 53 sites, whereas stimulation of 51 sites induced behavioural disorders of 3 types: 1) hypoactivity state with loss of food motivation (28 sites), 2) hyperactivity (16 sites) and 3) stereotypias (7 sites). The abnormal movements were induced by stimulation of both anterior and posterior striatum with all explored parameters. The behavioural disorders were induced mainly by long-train stimulation of the anterior striatum. Histological reconstruction showed that abnormal movements and hyperactivity sites were localized in the dorsal striatum, whereas hypoactivity and stereotypias sites were localized in different regions of the ventral striatum.

Conclusions: This study provides the evidence that behavioural disorders could be produced by electrical stimulation of the anterior striatum; the new DBS target for psychiatric disorders. Moreover, this study shows that long-train stimulation is the most effective parameter to induce behavioural disorders and could be used to identify the best target for DBS application to improve specific disorder.

Th-394

Involvement of human motor cortex in the recognition of handwritten or block letters – A TMS study

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Objective: To investigate the functional involvement of the primary motor cortex (M1) in recognizing letters using motor evoked potentials (MEPs) induced by transcranial magnetic stimulation (TMS).

Background: Why can humans recognize handwritten texts despite their extreme variability? One possible answer should be the observer's own knowledge about implicit motor program of orthography involved in writing. The measurement of MEPs induced by TMS, which is a non-invasive method that can evaluate the task-dependent excitability change of M1, was used to investigate the possible involvement of human M1 for writing muscles in recognizing letters.

Methods: Seven right-handed healthy volunteers with written informed consents were involved in the study. 30 letters were prepared as the stimuli; 10 small letters of alphabets, 10 Japanese hiragana letters, and 10 kanji letters of daily use in Japan. During the session, subjects were asked to look at the fixation point displayed at the center of the monitor, where the letter stimulus appears in a random order (duration: 400 ms, stimulus onset asynchrony: 8-12s). After each session, subjects answered the questionnaire to confirm that they paid attention to the stimuli. TMS was given at the hotspot for the right first digital interosseus (FDI) muscle. TMS pulses were applied to the site at the timings of 100, 200, 300, 400 or 500 ms following the onset of the presentation of each letter and MEPs induced by these TMS pulses were recorded from FDI. 20 MEPs were recorded while a subject was watching the fixation point, at the timings of more than 5 seconds before and after each stimulus onset, which were averaged and used as a baseline for each subject. The MEP ratios compared to the baseline MEP was used for the statistical analysis.

Results: The mean amplitude of baseline MEPs was 1113 ± 209 (mean ± SEM) μV. For handwritten letters, the mean MEP was significantly inhibited at 400 ms. For block letters, the mean MEP was not affected by the timing of TMS.

Conclusions: This result suggests that the hand area of human M1 might be involved in the neural network associated with letter recognition and that the brain representation of hand-written and block letters may be different. This modulation of M1 activity proved by TMS may be a neural shadow of implicit motor program of orthography involved in writing.

Th-395

Relation between post-movement-beta-synchronisation and corticomuscular coherence

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Objective: To analyse post-movement-beta-synchronisation in the EEG and EEG-EMG coherence simultaneously.

Background: The mechanisms and function of EEG synchronistion in the beta-band after the end of a short movement is not clear. The corticomusucular coupling during isometric muscle contractions

occurs in the same beta-band. It is unclear however, if these two features of cortical motor physiology are related.

Methods: 64-channel EEG was measured simultaneously with surface EMG of the right FDI-muscle in 11 healthy volunteers. Subjects kept a constant medium strength contraction of the FDI-muscle during the entire experiment. Superimposed on this they performed repetitive self-paced brisk short contractions. Time-frequency analysis including coherence over time was performed with respect to the onset of the brisk movements and averaged for 40 contrcations in each subject.

Results: Post-movement-beta synchronisation (PMBS) was found in the contralateral electrodes C1, C3 and C5 with a maximum 1-2.5 sec. after the brisk movements in the frequency range between 16 and 27 Hz for all the subjects. In 9 of the subjects there was coherence between the EEG recorded from these electrodes and the FDI in the same frequency range as the PMBS and with the maximum occuring at the same time. The other two subjects did not show any corticomuscular coherence.

Conclusions: Post-movement-beta-synchronisation coincides with corticomuscular coherence in the same frequency band. Thus PMBS is not merely a cortical phenomen but seems to involve the whole corticomuscular system, possibly reflecting recalibration after brisk movements.

CHOREAS (NON-HUNTINGTON'S DISEASE)

Mo-32

Paroxysmal choreathetosis in GLUT 1 deficiency syndrome-case report

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Objective: Report a case of GLUT1 deficiency syndrome (GLUT 1 DS) presenting as a paroxystic movement disorder.

Background: GLU-1 DS is caused by a defect in the facilitative glucose transporter GLUT1 with impaired glucose transport across brain tissue barriers causing hypoglycorrhachia. The spectrum of disease ranges from infantile-onset epileptic encephalopathy to a variety of paroxysmal neurological phenomena without epilepsy, including ataxia, dystonia, choreoathetosis, lethargy.

Methods: Clinical description.

Results: 7-year-old male, first child of healthy consanguineous parents, borned by caesarean section at 38 weeks of amenorrhea. A global developmental delay, both motor skills and expressive language, appeared. At 3 years of age he starts with paroxysmal episodes of dystonia and choreoathetoid movements. Those episodes occurred usually during the afternoon, had 1 or 2 h of duration and a frequency of 4 or 5 per month. At neurological examination, he presented dystonic postures, a mild ataxia and pyramidal signs. Extensive investigation was done. The only positive findings were hypoglycorrhachia with low ratio of CSF/blood glucose and low lactate, suggestive of GLUT-1 DS. The cerebral FDG-PET scan revealed a global and irregular decrease in glucose uptake, with more severe hypometabolism in frontal, temporal lobes and thalamus. The diagnosis was confirmed by a novel heterozygous mutation c.458G>A (p.Arg153His) detected in exon 4 of the SLC2A1 gene. Before diagnosis, a therapeutic trial with L-dopa/carbidopa and carbamazepine was done without improvement. Afterwards a ketogenic diet was also tried without compliance. Due to that, an alternative dietary regime, which included a high-carbohydrate diet fortified with uncooked cornstarch, was initiated. With this diet the episodes were less frequent and less severe.

Conclusions: This case draws attention to the association between paroxysmal dyskinesias and GLUT-1 DS and illustrates the importance of cerebrospinal fluid in detecting potentially treatable conditions in children with undiagnosed movement disorders. This new heterozygous mutation probably accounts for this mildly pathogenic form. In those cases, and especially if ketogenic diet is not tolerated, this dietary regime could be considered.

Mo-33

Painless legs, moving toes and fingers: Symptom variability related to hormonal state

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Objective: We present the case of a woman with abnormal involuntary movements of her toes and fingers, consistent with a diagnosis of "painless legs and moving toes", whose symptoms worsened while taking a progesterone-containing oral contraceptive, and improved during pregnancy and the lactating period.

Background: "Painless legs and moving toes" is a rare variant of "painful legs and moving toes", itself a very rare movement disorder. Because very few cases have been described, our knowledge about this condition's clinical spectrum remains limited.

Methods: Office evaluation with semi-annual follow-up, with videotaped examination; nerve conduction studies/electromyography (EMG-NCV), magnetic resonance imaging, serum studies, sleep study.

Results: Our patient developed, at age 26, small multidirectional involuntary movements of her toes and fingers. They were nearly constant in the toes and intermittent in the fingers. She also had tics, involving her face and arms, which she could fully suppress, whereas she was unable to completely suppress the involuntary finger and toe movements, though she could decrease their frequency and amplitude with effort. Unlike her tics, these movements were not associated with any urge, relief, and there was no associated pain. Past medical history included minor foot injuries. The finger and toe movements worsened while taking progesterone-only oral contraceptives, and gradually disappeared with the discontinuation of progesterone and during two pregnancies. The movements remained considerably reduced in frequency and intensity throughout the breast feeding period after each pregnancy, and then returned to their baseline severity, which has not changed for 6 years. EMG-NCV revealed evidence of bilateral carpal tunnel syndrome. A sleep study showed that the toe movements persisted through all sleep stages. There was no evidence of brain or cervical spine disease on MRI. Thyroid function studies, hepatic panel, CBC, ESR, ANA, electrolytes, glucose, creatinine were all within normal limits.

Conclusions: Conclusion: Our patient had involuntary movements consistent with a diagnosis of painless legs and moving toes. This is the first report, for this syndrome, of symptom variation related to hormonal changes, the mechanism of which is unclear.

Mo-34

Neuroacanthocytosis in Japan: Review of epidemilogical and neuropathological studies

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Objective: In order to clarify the incidence, clinical features and epidemiology of Neuroacanthocytosis, (NA) and review neuropathological findings in the autopsied cases in Japan.

Background: Since the first reports by Levine and Critchley et al. independently, many cases of chorea-acanthocytosis(ChAc) have been reported in various countries. But accumulation of the reports from Japan is rather prominent, when compared to other countries.

Methods: We searched ChAc and McLeod syndrome (MLS) from the Japana Centro Revuo Medicina(JCRV), which is a collection of abstract-form reports from about 4700 Japanese journals and periodical and PubMed. Neuropathologicl studies were done in the partly published case of our patient with the autosomal dominant inheritance with the review of 3 reported autopsied cases in Japan.

Results: Since the first Japanese ChAc report in 1974 till the end of 2008, 76 cases of probable ChAc and 14 cases of molecularly diagnosed MLS were found. The mode of ChAc transmission seems

to be predominantly autosomal recessive(AR), although there were 4 families which showed autosomal dominant(AD) inheritance with 2 molecularly diagnosed ChAc families. The patients with ChAc were widely distributed throughout including Hokkaido, Honshu, Sikoku and Kyushu Islands. The age onset was early thirty years, and more men suffered. Almost all the patients developed chorea with self mutilation of lips. Generalized seizures were reported in one third. IQ less than 80 was noted in the half. Caudate atrophy was documented in almost all the cases by CT or MRI. High CPK was reported in 80 %. Neuropathology of our AD-ChAc case with mutation of VPS13A revealed a marked atrophy of the caudate and putamen with small and medium-sized neuron loss and gliosis, which were quite similar to the findings in previously reported AR-ChAc. The unique finding was very wide distribution of atrophic neuron and astrogliosis over the entire cerebrum in our AD case, which is similar to the finding in Huntington' disease.

Conclusions: Our data suggest continuous publication of the cases of ChAc in Japan, although these include the heterogeneous group of NA disorders including ChAc and X-linked McLeod syndrome. Further advanced studies on NA in Japan are promising because of sustained high incidence of NA.

Mo-394

Hemichorea revealing Moya-Moya syndrome in neurofibromatosis 1

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Objective: To report the case of an 18-years old woman with neurofibromatosis 1 (NF1) who developed choreic movements revealing the presence of a moya-moya associated syndrome.

Background: Moya-moya syndrome has been reported as an extremely rare cerebrovascular problem in NF1. Chorea is also exceptional as a presenting feature of moya-moya. The involvement in the vasculopathy of the basal ganglia offers a substrate for the movement disorder.

Methods: Case study.

Results: An 18-years old woman patient, diagnosed at the age of 9 with NF1, presented for involuntary movements of her left body side. The neurological examination disclosed involuntary, jerky, chaotic movements, with no volitional control, involving her left arm and in a lesser degree the left leg and face. Although difficult to evaluate, she clearly had discrete left hemiparesis. Slight cognitive disability was noted. General examination revealed "café au lait" patches and xiphoid neurofibroma. In the past years, she has had two brain MRI (at age of 14 and 17) showing small cerebellar areas of high signal intensity and congenital hypoplasia of right internal carotid artery (ICA) consistent with NF1, with no other abnormalities. A new brain MRI was performed, disclosing a large cortical-subcortical right hemispheric area of high signal on T2-weighted and FLAIR images and significant parenchymal atrophy. Angio-CT showed already known congenital right ICA hypoplasia, distal rarefaction of right sylvian vessels supplied mainly by a proximal stenotic posterior communicant artery, stenosis of left ICA and its main branches within the circle of Willis, proximal stenosis of both posterior cerebral arteries, "puff of smoke" vascular network at the base of left brain. Moya-moya syndrome was diagnosed and the patient was referred for surgical treatment.

Conclusions: At our knowledge, no other case of hemichorea as presenting feature of moya-moya syndrome in NF1 has been previously described. In our case, the most obvious explanation for left hemichorea is the right hemispheric vascular involvement, including the basal ganglia. "Decompensation" of a congenital right hypoplasic ICA by the moya-moya process could possibly explain the obvious asymmetrical, right predominant, parenchyma sufferance.

Mo-395

Chorea presented in the syndrome of acute bilateral basal ganglia lesion in diabetic uremic patients

J.-J. Lin, K.-C. Yueh (Chushang Jenn, Nantou County, Taiwan)

Objective: To report two diabetic patients with chronic renal failure who developed sudden choreic movements associated with reversible bilateral basal ganglia lesions.

Background: Acute movement disorder associated with revesible bilateral basal ganglia lesions is an increasingly recognized syndrome, especially in patients with diabetic uremia. Most of patients with this syndrome have been reported in Asian patients and their clinical manifestations often presented parkinsonian symptoms. Brain MRI in these patients consisted of decreased signal intensity within the bilateral basal ganglia of T1-weighted images and increased signal intensity on T2-weighted images.

Methods: Case Report.

Results: The first case was an 82-year-old female with histories of NIDDM and hypertension for ten years. He had been diagnosed with chronic renal insufficiency 2 years earlier. Four days before admission, he suffered from an acute onset of generalized choreic movement in his distal limbs. The movements were not suppressible and sometimes interfered with voluntary movements such as standing and walking. Brain MRI showed a hypointensity in the bilateral basal ganglia on T1-weighted image and hyperintensity on T2-weighted image. His generalized chorea was complete remission 5 days after a supportive treatment. Follow-up MRI 45 days after admission showed diminution of the lesion on MRI images. The second case was a 57-year-old female with histories of NIDDM and hypertension for ten years. She knew chronic renal insufficiency 5 years ago and started to receive regular hemodialysis for the diagnosis of uremia two years ago. Two days before her admission, an acute onset of weakness on the right extremities, slurred speech andchoreiform movement on her right extremities. Brain MRI revealed a hypointensity in the bilateral basal ganglia on T1-weighted image and hyperintensity on T2-weighted image. After a supportive treatment, her hemiparesis, dysarthria and hemichorea were complete disappearance within 12 days. Follow-up MRI 3 months after admission revealed complete remission of the lesions in the bilateral basal ganglia.

Conclusions: In addition the parkinsonian symptoms, the syndrome of acute bilateral basal ganglia lesion in diabetic uremia can also present with acute choreic symptoms. Prognosis of the syndrome presented with choreiform movement is excellent.

Tu-35

Phenotypic variation in an Irish kindred with chorea-acanthocytosis

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Objective: To describe phenotypic variation within a kindred with Chorea-acanthocytosis.

Background: Chorea-Acanthocytosis is a recessive disorder of the *VPS13A* (*CHAC)* gene on chromosome 9q21, which encodes the chorein protein. Little is known about the function of the chorein protein *in vivo*. Clinical phenotypic variation within families has been previously described.

Methods: A 29-year-old previously healthy male presented with *de novo* status epilepticus. Involuntary orofacial movements were noted on examination. His brother was under investigation for a choreiform movement disorder. Another brother had a history of seizures. A detailed family history revealed that four paternal first-cousins-once-removed of the index case had a movement disorder with prominent orofacial involvement and psychiatric symptoms, all now deceased. There is no known consanguinity in the family.

Results: All affected siblings had evidence of a movement disorder with involuntary vocalisations, chorea and dystonia. Distal muscle wasting was noted in the index case. Eye movements were nor-

mal. Acanthocytes were detected on blood film of all affected siblings. McLeod blood group phenotype was negative. Serum CPK was markedly elevated in each of the three siblings. Lipoprotein profile and copper studies were normal. Huntington's and Torsion Dystonia mutation analysis was negative. Interictal EEG showed rhythmical delta activity consistent with diffuse encephalopathy. EMG showed myopathic motor units in the proximal upper limbs in the index case. The father of the affected brothers has acanthocytes on blood film but is clinically asymptomatic age 80. Western blotting from blood showed reduced expression of chorein in two of the siblings with a reduced, but still present band, in the 3rd affected sibling. An asymptomatic sibling and healthy control showed normal protein expression on Western blotting.

Conclusions: This kindred's clinical presentation is consistent with Chorea-Acanthocytosis, a recessive disorder of the *VPS13A* gene, which encodes the chorein protein. The phenotypic variation and the pattern of inheritance raises the possibility of incomplete penetrance of this autosomal recessive disorder or the interplay of other genetic factors which modify expression of chorein.

Tu-36

Ischemic stroke and movement disorder

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Objective: The goal of our study is to show the relationship between physiopathological aspects of the movement disorder and stroke.

Background: Movement disorder is an unidentified entity which has various geneses including degenerative origin. However, vascular etiology is also probable.

Methods: We report 125 cases of ischemic stroke collected in the department of neurology from January to October 2008, the lesions of the patients were repartitioned as follows: 60 patients (48 %) were affected in the central grey nuclei, 19 cases (15.2%) with impaired lenticular nucleus, 12 cases (9.6%) with thalamic lesions and 33 cases (26%) with lenticular and caudate nucleus. We specify that movement disorder was observed in two (3 %) of the sixty patients presenting an impairment of the central grey nuclei. The first case presented a right hemichorea associated to neurological deficits, while the second developed a dystonia of the left lower limb during the phase of recovery of his deficit.

Results: The MRI of the first patient showed multiple old ischemic lesions of the central grey nuclei which was asymptomatic, and the recent lesion causing the hemichorea was found in the fronto-parietal left cortico-sub-cortical in the diffusion images. Transient or developed ischemia could affect the central grey nuclei or their connections without involving movement disorder; consequently, movement disorder is associated to the occurrence of the cortico-sub-cortical lesion and its nucleus (Gionio et al. 1966; Johnson and Fahn. 1977).

Conclusions: Our study corroborate earlier literature supporting the physiopathological hypothesis of the movement disorder connected to stroke.

Tu-395

Peak-dose chorea secondary to "brivudine" treatment in patients with Parkinson's disease

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Objective: Peak-dose dyskinesia is a major and frequent problem in long term levodopa therapy of patients with Parkinson's disease (PD). Several reports indicate that some drugs or even some type of food increase the dopaminergic response and consequently producing a peak-dose chorea in PD patients. Brivudine is similar to acyclovir. It was shown to be a potent inhibitor of the herpes simplex virus Type 1 (HSV-1) as well as the varicella zoster virus (VZV). We haven't found any report in the medical literature about this potential effect with brivudine. We report here two cases in which the association between brivudine and dopaminergic treatment produced reversible peak-dose chorea.

Methods: A 57-year-old man and a 55 year-old woman with PD of 10 and 11 years of duration respectively. Disease severity was assessed with the UPDRS. They were treated with Brivudine due to herpes zoster cutaneous lesions. An intense peak-dose chorea was induced several minutes after the first dose of this drug and lasted for 24 hours. There were no recurrences of this event after discontinuing the Brivudine treatment (detailed information of the clinical characteristics of these patients will be presented in the poster).

Conclusions: There are no reports in the medical literature describing the possible association between Brivudine and peak-dose chorea in levodopa treated patients. The mechanism why this analogue of the nucleoside thymidine produces this effect remains unclear. There was an association between the administration of Brivudine and the development of this type of dyskinesia and no recurrences occurred after the discontinuation of the drug.

Tu-396

A case of amyotrophic lateral sclerosis with chorea

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Objective: To present a case of amyotrohic lateral sclerosis (ALS) with chorea.

Background: Involuntary movements in ALS are extremely rare.

Methods: Case.

Results: The patient is a 68-year-old woman with ALS presenting chorea. She noticed a walking difficulty due to motor weakness in her lower limbs and involuntary movement in the lower limbs was pointed out by her family at age of 63 years. She developed dysarthria and motor weakness in the right upper limb at age of 65 years. Since her dysarthria had worsened, she admitted to our department in December, the next year. She had a history of pulmonary emphysema and no family history of neurological disorders. At that time, neurological examination showed bulbar palsy, muscular atrophy, motor weakness in the upper and lower extremities and exaggerated deep tendon reflexes in lower extremities. Cortical function was normal. Chorea was seen in face, neck and the four limbs. Electromyography revealed fasciculation in the first doral interosseous. Changes in motor neuron units potentials including high amplitude and polyphasia were seen in examined muscles of four limbs and the paraspinal muscles. Brain magnetic resonance imaging (MRI) was normal. There was no abnormal expansion of CAG repeats indicating Huntington's disease, the spinocerebellar atrophy 1-3, 6-8, 12, 17, or dentatorubropallidolyusian atrophy. We diagnosed this patient as ALS based on those findings. During following two years, her motor weakness and muscular atrophy progressed, although choreic movement did not worsen. She admitted again for consideration of respirator and percutaneus endoscopic gastrostomy because of her progressed bulbar palsy and respiratory dysfunction at age of 68 years. She was put on the respirator and took percutaneus endoscopic gastrostomy during her admission.

Conclusions: This case demonstrates that some patients with ALS may have lesion not only in motor neuron system, but also in extrapyramidal system.

We-30

Chorea in iatrogenic hypocalcemia due to parathyroid gland removal during total thyroidectomy

A.Q. Rana (Toronto, Ontario, Canada)

Objective: To present an interesting case of chorea due to iatrogenic hypocalcemia resulting from removal of parathyroid glands during total thyroidectomy.

Background: Chorea is characterized by invlountary, unpredictable, brief, fleeting movements which appear to be flowing from one body part to another randomly. Chorea is the result of a list of genetic and acquired disorders. Chorea due to itarogenic metabolic causes is seen infrequently. Among these, one rare but important cause is prolonged hypocalcemia that in fact can be secondary to iatrogenic removal of parathyroid glands during total thyroidectomy.

Methods: We present a case of a 79 year old female originally from Sri Lanka, who had total thyroidectomy done 30 years ago in Sri Lanka after which she developed choreform movements. Corrected serum calcium was found to be significantly below the normal range and a significant improvement of choreform movements was seen upon introduction of calcium replacement therapy.

Results: CT scan of head showed calcification of basal ganglia.

Conclusions: Chorea can be a complication of total thyroidectomy due to parathyroid gland removal resulting in itarogenic hypocalemia and should be discussed with patients while offering these proceedures.

We-31

Movement disorders associated with diabetes mellitus: A prospective case series

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Objective: To describe the clinical characteristics of diabetic patients presenting with choreic movements and response to treatment at follow-up.

Background: Glucose dysregulation affects high metabolic rate cerebral regions including basal ganglia. Movement disorders as chorea and hemichorea-hemiballism had been associated with non-ketosic hyperglycemia (300-1000 mg/dl) and hyperosmolarity (300-390 mOsm/l). MRI usually shows putaminal hyperintensity. This abnormal movements had been described in older women with some cases remitting but other with persistence despite glucose control.

Methods: Charts from all movement disorder patients, excluding Parkinson's disease, hospitalized between 2005 and 2008 were reviewed resulting in eight patients with the diagnosis of hyperglycemic chorea, athetosis, ballism or chorea-ballism. We describe the demographical data, clinical presentation, image studies and treatment response.

Results: Our sample included 8 patients, 5 females and 3 males, with a mean age of 69.8 $\pm$ 9 years, mean glycemia on admission of 330 $\pm$ 117.4 mg/dl, mean HbA1c of 9.2 $\pm$ 3.7%, mean diabetes diagnosis time of 40.3 $\pm$ 31.4 months (two cases with chorea as first symptom). Movement disorder included hemichorea (4 cases), hemiballism (1 case), hemichoreo-ballism (2 cases) and generalized chorea (1 case). CT scan showed hyperdensity in basal ganglia in all cases and MRI showed basal ganglia hyperintensity in T1 and in 6 cases caudate hypointensity in T2 weighted and FLAIR images. Seven patients were treated with haloperidol and one with clonazepam and amantadine, acute glycemic control was achieved in all cases, chronic control was achieved in all but one patient. Follow-up ranged from 3 to 36 months with one loss, abnormal movement remitted in 3 cases, in two of them haloperidol was succesfully withdrawn. No correlation was found between clincal data and response to treatment.

Conclusions: Our case series had similarities with previously published reports about glucose levels on admission, age, gender and MRI findings of movement disorders in diabetic patients. More than half of the sample remains with abnormal movements despite adequate glucose control and neuroleptic treatment.

We-32

Choreatic movement disorder with non-ketotic hyperglycemia – A case report

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Objective: We describe a 87-year-old woman with transient choreoathetosis in hyperglycemia and review the literature.

Background: Choreoathetosis associated with non-ketotic hyperglycemia is a rare, usually benign syndrome in elderly persons. (1,2) The disorder usually improves soon after the onset of antidiabetic therapy. Until now about 130 cases have been described.

Methods: Case-report, video-ducumentation, review of the literature.

Results: A 87 year-old female patient complained of weakness in the left arm and hand for 5 days before admission to our hospital. The patient suffered from arterial hypertension and hypercholesterolemia. Neurological examination revealed a choreoathetosis of the left upper extremity. The reflexes of both arms could not be triggered and the Achilles tendon reflexes were absent. The remaining examination was unremarkable. The initial blood glucose level was 438mg/dl and HbA1c was 11.7%. No ketone bodies were found in the urine analysis. Cerebral MRI showed hyperintensity of the right putamen and globus pallidus on T1-weighted images, without gadolinium enhancement, no abnormalities on T2- and diffusion-weighted images. Two days after onset of antidiabetic treatment with insuline the patient's choreatic disorder improved and disappeared within two weeks, followed by hypokinesia and rigidity of the left upper extremity. DAT-Scan-Imaging revealed a reduced uptake of the right striatum. L-dopa test was negative (UPDRS III score before levodopa and DCI 19, after 200mg 18 points).

Conclusions: Choreoathetosis with non-ketotic hyperglycemia is a rare benign syndrome that improves after antidiabetic medication. In our case the patient showed hemi-parkinsonian features after treatment of the choreoathetosis, with reduced DAT-tracer uptake. Whether the patient suffers also from Parkinson's disease will be clarified in the follow-up. 1. Seung-Hun Oh. et al, Journal of the Neurological Sciences 2002; 200:57-62. 2. Branca D et al, Neurol Sci. 2005;26:275-7.

We-33

Acute hemichorea-hemiballism ipsilateral to ischemic stroke involving middle cerebral artery territory

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Objective: To better understand the pathophysiology of acute hyperkinetic movement disorders following stroke.

Background: Acute hyperkinetic movement disorders are rare presentations in acute stroke or may occur with some delay. These movement disorders are associated with stroke involving all levels of the contralateral frontosubcortical motor circuit including the sensorimotor cortex, basal ganglia, the thalamus, the substantia nigra, the cerebellum, the brainstem and their interconnecting pathways. Isolated cases of acute hyperkinesia ipsilateral to stroke have been reported.

Methods: We report a case of right acute hemichorea-hemiballism after right middle cerebral artery (MCA) ischemic stroke.

Results: Case Report. A 76 year old woman was admitted for acute left hemiparesis and right hemichorea-hemiballism. Her past medical hystory was negative for previous cerebrovascular events. Brain MRI with diffusion-weighted imaging showed acute ischemic stroke involving the right MCA territory. The ischemic areas included right caudate nucleus and right parietal cortex. EEG did not show epileptic activity. Hemichorea-hemiballism improved rapidly and disappeared a few days later.

Conclusions: Ipsilateral dyskinesia may very rarely occur in stroke. The presence of projections from the sensorimotor cortex to

the ipsilateral muscles has been established in humans. Damage to frontosubcortical motor circuit may modulate these ipsilateral projections and contribute to the pathogenesis of this uncommon movement disorder.

We-391

Neuroacanthocytosis – McLeod syndrome

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Objective: Neuroacanthocytosis (NA) is usually misdiagnosed until the disease is at an advanced stage. Our objective is to emphasize the importance of including these pathologies early on in the differential diagnosis of movement disorders.

Background: NA includes four mean types of neurodegenerative disorders presenting acanthocytes in blood sample, but some other pathology may present such erythrocyte abnormalities. On the other hand, the clinical heterogeneity of NA may lead into diagnosis error, making us mistake it for other pathologies that present movement disorders.

Methods: We attended a patient who presented mood and movement disorders (depression, obsessive behavior and tics) since childhood, but not correctly diagnosed until 29 years old, when he was evaluated by a neurologist specialized in abnormal movements. A differential diagnosis for Tourette syndrome, Wilson's disease, Hungtington disease (HD) and the four mean types of NA (Choreoacanthocytosis-ChAc-, Mc Leod syndrome, abetalipoproteinemia, PKAN) was performed.

Results: Neurological examination, laboratory analysis, neuroimaging, neurophysiological study, psychiatric and neuropsychological evaluations, HD and ChAc genetic tests, blood smear and inmunohematological study, were all tested resulting in favour of McLeod syndrome diagnosis.

Conclusions: Clinical heterogeneity, variability in the age of onset and difficulties in finding acanthocytes in some samples, sometimes make difficult an accurate and early diagnosis of these entities. Therefore, we advise considering the inclusion of NA in the differential diagnosis of movement disorders in every young patient, especially when these symptoms are associated with psychiatric disturbances or cognitive decline.

Th-396

Contrastive findings on PET images in two cases of hemichorea with hyperglycemia

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Objective: To present two cases of hyperglycemic hemichorea which showed opposite images by PET study with ^{18}F-Fluorodeoxyglucose.

Background: Patients with hyperglycemic hemichorea had reduced FDG uptake in the contralateral Basal Ganglion region in recent reports.

Methods: Patient 1 – A 73-year-old man was admitted for sudden onset of choreic movement on the right side. 10days before admission, hemichorea had developed suddenly. The hemoglobin A1c concentration was 7.9% and initial blood glucose level was 259mg/dl at admission. Brain FDG-PET was performed 2weeks after onset. Patient 2 – A 72-year-old man was admitted for sudden onset of choreic movement on the left side. 2weeks before admission, Hemichorea developed suddenly. The hemoglobin A1c concentration was 12.0% and initial blood glucose level was 507mg/dl at admission. Brain FDG-PET was performed 3weeks after onset. Both patients had a history of diabetes mellitus for many years and poor hypoglycemic control with oral agents and had no other cause of chorea except for hyperglycemia.

Results: Patient 1 had increased FDG uptake in the left Basal ganglion region. On the contrary, patient 2 had markedly reduced FDG uptake in the right Basal ganglion region.

Conclusions: Contrasive PET images in two cases of hyperglycemia induced hemichorea suggest that metabolic derangement associated with hyperglycemia, whether it is hypermetabolic or hypometabolic, can result in regional metabolic failure in the basal ganglia and seems to have close relevance to the mechanism of hemichorea.

CLINICAL ELECTROPHYSIOLOGY

Mo-35

Facial reflex hyperexcitability in geniospasm suggests a brainstem origin

A. Aggarwal, J.E. Warren, J.D. Warren, P.D. Thompson (Adelaide, Australia)

Objective: To report geniospasm (OMIM 190100) in 2 Australian families. To examine the mentalis acitivity and facial nerve excitability in a patient with geniospasm.

Background: Geniospasm is an inherited movement disorder characterized by involuntary contraction of the mentalis mucle manifesting as chin quivering. The nosology and origin of geniospasm remain unclear.[1]

Methods: The clinical features and disease course of geniospasm was recorded in both families. Electrophysiological characteristics of geniospasm were studied in a 42 year man from the first family. Muscle activity was recorded (surface and needle electrodes) from bilateral mentalis and orbicularis oculi (OO) muscles. The supraorbital nerves (SON) were stimulated in the supraorbital groove and responses recorded (surface electrodes) over both OO and mentalis muscles. Responses to facial nerve stimulation at the tragus were recorded in ipsilateral mentalis muscles.

Results: Geniospasm showed an autosomal dominant pattern of inheritance in both families with clinical characteristics similar to those described previously. The mentalis muscle activity responsible for geniospasm comprised bilateral brief motor unit action potentials of normal morphology. Voluntary contraction produced normal recruitment pattern, interrupted by geniospasm. Facial nerves latencies were normal and symmetrical. On SON stimulation, normal blink reflexes (R1 and R2) were recorded from bilateral OO. Responses corresponding to R1, R2 and R3 components of the blink reflex were recorded from both mentalis at 14ms, 42ms and 90ms respectively. R1 responses were variable and largely unilateral.

Conclusions: This report describes two Australian families with geniospasm. The observations that i) the geniospasm resulted from spontaneous arrhythmic discharges of normal motor units in both mentalis muscles, ii) the lack of peripheral facial nerve hyperexcitability or denervation and iii) the presence of bilateral facial nuclear hyperexcitability demonstrated by spread of facial reflexes to the mentalis muscles and R3 facial reflex response, indicate a central origin of geniospasm.[1] [1] Aggarwal A, Warren JE, Warren JD, Thompson PD. Facial nerve hyperexcitability in geniospasm sufggests a brainstem origin. Mov Disord 2009, in print.

Mo-36

Cognitive activity promotes oscillatory changes in the subthalamic nucleus. Intracerebral recording study

M. Balaz, P. Jurak, M. Bockova, I. Rektor (Brno, Czech Republic)

Objective: According to our previous data the cognitive activities in the STN are processed outside the typical cortico-basal ganglia-thalamic-cortical circuitry.

Background: We studied changes in STN local field potential activity related to purely auditory cognitive task.

Methods: 5 patients with late motor complications of Parkinson's disease who were indicated for deep brain stimulation surgery were

included in the study. The local field potentials of the subthalamic nucleus related to the non-motor, pure auditory P3 wave were analyzed.

Results: We have observed the gamma band power increase related to cognitive task on the contacts within the subthalamic nucleus.

Conclusions: We presume that these changes reflect the oscillatory nature of the STN cognitive activity.

Mo-37

Executive functions processed in the subthalamic nucleus. An intracerebral recording study

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Objective: To study the involvement of the subthalamic nucleus (STN) in the neurocognitive networks of the executive functions during four visuomotor cognitive tasks of single letters writing and counting with increasing cognitive and executive load.

Background: Five Parkinson's disease patients with externalised deep brain stimulation electrodes localized bilaterally in the STN and within its immediate vicinity performed four tasks of the experimental protocol: 1. single letter counting, 2. copying, 3. writing another letter (planning, inhibition of automatic responses) and 4. writing another letter inversed (planning, inhibition of automatic responses, mental inversion).

Methods: The alpha and beta ERD/S (event- related desynchronization/synchronization) were analysed.

Results: The alpha and beta ERD as the activational correlate were detected only during the two more complex tasks with increased demand on the executive functions: task 3 (in three of five subjects) and task 4 (in four of five subjects).

Conclusions: The involvement of the STN in cognitive activities is selective and specific and increases with the higher demand on the executive function. The results confirm the findings of a previous study (Baláž, 2008), that demonstrated specific activation evoked by an executive function task but not by a simple oddball task in the STN.

Mo-38

Integrative function of single neurons in the human subthalamic nucleus during checking behavior

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Objective: To study the role of the subthalamic nucleus (STN) in the processing of cognitive information during checking behaviour in patients with obsessive compulsive behaviour (OCD).

Background: Human behavior depends on complex interactions between cognition and emotion. How does the brain combine these two dimensions to make a decision and elaborate a goal-directed action remains unclear. One hypothesis is that such an integrative process might occur owing to the convergence of information through the basal ganglia. Recently, the associative and limbic STN have been proposed as potential targets for deep brain stimulation in patients with medically-resistant form of OCD[1]. We took the opportunity of the last study to investigate the role of STN neurons in the processing of cognitive information.

Methods: We used an instrumental task (CT), adapted from a matching to sample-task, that specifically offered the opportunity to verify once one subject has made a choice[2]. Single unit neuronal activity was recorded in the STN whereas patients with obsessive compulsive disorders (OCD) performed the CT.

Results: Among 125 single neurons recorded during task performance, 45 (36%) were task-related. Modifications of activity were observed in relation with: visual information during the study phase (28%), the choice phase (22%), or the checking phase (20%), movement execution during the choice phase (37%), or the checking phase (35%) and during the evaluation phase at the end of the task (56%). We found that STN neurons frequently responded in a polymodal manner to cognitive, premotor and emotional events. Moreover, discharge frequency was influenced by checking behavior.

Conclusions: These results suggest that STN neurons process multiple sources of information in accordance with the model of information convergence within the basal ganglia. They also demonstrate that the STN play a part in the physiology of doubt, a critical feature of OCD pathophysiology. 1. Mallet L, et al. STOC Study Group. N Engl J Med. 2008 Nov 13;359(20):2121-34. 2. Rotge JY, et al., Acta Psychiatr Scand. 2008 Jun;117(6):465-73.

Mo-396

Homeostatic metaplasticity of the trigeminal blink reflex in healthy humans

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Objective: To provide evidence of homeostatic metaplasticity in the brainstem circuitry of the trigeminal blink reflex in healthy subjects.

Background: It is unknown whether homeostatic mechanisms, defined as metaplasticity, operate in the human brainstem.

Methods: We examined the effects and interactions of two consecutive (i.e. pre-conditioning and conditioning) high frequency electrical stimulation sessions of the supraorbital nerve, on both electromyographic and kinematic variables of the blink reflex. In the main experiment the effects of three patterns of pre-conditioning stimulations: facilitatory, inhibitory or control, were tested on the long-term potentiation of the blink reflex, induced by the conditioning stimulation. In the control session the effects of two consecutive control stimulations were tested.

Results: Different patterns of stimulation of the supraorbital nerve induced either long term potentiation/depression-like or no effects on both electromyographic and kinematic parameters of the blink reflex. We found that, regardless the pattern of the pre-conditioning stimulation (facilitatory, inhibitory or control), the effects of the subsequent conditioning facilitatory stimulation were inhibited. In the control session we nevertheless observed a marked inhibition of the blink reflex after the conditioning control stimulation. Taking into consideration the inhibitory effects observed in the control session, we observed that the effects of the conditioning facilitatory stimulation on electromyographic, but not kinematic variables of the blink reflex were slightly but significantly enhanced by a pre-conditioning inhibitory stimulation.

Conclusions: We suggest that homeostatic mechanisms contribute in regulating brainstem synaptic plasticity in healthy humans. Metaplasticity of the trigeminal blink reflex should be studied to better clarify the pathophysiology of movement disorders involving the cranial region.

Mo-397

Cutaneous and mixed nerve silent periods in paroxysmal dystonia

J. Cogez, O. Etard, N. Derache, G. Defer (Caen, France)

Objective: To study neurophysiological interactions between Cutaneous and Mixed Nerve Silent Period (CuSP,MNSP) in two patients with paroxysmal dystonia.

Background: Underlying circuitry of MNSP and CuSP remain uncertain. CuSP could be based on high-threshold thinly myelinated fibers and oligosynaptic inhibitory medullary neural networks. MNSP could occur in three portions including collision of antidromic with orthodromic motor impulses, Renshaw cell inhibition activated by antidromic motor volley and cutaneous fiber activation. This latter portion has been suggested to share a common inhibitory pool with CuSP.

Methods: Two 55 and 58 year old women who had recently developed involuntary tonic contraction of upper and lower limbs were studied. In both patients, spinal cord MRI showed T2-weighted signal hyperintensities at the cervical level with no contrast enhancement in T1-weighted images. Diagnostis of idiopathic acute transverse myelitis was performed for the first patient; the second had secondary progressive multiple sclerosis since 40 years. For comparison, CuSP and MNSP were tested in 11 healthy subjects (4 males, 7 females mean age 46 years). Median nerve stimulation at the wrist (MNSP) and forefinger (CuSP) were applied during isometric contraction of the thumb to evoke a silent period recorded from the abductor pollicis brevis. Eight records for each subject and each test were rectified and averaged. CuSP and MNSP were automatically defined when EMG drops below 50% of the baseline preceding the stimulus.

Results: In both patients, the latter portion of MNSP was absent irrespective of stimulation intensity while CuSP was present. Thus the preservation of the CuSP shows that isolated stimulation of the thinly myelinated fibers could induce inhibition of the motoneuron. However, stimulation of the same fibers in the mixed portion of the median nerve couldn't induce this inhibition.

Conclusions: These results suggest that paroxysmal dystonia induced by spinal lesion is based on a lack of inhibition of the motoneuron secondarily induced by antidromic motor impulses.

Tu-37

Increased excitability induced by tDCS can unmask mirror movements

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(Perth, Western Australia, Australia)

Objective: To report a case of TMS-evoked mirror movement observed following unilateral M1 stimulation tDCS.

Background: Mirror movements (MM) are characterized by activity in fast-conducting corticospinal projections from the hand area of one primary motor cortex to both sides of the spinal cord, and can be evoked as simultaneous bilateral MEPs from unilateral motor cortex using focal single-pulse TMS. Previous studies have shown that unwanted mirror activity in the ipsilateral pathway can be suppressed by learning in some individuals. Anodal tDCS increases excitability in the cortical area directly beneath the stimulating electrode and connected neural pathways including interconnected motor areas. Here we investigate whether the increased excitability induced by tDCS can facilitate mirror movements.

Methods: Anodal tDCS was applied unilaterally to the left motor cortex for 10 minutes in a healthy, normal 19 year old male. Changes in corticomotor excitability were measured by focal single-pulse TMS applied separately to each motor cortex. MEPs were measured by EMG from the FDI muscles of both hands.

Results: Following tDCS, TMS evoked simultaneous bilateral MEPs recorded from the FDI muscles of both hands. Contralateral avMEP amplitude increased, as expected, and ipsilateral MEPs were consistently smaller than contralateral ones. MEP latency was identical on both sides.

Conclusions: Anodal tDCS can produce neurophysiological features of mirror movement presumably by enhancing activity in normally latent ipsilateral pathways as well as contralateral pathways.

Tu-38

EEG biofeedback training for Parkinson's disease with levodopa-induced dyskinesia

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Objective: To examine the effects of EEG biofeedback training on clinical features of Parkinson's disease, specifically levodopa-induced dyskinesia (LID).

Background: EEG biofeedback is a therapy that allows one to alter one's own cortical electrical activity when offered feedback on it, training changes that correlate with symptom alleviation into long-term improvement through operant conditioning. Neurofeedback specialists across the country have claimed success using the therapy with individuals with Parkinson's disease, but there has yet to be any research examining these assertions.

Methods: Nine subjects with IPD who experienced dyskinesia at least 20% of the waking day were randomized into a treatment or control group and underwent 30 sessions of either real feedback or mock feedback training over 15 weeks. Training protocols focused on rewarding decreases in 4-8 Hz coherence activity or increases in 12-15 Hz activity, and on inhibiting excess 4-8 Hz and 22-34 Hz activity across various electrode pairings (usually Fz & Pz, or T3& T4). At the end of the training, QEEG analyses and clinical assessments administered pre and post training were compared.

Results: Training with reward frequencies of 8-15 Hz corresponded with decreases in dyskinesia and increased feelings of well-being among subjects' self reports. Significant interaction effects were detected at posterior and frontal regions for relative and absolute power values ($P<0.001$), and in posterior regions for bursts per second and phase resests per second values ($p<0.005$). Paired-sample t tests showed that these interactions were accompanied by significant reductions in high beta activity ($p <0.01$). Interactions within the right posterior region were accompanied by increases in alpha relative and absolute power ($p< 0.01$), and decreases in alpha phase resets per second ($p < 0.001$). Dyskinesia measures taken pre and post training showed a decrease in the severity of dyskinesia at the end of training for cases and not controls, but the difference was not significant.

Conclusions: These results indicate that EEG biofeedback training can affect the spectral EEG topography of individuals with PD and LID, and that training to increase 8-15Hz activity and decrease 22-34Hz activity is associated with a decrease in dyskinesia and an improved sense of well-being.

Tu-39

Idiopathic spinal myoclonus: A clinical and neurophysiological assessment of a movement disorder of uncertain origin

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Objective: To assess the utility of clinical observation and neurophysiological measurements, particularly the Bereitschaftpotential, in the evalutaion of "idiopathic spinal myoclonus".

Background: Spinal Myoclonus (SM) is characterised by brief and sudden movements caused by the activation of muscles belonging to adjacent spinal myotomes. It can be subclassified into segmental and propriospinal forms. SM can occur in association with spinal cord lesions, but in idiopathic cases the question of a psychogenic origin is sometimes raised. Recent reports have indicated that "typical" clinical and electrophysiological features of propriospinal myoclonus can be mimicked voluntarily. A useful tool that can distinguish between organic and psychogenic jerks is the detection of a Bereitschaftspotential (BP) via jerk locked back averaging (BA) analysis.

Methods: A clinical and neurophysyological assessment of 20 patients affected by idiopathic SM was performed. A video EEG-EMG multichannel recording was performed in each patient to identify the muscles involved and to detect BP. An expert neurophysiologist blinded to the clinical details reviewed the BP recordings and divided them into those showing a *definite*, *possible* and *no* BP. A clinical assessment was performed by two neurologists expert in movement disorders who viewed the video recording of each patient, blinded to the clinical details, and indicated if the movements seen were compatible with organic (OM) or psychogenic (PM) myoclonus.

Results: A definite or possible BP was recorded in 15 out of 20 patients. Clinical raters agreed in their clinical opinion on 15 patients

(75%) but there was disagreement regarding the remaining 5 patients (25%). In patients where both raters agreed the movements appeared to be organic, all patients had a definite or possible BP.

Conclusions: BP are commonly seen in patients with idiopathic propriospinal or spinal segmental myoclonus. There is disagreement between clinicians in their clinical rating of spinal myoclonus as organic or psychogenic, but even in those patients where movements appear clinically to be organic, a BP is commonly detected. This suggests that BP recordings are a useful adjunct to clinical assessment in the diagnosis of patients with idiopathic spinal myoclonus.

Tu-40

Comparison of extensor-digitorum-brevis (EDB) test vs mouse diaphragm assay (MDA) as indirect test methods for detection of botulinumtoxin A (BTXA) antibodies in clinical practice

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Objective: To compare EDB and MDA in patients with clinical secondary non-responsiveness (SNR) to BTXA treatment as indirect test methods for detection of BTXA antibodies.

Background: SNR to BTXA injections may be associated with production of BTXA antibodies. EDB and MDA have been suggested to indirectly quantify BTXA antibodies.

Methods: 14 patients (13 cervical dystonia, 1 spasticity, median age 55 years) with clinically SNR to BTXA were enrolled in this study. SNR was defined as initially good (visual analogue scale (VAS) $\geq$ 60%) clinical response to BTXA injections, followed by at least two consecutive intramuscular injections in adequate doses with a clinical response of $\leq$ 30% (VAS) symptom reduction. All subjects underwent an EDB test, and blood samples were concomitantly analysed with MDA (Institute of Toxicology, Hannover). EDB test was performed injecting 6 mouse units (MU) BTXA (Botox®) in one and 12 MU in the other EDB. Compound muscle activities following suprathreshold peroneal nerve stimulation at the ankle were recorded before and two weeks after injection of BTXA. EDB was also examined in 20 healthy controls to establish a cut off value for pathology.

Results: Mean amplitude reduction 14 days after injection of 6 MU BTXA in healthy controls was 47,6 $\pm$ 18% (SD). In contrast patients with SNR displayed 23,5 $\pm$ 24% (SD) mean amplitude reduction, means being significantly different from each other ($p<0,005$). Mean amplitude reduction using 12 MU BTXA was also significantly different comparing patients and healthy controls (values not displayed). Applying a cut off value for a pathological EDB calculated by substracting 2 SD's from mean amplitude reduction, 6 of 14 patients had pathological values using 6 MU BTXA, and 3 patients using 12 MU BTXA. 6 of 14 patients had pathological MDA values, while 2 of them also displayed a concomitant pathological EDB result.

Conclusions: EDB and MDA both show high variability and seem to be unreliable for detection of antibodies in patients with SNR to BTXA treatment. Considering mean values of amplitude reduction in EDB being significantly different in healthy controls and patients, EDB could in some cases add valuable information to the clinical impression of SNR.

Tu-397

Effects of continuous magnetic theta-burst stimulation on early motor learning and retention of simple fast finger movements

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Objective: In this study we investigated whether continuous theta-burst stimulation (cTBS), a novel technique supposed to induce long-term depression (LTD)-like after-effects, could be an effective approach to modulate early motor learning and retention of a voluntary motor task.

Background: Early motor learning and motor retention involve changes in neural circuits of primary motor cortex (M1), presumably related to long-term potentiation (LTP) phenomena.

Methods: Eleven right-handed healthy subjects (9 men, 2 women; mean age: 30 $\pm$1.57 years) randomly received real and sham cTBS over the left M1. cTBS consisted of bursts of three pulses at 80 % of active motor threshold delivered at 50 Hz frequency and repeated every 200 ms in a continuous train lasting 40 seconds for a total number of 600 pulses. M1 excitability was assessed measuring 20 motor potentials (MEPs) evoked by single magnetic pulses at the baseline (T0) and seven minutes after cTBS (T1). Immediately after T1, subjects were asked to perform 160 index finger voluntary abductions in blocks of 20 movements. To test motor retention a further block of 20 movements was repeated 30 minutes after the execution of 160 voluntary finger movements. Kinematic variables (mean amplitude, mean peak velocity and peak acceleration) of the simple finger movements were measured. We compared the effects of real and sham cTBS on M1 excitability and on kinematic variables of the finger movements.

Results: ANOVA showed that real but not sham cTBS significantly reduced M1 excitability. In addition, real but not sham cTBS applied before the execution of 160 index finger abduction movements significantly reduced the increase in peak velocity and peak acceleration seen as practice of finger movements progresses. Similarly real cTBS decreased peak velocity and peak acceleration of the 20 movements executed 30 minutes after the execution of the 160 movements.

Conclusions: Real cTBS deteriorated practice-related changes in motor performance and early retention of the motor task.

We-34

Modulation of premotor cortex activity normalises measures of spinal and cortical inhibition without affecting MEPs in dystonia

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Objective: To compare the effect of repetitive transcranial magnetic stimulation (TMS) over premotor cortex in healthy subjects on short interval intracortical inhibition/facilitation (SICI/ICF) and spinal reciprocal inhibition (RI) in healthy subjects, patients with writer's cramp and DYT1 gene carriers.

Background: It has been reported that low frequency rTMS over premotor can alleviate some of the symptoms of focal dystonia, presumably through the suppressive effect on M1that has been clearly shown in healthy subjects. However, the modulating of premotor cortex stimulation has never been studied in dystonia.

Methods: Theta burst transcranial magnetic stimulation (TBS) was applied to the dorsal premotor area (PMd) and its after effects were quantified by measuring the amplitude of MEPs evoked by single pulse TMS over the primary motor cortex (M1), SICI and the third phase of RI between forearm extensor and flexor muscles. Continuous TBS (cTBS) with 300 and 600 pulses (cTBS300 and cTBS600, respectively) were studied in separate experiments in control subjects and patients with writer's cramp; and cTBS300 in clinically manifesting and non-clinically manifesting carriers of the DYT1 mutation (MDYT1 and NMDYT1, respectively).

Results: In healthy subjects both forms of cTBS over left PMd suppressed MEPs for over 30min; cTBS600 over left PMd reduced SICI and the third phase of RI. In contrast, neither cTBS300 nor cTBS600 over left PMd had any significant effect on MEPs in patients with dystonia, while cTBS600 over left PMd tended to normalise SICI and RI. NMDYT1 had a normal response to cTBS300 over left PMd.

Conclusions: We suggest that at rest there is a mixture of tonic excitatory and inhibitory connections from PMd onto MEPs, SICI and RI. In healthy subjects and NMDYT1 patients, this is weighted such that disruption with cTBS leads to decreased MEPs, SICI and RI. However, in dystonia, the resting balance shifts such that interfer-

ence by cTBS leads to a different set of effects: increased effectiveness of SICI and RI but no net effect on MEPs.

We-35

Abstract Withdrawn.

We-36

Human subthalamic nucleus neuronal activity participates in visuomotor learning

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Objective: To study the human subthalamic nucleus and its role in motor learning during neurosurgery for Deep Brain Stimulator (DBS) implantation.

Background: It has been difficult to study human neural activity under as controlled behavioral conditions as in animal experiments. Although we know in general that the human STN is involved in movement, how this structure participates in simple adapted arm movements is unclear.

Methods: Single and multi-unit neuronal activity and kinematics were recorded and analyzed from 7 Parkinson patients during 15 – 30 minute intraoperative experiments approved by the U of C's Institutional Review Board. The task involved simple visuomotor targeted arm movements with a digitizing tablet and pen during a "Learning" condition (L) requiring adaptation of movements over time to bring a cursor to a target and a "Non-learning" condition (NL), during which adaptation could not occur. Off-line discrimination and analysis of kinematics and neural activity was performed for 75 neuronal units (both single and multi-neuronal). The firing rate was averaged for 1.5s from presentation of the Go Cue. Instantaneous velocity and firing rate were analyzed using a mutual information (MI) analysis (Cover and Thomas, 1991).

Results: The STN neurons responded during arm movements as well as participated differently for Learning versus Non-Learning phases. Thirty to sixty percent of units showed significantly different firing rates in L compared to NL ($p < 0.05$, 2-way ANOVA). Also, the mean firing rate changed significantly for the different learning conditions only during the L phase ($p<0.05$, 1-way ANOVA). MI results indicated that instantaneous velocity measured at one time point was predictive of the firing rate of many STN neurons with a lag time of between 50–250 ms and that information and lag were significantly different in L vs NL ($p<0.05$, ANOVA). Additionally, during learning, the velocity/firing rate relationship was significantly more predictive during the closed-loop phase of the movements, from peak velocity to the end of movement ($p<0.05$, ANOVA) than during NL.

Conclusions: These results suggest that human STN activity participates in movement and movement adaptation by encoding velocity, especially during corrections.

We-37

The oscillatory activities in the human putamen

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Objective: Five epilepsy surgery candidates with temporal lobe epilepsy had depth electrodes implanted in the hippocampus, temporal, cingulate, prefrontal and orbitofrontal cortices. All patients had diagonal electrodes targeted in hippocampus with contacts in basal ganglia, namely in putamen.

Methods: The principal component analysis, the time frequency analysis, the power spectral analysis, the spectral and time coherence were used for analysis of preictal and ictal EEG.

Results: 1. Significant frequency components of 2-10Hz were constantly observed in BG. 2. There is a significant increase of power spectral density across all structures in all frequency ranges during an epileptic seizure. Number of seizures with significant spectral power increase was highest in BG. 3. There is a significant coupling between the basal ganglia activity and amygdalo-hippocampal activity during an epileptic seizure. The relationship between the epileptic activity in BG and other studied structures is less significant.

Conclusions: At variance with the increase in 4 ± 10 Hz activity described in hyperkinesias and dystonia (Silberstein 2003) the frequency of this significant component was reduced during an epileptic seizure in BG.

We-392

Magnetic brainstem stimulation study and multimodal evoked potentials in patients with Adrenoleukodystrophy

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Objective: The aim of this paper is to localize functional motor tract lesions in cerebral adrenoleukodystrophy (cALD) and adrenomyeloneuropathy (AMN) and to compare the results of motor evoked potential (MEP) and those of several kinds of evoked potentials.

Background: Single- or double-pulse magnetic brainstem stimulation (BST) can activate the corticospinal tracts at the level of the pyramidal decussation (Ugawa et al. 1994; Matsumoto et al. 2008). Its combination with transcranial magnetic stimulation over the motor cortex gives us the cortical-brainstem and brainstem-cervical conduction times.

Methods: One patient with adolescent cALD and 9 patients with AMN were recruited. MEPs were recorded from first dorsal interosseous (FDI) and tibial anterior (TA) muscles of the more affected side. For both muscles, central motor conduction time (CMCT) was measured. For FDI, BST was also performed in 9 patients except 1 AMN patient. When single BST could not elicit any MEPs, double BST at 2 ms interstimulus interval was added for more powerful

stimulation. The median and tibial nerve somatosensory evoked potentials (SEPs), auditory brainstem response (ABR) and visual evoked potentials (VEP) were recorded.

Results: CMCT was abnormal for FDI in 8 patients and for TA in all 10 patients. For FDI, MEP latency to BST could be measured in only 5 out of 9 patients. Two with AMN showed no CMCT prolongation. Markedly prolonged cortical-brainstem and mildly prolonged brainstem-cervical conduction times were revealed in one with AMN. The others (cALD and AMN) showed only prolonged cortical-brainstem conduction time. Abnormal SEPs were observed in all 10 patients, abnormal ABR in 9 (cALD and AMN), whereas VEP was abnormally prolonged in only 1 AMN patient.

Conclusions: The abnormalities of MEP, SEP and ABR are often observed in AMN patients. Severe intracranial pyramidal tract involvement was detected not only in cALD patient but also in AMN patients. The result supports the presence of cerebral involvement also in AMN patients.

Th-35

Real-time analysis of EEG in the elucidation of volition

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Objective: To predict the movements of healthy subjects in order to assess their movement intention and response to preemptive predictions.

Background: Cortical activity (movement related cortical potentials and event related desynchronization) preceding movement intention is well documented. Recent studies have found that the awareness of the intent to move has a more complex relationship to brain activity, with the intention being progressively more perceptible. Additionally, the study of patients with Tourette syndrome and psychogenic movement disorders highlights the discrepancy between the sense of volition and the brain's movement-initiating activity. Subjectivity has limited the study of this phenomenon; however, better volition-brain activity discrimination lies at the core of the study of many movement disorders.

Methods: 20 healthy, adult participants underwent 29-channel EEG recording during isolated right wrist extension which caused a light to turn on. Subjects were instructed to move as spontaneously as possible, with no external cues. Data was gathered on 120 movements over two calibration sessions and processed to predict movement prior to its occurrence. A threshold was researcher-chosen, after EEG power spectrum analysis, to ensure $>50\%$ true positives and $<10\%$ false positives in the predictions made by the model. When a prediction was made the light was turned on. Validation sessions used the model to perform >50 predictions per subject. The subjects reported their thoughts (intention or not) at the time of prediction. Movement was verified with on-line EMG analysis.

Results: The predictions captured movements with (51%) and without (3%) intention as well as non-movements with (16%) and without (30%) intention. Subjects reported feeling frustrated in response to the predictions; that is, when the light turned on prior to their own movement.

Conclusions: It is possible with EEG analysis to predict movement prior to its occurrence. In such situations, subjects are aware only some of the time that they are intending to move. This demonstrates objectively that movement is initiated subconsciously. When the "effect of the movement" occurred prior to movement, this produced a sense of frustration, likely due in part to a distorted sense of agency.

Th-36

Neuronal mechanisms of motor signals transmission in nonspecific (CM-Pf) and motor (Voi) human brain thalamic nuclei in spasmodic torticollis patients

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Objective: The aim was to reveal cellular mechanisms for transmission of the motor signal in CM-Pf and Voi thalamic nuclei during voluntary and involuntary pathological movements in spasmodic torticollis patients.

Background: At present time pathophysiology of spasmodic torticollis and specific neuronal structures involved in this pathology remain unknown. There are few models of cervical dystonia described in the literature. They suppose participation of some thalamic, basal ganglia and midbrain structures, but neuronal mechanisms for transmission of "normal" and pathological signals in these structures are little investigated.

Methods: The extracellular neuronal activity obtained by means of microelectrode technique during stereotaxic neurosurgical operations on spasmodic torticollis patients was analyzed by means of some mathematical methods including auto- and crosscorrelation, spectral analysis, wavelet analysis and some others. Human brain neurons were tested by means of verbal stimulus, motivated to performing of voluntary movements with and without neck muscle activation.

Results: The following data were obtained in CM-Pf and Voi thalamic nuclei: 1) peculiar properties of neuronal organization of these thalamic nuclei; 2) differences in the neural mechanisms of motor signal transmission during the performance of voluntary movements with and without axial neck muscular contraction and involuntary pathological dystonic movements; 3) importance of sensory neuronal component during the realization and finishing of voluntary and spontaneous involuntary dystonic movements; 4) significance of neuronal synchronization and 3-5 Hz oscillations for voluntary and involuntary movements. It was also revealed similarity and distinction of motor signal transmission in Voi and CM-Pf thalamic nuclei.

Conclusions: Our data suggest direct or mediate connection of motor (Voi) thalamic nucleus and nonspecific (CM-Pf) nucleus neuronal activity with spasmodic torticollis. It proves system multistuctures nature of this disease.

Th-37

Synaptic plasticity at brainstem and cortical level in Tourette syndrome

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Objective: We investigated synaptic plasticity in Tourette syndrome (TS) delivering two paradigms of stimulation that induce long-term potentiation (LTP)-like plasticity at brainstem and primary motor cortex (M1) level.

Background: Abnormal excitability at the level of the brainstem and M1 has been reported in TS.

Methods: Ten healthy subjects and ten patients with TS participated. Patients were clinically evaluated using the Yale Global Tic Severity Scale (YGTSS). The conditioning brainstem stimulation consisted in electric high frequency stimulation (HFS) (3 blocks with 5 min intervals, each block consisted in 4 trains and each train in 9 stimuli at 400 Hz) over the supraorbital nerve (SO) at the same time of R2 response of the blink reflex (BR). The test stimulation consisted in ten electric stimuli over the right SO to elicit the BR from right orbicularis oculi muscle before and after HFS. The intensity of electric pulses was set at two times the threshold for BR. The conditioning M1 stimulation consisted in intermittent theta burst stimulation (iTBS) (20 trains of 2 s repeated every 10 s, each train consisting in bursts of 3 pulses at 50 Hz, repeated at 5 Hz, intensity of 80% of active motor threshold). The test stimulation consisted in 20 motor evoked potentials (MEPs) recorded from right first interosseous muscle before and three times (5, 15, 30 min) after iTBS. The intensity was fixed before iTBS to evoke MEPs of 1 mV. We used between-group ANOVA to compare MEPs and R2. Spearman test was used for correlation between clinical and experimental data.

Results: At brainstem level, although R2 area was similar in TS and healthy subjects before HFS ($p=0,42$), R2 area was significantly enhanced after HFS in healthy subjects ($p=0.03$) but not in TS patients ($p=0.44$). TheYGTSS score negatively correlated with R2

enhancement after HFS (r=-0.73; p=0.02). At M1 level, iTBS significantly increased MEPs size in both TS (p =0,03) and healthy subjects (p=0.01). The YGTSS score did not correlate with the MEPs size enhancement after iTBS (r=0.14;p=0.7).

Conclusions: Synaptic plasticity tested by facilitatory paradigms (HFS and iTBS) is abnormal in TS at the level of the brainstem but not at M1.

Th-38

Post-movement beta synchronization in Wilson's disease

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Objective: To analyze the post-movement beta synchronization (PMBS) of the electroencephalogram (EEG) in Wilson's disease.

Background: Wilson's disease is an autosomal recessive inherited disorder of copper metabolism. Its most common neurological symptoms (tremor, parkinsonism, dystonia, ataxia, chorea, dysarthria) are mainly related to dysfunction of the basal ganglia-thalamo-cortical and the cerebello-thalamo-cortical pathways. Post-movement beta synchronization is a transient power increase in the beta frequency band, which can be detected above the sensorimotor cortex 1-2 s after the termination of the movement. It is postulated that it reflects active inhibition and information processing. In essential tremor normal PMBS power but increased latency can be measured whereas in Parkinson's disease PMBS latency is normal but its power is decreased.

Methods: Ten patients with neurological manifestation of Wilson's disease and ten controls performed self-paced movement with the dominant hand during EEG acquisition. Five electrodes located in the region of the sensorimotor cortical areas were selected for evaluation (C3, C1, Cz, C2, C4). The power and latency of post-movement beta synchronization were calculated after power spectral analysis with multi taper method.

Results: PMBS power contralateral to the movement was significantly lower in patients with Wilson's disease (1,94±0,7%) than in controls (2,5±0,7%; p=0,01). In all electrode position the latency of PMBS was significantly longer in the Wilson group (1,34±0,45s) compared to controls (0,93±0,44s; p=0,005). The severity and type of neurological symptoms and the location and size of the MRI abnormalities were not correlated with the changes of PMBS. However, alterations of PMBS tended to be more pronounced in patients with more severe neurological symptoms.

Conclusions: PMBS is affected in Wilson's disease with neurological manifestation indicating altered information processing in the sensorimotor cortex. PMBS abnormalities are the combination of changes observed in Parkinson's disease (decrease of power) and essential tremor (elongation of latencies). This may reflect the pathological changes in both the basal ganglia-thalamo-cortical circuit and cerebello-thalamo-cortical loop in Wilson's disease.

Th-39

Subthalamic neuronal activity in patients with obsessive-compulsive disorders or Parkinson's disease

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Objective: Study the subthalamic (STN) neuronal activity in patients with Obsessive Compulsive Disorders (OCD).

Background: Dysfunction in the basal ganglia circuitry has been implicated in obsessive and compulsive disorder (OCD). In a recent clinical research program, high frequency electrical stimulation of the STN has proved to be efficient in alleviating obsessions and compulsions in OCD patients and permitted to study neuronal activity in this disorder (Mallet et al, 2008).

Methods: Unit neuronal activity of STN neurons were recorded in awake OCD patients at rest and compared to data obtained in patients with Parkinson's disease (PD). The mean firing rate and interspike intervals were calculated for each cell. The firing pattern was classified as regular, irregular or bursting (Kaneoke and Vitek, 1996). Neuronal activity was also sampled for each period and epochs of elevated discharge rate were classified as burst using a Poisson surprise analysis. Spike trains with $S \geq 3$ were considered to be bursts. Percentages of action potentials and duration with $S \geq 3$ and mean S value were calculated for each cell. The precise localization of neuronal activity recordings was performed using a 3-D deformable basal ganglia atlas with a particular reference to STN subterritories.

Results: 156 STN neurons were isolated in 11 OCD patients and 113 neurons in 10 PD patients. In comparison to PD, the mean discharge frequency of STN neurons was lower in OCD patient (24.1 ± 14.1 Hz vs 32.1± 17.7 Hz, P<10-3) with a higher burst type activity (p<0.03). The mean S value was higher in OCD patients (7.0 ± 3.5 vs 5.9 ± 1.9, P<10-2) with a higher mean percentage of action potentials (39.0 ± 13.5 vs 32.8 ± 14.4 %, P<10-3) and duration with $S \geq 3$ (17.7 ± 4.7 vs 14.9 ± 5.6 %, P<10-4).

Conclusions: In OCD patients, the subthalamic neuronal activity seems abnormal with an increase in the bursting type activity. This is in line with the hypothesis of the role of basal ganglia, and the subthalamic nucleus, in the physiopathology of this disorder. Mallet et al, N Engl J Med, 2008 Nov 13;359:2121-34. Kaneoke and Vitek, J Neurosci Methods, 1996 Oct;68:211-23.

Th-397

High frequency oscillation in adrenoleukodystrophy

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Objective: To detect subclinical lesions in the sensory tracts in patients with adrenoleukodystrophy (ALD) using high-frequency oscillations (HFOs) of somatosensory evoked potentials (SEPs).

Background: ALD is a X-linked neurogenerative disorder caused by an impairment of peroxisomal beta-oxidation due to ABCD gene defects. Adult onset ALD is characterized by progressive demyelination within the central and peripheral nerve systems. In ALD patients, SEPs often reveal subclinical involvements of the afferent pathways which were not detected by neuroimaging techniques. HFOs of SEPs may give some new information about the sensory systems in ADL patients.

Methods: Subjects were 4 ALD patients and 15 age-matched healthy volunteers. SEPs filtered at 10-3000Hz were recorded after the median nerve stimulation at the wrist. HFOs were obtained by digital filtering raw SPEs from 500 to 1000Hz. The latencies and amplitudes of P9, N13, N20, and P25, and HFOs were compared between ALD patients and normal subjects.

Results: The onset to peak latency of N20 was significantly prolonged in ALDs. In these patients, the amplitudes of both N20 and HFOs were abnormally decreased, and the size ratios of HFOs to N20 were significantly lower than normal subjects.

Conclusions: The prolongation of N20 onset-peak latency might be explained by a delayed conduction time and temporal dispersion in the thalamo-cortical pathways in ALD. Although the amplitude reduction of both HFOs and N20 might be accounted for by temporal dispersion of sensory inputs to the sensory cortex, the reduction of size ratio of HFO to N20 suggested that HFOs are more susceptible to demyelination process than N20 component. These findings support the idea that HFO is a sensitive tool to detect clinically undetectable lesions in ALD patients, because of increased variability in conduction properties produced by demyelination.

DRUG-INDUCED MOVEMENT DISORDERS

Mo-39

Reversible hyperkinetic movement disorder related to quetiapine withdrawal

M.T. Ahmad, K.M. Prakash, C.W. Yip (Singapore, Singapore)

Objective: To report an unusual case of reversible generalised hyperkinetic movement disorder secondary to quetiapine withdrawal.

Background: Quetiapine is used in treatment of schizoaffective and bipolar disorders as well as psychosis in Parkinson's disease patients. Neurological side effects are not uncommon with this drug however there is limited knowledge about quetiapine withdrawal extrapyramidal side effects.

Methods: A 30-year old Caucasian man with schizoaffective disorder presented with acute onset of tachycardia, incoherent speech and generalised hyperkinetic movements.

Results: Routine laboratory investigations, toxicology, infective and inflammatory markers were normal. His electroencephalography and brain imaging were normal as well. Further history revealed that he had discontinued his regular quetiapine for several days. Re-introduction of quetiapine lead to complete resolution of his abnormal movements within 3 days.

Conclusions: Acute quetiapine withdrawal may result in hyperkinetic movement disorders. With this atypical antipsychotic drug becoming widely used in various neuropsychiatric disorders, awareness among physicians about this phenomenon will avoid unnecessary investigations as well as delay in the treatment.

Mo-40

Tardive chorea secondary to low dose quetiapine

F. Amjad, S.E. Lo (Washington, District of Columbia)

Objective: To report the case of a dopamine receptor blocker-naïve patient who developed tardive chorea with low dose quetiapine.

Background: Tardive syndromes (TS), characterized classically by oral-buccal-lingual dyskinesias and axial-cranial dystonias, and less commonly by chorea, are most commonly induced by dopamine receptor blockers (DRBs), such as 1st generation neuroleptics, and less often by 2nd generation "atypical" neuroleptics. Quetiapine has one of the lowest rates of TS, related to its low affinity for D2 receptors. Because of this, quetiapine is favored by movement disorder specialists, and may even be used to treat TS.

Methods: Design: Case report and literature review, accompanied by video.

Results: 53 year-old woman developed choreic movements in her lower extremities and trunk after taking relatively low doses of quetiapine (100-150 mg) for 12 months for insomnia. No prior history of psychiatric disorders or exposure to other DRBs. No akathisia. Huntington's and Wilson's disease and neuroacanthocytosis were ruled out. Quetiapine was tapered off, but chorea has persisted for 1.5 years. Clonazepam and levetiracetam were ineffective. Tetrabenazine (TBZ) greatly diminished the chorea, but induced severe parkinsonism and akathisia, requiring the use of a walker. Amantadine 400 mg/day briefly improved the chorea. Tapering TBZ below 50mg/day worsened the chorea. Given the unacceptable parkinsonism, dopaminergic therapy and deep brain stimulation of the globus pallidi may need to be considered. Review of the literature revealed a total of 11 cases of quetiapine-related TS, but most had prior exposure to DRBs and prior psychiatric disorders, and none reported truncal chorea similar to our patient.

Conclusions: Conclusion: Tardive syndromes rarely occur in patients on low dose quetiapine, and are even more rare in patients naïve to DRBs. Truncal chorea may be added to the spectrum of TS seen with quetiapine. Although quetiapine remains among the least offensive neuroleptics, our patient demonstrates that caution is still required when using this agent in potentially vulnerable movement disorder patients.

Mo-41

Could tardive dystonia be cured with botulinum toxin treatment?

M. Anca-Herschkovitsch (Holon, Israel)

Objective: To assess the dynamic of clinical dystonia in time under the treatment with BTX-A in tardive syndromes.

Background: Tardive dystonia (TD) is a form of tardive dyskinesia for which there is little satisfactory treatment. Botulinum toxin Type A (BTX-A) provided symptomatic treatment for localized dystonia in patients with TD unresponsive to other treatment. The improvement induced by BTX-A in dystonia is supposed to be independent from the pathophysiology. The literature provides evidence that the improvement from the administration of BTX-A in cervical dystonia, idiopathic or tardive is similar.

Methods: We describe 14 patients (8 male), referred for tardive type dystonic syndromes with multiple localizations :10 cervical dystonia, 8 facial dystonia (oromandibulat dystonia, palatal myoclonus, blepharospasm), 2 lower limb dystonia. All patients suffered from disorders treated by neuroleptic drugs (haloperidol, risperidone, perphenazine, olanzapine, ziprasidone): 7 psychiatric disorders, 3 Tourette syndrome, 1 Huntington's disease, or were exposed for years to cannabis (2). No family or past personal history of dystonia were reported. All patients were previously treated with oral drugs without benefit.

Results: The patients mean age is 45.9+/-9 years, mean interval of drug exposure before TD 3+/-9 years, the mean TD duration before treatment 6.6+/-4 years, mean period of treatment 2.8+/-1.8 years, mean interval of significant improvement with BTX-A 1.1+/-0.5 years. In 12 patients significant improvement was noted after the first 2 injections. Five (35%) returned to normal function with minimal residual TD reducing the therapy from 4 to 1-2 injections per year.1 patient (facial dystonia) after 2 injections refused the treatment because lack of benefit. He smoked grass during the treatment. 1 patient (lower limbs dystonia) with partial response during 4 years was continuously treated with neuroleptics and injected at large intervals (6-8 months).

Conclusions: Our experience rises the possibility that contrary to idiopathic dystonia, usually invalidant for life, in TD the BTX-A treatment might in short time significantly minimize the dystonia allowing normal function. One could draw the conclusion that different underlying mechanisms allow to BTX-A to change more efficiently the natural history of TD to a curable disorder. Future controlled trials are required to explore this possible benefit.

Mo-42

New treatment (BN82451) and assessment for L-dopa-induced dyskinesias in parkinsonian macaques

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Objective: To evaluate the anti-dyskinetic effect of treatment with a novel multitargeting molecule, BN82451, on levodopa induced dyskinesias in a primate MPTP model of Parkinson's disease.

Background: L-DOPA pharmacotherapy is very effective in alleviating parkinsonian symptoms but with time induces abnormal involuntary movements (AIMs) in the majority of patients.

Methods: Five adult male macaques (*M.fascicularis*) received daily injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP;0.2mg/kg i.m.) and then chronic increasing daily L-Dopa doses (100:25mg levodopa:benserazide) that induced AIMs. Acute and subchronic 5 day treatments with BN82451 (5mg/kg; base form), Amantadine (5mg/kg) or their solvent polyethylenglycol 400 (PEG400) were administered. L-Dopa was co-administered and animals were filmed for 6 hours on the 1st and 5th day of treatment. Ethovision® software was used to track spontaneous locomotor activ-

ity (total distance moved, TDM) and The Observer® software to quantify the incidence of AIMs.

Results: On day 1 of BN82451 injection the AIMs score was reduced in 3 monkeys and remained unchanged in the other 2. By day 5, all animals benefited from BN82451 treatment with an overall AIMs decrease of 34%, affecting all types of abnormal movements in the different parts of the body studied. This effect was not associated with a reduction in TDM. On day 1 of Amantadine treatment the AIMs score was reduced in 1 monkey, increased in 2 monkeys and remained unchanged for the other 2. At day 5, only 1 animal presented a slight reduction in AIMs score and an increase in TDM. All other animals presented concomitant increases and decreases in AIMs score and TDM respectively. Acute injection of 5mg/kg BN82451 2 hours before L-Dopa administration yielded a significant 43% reduction of the AIMs while increasing TDM in 4/5 animals compared to control.

Conclusions: Results show that in our model administration of BN82451 is more efficacious than Amantadine since it significantly decreases the total AIMs score in all parkinsonian animals without impairing their spontaneous locomotor activity. Moreover, differed acute administration of BN82451 and L-Dopa increases the reduction in dyskinesias while improving locomotor activity.

Mo-43

Long-term outcomes after pallidal deep brain stimulation for tardive dystonia/dyskinesia

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(San Francisco, California)

Objective: To evaluate the long-term effectiveness of bilateral pallidal deep brain stimulation (DBS) in patients with tardive dystonia.

Background: Tardive dystonia/dyskinesia can be a highly disabling, permanent condition related to the use of dopamine receptor-blocking medications which is often treatment resistant. Significant short-term benefits of DBS for treating intractable tardive dystonia/dyskinesia have been reported, however, long-term outcomes are unclear.

Methods: Five consecutive patients (2M, 3F) with disabling tardive dystonia/dyskinesia (3 generalized; 2 segmental dystonia) who underwent stereotactic placement of bilateral DBS leads for severe refractory tardive dystonia at our center between 1999-2006 were included in this study. All patients had history of a mood disorder or schizophrenia previously treated with a neuroleptic medication. Mean age at surgery was 41.2 yrs (28-59) and mean duration of motor symptom was 10.2 yrs (4-20). Patient history, physical examination, surgical records and baseline and follow-up outcome data were reviewed. Dystonia severity was determined by a blinded movement disorders neurologist by reviewing pre- and post–operative videotaped exams using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) movement score, and dyskinesia severity was measured by the Extra-Pyramidal Rating Scale (EPRS) dyskinesia subscale.

Results: The mean baseline BFMDRS and EPRS scores were 46.5 (10-80) and 19.2 (4-34), respectively. Overall, we observed a mean reduction of 52.7% in the BFMDRS within the first year after surgery (26 to 80%, range; P=0.001, paired t-test). Four patients had long-term improvements. One patient experienced a venous infarct peri-operatively and had only minimal improvement. Group analysis revealed persistent improvement of dystonia with last follow-up ranging from 2 to 8 years (mean 3.4 yrs) after surgery. Dyskinesia EPRS scores were also improved by 37% on average, but did not reach statistical significance (-21 to 77%, range; P=0.18, paired t-test). DBS stimulation parameters ranged from 2.5-3.6 V, 180-210 μsec, 60-185Hz.

Conclusions: Pallidal DBS can be an effective therapy with long-term benefits for patients with tardive dystonia/dyskinesia. Further studies are needed to validate these results in larger patient populations and to determine factors associated with better or worse prognosis.

Mo-44

Towards optimization of the rat model of L-dopa induced dyskinesia

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Objective: The present studies were aimed at further validating and optimizing the process of priming for L-DOPA induced dyskinesia (LID) in rats.

Background: Pharmacological replacement of dopamine with L-DOPA in Parkinson's disease patients provides a clear-cut therapeutic benefit. However, most patients develop L-DOPA induced dyskinesia (LID) and motor fluctuations within a few years of treatment. In the past decade, a new rodent model of LID has been developed (see Cenci *et al.,* Eur J Neurosci **10:** 2694-2706, 1998). This approach may markedly speed up search for antidyskinetic drugs.

Methods: Unilaterally 6-OHDA lesioned rats were treated with L-DOPA for a period of 22 days. During this period the animals were scored for abnormal involuntary movements (AIMs). Two separate sets of experiments were carried out. In the first study, a correlation between amphetamine (AMPH) and apomorphine (APO)-induced rotation, forelimb use asymmetry (cylinder test) and the development of LID was assessed. In the second study, effects of different L-DOPA administration regimes on LID development were investigated. Four groups of rats were used: (1) L-DOPA-treated daily for 22 days, in home cages; (2) L-DOPA-treated over 22 days, 5 times a week, in home cages; (3) L-DOPA-treated daily for 22 days, in test cages and (4) L-DOPA-treated only on test days, in test cages. All groups were tested every 3-4 days during the 22-day priming period (7 times).

Results: A correlation was only found between APO-induced rotation and LID development and between APO-induced rotation and forelimb use asymmetry. The histological analysis (tyrosine hydroxylase immunocytochemistry) is still ongoing. No significant differences were found in LID development between groups with different L-DOPA administration regimes. Furthermore, AIMs scores were found to reach stable levels after approximately one week of L-DOPA treatment, which confirms previously unpublished data from our lab.

Conclusions: Degree of asymmetry, measured by either AMPH-induced rotation or forelimb use test does not adequately predict the subsequent development of LID in unilaterally 6-OHDA-lesioned rats. Chronic daily treatment with L-DOPA for 3 weeks may not be necessary to induce a stable level of LID.

Mo-398

Copulatory dyskinesia with an outstanding response to tetrabenazine

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Objective: We report on a patient who presented with invalidating progressive copulatory dyskinesia while receiving different kind of neuroleptic drugs for a psychiatric disorder.

Background: Tardive dyskinesias (TD) are a sort of delayed-onset involuntary movements induced by dopamine receptor block agent. The most common of them, usually affecting elderly subjects, are bucolinguo masticatory dyskinesia. Body rocking and swaying motions of the trunk together with pelvic thrusts, also known as copulatory dyskinesia, are sometimes part of the syndrome.

Methods: Case report

Results: The clinical features and different drug-induced movements scales showed an outstanding improvement after tetrabenazine was started.

Table (Mo-398). Rating scales to assess Copulatory Dyskinesia

	Initial	After 8 months with tetrabenazine
Total score in AIMS	11/28	4/28
Global judgement in AIMS	8/8	3/8
Questionnaire ESRS	21/21	6/21
Examination ESRS Parkinsonism	35/42	9/42
Examination ESRS Dystonia	0/6	0/6
Examination ESRS Dyskinetic movement	11/42	1/42
Clinical global impression of severity (CGI-s) of Dyskinesia in ESRS	8/8	1/8
CGI-s of Parkinsonism in ESRS	5/8	1/8
CGI-s of dystonia in ESRS	0/8	0/8
CGI-s of akathisia in ESRS	5/8	2/8
DISCUS total score	7/60	2/60

All rating scales showed better scores after 8 months of treatment with tetrabenazine. An exception was dystonia rating in ESRS as she did not present it. We have to bear in mind this patient was unable to walk and she did not follow any order. Thus, gait and tongue movements could not be assessed initially. (AIMS): Abnormal Involutary Movement Scale; (ESRS): Extrapyramidal Symptom Rating Scale; (CGI-s): Clinical Global Impression of severity; (DISCUS): Dyskinesia Identification System.

Conclusions: To our best knowledge, this is the first published copulatory dyskinesia with good evolution and control of dyskinesias after treatment with tetrabenazine.

Tu-41

Drug-induced parkinsonism in hospitalized patients

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Objective: The aim of this study was to determine the incidence of Drug-Induced parkinsonism in hospitalized patients.

Background: Drug-induced parkinsonism is a common adverse drug effect of certain drugs (Anti-psychotics, Gastrointestinal Prokinetics, others) and a frequent cause of ambulatory consultation.

Methods: We performed this study within the Pharmacovigilance System of the Argerich Hospital (a tertiary care hospital) in Buenos Aires, Argentina, between July and December of 2008. For each drug adverse event the Naranjo Score was used to assess causality of drugs. All cases that were probably or highly probably ADRs – according to that Score – were included.

Results: There were 7,200 hospital admissions during that period. We detected 528 ADRs, 43% in females and 57% in males. The average age was 59 years. There were six cases (1.13% of the total ADRs) of drug-induced parkinsonism, drugs involved being: Haloperidol (2 cases), Aripiprazole, Phenytoin, Morphine and Salbutamol. Those ADRs occurred in four cases in males and in two cases in females. No admissions happened because of drug-induced parkinsonism.

Conclusions: Drug-induced parkinsonism represented only a 1.13% of all ADRs and only three cases were caused by Anti-psychotic drugs. We suggest it was because the consumption of Anti-psychotics is low in our hospital (2.6 Definite Daily Dose per 100 beds per day) and because the Emergency Room is not under the Hospital Pharmacovigilance System's surveillance.

Tu-42

Manganese-induced extrapyramidal symptoms: Methcathinone encephalopathy

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Objective: Exposure to high levels of manganese or hepatic failure leading an increase in blood levels of manganese can cause neurotoxicity. Manganese intoxication may cause a extrapyramidal syndrome with psychiatric symptoms.

Background: Similar clinical pictures were reported in psychoactive substance abusers using intravenous methcathinone.

Methods: case report.

Results: Case 1. 31- year- old male presented with speech disorder and involuntary movements. Neurologic examination revealed dysarthria, increased deep tendon reflexes, generalized dystonia. Blood analysis for dystonia etiology was normal. Serum hepatitis C antibodies were positive and his liver function tests were high. Cranial magnetic resonance imaging(MRI) was normal. *dyt-1* gene analysis was negative. After exclusion of possible etiologies, requisitioning of the patient revealed a history of a mean of 4 years methcathinone use before formal development of clinical signs. The patient's dystonia was found to be a result of manganese neutoxicity caused by potassium permanganate used in methcathionone manufacturing. Administration of levodopa produce 10% symptomatic change measured with Unified Dystonia Rating Scale (URDS). Case 2. 24-year-old male was admitted with speech disorder, slowing of movements and balance problems. His complaints started 5 years ago, when he began to use intravenous mixture containing methcathionone. Neurologic examination revealed facial grima, dysarthric and explosive/detonative/eruptive bilateral postural tremor with left-sided dominance, bradykinesia, postural instability and segmental dystonia (oromandibular, cervical and left hand) with slow and unbalanced gait similar to Case 1. Routine blood tests, serum copper and ceruloplasmine levels, electromyography was in normal limits. Cranial MRI showed no specific significance attributable to basal ganglia disorder. 6-[^{18}F]-Fluorodopa positron emission tomography was normal.

Conclusions: The extrapyramidal signs observed in these two methcathinone users are compatible with manganase intoxication caused by potassium permanganate injection. The most common reported sign of manganese neurotoxicity is parkinsonism. Taking a detailed history of the patient is important in dystonia etiology. Treatment strategies are similar to other dystonia cases but response to treatment differs.

Tu-43

Levosulpiride-induced hemichorea

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Objective: To report unusual case of hemichorea due to levosulpiride, providing new insights into drug-induced hemichorea.

Background: Levosulpiride is a selective dopamine D_2-receptor antagonist that is widely used for the treatment of functional dyspepsia in Korea. Several drugs such as dopamine receptor blocking drugs, stimulants, oral contraceptives, and anticonvulsant are known to be the cause of chorea. In addition, it was reported that some drugs and systemic illness were related to hemichorea. This is the first report of levosulpiride-induced hemichorea.

Methods: Case description.

Results: A 63-year-old, right-handed woman with a history of hyperlipidemia visited to our clinic for the evaluation of brief, irregular, purposeless, involuntary movements of her lip, left arm and leg. 10 days ago, her daughter noticed these abnormal movements. The patient came to our clinic because the symptoms became worsened. Neurological examination was normal except the involuntary movements. Brain MRI including DWI was performed with normal results. Her laboratory findings were unremarkable including oral glucose

tolerance test. Detailed medication history revealed that several drugs had been used for her arthralgia and gastrointestinal discomfort for about two months: levosulpiride, talniflumate, ranitidine, afloqualone, calcium polycarbophil. After stop all medications, her involuntary movements were significantly reduced for five days. Single photon emission computed tomography (SPECT) using ^{99m}Tc-HMPAO, performed at days 5, showed mild hypoperfusion in the right basal ganglia, especially caudate nucleus. Because she complained her symptoms in spite of improvement, Quetiapine 12.5 mg was prescribed at night. She reported that she was reluctant to use because of drowsiness and used it intermittently for one month. Her hemichorea was completely resolved at one month with medication. During the 4-month follow-up period, there was no recurrence without medication.

Conclusions: Levosulpiride was the most likely cause of her hemichorea as a result of the extensive investigation. Detailed medication history is important in any kind of involuntary movement with acute or subacute onset.

Tu-44

Clinical course of ephedronic encephalopathy

M. Kapianidze, I. Khatiashvili, M. Megrelishvili, N. Kvirkvelia (Tbilisi, Georgia)

Objective: To evaluate the clinical course and clinical-radiological correlation in patients with ephedronic encephalopathy (EE).

Background: Injections of hand-made drug ephedrone is the cause of an already well-known syndrome. The development of the symptoms seems to be different in separate cases as opposed to MRI pictures, that are more or less typical.

Methods: We evaluated clinical and MRI records of 20 patients with EE.

Results: Fifteen patients were included in the group of "new" EE. The length of ephedrone abuse was 6-18 months. EE in patients from this group started with psychosis in 2 cases, with apathetic syndrome in 4 cases, with dysarthria and\or gait difficulties in 9 cases. Clinical presentations of all of them at the time they admitted to the clinic were similar: apathy, mild to moderate hypokinesia, hypomimia with forsed smile while talking, spastic- hypokinetic dysarthria, gait disturbances and postural instability with falls. Memory and intellect were preserved. The T1-weighted MRI images of most of them demonstrate an increased signal in globus pallidus and substantia nigra, in some cases in cerebellar nuclei too. In six cases symptoms had gradually deteriorate over time, in other cases symptoms remained stable. Five former ephedrine users (in late 1990-ies) have not received any treatment. Main problem for these patients was severe dystonia especially in legs that interferes in walking, and/or postural instability. Several years after stopping the injections of ephedrone these patients MRI pictures don't show T1 hyperintensity in basal ganglia.

Conclusions: The natural history of EE is quite similar in majority of patients. At the beginning of the disease leading symptoms are hypokinetic dysarthria and postural instability, while subsequently dystonia become most disabling problem. There are examples of relatively benign course when patients are almost fully recovered (if not a dystonia in legs), and malignant cases with deeply disabled patients. There seems not to be any strong clinical-MRI correlations.

Tu-45

Ephedrone encephalopathy: Treatment approaches

I. Khatiashvili, M. Kapianidze, M. Megrelishvili, K. Akhvlediani (Tbilisi, Georgia)

Objective: The goal of our study was to assess the effectiveness of different approaches to treatment of ephedrone encephalopathy.

Background: Ephedrone encephalopathy is unique syndrome caused by injections of home-made compound consisted from pseudoephedrine, potassium permanganate, aspirin and water. The victims suffer from bradykinesia, dysarthria, gait disturbances, postural instability, pseudobulbar syndrome and dystonia. Antiparkinsonian medications are usually not effective. There is some improvement of dystonia on trihexfenidil.

Methods: We evaluate medical records of 12 patients who were referred to the clinic in 2007-2008. All of them were men, (age range 21-45 years old). The length of period of ephedrone injections varied from 2 months to 1 year. The time from injections' cessation was from 6 months to 6 years. All of them were evaluated clinically using UPDRS, Tinnetti scale, Beck Depression Scale. They have been observed by neurologist on first visit and then followed up in every 2 months. 7 patients received infusions of tioctacide, were switched subsequently to oral tioctacide with addition of oral venlafaxine (group 1), and 5 received venlafaxine only (group 2).

Results: In 1st group 4 patients experienced moderate improvement of gait, postural stability and considerable improvement of articulation and phonation. In 2 cases symptoms remained unchanged and in 1 case deteriorated gradually. 2 patients with initial improvement experienced recurrence of symptoms severity after quitting oral tioctacide. 4 patients in 2nd group had remarkable improvement of speech, phonation and gait stability. In two cases venlafaxine cessation caused reappearance of dysarthria and postural instability, which improved when the drug was started again. Involuntary laughing disappeared in all cases.

Conclusions: Effectiveness of tioctacide can be attributed to it's property to act against metal intoxication, therefore the results were seen mostly in patients with relatively short history of neurological symptoms' manifestation. The benefit of SNRI venlafaxin on gait and articulation might be due to enhancement of norepinephrine and serotonin in prefrontal regions and some brainstem structures involved in gait and posture regulation mechanisms. Our observation on certain effectiveness of tioctacide and venlafaxine needs further confirmation.

Tu-46

Akathisia and second-generation antipsychotic drugs

R. Kumar, P. Sachdev (Woden, ACT, Australia)

Objective: To review recent literature relevant to second generation antipsychotics (SGAs)-induced akathisia.

Background: Akathisa is one of the most common and distressing neuroleptic-induced extrapyramidal side effects (EPSE). Although it is well recognized in the context of conventional antipsychotic medications, there have been recent concerns raised by clinicians and researchers that this syndrome is overlooked in relation to second generation or atypical antipsychotics.

Methods: Review of published literature from 2006 to 2008.

Results: Recent studies using large databases clearly indicate that EPSE, in particular akathisia, do occur with the SGAs although the frequency is not as high as with the conventional antipsychotics. Risk factors include use of high doses, high potency SGAs, or combinations of SGAs with other psychotropic drugs, bipolar depression, palliative care settings, and co-morbid substance abuse in psychosis. The dopamine hypothesis remains plausible for understanding the pathophysiology of akathisia. There is emerging evidence that mirtazapine may be useful in the treatment of acute akathisia.

Conclusions: Even though akathisia is less prevalent with SGAs than the first generation drugs, it remains clinically important, and all clinicians should be conversant with its recognition and management.

Tu-398

Parkinsonism due to chronic artemisinin use

L.B. Bahroo, R.P. Gandhy, F.L. Pagan (Washington, District of Columbia)

Objective: To describe parkinsonian symptoms due to Artemisinin exposure.

Background: Artemisinin is an effective anti-malarial and anti-neoplastic medication. Artemisinin causes neurotoxicity by acting on the cytoskeleton and the mitochondria. Clinically in animal models, it is known to cause brainstem dysfunction resulting in gait disturbance, balance difficulty, ataxia and hearing impairments. One case of short term oral toxicity demonstrated reversible brainstem findings with the MRI significant for punctuate T2/FLAIR hyperintense lesions bilaterally involving the superior colliculi, periaqueductal grey, and the dentate nucleus.

Methods: Case study with review of relevant literature.

Results: 66 year old male presented with three year history of progressive gait and balance difficulty, bradykinsia and ridgity without rest tremor. Past medical history significant for breast cancer and ten years of exposure to artemisinin (which he felt was neuroprotective). Examination was significant for masked face, hypophonic speech, bradykinesia in all extremeties, cervical dystonia, and axial rigidity. Additionally, he had balance difficulty on pull testing, impairment and on tandem gait testing. Brain MRI findings were significant for moderate cortical and cerebellar vermis atrophy, subcortical white matter disease and midbrain atrophy. Para-neoplastic and antigliadin antibodies were negative.

Conclusions: The impairments in the case correspond to the animal toxicity data. Additionally, the MRI findings are similar to the previously known findings. While the cessation of Artemisinin did not result in clinical improvement, the patient has not declined significantly over the past year. To our knowledge, this is the first human case of long term oral exposure to Artemisinin.

We-38

Ephedrone and motor neuron damage – Can there be a relationship?

N. Lobjanidze, I. Khatiashvili, M. Okujava, K. Akhvlediani, N. Kvirkvelia (Tbilisi, Georgia)

Objective: The aim of the study was evaluation of clinical, radiological and ENMG characteristic of ephedronic encephalopathy(EE).

Background: The ephedrone abuse is widely spread among young people in some of the eastern European countries in transition. That mixtures used to be made from medicines containing pseudoephedrine and potassium permanganate (KMnO4) to produce the oxidant reaction and get methcationine. MRI picture and the clinical syndrome caused by ephedrone injections are relatively well known. It is consisted with parkinsonism-like syndrome, dystonia, gait and postural disturbances, pseudobulbar signs, neuropsychologic disorders. It is characterized by MRI picture showing manganese deposition in basal ganglia, brainstem and cerebellar nuclei. We have observed some cases clinically and radiologically different from those relatively typical features.

Methods: MRI, ENMG investigation of patients with EE.

Results: Case reports. We observed three patients, 25, 23 and 53 years old men. All of them injected ephedrone regularly during 1-1,5 year and subsequently developed hypophonia, propulsions, bradykinesia, dystonia and emotional incontinence. Brain MRI scan in one case was performed after more than 1 year from injection's cessation and didn't show any hyperintense T1 signals consistent with manganese deposition in basal ganglia. Instead, the elevated T2 signals from pyramidal tracts bilaterally were found. This 23 years old patient had widespread fasciculations, muscle atrophy and ENMG signs of spinal anterior horn damage. He died from breath insufficiency. Two other patients both had T1 hyperintensity in basal ganglia as well as T2 signal elevation from corticospinal tracts. One of them also had ENMG findings of lower motoneuron dysfunction. Neither of them had fasciculations or muscle wasting.

Conclusions: Upper and lower motor neuron damage is not typical for ephedronic encephalopathy. Nevertheless, taking the cases described above, it is possible to speculate about some cause-effect relations. That needs further investigation to rule out simple coincidence with genuine ALS development, or influence of some other toxic factors (chemicals, metals etc.).

We-39

A patient-centric disease framework for Parkinson's disease levodopa induced dyskinesia

A.L. Shields, U.G. Mallya, R.M. Lane, S.K. Thomas (East Hanover, New Jersey)

Objective: To develop a patient-centric disease framework that delineates disease-related impact and patient outcomes associated with Levodopa Induced Dyskinesia (LID).

Background: LID can pose significant burden to the care for patients with Parkinson's disease (PD). In addition, LID can limit optimal use of levodopa drug therapy resulting in sub-optimal management of PD symptoms. Nonetheless, a comprehensive characterization of all the symptoms and disease-related impact of LID among patients developing LID has not been well established and understood.

Methods: A systematic search of the empirical literature using the PubMed and PsychInfo databases was conducted to describe the cause, progress and patient impact of LID. Meta-analytic and qualitative review papers were also extracted to map out various components of the LID signs and symptoms.

Results: A comprehensive disease framework depicting signs, symptoms and patient impacts of LID was constructed. This framework shows that in addition to motor fluctuations and dyskinesias, a variety of symptoms including sensory and behavioral fluctuations are also commonly expressed among patients with LID. Patients also experience different types of dyskinetic movements and sequelae during the ON and OFF states of levodopa effects. The impact of LID seen in these patients are those that impair their physical (mobility, speech, falling, daily activities), social (communication, social activities) and emotional (depressed mood, anxiety, stigma, embarrassment) functioning. Moreover, the framework highlights the differential impact expressed by the types of dyskinetic movements among patients with LID.

Conclusions: LID impacts patients on physical, emotional and social levels. A patient-centric approach that specifies tailored therapeutic strategies for these patients to address their varying needs is recommended. Further research is warranted to validate these findings.

We-40

Neuroleptic malignant syndrome complicating alcohol withdrawal

C. Mihailescu, G. Mihailescu (Bucharest, Romania)

Objective: To prospectively evaluate the efficacy of an L-Dopa-based treatment of neuroleptic malignant syndrome developed during alcohol withdrawal.

Background: The neuroleptic malignant syndrome (NMS) represents an infrequent but serious condition, mainly concerning patients under psychiatric treatment, even after the occurence of the so-called low-risk atypical neuroleptics. Currently, little is known about risk factors and susceptibility for developing NMS which can occur at any age and irrespective of gender and comorbidities. NMS is feared due to its poor prognosis, especially when left untreated, due to underdiagnosis, when it could lead to fatalities. Recent data about treatment, as early as possible, with L-Dopa and it's combinations is encouraging.

Methods: We present 3 cases of neuroleptic malignant syndrome developed in patients with no significant concomitant pathologies, treated for psychomotor agitation during alcohol withdrawal.

Results: The signs and symptoms developed after a mean of 2 days after administration of the neuroleptic (mainly Haloperidol) but, under such difficult circumstances, diagnosis and treatment (L-Dopa-based regimen) occured only after a mean of 5 days. Each case submitted is discussed with regard to dosage administered and to the the evolution of the clinical and laboratory parameters under treatment.

Conclusions: NMS signs and symptoms can develop in patients with alcohol withdrawal treated with neuroleptics for psychomotor agitation, thus complicating its diagnosis and the clinical outcome. The treatment with L-Dopa proved effective in these patients, confirming recent data. Heavy alcohol consumption and alcohol withdrawal could prove to be a risk factors for NMS. These conclusions warrant further confirmation in larger-scale studies.

We-41

Class specific manifestation in drug induced parkinsonism

R.P. Munhoz, H.A. Teive, L.C. Werneck (Curitiba, PR, Brazil)

Objective: To analyze the demographic and clinical profile of cases of parkinsonism induced by dopamine receptor blockers (DRB) and calcium channel blockers (CCB).

Background: Drug induced parkinsonism (DIP) is classically described in patients taking DRB such as neuroleptics and antiemetics. In countries where CCB are available, this drug class also plays a significant role as causative agents in DIP. As these drug classes cause motor symptoms via different mechanisms, it should be expected that their manifestations also differ.

Methods: All patients with a clinical diagnosis of DIP according to established criteria were assessed. Patients were divided according to drug class involved, DRB or CCB. Those using both or an additional causative drug were excluded. Assessments included demographic, clinical data and neurological examination.

Results: A total of 120 cases of DIP were assessed. A total of 17 different drugs were detected, flunarizine was the most common in 34 cases, followed by haloperidol in 20, levomepromazine in 16, cinarizine and valproate in 13, risperidone in 12, chlorpromazine in 7, thioridazine in 6, metoclopramide in 5, sulpiride and zuclopentixol in 3, lithium and amlodipine in 2 and bromopride, ciclosporine A, trifluoperazine and verapamil in one case. The subgroups included 57 cases using exclusively DRB and 47 using CCB, accounting for 86,67 % of the whole sample. In the sample 78 (65 %) were female, mean age was 68,81 years, mean age of onset was 66,3 and mean duration was 2,51 years. Comparison of subgroups showed a significantly lower frequency of male cases was found in the CCB group, 25,61 % versus 47,42 %. The groups also differed in regards to mean age, 66,16 for the DRB group versus 73,64 in the BCC (p: 0,0016), mean age 63,93 versus 70,59 (p: 0,004) and mean duration 3,04 in the CCB group versus 2,23 in the DRB (p: 0,039). Cases with rigid akinetic parkinsonism were more common among DRB while tremor dominant cases were more common among CCB. H&Y scale scores were significantly worse for the DRB group (p: 0,046).

Conclusions: Cases with DIP, related to DRB and CCB differ in most demographic and clinical aspects that may be important clues for diagnosis and the understanding of specific physiopathology.

We-42

Catamenial and oral contraceptive-induced exacerbation of chorea in chorea-acanthocytosis: Case report

R.P. Munhoz, P.A. Kowacs, M.G. Soria, S. Raskin, H.A. Teive, R.D. Ducci (Curitiba, PR, Brazil)

Objective: To report for the first time the catamenial exacerbation of chorea in Chorea Acanthocytosis (ChAc) and further deterioration during treatment with an oral contraceptive (OC).

Background: Several endocrine and hormonal disturbances, especially those linked to estrogen, can influence the occurrence and severity of movement disorders including parkinsonism, chorea, dystonia, tics, and myoclonus. Autosomal recessive ChAc is neurodegenerative disorder with diverse neuropsychiatric presentations including behavioral, cognitive and movement manifestations, the latter typically chorea and oroligual dyskinesias.

Methods: Single Case Report.

Results: A 38-year-old female with epilepsy since the age of 18 years was initially evaluated at the age of 33 when she started to experience mild upper extremities chorea. After about one year, overt chorea became evident, including oro-lingual dyskinesias. This symptoms was associated with obsessive-compulsive behavior, depression and motor tics (eye blinking and lip smacking). She was the first of four siblings, parents had remote consanguinity. Peripheral red blood cell analysis revealed acanthocytes; the diagnosis of ChAc was made after Western blot analysis of erythrocyte membrane preparations revealed absent levels of chorein. She was started on quetiapine 50mg bid, paroxetin 20mg qd, clonazepan 2mg qd and tetrabenazine 25mg tid with good response. After 6 months, she complained of exacerbation of chorea during the three days that preceded her menses for the previous four cycles. Continuous oral desogestrel 75 microg/day was started. During the first days, she experienced an abrupt and dramatic worsening of chorea, which became generalized and interfered with daily activities and feeding. Hormonal treatment was withdrawn and movements gradually returned to baseline.

Conclusions: The association of OCs and chorea is widely recognized. While most of such cases have been hypothesized to be related to reactivation of Sydenhan's chorea and the use of estrogens, these history is not found in some patients, as in the case presented here which was using a progestagen. This case is alse the first case of a patient with ChAc presenting with catamenial worsening of chorea and its' even more dramatic exacerbation after starting an OC.

We-43

Effects of risperidone at "protective" doses on balance control in healthy individuals

E. Pourcher, H. Cohen, P. Corbeil, M. Simoneau, J.-F. Rodrigue (Quebec, Quebec, Canada)

Objective: Second generation anti-psychotics (SGA) with mixed D_2 /$5HT_2$ blocking properties have been developed to minimize extra-pyramidal side-effects (EPS) which include, following single dose, tremor, dystonia and bradykinesia (Tandon et al 2002). This study aimed at determining the effect of a single dose of the prototypical SGA Risperidone at dose considered clinically protective (meaning 3mg in young adults and 1mg in elderly) on balance control in young healthy individuals. It is hypothesized that measuring balance control (posturography [PG]) is an objective means to detect subtle motor behavioural changes caused by risperidone.

Methods: 12 healthy male subjects (mean age: 28.5 ± 3.7 years), with no history of neurological disorders nor prior treatments with antipsychotic agents participated. PG assessments included the Sensory Organization Test (SOT) and the Adaptation Test (ADT). The SOT quantifies the patient's ability to maintain upright balance under various sensory conditions (firm surface/sway referencing and/or eyes open/closed conditions) and the ADT assesses the patient's ability to control sway when the support surface rotates unpredictably (Equitest®, USA). Using a 3 way-crossover design, subjects received either a placebo or risperidone (either 1 mg or 3mg according to a randomization schedule). PG assessments were performed immediately pre- and 1, 3, 6, and 9 hours post-dosing. A 2 week washout period was applied between treatments. The body's net center of foot pressure (CoP) and center of mass (CoM) displacement were analysed. Results were submitted to a two-way repeated measures ANOVA, with Dose and Phase as within factors ($\alpha = 0.05$).

Results: Results revealed that, compared to the placebo, risperidone (i.e., both doses) increased the range of the CoP during all SOT conditions (ΔCoPs $> 2\%$, $p < 0.005$). Remarkably, the Dose by Phase interaction showed that even when visual control was available while standing on a firm surface, both doses of risperidone, led to a larger CoP sway 3 and 6 hours post-dosing. This increase in CoP sway was exacerbated in the more challenging conditions of the SOT ($p < 0.001$).

Conclusions: Our preliminary results suggest that balance control is negatively affected by striatal D_2 receptor occupancy at doses of risperidone clinically considered not to induce EPS.

We-44

Acute onset tremor associated with combination of chipmax and fluoxetine

A.Q. Rana (Toronto, Canada)

Objective: To report an interesting case of an acute onset severe disabling action tremor from combination therapy of chipmax and fluoxetine.

Background: Chipmax is a new drug used for smoking cessation. It is vareniciline tartarate which binds to alpha 4, beta 2 nicotine acetylcholine receptor with simultaneous partial agonist and antagonist activity which is believed to play a major role in addiction pathway. It partially stimulates dopamine release and prevents binding of nicotine. Slective serotonine reuptake inhibitors are frequently used to treat depression associated with Parkinson's disease and are considered to have a very low side effect profile in terms of exacerbating tremor and parkinsonism.

Methods: We report a case of a 66 year old female who was started on chipmax to help quit smoking. One month later while she was chipmax, she was started on fluoxetine 20 mg for depression and within few days she developed a high amplitude, 10-12 Hertz disabling, flexion, extension, symmetrical, postural and kinetic tremor of both upper extremities.

Results: On lowering the dose of fluoxetine to 10 mg the tremor improved significantly.

Conclusions: Movement Disorders could be potential and serious complications of any new drugs especially affecting addiction pathways as shown by this case. This should be kept in consideration when SSRIs are started in patients on new drugs such as Chipmax.

We-393

Tricyclic antidepressant-induced myoclonus: Case report and literature review

Y.-D. Kim, K.S. Yum (Daejeon, Korea)

Objective: To report a case of tricyclic antidepressant-induced myoclonus and review about relation with tricyclic antidepressant and myoclonus.

Background: Myoclonus is defined as sudden, brief, shock-like, involuntary movements. It is classified as either positive or negative. Symptomatic myoclonus is the most common etiology of this disorder, followed by epileptic myoclonus, and then essential myoclonus. Drug-induced myoclonus is also common form. Many drug, include toxin, psychotropics, anticonvulsant, antineoplastic drug, narcotics, cardiovascular drug and antibiotics can cause myoclonus. Tricyclc antidepressant (TCA) is known to cause of myoclonus, but it is rare case.

Methods: Report of case that development of myoclonus after administration of amitriptyline. Pubmed search of case report that TCA –induced myoclonus was performed from 1970 to 2008. Total of 8 cases were identified.

Results: A 64-year-old man was admitted to our hospital. He complained 1-day of involuntary movement on upper extremities and face. He didn't have medical history include hypertension, diabetes mellitus, seizure and stroke. There were no physical or neurological disorders in his familial history. Before eight days, he was treated with amitriptyline, 15mg/day, for tension type headache. Multifocal myoclnus was observed involving the face and upper extremities. We performed electroencephalogram and there was no epileptic spike and wave discharge. Patient's brain magnetic resonance imaging didn't show any focal abnormality. Thyroid function test, liver function test, blood urea nitrogen, creatinine and electrolyte were normal. Antinuclear antibody, lupus anticoagulant, anti-dsDNA antibody, amti-SSA(Ro), anti-SSB(La), rheumatoid factor and ANCA were normal. We administrated 1mg of clonazepam and then myoclonus was resolved completely. After re-administration of amitryptiline, myoclonus was induced again. He stopped amitryptiline and myoclonus wasn't observed anymore.

Conclusions: We report case of TCA-induced myoclonus. Many drugs can be cause of myoclonus, but TCA-induced myolonus is rare. The underlying pathophysiologic mechanism is known to be mediated through enhancement of serotonin and γ-aminobutyric acid. Identification and cessation of offending drug is important.

Th-40

Recurrent acute dystonic reaction and oculogyric crisis despite withdrawal of dopamine receptor blocking drugs

S.A. Schneider, V. Udani, C. Sawant, K.P. Bhatia (Luebeck, Germany)

Objective: To raise awareness for the existence of recurrent acute dystonic reaction and oculogyric crisis despite withdrawal of dopamine receptor blocking drugs.

Background: Adverse events of dopamine blocking agents include acute dystonic reactions and oculogyric crises (OGCs). OGCs may be recurrent on maintenance of or re-exposure to the drug. Thus, complete withdrawal is recommended. Recurrent episodes of acute dystonia *despite withdrawal* and in the lack of further exposure to antidopaminergic agents are usually not seen.

Methods: Here we report three cases with recurrent OGCs despite complete withdrawal of neuroleptics. Triggering/priming factors were a single dose of haloperidol in two cases and a single dose of metoclopramide in one case. Episodes re-occurred spontaneously but responded to anticholinergics.

Results: The pathomechanisms of acute dystonic reactions and OGCs remain unclear. Parallels to levodopa-induced dyskinesias in Parkinson's disease, as well as dopa-responsive dystonia, paroxysmal dyskinesias and channelopathies are discussed. Whether there is a genetic susceptibility or some other reason for only some patients developing this phenomenon remains unclear.

Conclusions: In rare cases, patients may exhibit recurrent acute dystonic reaction and oculogyric crisis despite withdrawal of dopamine receptor blocking drugs.

Th-41

Two year follow up in ephedrone induced parkinsonism with dystonia

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Objective: to monitor the disease course of ephedrone induced parkinsonism with a serial clinical and imaging study.

Background: A neurological syndrome characterised by l-dopa unresponsive bradykinesia, retropulsion with falls backwards, dysarthria, gait disturbance and dystonia has been recently identified in drug addicts within the former USSR and Eastern Europe, following the prolonged intravenous use of ephedrone (methcathinone), a central nervous stimulant prepared from pseudoephedrine, potassium permanganate and vinegar. The clinical and radiological picture closely resembled previous reports of chronic manganese poisoning. Olfaction and DAT SPECT scan were normal. The disease course remains unclear.

Methods: 13 male patients has been carefully studied over several years and serial UPDRS, MMSE, FAB, BDS, repeat MR brain scans been carried out. Pubic hair was sampled for manganese.

Results: Neurological symptoms began on average 8.5±3.2mths after daily IV Ephedrone abuse, with a daily dose 20 to 120 ml. Progression was rapid over the first six weeks with increasing apathy, speech, balance disturbance and slowness in movement. ADL started to improve in 4±3 mths after drug cessation. During two year study, started 2.0±1.5 yrs after the last Ephedrone exposure, a stepwise deterioration of dystonia (5) and parkinsonism (1) was noted, two lost speech, a violent asymmetrical kinetic hand tremor developed in 3. By 4±2 yrs without drug exposure ten had a marked to severe spastic, hypophonic dysarthria; loss of postural Rx on retropulsion;

dystonic cock gait with an upright posture (8); marked eyelid opening apraxia (6); severe hand dystonia (3); bradikinesia (10), micrography (4). Memory remained intact. UPDRS score was 49±11 (ND) at disease duration 2.2±1.4yr and 55±20 two years later. Whereas initial MRI showed symmetrical hyperintense T1-weighted signals in the globus pallidus, putamen, STN and less intense abnormalities in SN, nn. caudatus and dentatus, MRI on the follow up study was normal. Mn level in pubic was normal after a year after ephedrone cessation.

Conclusions: Ephedrone abuse results in disabling irreversible neurological disorder with delayed stepwise progression despite drug cessasion. Public prevention and early drug elimination are vital.

Th-42

Tardive tongue dyskinesia and burning mouth syndrome: Successful concurrent treatment with botulnum toxin A

M.-W. Seo, M.-H. Lim (Jeonju, Jeonbuk, Republic of Korea)

Objective: We report a case of tardive tongue dyskinesia and burning mouth syndrome, which symptoms were simultaneously treated with botulinum toxin A(BTX-A).

Background: Tardive dyskinesia(TD) is a serious motor side effect of chronic neuroleptic therapy. Burning mouth syndrome (BMS) is an intra-oral burning sensation for which no medical or dental causes can be found and in which the oral mucosa has a grossly normal appearance. We have experienced a case of tardive tongue dyskinesia and BMS. Both symptoms were simultaneously treated with botulinum toxin A (BTX-A).

Methods: Case report We describe a 54-year-old female patient who developed disabling involuntary choreic movements of the tongue characterized by continuous, irregular, writhing movements during mouth closing. The patient also complained of severe mouth burning symptoms. Tongue dyskinesia and BMS developed about five years after neuroleptic drugs were started. For treatment, fifty units of BTX-A (Dysport) was injected into the tongue muscles under EMG guidance. Tongue dyskinesia and burning symptoms improved about ten days after BTX-A injection. She was very pleased with symptom improvement. She has been injected BTX-A every month for two years since her first visit.

Results: Primary and secondary changes in the function of dopamine receptors lead to opposing pathological changes in the activity of neuronal pathways connecting the basal ganglia. Neuroleptic-induced lesions of the striatal neurons and genetic predisposition can also influence TD In a recent PET study demonstrated presynaptic dysfunction of the nigrostriatal dopaminergic pathway in BMS, which might be a common disease mechanism with TD. BTX-A can treat both hyperkinetic diseases and pain conditions by: 1) Inhibition of peripheral and central sensitization. 2) Chemodenervation of the motor endplate, 3) Anti inflammatory effects.

Conclusions: Dysfunctions of the nigrostriatal dopaminergic system might be commonly involved in the development of TD and BMS. BTX-A could concurrently treat tardive tongue dyskiniesia and BMS.

Th-43

New treatment (BN82451) and assessment for L-dopa-induced dyskinesias in hemiparkinsonian rats

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Objective: Development of L-DOPA-induced dyskinesia (LID) remains a major problem in the long-term treatment of Parkinson's disease (PD). The present study was aimed at assessing behavioural and biochemical evaluation of treatment with a novel multitargeting molecule, BN82451, on LID in a rat model of PD.

Background: BN82451 counter the pathways involved in neuronal degeneration by sodium channel blockade (neuronal excitotoxicity), reactive oxygen species scavenging (oxidative stress), and cyclooxygenase and/or lipoxygenase inhibition (neuro-inflammation). Reduction in mitochondrial swelling and cytochrome c release (mitochondrial protective action) is an additional neuroprotective effect.

Methods: Rats were submitted to two unilateral injections of 6-OHDA in the striatum. Four weeks later, the animals were treated chronically with increasing daily doses of L-DOPA. During 4 weeks of treatment, L-DOPA-treated rats developed abnormal involuntary movements (AIMs) classified as locomotive, axial, orolingual and forelimb dyskinesia. For quantification of dyskinesia, rats were observed individually every 30 minutes from 30 to 180 min after the injection of L-DOPA. For acute and subchronic determination, BN82451 treatment was administered orally at 10 mg/kg on Day 1 and pursued the 3 consecutive days and AIMs and spontaneous motor activity were measured at Day 1 and Day 5. Blood and CSF were taken at the end of the experiment to assess biological parameters.

Results: Acute treatment with BN82451 (10 mg/kg/day) resulted in a potent reduction in AIMs score without reducing rat activity. Rotational behaviour induced by L-DOPA was also significantly decreased by BN82451. Moreover, at day 5, after a 4 day subchronic treatment and 24 hours after the last administration, the AIMs were always significantly reduced (50% in comparison with controls). These effects were paralleled by an attenuation of biological changes associated with the dyskinesiogenic action of L-DOPA.

Conclusions: These data demonstrate that BN82451 produces strong anti-dyskinetic effects in an animal model of PD and may represent a treatment option for managing dyskinesia.

Th-398

Anticholinergics use in elderly with Parkinson's disease may lead to the development of chorea

A.Q. Rana (Toronto, Canada)

Objective: To report a case of severe generalized chorea and orofacial dyskinesia in a Parkinson's disease patient with exposure to trihexyphenidyl.

Background: Anticholinergic medications are used in Parkinson's disesease for control of resting tremor. In additon to the anticholinergic side effects, there have been reports in literature of chorea caused by anticholinergic medications especially in the elderly patients with Parkinson's disease although the exact mechanism by which they cause chorea is unknown.

Methods: We report a case of an otherwise healthy 81 year old female who was seen with a tremor dominant Parkinson's disease and was started on trihexyphenidyl. Although she had no side effects but because of her age and increased risk of anticholinergic side effects in elderly, 6 weeks later trihexyphenidyl was stopped and she was advised to take levodopa but unfortunately she never started herself on levodopa and continued taking trihexyphenidyl through her family physician. She did not come for a follow up visit to Parkinson's clinic. Three years later she was referred to the Parkinson's clinic for severe generalized choreform movements and orofacial dyskinesias by her family physician. Trihexyphenidyl was stopped and choreform movments improved.

Results: MRI and blood tests were unremarkable.

Conclusions: Anticholinergic medications can cause a very disabling chorea and orofacial dyskinesias, especially in the elderly patients with Parkinson's disease and should be used with caution.

Th-399

Involuntary movements and electroencephalogram (EEG) features in cefepime induced encephalopathy with renal insufficiency

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Objective: To report two patients with renal insufficiency who presented with involuntary movements due to cefepime induced encephalopathy.

Background: Cefepime, a fourth generation cefalosporins, is a widely used antibiotic. Recently, it has been reported that cefepime has neurotoxicity mainly in patients with renal failure. The common symptoms are consciousness disturbance and myoclonus. We have experienced two cases that showed involuntary movements probably due to cefepime-induced encephalopathy.

Methods: Case reports.

Results: Patient 1 is a 85-year-old woman on hemodialysis for chronic renal failure. She presented action myoclonus in the extremities and face after receiving 1g of cefepime every 24 hours and vancomycin, the dose of which was carefully monitored, for her osteomyelitis for 4 days. Although she showed neither severe consciousness disturbance nor generalized convulsion, she gradually became unable to speak possibly because of facial myoclonus. Electroencephalogram (EEG) taken 6 days later showed marked generalized high amplitude, sharp waves, which looked like periodic synchronous discharges (PSDs). Cefepime was discontinued and the myoclonus and EEG abnormality subsided gradually. Patient 2 is a 89-year-old man supported by mechanical ventilation because of respiratory dysfunction. He could respond to verbal command with hand movements. He was given 1g of cefepime every 8 hours for treatment of cholangitis. One day after, he showed intermittent jerky head-shaking movements. His responsiveness was relatively preserved. EEG showed generalized sharp waves similar to those of the patient 1. He had developed acute renal dysfunction probably due to sepsis on the same day. Involuntary movement and EEG abnormality disappeared soon after cefepime was discontinued.

Conclusions: These patients showed jerky involuntary movements and marked EEG abnormalities indicating cefepime-induced encephalopathy in spite of little consciousness disturbance. Patients with renal insufficiency often show myoclonus without significant EEG abnormalities, but acute-onset jerky involuntary movements could be the initial sign of drug-induced encephalopathy.

DYSTONIA

Mo-45

To report a patient with familial bilateral striopallidodentate calcinosis

P. Agarwal, A. Griffith, M. Borromeo-Wesner (Kirkland, Washington)

Objective: To report a patient with familial bilateral striopallidodentate calcinosis.

Background: Bilateral striopallidodentate calcinosis involves bilateral calcification of the striatum and pallidum, with or without deposits in dentate nucleus, thalamus and white matter. The underlying metabolic and genetic etiology remains unknown. One large family has been linked to a region on chromosome 14q, but the gene has not been identified. Patients have a broad range of clinical phenotypes, ranging from completely asymptomatic to fairly marked parkinsonism. Other associated phenomenon have included ataxia and various psychiatric and behavioral abnormalities.

Methods: A retrospective chart review was conducted of a patient presenting with generalized dystonia and calcifications in basal ganglia on CT scan of head.

Results: A 52 year old female presented with severe pain from generalized dystonia. She had no ataxia or parkinsonism. Symptoms started at age 45 with trouble gripping a pen and extensive work up for other causes of dystonia was negative. She is adopted with family history unknown. CT scan of brain revealed significant dense calcifications bilaterally and fairly symmetrically of the globus pallidus with definite but lesser calcification bilaterally of dentate nucleus in the posterior fossa and a small amount of calcification in the internal capsule. The CT scan of her 22 year old son also showed significant bilateral calcifications of globus pallidus with smaller amount of calcification in head of caudate. Her 28 year old daughter with bipolar disorder also has calcifications of basal ganglia and her 3.5 year old son has an unusually large head but no basal ganglia calcifications.

Conclusions: Bilateral striopallidodentate calcinosis is presumed to an autosomal dominant disorder with a 50% risk to children of an affected person. The penetrance is variable. In this family the patient's two children have calcifications of basal ganglia and one grandchild with unusually large head but no calcifications on CT head. This pattern does seem consistent with autosomal dominant inheritance with variable penetrance. Further studies need to be done to try to identify the gene associated with bilateral striopallidodentate calcinosis and to analyze the reason behind high variability of clinical manifestations. This patient benefited from botulinum toxin injections for dystonia.

Mo-46

Retrospective evaluation of 29 oromandibular dystonic cases who underwent botulinum toxin treatment

O. Burclukose, F. Selcuk, A.Y. Akin, C.M. Akbostanci (Ankara, Turkey)

Objective: In this article the aim is to investigate the efficacy of botulinum toxin, the initial time of impovement, the durability of improvement, improvement rate, the adverse effect by the treatment duration and the the rate of this adverse effects in patients with oromandibuler dystonia.

Background: Botulinum toxin treatment is a method of proved efficacy in patients with oromandibuler dystonia. This treatment has curable effects on patients by some adverse effects.

Methods: This is a retrospective study. Between July 1996- January 2009; 80 sessions of botulinum-A toxin injection is applied to 29 patients with oromandibuler dystonia in our Movement Disorder Unit of Neurology Department. All sessions were proceded with the help of EMG.

Results: An average value of 86.2 units (Botox equivalent dose) has been applicated to the patients. The patients felt the first improvement after 8.7 days and they returned to their conditions before injection after 2.8 months. The patients expressed averagely %55.2 improvement. In %80 of injections no adverse effect was observed, in %12.9 dysphagia, in %3.2 nausea, in %1.6 difficulty to open mouth, in %1.6 headache, in %3.2 othalgia, in %2.7 weakness of tongue, in %1.6 jaw pain while eating was detected.

Conclusions: Botilinum toxin injection treatment in oromandibular dystonia has been accepted as a safe and efficacious modality. The overall complication rate in our study was low and the results were similar to the studies that reported before.

Mo-47

Oromandibular dystonia due to cerebellar infarct: A case report

F. Selcuk, C.M. Akbostanci (Ankara, Turkey)

Objective: Oromandibular Dystonia (OMD) is a focal dystonia involving the mouth, jaw, and tongue causing involuntary mouth closure or opening, deviation of the jaw, facial grimacing, or tongue movements. It often interferes with chewing, swallowing, and speaking.

Background: OMD affects more women than men with a mean age of symptom onset between 31 and 58 years. It is not uncommon for patients to report a precise onset of the first OMD episode. In studies by Tan and Jankovic, the majority is idiopathic in etiology, accounting for 63% of cases reported. Other possible etiologies include drug-induced OMD (22.8%), peripheral-induced OMD (9.3%), postanoxia OMD (2.5%), neurodegenerative disorder-associated OMD (1.8%), and head injury-associated OMD (0.8%).

Methods: 65 year old woman reffered to Neurology Service due to sudden onset of involuntary mouth opening, deviation of the jaw, facial grimacing, and tongue movements. In her medical history she had hypertension, type two diabetes mellitus. It was six months ago when she had sudden onset of gait problem and involuntary jaw movements. At that time neuroimaging studies showed left cerebellar artery infarction. In her neurologic examination she had jaw opening

and left side dominant bilateral jaw deviation. Cerebellar tests were impaired at left side and her gait was ataxic. She was treated with Botulinum toxin A injections.

Results: This case shows that ischemic stroke in cerebellum may have a casual relationship with OMD. A similar case was reported in 1990 in which left cerebellopontine angle meningioma appeared to act as a triggering mechanism for the development of blepharospasm-oromandibular dystonia.

Conclusions: Brain stem/cerebellum lession could trigger the mechanism for OMD.

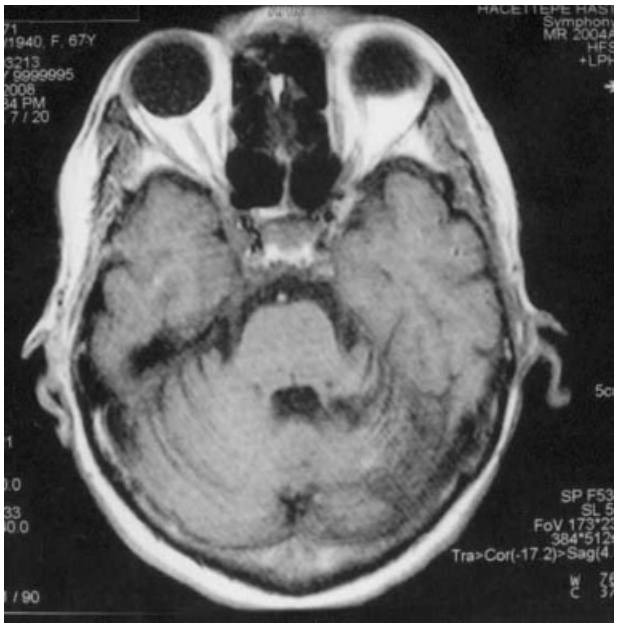

FIG. 1 (Mo-47).

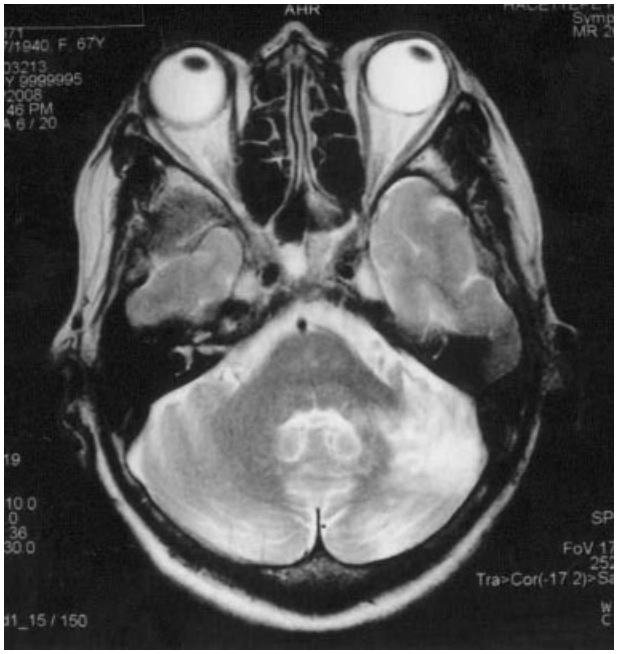

FIG. 2 (Mo-47).

Mo-48

Hallervorden-Spatz syndrome: A clinical and genetic study of 10 patients

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Objective: To report clinical findings in ten children affected by Hallervorden-Spatz with two unusual features at the onset of the disease: behavioural disturbance and cerebellar ataxia.

Background: Hallervorden-Spatz Syndrome (HSS) is a rare autosomal recessive neurodegenerative disorder of childhood characterized by progressive extrapyramidal manifestations and iron accumulation in the brain. Classical and atypical clinical presentations are known. Many patients with this disease have mutations in the gene encoding pantothenate kinase 2 (PANK2).

Methods: We report ten patients from 3 families that fulfilled HSS clinical criteria. Diagnosis was made between 1997 and 2008. They were examined at different stages of the disease. MRI was performed in five patients from the 3 families. Mutations analysis in the PANK2 gene was performed in all the patients.

Results: Mean age at onset of the disorder was 5 years and 8 months. Hyperkinetic syndrome and concentration difficulties were the first and striking features observed by the parents in all the patients. Other precocious signs described by the parents were abnormal falls, gait or postural difficulties. These features were followed by dysarthria, dystonia including retrocolis, oromandibular-facial dystonia, pyramidal signs, cognitive impairment. Pigmentary retinopathy was observed in all the patients. Progression was rapid with loss of independent ambulation at a mean age of 11 years with generalized dystonia and painful paroxystic rigidity. Magnetic resonance imaging (MRI) showed specific pattern of globus pallidus known as the eye of the tiger sign. PANK2 mutations were observed in the ten patients. We identified 2 homozygous truncating mutations segregating in 2 of these families. One of these mutations was found at the compound heterozygous state in patients of the third family together with two missense variations that were not detected in control chromosomes. The deleterious effect of these missense variations is not understood yet.

Conclusions: All cases had classical signs of HSS with progressive dystonia, pigmentary retinopathy, specific MRI pattern and PANK2 mutations. Nevertheless, unusual clinical features like major hyperactivity and ataxia which were precocious signs of the disease are scarcely described in the literature.

Mo-49

Anticipation in DYT1 dystonia

E.U. Augustine, J.W. Mink (Rochester, New York)

Objective: To describe the age at onset and clinical features of DYT1 dystonia in a family.

Background: DYT1 dystonia is a dominantly inherited disorder with incomplete penetrance, caused by a mutation in chromosome 9q34. Intrafamilial variability of phenotype has been well described. However, anticipation is not characteristic of this disorder. We describe a family who demonstrates evidence of anticipation in terms of age of onset and clinical severity.

Methods: Five patients from a single kindred were evaluated in the Movement Disorders clinic in Rochester, NY between 2001 and 2008. Available at-risk relatives were interviewed. The diagnosis of DYT1 dystonia was confirmed with molecular genetic analysis of the DYT1 gene in patients 1 and 3.

Results: Ten individuals in four generations were found to be affected. Age of onset ranged from 7 to 24 years. Presentation was most commonly with writer's cramp (four) or focal leg dystonia (four). Over time, dystonia remained focal in three, progressed to involve two limbs in four, and generalized within one to three years in three. Clear age of onset and specific clinical symptoms could not be determined for one individual (deceased). Onset in the first decade of life for all five patients of the youngest generation was striking when compared to second or third decade onset in prior generations. Three of these five had generalized dystonia, including two with severe, rapidly progressive, generalized dystonia refractory to medical therapy, eventually requiring DBS placement. The remaining two have involvement of more than one limb, in contrast to older generations, where three of five had action or task-specific dystonia confined to one limb.

Conclusions: The clinical spectrum of DYT1 dystonia is known to demonstrate significant intrafamilial variation, and it is possible that the early age of diagnosis is in part due to heightened awareness of the disorder within this family. However, the broader anatomic distribution of the dystonia, rapid generalization, and significant impairment in the youngest generation supports anticipation. Unexplained by the presence of a DYT1 mutation alone, there appears to be a role for additional genetic or environmental factors modifying the expression of the mutated DYT1 gene. Further study of this family may have implications for evaluation of rare occurrences of anticipation in other genetic diseases where this is an atypical feature.

Mo-50

Deficient consolidation of new motor memories in dystonic patients

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Objective: Our aim was to test whether dystonia patients will show normal performance gains following motor training of a new fingers sequence.

Background: It is not clear yet whether dystonia patients have difficulties in learning new motor skills. Indirect evidence to this open question comes from a study that tested motor sequence learning in a group of non-manifesting DYT1 carriers. The carriers had normal movement speed and accuracy when they performed simple motor tasks but marked impairment in the learning of new motor sequences.

Methods: Eighteen writer's cramp patients (mean age 48.3 sd 3.4) and 24 healthy controls (mean age 48.3 sd 2.4) practiced simple and complex 8-digits sequences during 45 minutes (simple sequence: 1-2-3-4-1-2-3-4; an example of a complex sequence: 2-1-4-1-3-2-4-3, the index finger is "1"). During practice the finger taps were 1.5Hz paced to control for the number of completed sequences. The speed and accuracy of the finger movements were recorded by 4-buttons response box connected to a PC. To quantify the performance gains of the complex sequence three speed tests were applied: before training (Test1), immediately after training (Test2) and 24 hours post-training (Test3). Test2 measured the performance gains related to training and Test3 the delayed gains considered to reflect overnight procedural memory consolidation processes.

Results: Figure 1 shows the average number of correct sequences completed by each group in the three tests. Both groups showed significant training gains (Test1 to Test2) however only the controls showed the expected delayed gains (Test2 to Test3) (significant ?interaction). No significant differences between the groups were found in number of erroneous sequences (Figure 2) or velocity of performance.

Conclusions: Our results show for the first time direct evidence for an impaired motor learning in dystonia. The patients benefited from motor training and showed early performance gains related to training. However, they did not show the delayed performance gains related to consolidation of the new motor sequence in memory. Consolidation refers to the processing of motor memory that occurs off-line, i.e. in the absence of any further practice, and leads to improvement in motor performance.

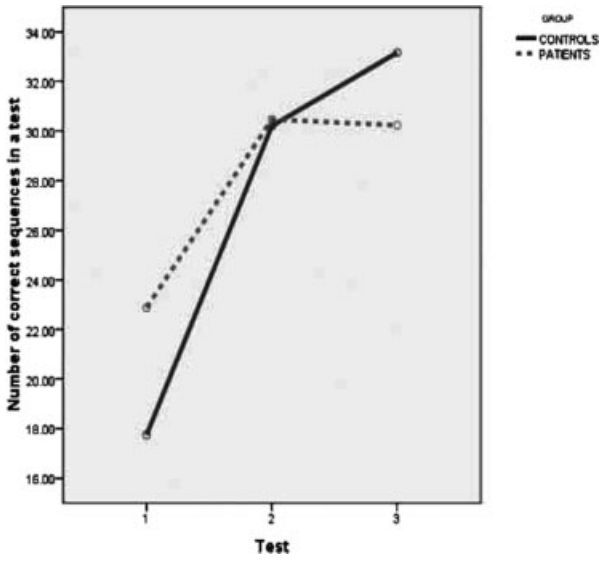

FIG. 1 (Mo-50).

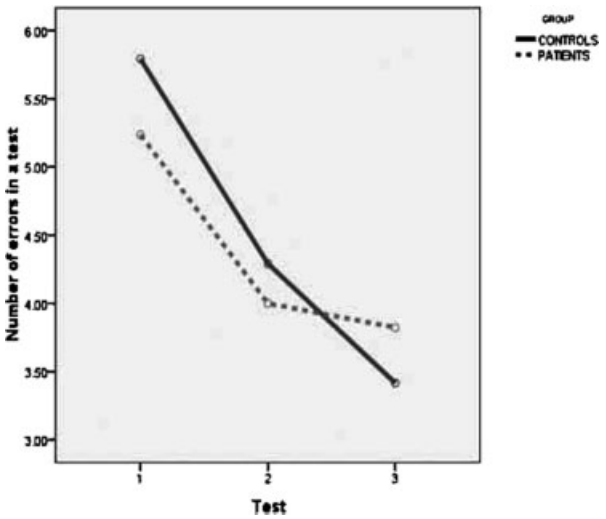

FIG. 2 (Mo-50).

Mo-51

Increased inhibition from the left dorso-lateral premotor cortex in focal hand dystonia

S. Beck, E. Houdayer, S. Pirio Richardson, M. Hallett (Bethesda, Maryland)

Objective: The aims of this study were to assess the role of the ipsilateral PMd in patients with focal hand dystonia (FHD) and in the genesis of surround inhibition, which is known to be deficient in FHD patients.

Background: Ipsilateral dorso-lateral premotor cortex (PMd) plays an important role in movement selection and has been shown to be over-active in patients with focal hand dystonia (FHD).

Methods: Using the abductor pollicis muscle (APB), a surrounding, non-synergistic muscle, as target muscle, single and paired pulse transcranial magnetic stimulation (TMS) was applied during different phases of an index finger movement. In the paired pulse paradigm, a sub-threshold conditioning pulse was applied to PMd 6 ms before the test pulse, given to the primary motor cortex (M1).

Results: There was surround inhibition during movement initiation in the control group, but not in FHD patients. In contrast, the FHD patients, but not the control group, showed premotor-motor inhibition (PICI) at rest. During movement, PICI was abolished in both groups.

Conclusions: We conclude that PICI may not play a key role in the formation of surround inhibition, since it was not enhanced during movement initiation in the control group. However, inhibition from PMd on M1 was significantly greater in FHD patients compared to controls at rest suggesting that PMd is involved in the pathophysiology of FHD. Increased PICI at rest may be compensatory and thereby explain beneficial effects of PMd stimulation with low-frequency repetitive TMS.

Mo-52

Cervical dystonia: Clinical and therapeutic features in 85 patients

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Objective: The objectives of this study were to identify the clinical profile of 85 patients with cervical dystonia and to analyze their response to treatment with botulinum toxin A (BoNT/A) in terms of the severity of the motor alterations and pain.

Background: Dystonia is defined as a syndrome characterized by prolonged muscle contraction causing twisting, repetitive movements or abnormal posture. Most voluntary muscles can be affected and, in the case of the neck muscles, the condition is referred to as cervical dystonia. A wide range of therapies are available for cervical dystonia, from clinical treatment to brain surgery (pallidotomy and deep brain stimulation) or even peripheral surgery. However, BoNT/A is currently considered the treatment of choice.

Methods: The inclusion criteria were: (1) the presence of cervical or segmental dystonia; (2) the presence of generalized dystonia, hemidystonia or multifocal dystonia, with referral for botulinum-toxin-A treatment for cervical dystonia. The choice of muscle, location and amount of BoNT/A for each muscle were determined based on clinical evaluation with the aid of electromyography. Patients received botulinum-toxin-A therapy (Botox®, Allergan, Irvine, CA, USA) in dosis varied from 100 to 280 U. The patients were assessed on admission and approximately 14, 30 and 120 days after the treatment had started to compare severity, disability and pain using the Toronto Western Spasmodic Torticollis Rating Scale; Fahn-Marsden dystonia scale, Jankovic disability; and visual analog pain scale.

Results: The average ages at onset of focal dystonia and segmental dystonia were greater than for generalized dystonia ($p<0.0003$). The severity of the abnormal head-neck movements were more severe among the patients with generalized dystonia ($p<0.001$). Pain in the cervical area was noted in 59 patients. It was not possible to determine the etiology of the disease in 62.3% of patients. Tardive dystonia was the most common secondary etiology.

Conclusions: A major improvement in the motor symptoms of CD and pain was observed in patients following treatment with BoNT/A. The tardive dystonia subgroup did not respond to the treatment. Dysphagia was observed in 2.35% of the patients.

Mo-53

Psychiatric disorders in patients with primary focal distonia

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Objective: We studied the frequency of psychiatric disorders in patients affected by various clinical forms of adult onset focal dystonia.

Background: Adult onset focal dystonia can be associated with psychiatric disorders, particularly anxiety, depression and obsessive-compulsive disorder (OCD).

Methods: We enrolled 67 patients with primary focal dystonia: 31 with cervical dystonia (CD, mean age 57.2 ± 17.7), 22 with blepharospam (BSF, mean age 68.2 ± 9.3), 7 with arm dystonia (AD, mean age 50.3 ± 15.6) and 7 with laryngeal dysphonia (LD, mean age 56.7 ± 10.7). Patients were recruited at the movement disorders outpatient clinic of the Department of Neurological Sciences, Sapienza University of Rome. Results were compared with those of 15 patients with hemifacial spasm (HFS, mean age 60.4 ± 13.4) and those of 42 healthy subjects (HS, mean age 54.6 ± 13.5). CD was rated with the Toronto Western Spasmodic Torticollis Scale, BSF with the Blepharospasm Severity Scale, AD with the Arm Severity Section of the Dystonia Movement Scale and LD with a three-point clinical scale. Psychiatric evaluation was performed with the Structured Clinical Interview for DSM-IV. OCD was assessed with the Yale-Brown Obsessive-Compulsive Scale, anxiety with the Hamilton Anxiety Scale and self-reported level of depression with the Beck Depression Inventory.

Results: In CD the most frequent psychiatric disorder was major depressive disorder (MDD, 25.8%), followed by anxiety NOS (13%), generalized anxiety disorder (GAD, 6.5%), adjustment disorder (6.5%), panic attack (3%), OCD (3%), and dysthymia (3%). In BSF the most frequent psychiatric disorder was GAD (27.2%), followed by MDD (22.7%), dysthymia (13.6%) and anxiety NOS (4.5%). One of the seven patients with AD had OCD and 1 had adjustment disorder. Two of the 7 patients with LD had MDD and 1 had GAD. Five out of the 15 patients with HFS and 12 of the 42 HS had a diagnosis of psychiatric disorder (including anxiety, depression and OCD).

Conclusions: Patients with primary focal dystonia in comparison to patients with HFS and healthy subjects have an increased frequency of psychiatric disorders, mainly major depression and generalized anxiety disorder.

Mo-54

Chylomicron retention disease: Dystonia as a new clinical feature

G. Bernard, M. Panisset, A. Sadikot, S. Chouinard (Montreal, Quebec, Canada)

Objective: We wish to report three cases of chylomicron retention disease presenting a new clinical feature: dystonia and the response of one of these patients to deep brain stimulation.

Background: Chylomicron retention disease is a rare autosomal recessive condition characterized by malabsorption of dietary fat, cholesterol and liposoluble vitamins causing failure to thrive, developmental difficulties, as well as neurological signs and symptoms, including abnormal vibration sense and decreased or absent deep tendon reflexes. This genetic condition is usually diagnosed by demonstrating accumulation of lipid droplets in the enterocytes at the jejunal biopsy. The majority of cases are caused by mutations of the SAR1B gene on chromosome 5 but the genetic testing is still unavailable clinically.

Methods: We reviewed the chart of three patients affected by this disorder.

Results: Our three patients presented in early childhood with some degree of malabsorption resulting in failure to thrive. They were all of subnormal intelligence, developed decreased vibration sense and absent deep tendon reflexes. The diagnosis was confirmed in all by a jejunal biopsy demonstrating lipid droplets accumulation in the enter-

ocytes. Their clinical picture was somewhat atypical in that all three of them developed a dystonic tremor in adolescent or early adult years. The dystonic tremor of all was resistant to medications. One of the patient had a dystonic tremor involving one side more than the other, resulting in very significant impairment of his quality of life. He underwent implantation of deep brain stimulator in the contralateral thalamus with major improvement of his tremor.

Conclusions: Chylomicron retention disease is a rare genetic disorder which may have, among other more typical clinical manifestations, dystonia with a dystonic tremor. The good results obtained with deep brain stimulation of the thalamus in one of our patient suggest that this modality of treatment should be investigated further in this population.

Mo-55

Neurostimulation therapy for primary and secondary dystonia: The Venetian experience

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Objective: To report the motor outcome of neurostimulation therapy in patients with primary and secondary dystonia undergone surgery in Venice.

Background: Neurostimulation is becoming a recognized treatment option for segmental and generalized dystonia refractory to medical therapy; however the indications for surgery are still debated.

Methods: Since December 2005 to December 2008, twelve dystonic patients (6M, 6F) have been undergone surgery in Venezia-Mestre, Italy. Ten patients (3 with primary segmental dystonia, 1 with post-meningoencephalitis segmental dystonia, 5 with primary generalized dystonia), underwent bilateral GPi-DBS. One patient with post-stoke hemidystonia underwent implantation for unilateral Motor Cortex Stimulation (MCS) and 1 patient with DYT11 positive generalized dystonia with severe atrophy and vascular encephalopathy underwent bilateral MCS. All the surgical procedures were performed with intraoperative neurophysiological monitoring. No adverse events were observed after surgery. In the post-op period all patients were included in a rehabilitation program for at least 3 weeks. Patients were evaluated pre and post surgery with the BFMDRS and TWSTRS.

Results: At 3 months, motor scores improved in all DBS-patients with 40% to 80% reductions in the BFMDRS. Further improvements were observed throughout the next 12 months and these persisted in long term follow-up (36 months). The most significant responses were seen in patients with primary dystonia. None of the patients worsened cognitively, and most reported improved mood. The post-op intensive and personalised physical therapy accelerated the time of improvement of dystonic symptoms. We did not observe any significant clinical improvement in the two patients undergone MCS although different patterns of stimulation have been tried. Only after surgery and for few weeks these patients showed a small clinical benefit probably due to the physical therapy.

Conclusions: GPi-DBS is an effective treatment for primary dystonia and some forms of secondary dystonia refractory to medical therapy. A post-op intensive and personalised rehabilitation program seems to accelerate the time of improvement. Although more data are needed, we did not observed significant benefit for MCS dystonic patients.

Mo-56

Autosomal dominant mirror movement in a French family

S. Billot, C. Depienne, S. Meunier, A. Brice, M. Vidailhet, E. Roze (Paris, France)

Objective: To describe five patients from the same French family with autosomal dominant mirror movements.

Background: Mirror movements (MM) are characterized by simultaneous, involuntary, controlateral identical movements that are induced by voluntary movements. MM are normal in young children but do not usually persit beyond age 10, when full myelinisation of the corpus callosum is achieved. In older patients, MM can be observed in association with various neuropsychiatric conditions including congenital and acquired disorders. By contrast, MM can be rarely found in the absence of additional neurological manifestation.

Methods: The patients had standardized interview, neurological examination and videorecording. Linkage analysis, neuroimaging studies using fMRI and MR-DTI with fibber tracking and neurophysiological studies using transcranial magnetic stimulation are under process.

Results: Five patients of a four generation pedigree were classified as affected on the basis of clinical findings. All patients had a very similar phenotype. MM have been noticed from early childhood and did not worsen with aging. They predominantly involve the hands, especially the fingers. They are of lesser amplitude as compared with the voluntary movement and increase with task complexity and effort and cannot be voluntary suppressed. Two of these patients have severe writing difficulties. When writing, they must stop after after a few words due to painful contraction of the hand. External blocking of the controlateral hand prevents the occurence of this disabling contraction so that the patients can write almost normally. It may be interpreted as a "double mirror" phenomenon. The transmission pattern in this family was highly suggestive of an autosomal dominant disease with incomplete penetrance.

Conclusions: Familial MM is a benign neurological condition although severe writing difficulties can occur in the course of the disease. In keeping with the hypothesis on the underlying mechanism of MM, genetic analysis of such rare families may allow identifying genes involved in the regression of the ipsilateral pyramidal tract or in the corpus callosum maturation.

Mo-57

Long-term (7-year) cervical dystonia safety study with Myobloc®

W. Birmingham, E. Salazar-Grueso (Malvern, Pennsylvania)

Objective: Summarize the results of a 7-year cervical dystonia (CD) safety study with Botulinum Toxin Type B (BoNT-B).

Background: As a US post-approval commitment, patients with CD were enrolled in this study to evaluate the safety, efficacy and immunogenicity of repeat doses.

Methods: This was a multicenter, open-label study enrolling patients who were serotype type A responsive or unresponsive. Safety assessments, patient rated efficacy scores and serum samples for neutralizing antibodies were collected.

Results: Of the 502 patients enrolled, 48 were serotype A resistant and 454 were serotype A responsive. Mean age was 54 years; the majority of patients were white (96%) and female (68%). The mean dose was 16,227 Units; the median was 17,500 Units (min 5,000 Units, max 25,000 Units). Mean time between injections was 91.33 $\pm$ 31 days. Mean duration of treatment was 3.4 years or about 14 treatment sessions. Mild to moderate dry mouth or dysphagia was experienced by 63% and 26.1% of patients, respectively, following up to 7 years of treatment. No events of aspiration, aspiration pneumonia or botulism were reported. Few (5) treatment-related serious adverse events (AE) were reported. Twenty-nine patients withdrew due to AEs; 14 patients withdrew due to treatment-related AEs. Five deaths unrelated to treatment were reported. No notable findings were observed among laboratory tests, physical and neurological examinations, and vital signs. Mean patient efficacy ratings were slightly to moderately improved over all treatment sessions (1-28) for both A-responsive and A-unresponsive patients on a 7-point scale. Immunogenicity data is being compiled.

Conclusions: Repeat doses of BoNT-B were safe, well tolerated, and had a beneficial effect during long-term use in patients with

CD. Prior history of being A-unresponsive did not appear to have an effect on efficacy.

Mo-58

A family with a hereditary form of torsion dystonia from Northern Sweden treated with bilateral pallidal deep brain stimulation (DBS)

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Objective: To evaluate pallidal DBS in a non-DYT1 form of hereditary dystonia.

Background: Pallidal DBS has emerged as an effective treatment particularly for DYT1 dystonia. Little is however known about the effectiveness concerning other forms of hereditary primary dystonia. We present the results of pallidal DBS in a family with non-DYT1 hereditary dystonia following an autosomal dominant pattern in inheritance, where identification of the mutated gene has failed so far. All affected individuals are descendants of three couples living in the 17th century in a village in Northern Sweden. Ten members had definite dystonia and five had dystonia with minor symptoms. Six generalized, 3 multifocal and 1 segmental. 4 of the remaining 5 cases had blepharospasm combined with dystonic posture of an upper extremity, action tremor or problems with alternating movements. The presenting symptoms were in the head/neck area and age at onset around age 25 (range 14-50).

Methods: 4 patients (3 males) received bilateral pallidal DBS. Mean age was 47 years (range 35 -55), and duration of disease 22 years (range 19 – 28).

Results: Mean BFM score decreased by 79 % on stimulation, from 42.5±24 (22-72.5) to 9±6.5 (3-18.5) at the last evaluation. Cervical involvement improved by 89%. Similarly. The two patients with oromandibular dystonia and blepharospasm responded well, with a reduction of 95 % regarding these symptoms.

Conclusions: The present study confirms the effectiveness of pallidal DBS in a new family with hereditary primary segmental and generalised dystonia characterised by prominent cervical and craniofacial involvement.

Mo-59

Further evidence for pallidal output abnormalities in cervical dystonia

A.J. Blood, J. Kuster, T.J. Multhaupt-Buell, N. Makris, M.L. Makhlouf, L.R. Sudarsky, N. Sharma (Charlestown, Massachusetts)

Objective: To further investigate white matter microstructure medial to the pallidum in cervical dystonia patients.

Background: We previously showed that a cohort of cervical dystonia patients exhibited a white matter microstructural abnormality medial to the pallidum (Blood et al., 2006). Here, we present data validating this finding in a larger cohort, and further characterize the finding by comparing mean diffusivity (MD) with fractional anisotropy (FA) measures. We also evaluated several other regions based on predictions from a recent model for dystonia (Blood, 2008).

Methods: 11 patients with cervical dystonia and 11 matched control subjects were scanned with a diffusion tensor imaging (DTI) sequence on a Siemens 3T scanner. All patients were either botulinum toxin (BTX) naïve or at the end of a BTX treatment period, when BTX was least effective. DTI images were processed using FSL software. Whole brain contrasts were conducted for FA and MD maps in patients versus controls, and resulting statistical maps evaluated for group differences.

Results: Patients exhibited large clusters of reduced FA relative to controls in white matter medial to the pallidum, which swept out of the pallidum and caudally toward the thalamus. The difference was greater and extended more rostrally in the left hemisphere. We also observed FA differences in patients along the superior cerebellar peduncle, in supplementary motor area white matter, and in the red nucleus/Forel's field H region. Although MD values were also different in some regions, no MD differences were observed between patients and controls where FA was reduced medial to the pallidum.

Conclusions: These results replicate earlier findings of altered FA medial to the pallidum in cervical dystonia patients. The anatomy of these clusters and presence of altered FA in regions to which these fibers project, further supports the hypothesis that pallidal output fibers are altered in cervical dystonia. The absence of MD abnormalities in this region suggests that decreased FA reflects a change in axonal coherence or microstructure, rather than reduced fiber density. References: Blood AJ, Tuch DS, Makris N, Makhlouf ML, Sudarsky LR, Sharma N. NeuroReport 2006; 17(12):1251-5. Blood AJ. Bioscience Hypotheses 2008; 1(1):14-25.

Mo-60

Profound generalized dystonia and psychomotor delay without hyperphenylalaninemia – A novel phenotype of GTP cyclohydroxylase 1 deficiency associated with a GCH1 promoter mutation

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Objective: To analyze the *GCH1* gene in a patient with infantile-onset generalized dystonia, severe psychomotor delay, and a family history of dopa-responsive dystonia.

Background: GTP cyclohydrolase 1 (GTPCH), encoded by the *GCH1* gene, leads to the synthesis of tetrahydrobiopterin, which is a cofactor of aromatic amino acid hydroxylases in synthetic pathways of several neurotransmitters, including dopamine. The clinical presentation of GTPCH deficiency depends on the genetic defect, and may take the form of mild autosomal dominant dopa-responsive dystonia, if only one *GCH1* allele is mutated, or severe autosomal recessive syndrome with hyperphenylalaninemia (HPA), if both alleles are inactivated. None of more than 100 *GCH1* mutations reported so far were identified within the promoter.

Methods: Sequencing analysis of the entire *GCH1* gene.

Results: *Patient.* The eight-year-old boy with infantile-onset of generalized dystonia and profound psycho-motor delay was born to a mother with dopa-responsive dystonia (DRD). His father had had a non-progressive hemiparesis of unknown cause since childhood. The patient had normal MRI scans of his brain, and a metabolic screen excluded inborn errors of metabolism, including HPA. *Genetic analysis.* The standard sequencing of the *GCH1* coding region revealed a heterozygous c.614T>G (V205G) mutation in both the patient and his mother. The mutation was associated with DRD in previous reports. Further analysis of the non-coding regions led to the identification of a 18-nucleotide deletion within the *GCH1* promoter. The same mutation was also detected in the patient's father, thus proving the compound heterozygosity status of the patient. The promoter mutation overlapped the cAMP response element (CRE), and animal studies showed that cAMP is critical to *GCH1* expression in certain (but not all) cell types, including midbrain and hypothalamus dopamine neurons.

Conclusions: The patient may have selective central GTPCH deficiency, which explains the severity of his neurological syndrome, with some residual GTPCH activity, preventing generalized HPA, in extraneural tissues, which are less dependent on cAMP stimulation.

Mo-61

Temporal discrimination thresholds in familial AOPTD Pedigrees – Use of a new endophenotype

D. Bradley, R. Whelan, R. Walsh, R. Reilly, S. Hutchinson, F. Molloy, M. Hutchinson (Dublin, Ireland)

Objective: To examine Temporal Discrimination Thresholds (TDTs) in familial and sporadic AOPTD patients, their unaffected

relatives and control subjects and to apply the technique as an endophenotype in familial AOPTD pedigrees.

Background: Familial adult onset primary torsion dystonia (AOPTD) is an autosomal dominant disorder with markedly reduced penetrance. Most AOPTD patients are sporadic cases. Sensory processing abnormalities in unaffected relatives of AOPTD patients may indicate non-manifesting gene carriage (act as an endophenotype). Temporal discrimination thresholds (TDTs) are abnormal in AOPTD but they have not been applied as an endophenotype.

Methods: 32 AOPTD patients (15 familial, 17 sporadic), 40 unaffected first degree relatives (24 related to familial cases and 16 related to sporadic cases), 17 unaffected second degree relatives (all related to familial cases) and 43 control subjects were examined. TDT was measured using visual and tactile stimuli. Of these subjects, 12 AOPTD patients, 24 first degree relatives and 17 second degree relatives came from 6 multiplex families with at least 3 affected patients.

Results: The mean TDT in 26 controls <50 years was 22.85ms and in 17 controls >50 years was 30.87ms. The upper limit of normal was defined as control mean +2.5 SD. Z-Scores were calculated for all subjects. 27/32 (85%) AOPTD patients had abnormal TDTs with similar rates in sporadic and familial cases. 20/40 (50%) unaffected first degree relatives had abnormal TDTs with similar rates in relatives of sporadic and familial AOPTD cases. Abnormal TDTs were found in 7/17 of second degree relatives. Using TDT testing in 52 individuals in the six multiplex families, 22 had normal TDTs, one of whom had spasmodic dysphonia and 30 abnormal TDTs were identified in 10 affected individuals, 1 obligate carrier and 19 unaffected relatives (12 first degree and 7 second degree). Using TDT we identified twice as many endophenotype carriers as clinically manifesting individuals, no individual with a normal TDT was found to have an offspring with an abnormal TDT, and an autosomal dominant transmission was demonstrated.

Conclusions: The prevalence of abnormal TDTs in AOPTD patients and relatives follows the rules for a useful endophenotype. Based on performance in 6 families, TDT may be an effective tool in AOPTD research.

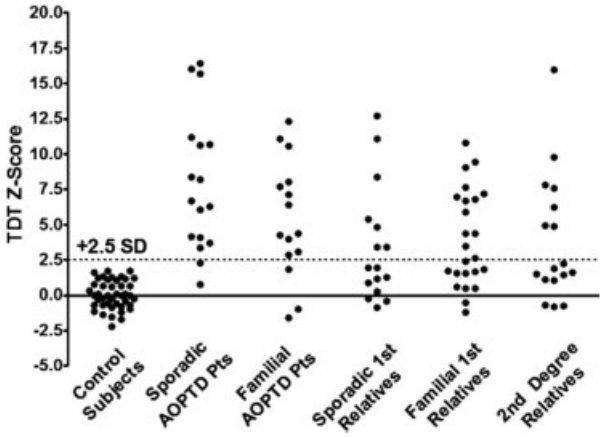

FIG. 1 (Mo-61).

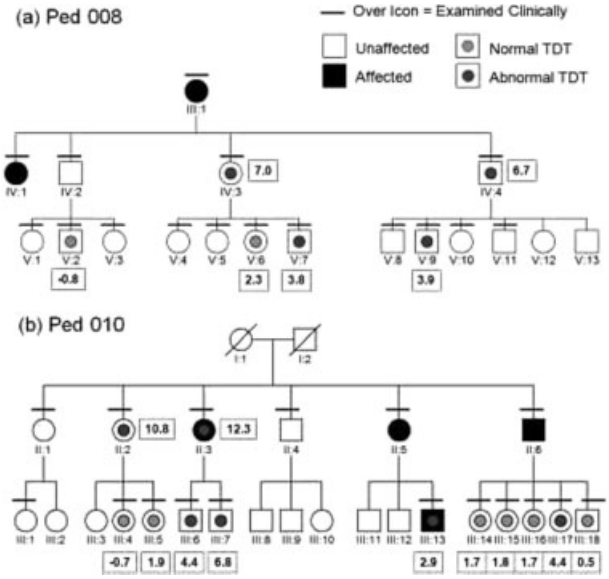

FIG. 2 (Mo-61).

Mo-62

Genotypic changes in cerebello-thalamo-cortical connectivity in primary dystonia

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Objective: (1) To assess the integrity and the functional role of cerebello-thalamic-cerebral (CBTC) pathways in primary torsion dystonia (PTD). (2) To explore mechanisms of penetrance in PTD.

Background: Increasing evidence implicates abnormalities in cerebellar function in dystonia, particularly in PTD.

Methods: We used diffusion tensor MRI (DTI) to track white matter fiber pathways in 20 manifesting (MAN) and non-manifesting (NM) dystonia gene carriers (age: 42.9 ± 13.4 years, mean/SD; 11 DYT1 [7 MAN-DYT, 4 NM-DYT1]; 9 DYT6 [5 MAN-DYT6, 4 NM DYT6]; median BFM score in all MAN: 13.8, range 1-51) and in eight age-matched gene-negative controls (age: 40.3 ± 19.0). CBTC pathway connectivity was quantified with probabilistic tractography using seed masks below and above the decussation of the CBTC (bilateral superior cerebellar peduncles and suprapontine brainstem regions respectively). Voxel-based group comparisons of the DTI based CBTC tracts were performed using SPM5. Additionally, all DYT1 carriers were scanned with $H_2{}^{15}O$ PET while performing a simple motor task. Measures of CBTC connectivity were used as covariates for $H_2{}^{15}O$ PET analysis to estimate the functional role of path disruptions.

Results: A highly localized reduction in connectivity was present in DYT1 and DYT6 carriers ($p<0.001$), involving fiber tracts connecting the dentate nucleus and the ventral thalamus. This disruption of cerebellar outflow projections was relatively greater in MAN carriers. Importantly, NM carriers exhibited a second area of reduced connectivity along the CBTC pathway, affecting distal thalamo-cortical projections in the vicinity of the sensorimotor cortex. Interestingly, clinical penetrance was predicted by a combination of the two serial tract lesions ($p=0.003$). Moreover, the reduced measures of connectivity along the CBTC tract in DYT1 carriers were associated with increased motor activation in the ventrolateral thalamus, primary motor cortex, and supplementary motor area ($p<0.001$).

Conclusions: Our results support the idea of a cerebellar origin of PTD, which is likely neurodevelopmental in origin. Additionally, our data suggest a completely novel mechanism for penetrance: Penetrance appears to be mediated by the combination of discrete areas of abnormal structural connectivity occurring in tandem along the CBTC pathways.

Mo-63

Imagination of writing reveals a primary deficit of basal ganglia-premotor activation in patients with idiopathic focal hand dystonia

F. Castrop, C. Dresel, A. Hennenlotter, C. Zimmer, B. Haslinger (Muenchen, Germany)

Objective: To investigate the neural correlates of non-lexical writing without motor output in patients with writer's cramp.

Background: The pathophysiology of idiopathic dystonias seems to encompass deficient inhibitory basal ganglia function and altered sensory processing, though the relation of these mechanisms to each other remains unclear. To deal with this question and to address the basal ganglia circuitry dysfunction without interference by abnormal sensory processing, tasks without motor execution might be promising.

Methods: Event-related fMRI was carried out in 10 patients with writer's cramp and 10 healthy controls during 2 experimental tasks: 1) kinesthetic motor imagery: here subjects were instructed to imagine continuously drawing visually presented geometric figures without movement execution. 2) observation task: subjects passively watched videos showing hands drawing geometric figures.

Results: In both groups, motor imagination and observation activated a widespread overlapping cortical and subcortical network including the bilateral dorsal and ventral lateral premotor cortex, the mesial premotor cortex, the superior and inferior parietal lobule, the bilateral lentiform nucleus, the thalamus and the cerebellar hemispheres. Compared to controls, patients showed deficient activation of the left PMd, the SMA proper, the lentiform nucleus and thalamus during imagination, whereas no significant signal differences between groups were revealed during observation.

Conclusions: We demonstrate that patients with writer's cramp show deficient activation of basal ganglia-premotor circuits during motor imagination. While visual signal processing and observation-induced motor activation seem to be comparable between both groups, as underlined by a lack of intergroup signal differences during motor observation, internal movement simulation and planning during imagination seem to be dysfunctional in patients with focal dystonia. We suggest that this is in line with the concept of a disrupted basal ganglia center-surround inhibition leading to deficient focusing and selection of motor programs. As shown here, this seems to be a primary deficit that is independent of abnormal somatosensory input.

Mo-64

Sonography during writer's cramp treatment with botulotoxin injections

T. Charnukha, S. Likhachev, N. Charnenka (Minsk, Belarus)

Objective: To study forearm soft tissues sonography the possibilities of for safe points determining for botulotoxin A injections in patients with writer's cramp.

Methods: 3 patients with writer's cramp have undergone sonographic analysis of the forearm soft tissues in the area of supposed injection before the procedure of botulotoxin A introduction. Nerves and vessels position, thickness of subcutaneous fat and forearm muscles have been determined. Ultrasound analysis has been held by means of apparatus HD 11XE, linear measuring device with scanning frequency 5-12 MHz in grey-scale and colour Doppler ultrasonography modes.

Results: Supposed muscles for botulotoxin injections were determined during visual assessment, palpation, electromyography. After that sonography was held in course of which a projection of neurovascular fascicles was drawn on the forearm skin and injections points determinating. The thickness of subcutaneous fat, muscles depth, and optimal depth of needle introduction was shown in the schematic drawing. Nerves search was held with the help of bone landmarks during grey-scale analysis and due to arteries and veins position in Doppler ultrasonography mode. The injections were introduced into *m. flexor carpi ulnaris* and *m. flexor digitorum superficialis* muscles bellies in the amount of 100-150 U dysport. Handwriting improvement, increase of writing rate, hand tension and stiffness decrease during writing was observed in all patients. Adverse reactions and complications were not observed.

Conclusions: The use of soft tissues sonography for writer's cramp treatment with botulotoxin A helps to estimate individual size of the target muscle, to determine the depth of needle introduction, reduce the risk of the forearm nerves and vessels damaging.

Mo-65

Internal globus pallidus deep brain stimulation in status dystonicus: A study of eleven cases

L. Cif, V. Gonzalez, H. Elferitit, E. Andre, C. Geniez, P. Coubes (Montpellier, France)

Objective: The authors studied the influence of internal globus pallidus deep brain stimulation (DBS) on status dystonicus.

Background: Patients with dystonia of various aetiologies can develop severe long lasting generalized dystonia called status dystonicus usually refractory to standard drug therapy and requiring management in intensive care units. DBS of the internal globus pallidus (GPi) is an effective treatment in primary dystonia and is under assessement for secondary and degenerative dystonia.

Methods: Eleven patients (7 female, 4 male) exhibiting generalized dystonia and who developed during disease progression status dystonicus were included in the study. Only two patients were adults at the time they developped status dystonicus. Nine patients developped status dystonicus previous to DBS surgery and two patients during follow-up for DBS. Three primary dystonia (DYT1 positive in two cases), 2 PKAN, 1 Lesch Nyhan disease, 1 Whipple disease, and 4 secondary dystonia were included. All the patients received surgery for GPi DBS. Dystonia was assessed by the Burke Fahn Marsden's Dystonia Rating Scale. Evolution of dystonia, electrical settings, duration of the stay in intensive care unit and drug therapy changes following DBS have been studied.

Results: The mean of age at surgery was of 13.5 years (range, 8 to 33.5). The mean follow-up with DBS was of 4.3 years (range,1 month to 12.5 years). Eight patients were improved by GPi DBS allowing discharge from intensive care unit. The two DYT1 patients exhibited complete recovery and were off all drug therapy. The longest follow-up is of 12.5 years in the patient presenting with DYT1 negative primary dystonia. Significant clinical improvement was obtained in 5 patients but with more limited gain on disability scores. Three patients (one PKAN, one Lesch-Nyhan, one secondary dystonia) died during the follow-up. In one patient, DBS was completely ineffective. Mean of stay in intensive care unit was inferior to one month after DBS.

Conclusions: These results demonstrate that GPi DBS can be efficient in patients with status dystonicus. Clinical response is heterogeneous and usually occurs during the first months of DBS. The best and long lasting results are obtained in patients with primary dystonia.

Mo-66

Factors predicting improvement in primary dystonia treated by pallidal deep brain stimulation

L. Cif, X. Vasques, V. Gonzalez, P. Coubes (Montpellier, France)

Objective: To identify the factors predicting the degree of dystonia improvement with deep brain stimulation (DBS).

Background: Despite the beneficial effects of Globus Pallidus internus (GPi) deep brain stimulation (DBS) in patients with primary generalized dystonia (PGD), the degree of improvement varies from one patient to another.

Methods: We examined the effects of clinical (gender, DYT1 status, age at surgery, pre-operative assessment, age at onset) anatomical (volume of the GPi) and electrical variables (voltage, current, impedance, stimulated volume by the electric field using a stereotactic model of DBS) on the postoperative Burke-Fahn-Marsden Dystonia rating scale (BFMDRS) motor score in order to identify which factors may be predictive of the degree of improvement. We reviewed retrospectively the clinical records of 40 steady-state patients with PGD who had been treated by bilateral GPi lead implantation. The follow-up period was from 2 to 8 years. The correlation between the

electrical parameters (voltage, impedance and current) and the clinical outcome was studied. An analysis of covariance was performed to identify factors predictive of the magnitude of improvement.

Results: The most influential factors according to the model are as follows: the preoperative BFMDRS score ($p<0.0001$); age at surgery ($p<0.0001$); the right GPi volume ($p=0.002$); the left stimulated GPi volume ($p=0.005$). No significant correlation was found between the electrical parameters used and the mean motor scores in steady state.

Conclusions: By using this analysis of covariance, it would be possible to predict the postoperative motor score of the patients. However, other variables studied in a prospective manner (e.g. electrode position within the target) could represent predictors of the clinical outcome.

Mo-67

Cerebellar vermis hypoplasia in a case of Joubert syndrome associated with cervical dystonia

S.M. Cinar, S. Bilge, E.D. Polat, O. Akdemir, A. Yildirim (Istanbul, Beyoglu, Turkey)

Objective: We present clinical and radiologic findings a 27-year-old woman a case of Joubert syndrome associated with cervical dystonia.

Background: Joubert syndrome is a rare autosomol recessive disorder whose main characteristic imaging features are elongation and thinning of the pontomesencephalic junction, thickening of the superior cerebellar peduncles, aplasia or hypoplasia of the vermis and incomplete fusion of the halves of the vermis, creating a sagittal vermic cleft.

Methods: Our case had cervical dystonia since three years old, ataxia, motor delay, and cognitive impairment, diagnosed as cerebral palsy. Neurological examination revealed ataxia, intention tremor, dysarthri, cervical dystonia and a wide-based, shuffling gait.

Results: Magnetic resonance imaging showed vermian hyposplasia, consistent with Joubert syndrome. MRI scan of the brain were revealed dilatation of the fourth ventricle. CT and MRI showed hypoplasia of the cerebellar vermis. Cerebellar atrophy was established by cranial MRI. A renal cyst was revealed by ultrasound.

Conclusions: This case demonstrates that a patient with Joubert syndrome may survive into adulthood and present as a chronic neurologic disorder with cervical dystonia.

Mo-68

Deep brain stimulation for dystonia: Follow up at Sheba Medical Center

O.S. Cohen, H. Strauss, Z. Nitsan, R. Spiegelmann, S. Hassin-Baer (Ramat-Gan, Israel)

Objective: To present the results of GPi DBS in patients with dystonia at follow up in Sheba Medical Center.

Background: Deep brain stimulation (DBS) of the internal globus pallidus (GPi) has emerged as a useful therapeutic option for patients with intractable dystonia and insufficient response to medical therapy.

Methods: Patients were examined and data was collected from their files. Clinical efficacy of the stimulation was evaluated using the clinical global impression of severity (CGI-S) scale, the clinical global impression of change (CGI-C) scale and the disability subscore of the Burke-Fahn-Marsden Dystonia scale.

Results: Data concerning 13 pts. (9 males; age: 35.5 $\pm$ 12.7 yrs) with dystonia (11 generalized, 1 focal and 1 segmental dystonia), treated with GPi- DBS is presented. The time form surgery to evaluation was 3.4 $\pm$ 1.8 years (range 1-6yrs). The diagnoses were primary generalized dystonia (DYT-1) in 4 pts. Four pts. had tardive dystonia (TD) and 2 dystonia associated with cerebral palsy (CP). One patient had idiopathic oromandibular dystonia, one pantothenate kinase-associated neurodegeneration (PKAN), and one pallidoluisian atrophy (PLA). Three DYT1 pts. and a patient with the focal oromandibular dystonia had moderate to marked improvement. Of the 4 pts. with TD, an initial moderate to marked improvement was seen in 3 pts.but in 2 this favorable response waned off after less than a year. The fourth patient with TD had only a mild improvement. Four pts. (2 with CP, 1 with PKAN and 1 with PLA) had no benefit and the device was either switched off or removed. One DYT1 patient committed suicide 3 months following the operation, prior to optimization of stimulation parameters. For the patient who responded the mean time to optimal response was 7.5 $\pm$ 5.8 weeks. 6/8 patients had monopolar stimulation and 2 double monopolar in at least one contact. The mean stimulation parameters were: Amp. 3.2 $\pm$ 0.7V(range 2.5-4.2V), PW 112 $\pm$ 43 ms (range 60-210ms) and frequency 135 $\pm$ 17 Hz (range120 to 180Hz).

Conclusions: Our data reinforce previous reports that GPi DBS is a good treatment for certain types of dystonia mainly hereditary-familial generalized dystonia and idiopathic dystonia. Pts. with multisystem neurodegeneration or secondary dystonia did not obtain benefit. Pts. with TD may show a marked initial response but may deteriorate later.

Mo-69

Effects of muscle contraction on the efficacy of botulinum toxin treatment in patients with blepharospasm

A. Conte, D. Belvisi, L. Marsili, L. Rocchi, F. Di Stasio, G. Fabbrini, A. Berardelli (Rome, Italy)

Objective: Aim of the present paper is to determine if prolonged electrical stimulation of the injected muscle can increase the efficacy of BonTA treatment in patients with blepharospasm (BS) and assess the safety of BonTA by investigating whether BonTA injection could alter the excitability of blink reflex circuits in the brainstem.

Background: Pharmacological effects of botulinum toxin type A (BonTA) can be increased by muscle activation and by electrical stimulation performed immediately after the injection of BonTA and a study conducted in animals has demonstrated that BonTA is transcytosed to the afferent neurons in the brainstem.

Methods: Thirteen patients with BS were treated with injection of BonTA (Botox) in the orbicularis oculi muscle. In 7 patients, direct electrical stimulation of the orbicularis oculi muscle on one side was delivered for 30 minutes (4hz frequency) immediately after BonTA injection and in 6 patients stimulation was delivered for 60 minutes. Blink reflex recovery cycle was studied by paired electrical shocks to the supraorbital nerve at interstimulus intervals of 250 and 500 ms. Compound muscle action potential (CMAP) of the orbicularis oculi was measured by surface EMG after stimulation of the facial nerve. Clinical and neurophysiological assessment was performed before (T0) and 2 weeks (T1) after the injection of BonTA. CMAP amplitude, blink reflex recovery cycle at T0 and T1 were compared between the stimulated and the non-stimulated orbicularis oculi muscle.

Results: ANOVA showed that cMAP amplitude significantly decreased at T1 but did not differ between stimulated and non-stimulated orbicularis oculi in both groups of patients. BontA injection left the blink reflex recovery cycle unchanged in both groups regardless from the stimulated and non-stimulated side.

Conclusions: In patients with BS, one hour muscle activation performed immediately after BontA injection does not increase the efficacy of BontA. The observation that BontA injection does not alter the excitability of brainstem interneurons tested with the blink reflex recovery cycle suggests that in humans BontA injection does not produce functional changes at the level of the brainstem.

Mo-70

Botulinum toxin type B (BoNT-B) effects on pain associated with cervical dystonia: Results of placebo- and comparator-controlled studies

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Objective: The objective of this study is to evaluate the effect of BoNT-B on pain associated with CD using TWSTRS-Pain scale (TWSTRS-PS).

Background: Neck pain is reported to occur in 75% of cervical dystonia (CD) patients and contributes significantly to disability.

Methods: Response rates (RRs) and mean improvements (MIs: baseline minus endpoint) on TWSTRS-PS from two pivotal, placebo-controlled studies (AN072-301 and AN072-302) and one comparator-controlled study with non-inferiority design (AN072-402) were reviewed. AN072-301 (N=109) enrolled botulinum toxin type-A (BoNT-A) responsive subjects randomized to placebo (36), BoNT-B 5,000U (36) or 10,000U (37) group; AN072-302 (N=77) BoNT-A resistant subjects to placebo (38) or BoNT-B 10,000U (39) group; AN072-042 (N=111) BoNT naïve subjects to BoNT-A 150U (55) or BoNT-B 10,000U (56) group. Responders were defined as >20% improvement from baseline at Week 4 in TWSTRS-PS.

Results: In AN072-301, RR differences at Week 4 were -43% (95% CI: -64%, -22%) for placebo vs. BoNT-B 5,000U, and -36% (95% CI: -57%, -14%) for placebo vs. BoNT-B 10,000U. MI differences were -3.2 (-4.9, -1.4) for the former, and -3.8 (-5.8, -1.9) for the latter. In AN072-302, RR and MI differences for placebo vs. BoNT 10,000U were -30% (-50%, -10%) and -3.5 (-5.0, -2.0), respectively. Pooling data from AN072-301/302, RR and MI differences for placebo vs. BoNT 10,000U were -34% (-49%, -19%) and -3.6 (-4.8, -2.4), respectively. In AN072-402 (per-protocol-population), RR and MI differences for BoNT-A 150U (n=47) vs. BoNT-B 10,000U (n=46) were -23% (-42%, -3%) and -0.8 (-2.0, 0.4), respectively.

Conclusions: At Week 4 post injection, subjects treated with BoNT-B 5,000U to 10,000U in placebo-controlled studies were significantly more likely to meet responder criteria and showed significantly larger MI than those treated with placebo. In the comparator study, toxin-naïve subjects treated with BoNT-B 10,000U demonstrated a statistically significantly higher RR and a numerically larger MI than those treated with BoNT-A 150U.

Mo-71

Clinical and epidemiolgic profile of dystonia in El Salvador: 8 months of pursuit

E.A. Cornejo-Valse, E.P. Siliézar-Pineda, H. Orrego-Castellanos, M. Rubio (Delegacion Tlalpan, Ciudad de Mex, Mexico)

Objective: To describe (1) epidemiological characteristics, (2) clinical profile and (3) therapeutic effect, quantified in The Fahn-Marsden Scale (BFM) and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) of patients with dystonia.

Background: At the moment there aren't studies describing epidemiological or clinical profile of dystonias in the regíon of Central America.

Methods: Cross-sectional case series of patients evaluated at Salvadorean third level reference hospital for consider the use of botulinum neurotoxin (BoNT), from March 1st to October 31st 2008 period. Patients with complete laboratory investigation, electromyography and brain MRI, evaluated previously in a unit of Abnormal Movements. Continuous variables were described with mean and standard deviation. Discrete variables were described with absolute and relative frequencies. BFM and TWSTRS scales were applied by the same Neurologist in those patients who recieved BoNT at 0 and one month of treatment, and were compared with T-student.

Results: 46 patients were included, 29 (63%) female; mean age 56 ± 14.3 years (range 25-83). Idiopatic Hemifacial Spasm was the more frequent Dystonia 26 (56%); followed by Hemifacial Postparalitic Spasm and Blepharospasm 6 (13%) for each one; and Cervical Dystonia 4(8%). 31 patients recibed BoNT, and were applied BFM and TWSTRS Scales. The mean reduction in BMF scale was 15.4 ± 4.69 SD ($p < 0.01$) for dystonias with facial involment; for Cervical Dystonia there was a mean reduction of 17.9 ± 12 SD (p 0.59).

Conclusions: (1)Dystonias were more frecuent in females middle aged; (2)facial involvement was more frequent. (3) All patient had improvement of quantitative parameters with BoNT.

Mo-72

Decreased functional interactions in the motor network of patients with focal hand dystonia using fMRI

D. Coynel, M. Vidailhet, C. Delmaire, G. Marrelec, V. Perlbarg, A. Krainik, J. Doyon, S. Lehéricy, H. Benali (Paris, France)

Objective: We tested the hypothesis that functional interactions were altered in the motor network in patients with focal hand dystonia, using a measure of hierarchical integration (HI) to quantify functional interactions within networks [Marrelec et al, Med Im Anal, 2008].

Background: In focal hand dystonia, dysfunction of the sensorimotor system has been observed using functional imaging: decreased or increased activations in the sensorimotor and premotor cortex, and disorganized somatotopic representation of body parts in the putamen.

Methods: 14 right-handed patients with unilateral writer's cramp were compared with 13 right-handed healthy volunteers using fMRI at 1.5T. Subjects performed flexion/extension of right and left fingers and toes as well as lip contraction [Delmaire et al, Neurology, 2005]. Spatial Independent Component Analysis was used to identify task-related motor network maps from which we defined bilateral ROIs (SMA, M1, putamen, and thalamus). HI was used to quantify functional interactions within the motor network as well as within and between hemispheres for each experimental condition. As a control condition, we computed HI between regions of the visual network.

Results: In controls, there was no significant difference in HI in the motor network for hand, lip or foot movements. In patients, total and inter-hemispheric HI were significantly lower than in controls when performing hand and foot movements. Contralateral intrahemispheric HI significantly decreased in patients for both hand movements. The decrease was specific to limb movements as no significant difference was found between patients and controls for lip movements and within the visual network. Note that no difference between patients and controls was found in the motor network with SPM's GLM.

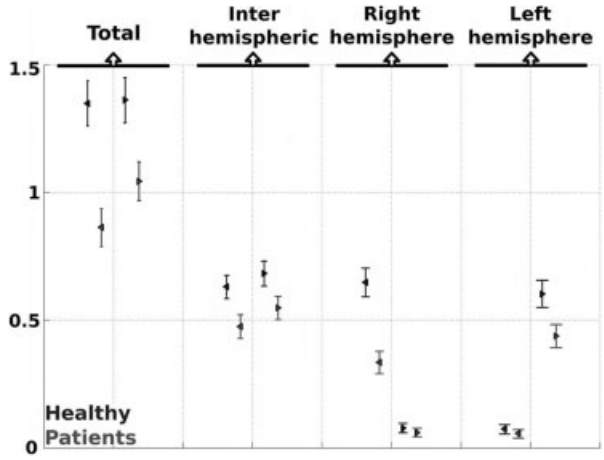

FIG. 1 (Mo-72). Integration values for Right (right-pointing arrows) and Left (left-pointing arrows) hand movements, for healthy volunteers and dystonic patients.

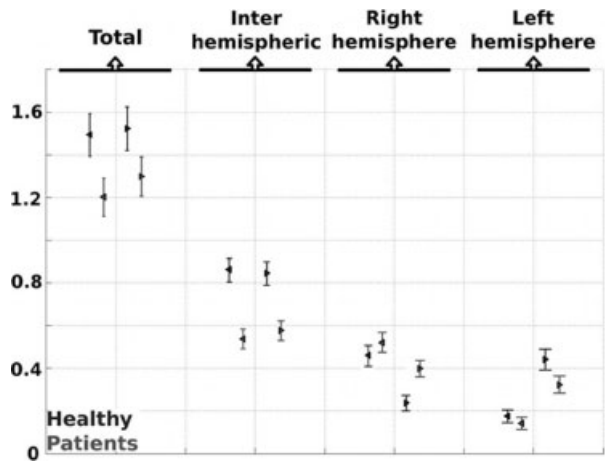

FIG. 2 (Mo-72). Integration values for Right (right-pointing arrows) and Left (left-pointing arrows) foot movements, for healthy volunteers and dystonic patients.

Conclusions: In patients, total, inter and contralateral hemispheric integration for movements of both affected and non affected hands were decreased. This suggests that information exchanges may be altered within the cortico/sub-cortical motor network of patients with writer's cramp. These data fit well with previous functional imaging studies that have demonstrated deficient activation of the primary motor and premotor cortex within the affected and non affect limb representation areas.

Mo-73

Secondary dopamine and serotonine deficiencies in children with movement disorders

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Objective: We aimed to describe secondary neurotransmitter (NT) abnormalities in pediatric patients with movement disorders (MD).

Background: MD are frequenly detected among children with neurologic disorders (ND), regardless of etiology. Primary or secondary dopamine deficiencies in children may cause dopa-responsive dystonia, rigid-akinetic syndrome and encephalopathy. Some evidence also suggests a role for serotoninergic system in the production of MD of basal ganglia origin. Homovanilic (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations in CSF reflect serotonine and dopamine turnover in the CNS.

Methods: NT metabolites in CSF of 191 patients (103 males, 88 females; mean age 3.5 years (SD 4.4y) range 1 month–20y) with ND of diverse etiology were analyzed by reverse phase HPLC with electrochemical detection. Reference values (RV) were established in a comparison population. Biochemical and molecular analysis ruled out a primary defect of NT. Chi-Square test was applied to search for the association between abnormal NT metabolites, age at lumbar punction, type of MD and MRI abnormalities.

Results: Ninety children (47%) showed MD (dystonia 37, tremor 14, chorea 11, myoclonus 14, rigid akinetic syndrome 2, complex dyskinesias 12). Basal ganglia lesions on MRI (23/170) were more frequently dectected in children with MD, especially in those with chorea and dystonia (χ^2 8.8, p=0.003). HVA and HIAA concentrations below our RV were detected in 35 and 42 children, respectively. Dopamine deficiency was detected in all age groups, whereas HIAA deficiency was more frequent in children above one year age (χ^2 5.6, p=0.018). In infants, HVA deficiency was associated with MD, especially choreo-dystonia ($\chi^2$4.6, p=0.031), and basal ganglia abnormalities (χ^2 9.9, p=0.002). These infants were mostly affected by genetic encephalopaties.

Conclusions: Secondary abnormalities of biogenic amines are detected in 20% of children with MD. Infants with genetic encephalopaties manifesting choreo-dystonia and basal ganglia abnormalities are at high risk of developing secondary dopamine deficiency. Treatment of these patients with levodopa might be considered in order to improve their motor disturbances.

Mo-399

To report two patients with Parkinson's disease and severe lateral trunk flexion with varying response to treatment

P. Agarwal, A.F. Griffith, M. Borromeo-Wesner (Kirkland, Washington)

Objective: To report treatment outcomes of two patients with Parkinson's disease and lateral flexion of spine.

Background: Lateral flexion of the spine may be seen in Parkinson's disease. The clinical characteristics of lateral flexion in Parkinson's disease vary. Clinically this has been classified into two types, the chronic and subchronic types. The chronic type of lateral flexion in PD appears subclinically and worsens, with progression of the disease. Flexion is towards the more affected side. The subchronic type of lateral flexion in PD develops subacutely and worsens rapidly over several months.

Methods: Retrospective chart review revealed two patients with Parkinson's disease and lateral flexion of spine.

Results: 65 year old female patient with Parkinson's disease developed after 6 years severe backpain and inability to stand straight. Over the months this was slowly progressive. At time of examination when she stood up she was stooped forward but on lying down she could completely straighten her back. On examination she had kyphoscoliosis of the spine. Though her other PD symptoms were levodopa responsive, her kyphoscoliosis was unresponsive to levodopa, amantadine, baclofen and muscle relaxants. She had modest posture improvement and significant pain relief with botulinum toxin injections to her paraspinal muscles. 73 year old patient with Parkinson's disease, diagnosed eight years ago, avid hiker and outdoorsman, who developed axial dystonia with acute worsening during a hike, associated with left lower back pain and bruising. He was able to sit upright, but on walking he leaned progressively to the right. The axial dystonia was levodopa-unresponsive. Physical therapy and a series of botulinum toxin injections to paraspinal muscles were ineffective. He underwent bilateral GPi DBS, with some improvement in motor symptoms after second programming session, but minimal change in posture. Programming is ongoing at this point.

Conclusions: Lateral flexion of the spine can be a severe complication of Parkinson's disease, significantly affecting quality of life. Although patients may respond to levodopa, botulinum toxin injections, and deep brain stimulation, others may be poorly responsive. Further research is needed to elucidate what clinical features may best respond to therapies.

Mo-400

Paroxymal nonkinesigenic dyskinesia: A case report

M.H. Sorgun, S. Erdogan, C. Yucesan, N. Mutluer, C.M. Akbostanci (Ankara, Turkey)

Objective: We describe a woman who had paroxysmal nonkinesigenic dyskinesia with an infarct in the nucleus lentiformis and caudatus.

Background: Paroxysmal nonkinesigenic dyskinesia (PNKD) is a rare disorder characterized by episodic hyperkinetic movement attacks. PNKD is usually inherited as an autosomal dominant trait. The most common cause of secondary PNKD is multiple sclerosis.

However, PKND has been reported in hypoglisemia, thyrotoxicosis, hypoparatroidism, inherited biopterin syntehesis defect, head injury.

Methods: In this report, we describe a woman with 45-year history of short-lasting paroxysmal nonkinesigenic dyskinesia. The episodes occurred 5 to 50 times per day, lasted from 10 to 30 minutes, and were not suppressed with sleep.

Results: EEG was normal. Neuroimaging studies showed an infarct in the nucleus lentiformis and caudatus. She have factor V Leiden mutation and responded well to carbamazepine (800 mg/d).

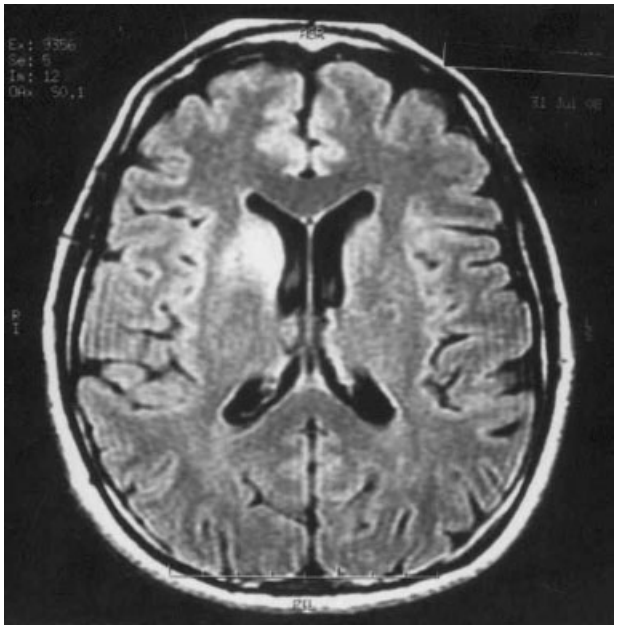

FIG. 1 (Mo-400).

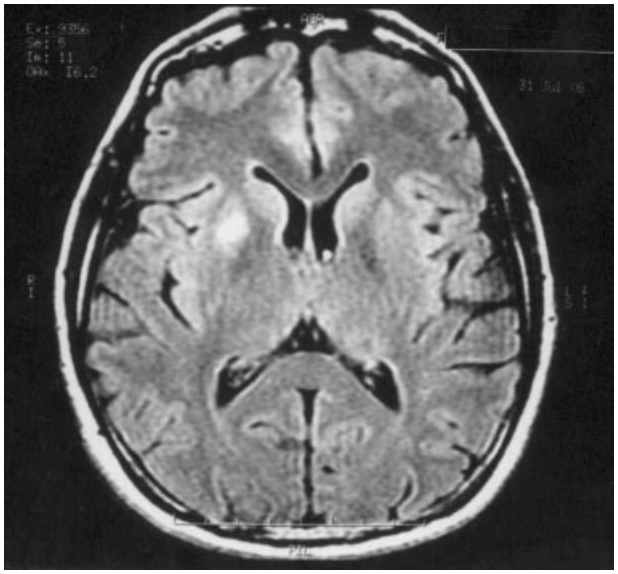

FIG. 2 (Mo-400).

Conclusions: This case shows that ischemic stroke in the nucleus lentiformis and caudatus may have a causal relationship with PNKD. In other reports, neuroimaging studies showed lesions in the basal ganglia.

Mo-401

Dystonic features in adult sporadic tremor dominant Parkinson's disease: A case series

N.N.P.S. Bajaj, V.K. Gontu, J. Birchall, D.G. Grosset, A.J. Lees (Nottingham, United Kingdom)

Objective: To study the presence of dystonia in adult onset, sporadic PD in the dopaminergic drug naïve state.

Background: Dystonia and parkinsonism can co-exist in both genetic and acquired dystonic syndromes. Genetic dystonia-parkinsonism is seen in X-linked dystonia-parkinsonism (Lubag)(DYT3), Dopa responsive dystonia (DRD- Segawa's syndrome)(DYT5), and Rapid onset dystonia-parkinonism (DYT12). Acquired dystonic syndromes can also feature parkinsonism e.g. neuroacanthocytosis, Hallervorden-Spatz, Fahr's disease, Mcleod's syndrome. FP-CIT scans in genetic forms of dystonia are generally normal. Dystonia may also be a feature of idiopathic or genetic Parkinson's disease (PD), the latter seen in parkin or PINK1 genetic variants, usually of childhood onset. In adult onset sporadic PD, dystonia is usually attributed to dopaminergic drug therapy. The occurrence of dystonic features in tremor dominant PD (TDPD) has particular diagnostic implications for differentiating these patients from patients with dystonic tremor where parkinsonian features can co-exist.

Methods: Video analysis of a case series of TDPD patients not previously exposed to dopaminergic therapy where dystonic features were noted from the outset. Patients were recruited prospectively as part of a study on patients featuring postural tremor with parkinsonism. Diagnosis of TDPD was based in all patients on FP-CIT scan, subsequent response to dopaminergic therapy and long term follow up.

Results: 10 cases of adult onset, drug naïve PD patients with dystonic features are described. The diagnosis of PD was made in all cases on the basis of an abnormal FP-CIT scan, appropriate subsequent response to dopaminergic therapy and long term follow up over an average period of 18.3 months (SD 15.6) Dystonic features notes in this series included dystonic posturing of limbs (4), torticollis (1) and retrocollis (1) and thumb hyperextension (4). Average age of onset was 64.8 yrs (SD 7.3).

Conclusions: Dystonic features can be seen in adult onset, sporadic TDPD in the dopa naïve state. This can make differentiation from dystonic tremor difficult and may limit the specificity of dystonic features as a differentiating sign between dystonic tremor and TDPD patients. Whether dystonia in idiopathic PD patients defines a further subset of PD remains to be determined.

Mo-402

Can handwriting distinguish dystonic pseudoparkinsonism from Parkinson's disease?

N.P.S. Bajaj, V.K. Gontu, J. Birchall, J. Patterson, D.G. Grosset, A.J. Lees (Nottingham, United Kingdom)

Objective: To distinguish dystonic pseudoparkinsonism from Parkinson's disease using handwriting samples.

Background: Patients with dystonic tremor are one of the causes of SWEDD (subjects with scans without evidence of dopaminergic deficit). Differentiating these cases clinically from PD can be challenging. Micrographia is a well reported feature of PD. Dystonic tremor to date has not been associated with any particular handwriting pattern.

Methods: Handwriting samples (Archimedes spiral, line drawing and standard sentence) were collected prospectively as part of a longer term study on the differential assessment of tremulous patients with parkinsonism. All of these patients had a working clinical diag-

nosis based on FP-CIT scan, long term clinical follow-up and response to dopaminergic agents. The handwriting samples of 8 tremor dominant PD (TDPD) and 20 dystonic SWEDD patients were assessed by three clinical reviewers blinded to the operational diagnosis and to any historical information on the patients. Reviewers were asked to give a diagnosis of PD, dystonic tremor, essential tremor or other on the handwriting samples.

Results: Of the 8 known TDPD patients, micrographia was identified by all three reviewers in 1 case, by two reviewers in 2 cases and by one reviewer only in 2 cases. 3 remaining cases of TDPD were not thought to have micrographia by any of the reviewers. False negative and positive rates for the diagnosis of PD based on micrographia were calculated for each reviewer and then averaged to determine an overall specificity and sensitivity for micrographia as a marker for PD in this study. Eight of the 20 dystonic tremor cases (40%) were noted to have large lettered, jerky, "childish" handwriting.

Table (Mo-402). Overall analysis from 3 reviewers

	False Negatives	False Positives	Sensitivity	Specificity
Reviewer 1	62.5	35	37.5	65
Reviewer 2	37.5	55	62.5	40
Reviewer 3	87.5	25	12.5	75
Average	62.5	38.3	37.5	63.3

Conclusions: In this study, micrographia as a means of diagnosing PD on a blinded handwriting sample showed a specificity of 63.3% and a sensitivity of 37.5%. The finding of large amplitude, childish handwriting in the dystonic tremor cases is worthy of further study.

Mo-403

Overall clinical efficacy and overall tolerability of NT 201; botulinum neurotoxin free from complexing proteins)

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Objective: Assessment of the overall clinical efficacy and tolerability of NT 201; Merz Pharmaceuticals, Germany). Additionally, the safety after the introduction of NT 201 into the European, Middle and Latin American markets is evaluated.

Background: NT 201 is a botulinum neurotoxin type A free from complexing proteins. NT 201 has not been associated with formation of neutralizing antibodies in animal models in contrast to another commercially available product*.

Methods: Efficacy in focal dystonia was analyzed on the pooled data from 2 pivotal clinical trials in blepharospasm and cervical dystonia (343 NT 201 patients; 340 BTXCo* patients) and 1 post-stroke spasticity trial (73 NT 201 patients and 75 placebo patients). For the safety analyses, 6 clinical trials (blepharospasm, cervical dystonia, and upper limb spasticity) have been included (n=539 NT 201, n=442 BTXCo and n=75 placebo subjects). For the post-launch evaluation spontaneously reported adverse events were analyzed.

Results: In the randomized, active-controlled, double-blind studies in focal dystonia NT 201 and one other Botulinum toxin (BTXCo) have been used with a dose ratio of 1:1. The results demonstrate equivalent efficacy between the NT 201 and BTXCo. Onset, waning, and duration of effect were comparable. These findings have been confirmed by the Physician's Global Impression of Efficacy: 70.6% of BTXCo patients and 71.8% of the NT 201 patients were rated as "good" or "very good". Additionally, in the placebo-controlled spasticity trial 62% of the caregivers rated the efficacy as good or very good compared to placebo (33%). 26.7% of patients in the NT 201 group, 26.0% in the BTXCo group, and 22.7% in the placebo group reported an adverse event. There were no clinically relevant differences between the two active treatment groups in the focal dystonia trials and between NT 201 and placebo in the post-stroke spasticity trial concerning safety aspects. All adverse reactions were either already known and/or were considered by the physician unlikely to be related to NT 201. More than 67,000 patients have been treated so far and no new safety concerns have been reported.

Conclusions: These analyses demonstrate that NT 201 is efficacious and well-tolerated for the treatment of focal dystonia and post-stroke spasticity. * BTXCo (Allergan, USA).

Mo-404

The thalamus revisited – A suitable target for deep brain stimulation in myoclonus dystonia

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Objective: To evaluate the most effective target by bifocal (pallidal and thalamic) deep brain stimulation (DBS) in a patient with myoclonus dystonia.

Background: The globus pallidus internus (GPi) has been established as the target of choice especially in DBS for primary forms of dystonia. Also, in myoclonus-dystonia the GPi has become the common target, nowadays. However, in earlier studies the nucleus ventralis intermedius thalami (Vim) was shown to be an option, in particular to treat the disabling myoclonic jerks.

Methods: A 34-year-old woman suffered since four years of myoclonic jerks involving the head and the upper extremities. She also presented with cervical dystonia and dystonic movements of both arms. She was diagnosed having segmental myoclonus-dystonia. Conservative treatment with propanolol, tiapridex, dopamine, trihexyphenidyl, cabergolin and clonazepam was uneffective especially for the myoclonic jerks. Also botulinum toxin injections did not show beneficial effects. Therefore, she was scheduled to undergo bifocal CT-stereotacic implantation of quadripolar DBS electrodes (3387, Medtronic) into the posteroventro lateral GPi and the Vim under local anaesthesia. The pallidal target was refined by intraoperative microelectrode recordings. The preoperative BFM motor and disability scores were 15 and 7, respectively.

Results: There were no surgically related complications. Postoperatively, extensive testing for alternative stimulation via the four externalized electrodes was performed. While on thalamic stimulation the patient experienced clearly a more pronounced effect for the myoclonic symptoms than with GPi stimulation. All four electrodes were connected via a y-switch to two IPGs (Soletra), while thalamic stimulation was switched on for chronic stimulation. In the follow-up there was an improvement in the BFM motor score by 60% at 6 months. In particular, the myoclonic jerks abated completely. The BFM disability score was improved by 67% at 6 months follow-up.

Conclusions: Although the GPi has been addressed as the target of choice for dystonia, thalamic Vim should not be forgotten. It may provide a more pronounced effect in case of refractory myoclonus-dystonia. Bifocal deep brain stimulation is an elegant method to determine the most beneficial target in those patients.

Mo-405

SPECT with dopamine transporter-specific radiotracer ^{123}I-FP-CIT in benign essential blepharospasm

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Objective: To explore by ^{123}I-FP-CIT SPECT the possibility of a hypodopaminergic status in BSP.

Background: Several lines of evidence raised the possibility that the nigro-striatal dopamine system contributes to the pathophysiology of primary BSP. In fact, BSP patients show an enhanced excitability of the trigeminal blink reflex circuit which is under dopaminergic control. Furthermore, in an animal model partial nigro-striatal dopamine depletion and weakening of the orbicularis oculi muscle may act synergistically on trigeminal sensory-motor blink reflex circuits initiating BSP.

Methods: Five consecutive patients suffering from primary BSP displaying normal MRI scan and botulinum-toxin were recruited, along with 8 PD patients and 11 age-matched ET patients. A standard protocol for ^{123}I-FP-cit SPECT imaging was adopted.

Results: As compared to ET, BSP patients showed non significant average 5% Putamen/Occipital reduction (range 0 to -11%) and 3% Caudate/Occipital increase (range +10 to -6%), whereas significant 47% Putamen/Occipital and 42% Caudate/Occipital decreases were found on average in PD patients. The side to side differences of Putamen/Occipital ratio were lower in ET and BSP groups than in PD patients (0.28 ± 0.15 vs. 0.3 ± 0.2 vs. 0.49 ± 0.17; PD different from the other groups, $p<0.05$). Similar findings were obtained when assessing Caudate/Occipital uptake.

Conclusions: we found that DAT level was normal in the BSP patients reported in the present study. These findings do not support a hypodopaminergic dysfunction involving presynaptic mechanisms in primary BSP. However, we cannot fully exclude the possibility that our patients could develop striatal dopamine decline and PD symptoms in the future.

Mo-406

Occupational focal dystonia and thalamic injury

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Objective: A thalamic injury can produce an occupational focal dystonia related to a very specific task.

Background: Several authors have reviewed the involuntary movements induced by thalamic injuries

Methods: We report a 20 years old left-handed man, whom, several months before the consultation, develops an abnormal position with forced extension of left wrist and external rotation of the hand, when painting and performing reiterative flexo-extension movements of the wrist. The exploration only shows a mild claudication of superior left extremity when Barré maneuver is performed.

Results: In the cranial RM appears a 14 mm image in right thalamus, that shows a heterogeneous intensity in all sequences performed, with a loss of signal in sequences T2 that suggests a cavernomatous injury.

Conclusions: Several authors have reviewed the involuntary movements induced by thalamic injuries. The present case illustrates the peculiarity of a thalamic injury that produces an occupational focal dystonia related to a very specific task, the repetitive flexo-extension of the wrist when painting. The basal ganglia- thalamus -cortex circuit seems to be the anatomical substrate of dystonia even the physiopathology of his type of movement disorder is not known exactly.

Tu-47

Postural stability in cervical dystonia and the effect of botulinum toxin

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Objective: To determine (1) whether cervical dystonia affects static balance and (2) the effects of botulinum toxin injection on static balance in patients with cervical dystonia.

Background: Cervical dystonia results from involuntary contraction of neck muscles leading to abnormal postures of the head. There are very few studies regarding the relation between cervical dystonia and postural stability, and the effects of botulinum toxin on static balance.

Methods: Nine patients with cervical dystonia and 12 age, sex and weight-matched healthy controls were included in this study. All subjects were evaluated with eyes open, eyes closed, head turn to right, head turn to left, and tandem on a static posturography force platform. Dystonia severity was assessed by TWSTRS scale. Evaluations of the patients were repeated 6 weeks after the injection.

Results: All postural stability measurements of the patienst were higher than the controls but none reached statistical significance with eyes open and eyes closed. Posturographic analysis during tandem test showed that patients with cervical dystonia had statistically higher values in all parameters of static balance ($p<0.001$). When the effects of botulinum toxin injection were evaluated, a significant decrease was found only in all parameters (except lateral sway) of tandem test.

Conclusions: Several previous studies failed to show abnormalities of static posturography in cervical dystonia compared with healthy controls. Although the number of cases in this study are few to draw conclusions, this preliminary data suggests that patients with cervical dystonia display static balance problems, if their area of stance decreases. Another important suggestion is that botulinum toxin injections help them not only with their head-neck posture, but also improve their balance.

Tu-48

Mapping muscle contraction patterns in rotatory cervical dystonia by multiple simultaneous paired intramuscular EMG

R.N. Dille, D.D. Duane (Scottsdale, Arizona)

Objective: To determine in rotatory cervical dystonia (RCD) the pattern of muscle involvement utilizing simultaneous paired intramuscular EMG.

Methods: Retrospective analysis of 57 patient charts (Arizona Dystonia Institute) evaluated between March 2002 and December 2008 undergoing dual channel EMG (TECA Neurostar, concentric needle electrodes) of at least 6 pairs of paracervical muscles (Sternocleidomastoid- SCM, Scalene complex -Scal, Splenius Capitis– Sp Cap, Oblique Capitis Inferior- OCI, Trapezius- Trap, Levator Scapulae- Lev Scap). Excluded were patients with prior cervical spine or nerve root surgery, anterocollis, > mild retrocollis, or only slight rotational torticollis. Laterocollis was recorded as ipsi- or contralateral to direction of rotation. Classification was made by Toronto Western Spasmodic Torticollis Scale (TWSTRS) and photo/video imaging. TWSTRS and EMGs were conducted by the same examiner (DDD) with patients in a seated upright posture, non-resistant to dystonic contraction.

Results: 26 patients met the above criteria: 20 female, 6 male; mean age 63 years (range 35-84); mean duration of symptoms 18 years (range 2-39). Laterocollis ipsilateral to RCD, N=17, 15 female; contralateral to RCD, N=9, 5 female. Mean TWSTRS severity 22/35 (range 15-30); mean TWSTRS pain 13/20 (range 0–20). **Muscle pattern in RCD:** EMG scores were normalized for each patient and expressed as a percentage for each muscle. R/L muscles are given as ipsi- or contralateral to direction of rotation. Muscles contributing >10% of total muscle activity: **Contralateral Laterocollis:** Ipsi– Sp Cap & OCI, Contra- SCM, Trap, Sp Cap, +/- Scal; additionally active, Ipsi– Trap N=5, Lev scap N=2; Contra– OCI N=5. **Ipsilateral Laterocollis:** Ipsi- Sp Cap, OCI, Scal; Contra- Sp Cap, +/- SCM; additionally active, Ipsi- Trap N=7, SCM N=6; Contra- OCI & Trap N=5.

Conclusions: Muscle involvement in RCD is always bilateral, involves at least 5 muscles, and although similarity in patterns occur, variability between patients is common and influenced in part by the direction of laterocollis. Antecedent knowledge of the pattern of muscle involvement in individual patients should initially influence amount/site of botulinum toxin injection or may optimize treatment outcomes for otherwise suboptimal responders.

Tu-49

Impaired somatosensory activation during tactile stimulation in orofacial dystonia

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Objective: To investigate whether central sensory processing is abnormal in orofacial dystonia despite the absence of a clinically apparent sensory deficit.

Background: The pathophysiology of focal dystonia is not well known. In addition to motor dysfunction, clinical, electrophysiological and imaging studies indicated sensory abnormalities in this disorder. A previous fMRI report revealed overactivation of somatosensory areas during a motor task in patients with orofacial dystonia. However, it is not clear whether abnormal somatosensory activation is related to motor execution or an independent finding in these patients.

Methods: A new MR-compatible stimulation device randomly applied punctate tactile stimuli (von Frey-filaments of normalized intensity) to the forehead, upper lip and hand in 16 patients with orofacial dystonia and 15 healthy controls during event-related fMRI. To study the effects of botulinum toxin (BTX) treatment, patients were scanned before and after BTX therapy.

Results: Patients with orofacial dystonia revealed a deficient activation of primary and secondary somatosensory areas during stimulation of the face and the right hand compared to controls. BTX treatment did not modulate somatosensory dysfunction but reduced the activation of the contralateral putamen and the bilateral thalamus during forehead stimulation.

Conclusions: Deficient somatosensory activation of affected as well as clinically unaffected areas indicates an intrinsic abnormality of the somatosensory cortex in orofacial dystonia. The level of basal ganglia activation during tactile stimulation was modulated by BTX treatment suggesting a defective sensory gating function of the basal ganglia. These results emphasize the role of the somatosensory system in the pathophysiology of orofacial dystonia.

Tu-50

Assessment of outcome following surgical treatment of paediatric dystonia with deep brain stimulation

P. Epaliyanage, J. Lin, R. Selway (London, United Kingdom)

Objective: To assess the surgical outcome of paediatric deep brain stimulation insertion for dystonia.

Background: Surgical outcome is often difficult to assess reliably. Many approaches are subjective and assessed by the surgeons themselves. Objective scoring systems may not address the issues from the patients' perspective. Children with severe dystonia provide a particularly challenging group in this respect. Multiple disabilities, communication difficulties and inter-patient symptom variability make single scoring system hard to use for qualitative data collection.

Methods: Consecutive patients with severe dystonia underwent comprehensive assessment before insertion of a pallidal deep brain stimulators. Before surgery a variety of assessments were tailored to individual patients including a disability and dystonia scale, pain, range of movement, communication, activities of daily living measurements and caregiver priorities. Discussion was documented specifically about family and patient concerns and expectations before agreeing a list of treatment aims and grading their importance. Finally a list of key goals was drawn up with patient and family with outcomes that can be measured.

Results: 30 patients underwent assessment, agreement of surgical goals and then surgery. The global dystonia scale (BFMDRS) improved in all patients but use of the scale was hampered by disabilities which exceeded the maximum score. Goals in each patient varied widely but recurring themes included reduction in pain, improved sleep and improved ability to transfer and be seated in a wheelchair, most of which are not considered directly in BFMDRS.

Conclusions: In complex conditions with variable disability, single outcome measuring tools are often inappropriate to address patient, carer and physician perspectives. Tailoring of outcome measures to the individual and agreeing goals in advance of surgery allows rigorous quality measurement. However such an approach is time consuming and requires meticulous multidisciplinary setup.

Tu-51

Speech disturbance in neurometabolic hyperkinetic disorder

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Objective: To refine the description of the speech disorders (SD) and to propose approaches for speech rehabilitation in pediatric and adult patients with speech disturbances due to a neurometabolic hyperkinetic disorder.

Background: Speech disturbance is a frequent and disabling feature in most patients with neurometabolic hyperkinetic disorder. It is often an early manifestation and remains prominent throughout the disease course. However, the clinical phenomenology of SD in this setting is poorly characterized and there are no guidelines for the rehabilitation of these patients.

Methods: We prospectively enrolled consecutive symptomatic patients seen for speech evaluation with a firm diagnosis of neurometabolic hyperkinetic disorder. Additional inclusion criteria were: i) Age over 3 years ii) French as mother tongue iii) No major cognitive impairment. The patients had a standardized interview, neurological examination and a comprehensive standardized speech examination. SD was evaluated with the Auzou's French adaptation of the Frenchay Dysarthria Assessment developed by Enderby and the Auzou's French adaptation of the apraxia of speech evaluation test of Duffy. Finally, the patients underwent a short non verbal neuropsychological test taking into account their motor and speech disabilities and their fatigability, using Raven Progressive Matrices.

Results: 14 patients were enrolled in the study, including 8 patients with glutaric aciduria type 1, 4 patients with Lesch-Nyhan disease and 4 patients with GM1 gangliosidosis type 3. In all patients, we found a very consistent pattern of complex speech alterations with combined features of hyperkinetic dysarthria and speech apraxia.

Conclusions: The original pattern of SD may be related to the lesion location and age at the time of initial damage, regardless of the metabolic disorders responsible for the disease. The characteristics of SD may then reflect the response of the developing brain to static damage that occurred early in life, rather than being an ongoing disease process. Our findings point to certain approaches for speech rehabilitation in this setting.

Tu-52

Lower limb occupational dystonia in a flamenco dancer

P.J. Garcia Ruiz, V. Sanchez (Madrid, Spain)

Objective: To describe a unique case of lower limb task-specific dystonia in a flamenco dancer.

Background: Task-specific dystonia is frequent among artists who engage in repetitive, highly skilled tasks (musicians). In general, task specific dystonia occurs in upper limb. Lower limb task specific dystonia is extremely rare.

Methods: Case report of a 30 years old lady of Japanese origin without personal or familial history of movement disorders. She moved to Spain several years ago. She was very fond of flamenco and began to practice flamenco many hours every day for several years. She began to note "mistakes' of her right leg while performing "zapateado" (rapid tap dance). She complained of lack of control of her right leg (especially right foot) only in this situation, otherwise she could walk, run and even practice other dances without any problem. First, she noted this difficulty after long sessions of dance, then she began to exhibit problems in "zapateado" just in the beginning of her dance sessions.

Results: VIDEO showed external deviation of her right foot during "zapateado". Rest of physical and neurological exam was normal. Ancillary tests were normal. She was treated with levodopa and benzodiazepines with no response.

Conclusions: This case probably represents a case of task specific dystonia of lower extremity (dancer dystonia).

Tu-53

Objective analysis of the voice in primary focal and segmentaries cranial dystonias (no larynges)

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Objective: We evaluate the voice disorders in patients (p) with primary focal and segmentary cranial dystonias (D).

Background: Since D is a more extensive process than we can clinically observe, we may find phonatory disorders even in asymptomatic p.

Methods: Ten p, 8 women, age 24 to 65 y.o, were included: 2 blepharospasm, 5 cervical D and 3 with D in more than one segment. The D was clinically evaluated by AIMS (Abnormal Involuntary Movement Scale). Program Analysis of Acoustic Signals of Speech (ANAGRAF) was used to get an objective voice analysis. The acoustic measures analyzed were: Fundamental frequency: frequency of vibration of the vocal cords; Jitter: changes in the frequency cycle to cycle of the fundamental frequency; Shimmer: variation of the amplitude cycle to cycle; H/N: Relationship between the energy component of the periodic signal respect to the noise components; Formants and bandwidth: natural resonance frequencies of the supraglottic cavities ordered from low to high. The results were classified by Yanagihara Dysphonia Classification (YDC) in four stages of severity, the stage 0 being normal and stage 4 being formants replaced by noise.

Results: While only 20% of p interviewed referred voice disorders, 100% of them showed alterations in the objective voice evaluation. Eighty percent of p had abnormal Jitter values, 70-100% abnormal values in Formants of the Voice and 90% with out of range H/N. YDC showed 80% of the p in stages1 and 2, 10% in stage 3 and the last 10% in stage 0. In 4 p with cervical D the fiberscopy evidenced a hypomobility of the vocal cords in the presence of hiatus, which was interpreted as secondary to mechanical phenomenon that causes the D in the neck. However, this finding cannot be dismissed as an expression of a dystonic phenomenon in the clinically asymptomatic vocal cords.

Conclusions: These findings suggest that primary focal and segmentary cranial D could have a subclinical disturbance of the voice. These results support the concept that D would be a more spread disorders than clinically observable.

Tu-54

Optimising outcomes following paediatric deep brain stimulation (DBS)

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Objective: To demonstrate the added value of focussed therapeutic intervention in optimising outcomes following DBS.

Background: The need to measure the effect of DBS using functional and participation outcome measures in conjunction with the Burke-Fahn-Marsden Dystonia Rating Scale (BFM) is paramount (Gimeno et al, 2008). This detailed assessment allows therapy intervention to maximise potential change.

Methods: Three illustrative DBS cases are described. Dystonia measured using BFM. Functional measures are described.

Results: Case 1: 11 yo primary dystonia. BFM improved 54-80% over 18 mo. Daily independence skills (ADL) plateaued (CP CHILD personal care improved 62% at 1 year, 60% at 18 months), with mismatch of motor ability & performance. 6 minute timed walk (6MWT) improved 40% with targeted strengthening, despite 12% deterioration in BFM. ADL assessment showed motor planning and organisational difficulties, with active therapy intervention required to optimise outcome. **Case 2:** 17 yo PKAN; BFM reduced 27% over 12 mo. Disability score unchanged (30/30). CP CHILD showed 12% improvement–most change in health section. Neither measure captured important change e.g. Washing/dressing assessment: 50% decrease time and 90% reduction in spasms. Therapy addressed seating and manual handling needs for school, with improvements after DBS allowing hoisting to be re-introduced and 80% increase in school attendance. **Case 3:** 18 yo primary dystonia. Improvement in all parameters following DBS, with 54-83% improvement in BFM over 3 months. Participation limitations greater than expected for level of disability highlighting attitudinal and environmental factors. Functional measures crucial in demonstrating progress, despite self perception of disability. BFM Movement and Disability scores deteriorated (-29%, -40%) with infected device removal at 5 mo. Interestingly, improvement remained in Melbourne right upper limb scores (+7%) and 6MWT (60%), with GMFM unchanged (-3%) despite progression of the dystonia following device removal. This could be due to effect of wires in situ or potential placebo effect.

Conclusions: Sole use of impairment measures (e.g. BFM) is inadequate in complex motor disorders and misrepresents the benefits possible with DBS. Outcomes following DBS are optimised by targeted therapy interventions.

Tu-55

Clinical assessment of patients with acquired hemidystonia: Selecting patients for deep brain stimulation treatment

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Objective: To assess the clinical, neurophysiologic and image studies of patients suffering from hemidystonia in order to identify potential candidates for DBS therapy.

Background: Hemidystonia refers to dystonia affecting unilateral face, arm and leg. The most frequent etiology is stroke, followed by perinatal injury and trauma. Usually dystonia develops after a brain insult with a variable delay ranging from months to years. It has been hypothetised that dystonia was secondary to abnormal reorganisation of motor circuits after the cerebral lesion.

Methods: We describe the clinical records of 10 patients suffering from hemidystonia. Patients underwent MRI, Motor (MEP) and Somatosensory evoked potentials (SEP), SPECT, and DaTscan. When possible patients were studied by functional MRI.

Results: We identified 10 patients (M:F=6:4). Different etiologies were reported: perinatal injury (2 strokes); childhood (<10 yr): stroke(1), cerebral hemorrhage(1), cranial trauma (1), unknown etiology (2). Finally two adults developed post-stroke hemidystonia. All the patients but one had initial reversible hemiparesis. Six patients had dyskinesias. Cerebral MRI showed lesions located in lenticular nucleus (6), unilateral striatum (1), thalamus (5). MEP were often normal; 4/8 patients had abnormal SEP. All patients showed hypoperfusion in SPECT. Dopamine transporter imaging showed reduced putaminal binding: 6 patients. Patients were poorly responsive to pharmacologic treatments, the most efficient being Benzodiazepines. Levodopa was globally non efficient. Four patients have been treated by Pallidal DBS: one of them (hemidystonia/hemiatrophy) has been refractory to Pallidal and afterwards to Thalamic DBS. fMRI of this patient showed bilateral activation of sensorimotor cortex, contralateral premotor, prefrontal, caudate and posterior putamen and ipsilateral cerebellar activation with non-dystonic hand movements. Dystonic hand mouvements activated bilateral asymmetric premotor and prefrontal cortex, without any activation in basal ganglia and cerebellum.

Conclusions: In our series delayed dystonia appeared after early brain injury during childhood, the leading cause being stroke. Presence of dyskinesias, and normal MEPs were the most important clinical features to consider DBS.

Tu-56

Effect of delayed use of reconstituted refrigerated botulinum toxin (BoNT) in hemifacial spasm (HFS) and blepharospasm (BS)

V. Goyal, G. Shukla, S. Singh, M. Behari (New Delhi, India)

Objective: To evaluate effect and adverse events BoNT injected after 7-14 days after reconstitution in patients with HFS and BS.

Background: Economic factor reduces BoNT utility in dystonia in developing countries. At our BoNT toxin clinic, it is common prac-

tice to use reconstituted refrigerated BoNT with in 7-14 days, if could not be utilized on the same day. It is known to be effective in laryngeal dystonia. There is no such report in HFS and BS.

Methods: This retrospective analysis of patients data, who had received reconstituted refrigerated BoNT ink Botulinum Toxin Clinic (of department of neurology, AIIMS, New Delhi, India). As a routine practice reconstituted BoNT if not utilized on the same day, is refrigerated at 2-8 degree Celsius and is used with in 2 weeks period. Effect of the BoNT in the form of onset of effect, efficacy (assessed by subjective global assessment scale, scoring 0-100% of pre-injection state), duration of effect and side effects were recorded. Patients had received Botox (Allergan), Dysport (Epson) and BTX-A (Intas). Dose of dysport was divided by factor of 3 to calculate equivalent dose of Botox.

Results: This study included 44 patients (30 of HFS and 14 of BS). Mean age of patients with BS was 48.92 ± 6.89years and of that of HFS was 47.41± 11.49 years. There were 24 males and 20 females. Mean dose of botulinum toxin injected in HFS was 25.35 ± 7.84IU and in BS was 48.92 ± 6.89 IU. Mean duration of injection since reconstitution was 8.47 ± 3.0 (range 7-14) days. Effect started in 4.31 ± 4.97 (median 3) days and mean benefit was 79.14 ± 18.16 % (> 50% benefit in 88.75% and > 75% benefit in 60.52%), which was same in both HFS and BS. Duration of effect was 15.75 ± 9.31 (median 14) weeks, which was slightly more in patients with HFS. Only minor side effects were observed in total 4 patients. There was no event of any infection at injection site.

Conclusions: This first Indian study to evaluate efficacy of reconstituted refrigerated BoNT injected after 7-14 days in patients with HFS and BS. It has shown effect onset in 3 days, efficacy of about 80% and effect lasting for about 16 weeks. These results are comparable to published effects with freshly diluted BoNT. Randomized control study will prove definite efficacy of delayed injection after reconstitution and refrigeration.

Tu-57

Assessment of the alterations in early & late components of contingent negative variation (CNV) in simple writer's cramp (WC)

C. Goyal, G. Shukla, A. Srivastava, K.K. Deepak, V. Goyal, M. Behari (New Delhi, India)

Objective: To evaluate amplitudes & latencies of early & late components of CNV in patients of simple WC as compared to normal individuals.

Background: CNV represents preparation and voluntary motor control**.** It reflects the neuronal activity necessary for sensorimotor integration. This study evaluates whether the brain activities that prepare movements are primarily disordered in WC.

Methods: CNV was done in 34 right handed patients of simple WC and 31 unrelated, gender matched, healthy individuals. In all the subjects (cases as well as controls), latencies and amplitudes were recorded for early and late components of CNV at Fz, Cz, Pz, C3, C3', C4, and C4' sites at baseline (BL) and after writing (AW).

Results: In this case-control study, the mean age of cases at the time of presentation was 34.78 ± 11.25 years, at onset was 28.86 ± 10.37 years and the mean duration of illness was 5.98 ± 4.07 years. When all the mean latencies, early (L1)as well as late (L2), recorded at BL and AW were compared between cases and controls, it was found that all L1 at BL were less in cases, whereas all L1 recorded AW were more in cases than controls. All L2 including those recorded at BL as well as AW were less in cases as compared to controls except L2 at BL at C3 which was similar in both the groups. When the mean amplitudes at BL and AW were compared in cases and controls, it was noticed that all the mean amplitudes of early (A1) as well as late CNV (A2) recorded AW were smaller in cases at all sites compared to BL values except A1 being more AW at Fz,A2 more at BL & AW at Fz,A2 AW more at C3',A2 more at BL & AW at C4, A1 & A2 more at BL & AW at C4' in cases. However,it was found that the difference of amplitudes for A2 at C4 AW between cases and controls ($p=.049$) & A2 at C4' AW between cases and controls ($p=.03$) could only reach unto statistical significance($p<.05$).

Conclusions: This study reveals significant laterality of the late CNV seen with the right-hand task in patients with WC pointing towards functional abnormality of motor cortices. CNV measures neuronal activity within a thalamo-cortical-striatal network and the cortico basal ganglia-thalamocortical circuit could play a significant role in the generation of the late CNV, hence this study shows involvement of basal ganglia circuits in pathophysiology of WC.

Tu-58

Frequency-specific effects of deep brain stimulation on hand motor function in patients with cervical dystonia

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Objective: To explore whether externally imposed synchronization through direct stimulation of the globus pallidus internus has frequency selective effects on motor performance in a simple unimanual tapping task in patients with cervical dystonia (CD).

Background: Deep brain stimulation (DBS) is a very effective treatment for patients with medically intractable CD. However, mild worsening of motor function in previously non-affected body parts has been reported (Ostrem et al. 2007). Further, slowing in tapping rate has been found in PD patients with relatively preserved baseline function during 20 Hz stimulation and HFS (Eusebio et al. 2007).

Methods: Tapping rates were recorded from 14 sides in 7 patients (2 male, mean age 60.3 yrs, SD 7.8) who underwent pallidal DBS for medically intractable CD. Tapping was performed for 30 s duration without DBS and during stimulation at 20 Hz, 50 Hz and high frequency (≥130 Hz, HFS). Repeated-measures ANOVA with the factor FREQUENCY (4 levels) was calculated and post-hoc paired t-tests were performed for absolute tapping rates.

Results: Tapping rate was significantly modulated by DBS and this effect was frequency selective (ANOVA main effect for FREQUENCY, $F=10.58$ [3;11], $p=0.001$). A significant slowing in mean tapping rate occurred during HFS (110.4 taps, SD 21.9) compared to OFF stimulation (119.1 taps, SD 18.8, $p=0.019$) with a mean decrease of 7.3 %. ($p=0.019$). In contrast, motor performance improved with 20 Hz stimulation (123.7 taps, SD 19.4, $p=0.015$) compared to OFF stimulation leading to a mean increase in tapping rate of 4 % ($p=0.035$).

Conclusions: Here we showed that motor performance in previously non-affected body parts can deteriorate during HFS in CD patients, possibly by removing any residual physiological neuronal activity in the cortex-basal ganglia motor loop. Conversely, 20 Hz stimulation may help to restore a balance between antikinetic and prokinetic frequencies in those patients leading to improved motor performance. Positive effects of low frequency stimulation on dystonic symptoms have been reported recently (Alterman et al. 2007) and deserve further investigation.

Tu-59

A qualitative approach to perceived changes in everyday life in patients with dystonia treated with deep brain stimulation (DBS)

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Objective: To explore in depth perceptions of changes in life in patients with dystonia treated with DBS.

Background: Dystonia often limits activity and participation with detrimental effects on life quality. DBS has emerged as an treatment for patients with severe refractory dystonia. Existing studies of DBS for dystonia have shown significant motor improvement, however, the patients experience of surgery has been less studied.

Methods: Thematic interviews were used to obtain information on the patients perceptions after DBS. 5 patients (4 women), aged 28-49 years were interviewed 1-3 years after pallidal DBS. 3 patients had generalized dystonia (2 DYT-1 positive), 1 myoclonic, and 1 cervical

dystonia. The interviews, 2-3 hours-long, were taped and transcribed verbatim, then analysed with Grounded Theory.

Results: Re-orientation was an overall theme in all interviews. Surgery led to a "huge" change "overnight". The patients wished for more psychological support and counselling to learn how to cope with the new life situation and to realise their "true" potential after DBS. They had aspirations for the future, but were uncertain what direction to take. Positive perceptions after DBS were physical and even more social/mental. The patients felt more confident after the operation. They were more mobile and could walk better, without or with less pain. They reported more control over the body, with improved speech and handwriting. They were less tired, felt more relaxed and had a better sleep. They perceived that they had more energy. Negative perceptions were less prominent: loosing the hair was perceived "hard" since it was a vital part of identity and appearance and was considered a compensation for the dystonia. Some patients had mood swings after DBS. The patients were very positive to the operation, they expressed that they had "nothing to lose" and did not regret it.

Conclusions: While pallidal DBS for dystonia provides patients with a potential for better mobility, less pain, and more confidence, the patients may still need support and counselling after surgery to re-orientate into the new life situation. These preliminary findings identify several areas of physical and psychosocial adjustment, which may guide future efforts to assist patients in life readjustment after surgery.

Tu-60

Musicians with embouchure dystonia show primary sensorimotor overactivity

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Objective: To investigate if sensorimotor activation is abnormal in musicians with embouchure dystonia (ED).

Background: ED is a very disabling focal task-specific dystonia affecting the lower facial and jaw muscles in musicians playing brass or woodwind instruments. Loss of embouchure control nearly always incapacitates the patients in playing their instrument on a professional level. Abnormal sensorimotor activation has been shown in previous imaging studies on other task-induced dystonias. However, little is known on the pathophysiological basis of ED.

Methods: An event-related fMRI paradigm was performed in 10 professional healthy brass players and 10 brass players with ED. The two experimental tasks involved buzzing into an instrument-specific fully functional mouthpiece or a 'neutral' task demanding simply blowing into a tube. Purpose-built acrylic glass mouthpieces and tubes were mounted on a MR-compatible acrylic-glass handhold. Functional data were acquired with a 1.5T scanner and analyzed with SPM5.

Results: Both tasks activated a widespread sensorimotor network in both groups. When directly comparing activations during buzzing at the mouthpiece, patients with ED showed significantly increased activation of somatotopic face representations within bilateral primary sensorimotor cortices and of the mesial premotor cortex.

Conclusions: We show abnormal primary sensorimotor overactivity in patients with ED during a specific motor task inducing dystonia. This finding substantially adds to previous studies in other task-specific dystonias like writer's cramp. It supports the concept of deficient subcortical (basal-ganglia) and intracortical inhibition as a crucial factor predisposing to the development of dystonic motor output in musicians with ED.

Tu-63

In vivo metabonomics of M1 hand area in patients with focal hand dystonia: A 3T MR spectroscopy study

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Objective: To quantify several neurotransmitters and brain metabolites with 1H Magnetic Resonance Spectroscopy (MRS) in patients with primary focal hand dystonia (FHD).

Background: Dystonia is a neurofunctional disorder. Its neurochemistry is not well known.

Methods: 10 patients and 10 healthy volunteers (HV) were scanned on a 3T GE scanner. 1H MR spectra were acquired from an 18 cm3 voxel centered at the contralateral hand knob. Spectra were also obtained from a voxel of V1 bilaterally. GABA was measured with a PRESS based J-editing method, under first order shimming, at TE of 68 ms. Lorentzian peaks were fitted with software that analyzes time domain spectra in two steps. First, the unedited spectra were fitted for the amplitudes of Cho, Cr, and NAA. Then, GABA peak at 3.01 was extracted. 1H spectra of 30 ms TE that yield multiple metabolite peaks were fitted with LCModel. To see the group differences we used a linear mixed effects model with an unknown covariance structure containing different covariance for any pair. As there were significant interactions for each of the two voxel locations separately, we examined group difference per metabolite for each voxel by using two-sample t-tests corrected for multiple comparisons.

Results: We found no significant differences in M1 or V1 for GABA/Cr between groups. We also compared GABA of M1 to V1 within each group and found no significant differences. For unedited short TE spectra no differences were detected for NAA, GPC, Cho, Cr-PCr, Glx, macromolecules and myo-Inositol. Other NMR visible metabolites did not survive a 16% Cramer-Rao lower bound, a measure of variance of estimation by the model.

Conclusions: The aim of this single voxel MRS study was to simultaneously characterize a number of brain metabolites and neurotransmitters in FHD. We found no differences between the patients and HVs. This is the first study to report on metabonomics of FHD. Imaging data have so far failed to show consistent structural or functional abnormalities in FHD. Our results suggest that many metabolites with various functions are also normal in patients with FHD. This finding fits well with the neuro-functional nature of the disorder, indicating that the symptoms of FHD are not due to a static neurochemical abnormality but likely due to a dynamic task specific abnormality.

Tu-64

Patients with adult-onset cervical dystonia and marked improvement to a sensory trick perform better in multimodal temporal discrimination

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Objective: To assess whether the presence of a sensory trick (ST) is associated with altered temporal discrimination in patients with adult onset primary cervical dystonia (AOPCD).

Background: One of the most distinctive features of AOPCD is the improvement with STs. The involvement of the sensory system is also reflected by subclinical impairment of tactile spatial and temporal discrimination.

Methods: Patients with AOPCD were included. TWISTER score was applied for clinical assessment. ST was scored according the TWISTER score with 0 point for an absent effect, 1 point for a partial improvement of abnormal posture and 2 points for a complete resolution of involuntary muscle activity. Temporal discrimination thresholds (TDT) were assessed using unimodal paradigms (two electrical (tactile) stimuli or two visual (LED) stimuli) and with a crossmodal paradigm (one tactile and one visual stimuli). Interstimulus intervals (ISI) were increased with steps of 10ms starting from an ISI of 0ms.

Results: 33 patients (24 f/9 m) with AOPCD were included. Mean age was 56 yrs with a mean disease duration of 12.3 yrs and a mean TWISTER score of 25. A complete ST was present in 23%, a partial in 52% and was absent in 21%. A shorter disease duration correlated with the presence of a ST ([cc:-0.382] $p=0.028$) but not with current age [cc:-0.017]. Tactile and crossmodal (cm) TDTs were lower in patients with a complete ST (cm TDT: 106.8ms; cm TOJ (temporal

order judgment): 115.9ms) compared to patients without the presence of a ST (cm TDT: 136ms; cm TOJ: 141ms). In female patients the presence of a ST was significantly correlated with lower TDT's in the crossmodal paradigm (TDT: [cc:-0.560] p=0.004; TOJ: [cc:-0.579] p=0.003) whereas unimodal (tactile or visual) TDT's didn't reach significance. In all dystonia patients (f + m) there was a strong trend (cm TDT: [cc:-0.333] p=0.058) without reaching significance.

Conclusions: The presence of a ST is strongly correlated with better performance in crossmodal (tactile/visual) temporal discrimination in female patients with AOPCD. The parietal cortex is an important structure of multimodal sensory integration and also shows activation (superior and inferior parietal lobule) during ST application in functional imaging studies.

Tu-65

Complications of deep brain simulation for primary and secondary dystonias in children

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Objective: To evaluate complications of deep brain stimulation (DBS) therapy in children with dystonia.

Background: Deep brain stimulation is a recognised treatment for dystonia and Parkinson's disease (PD). The results and complications of DBS are reported mainly in cohorts of adults with PD. Data on paediatric patients being often included in adult series.

Methods: 30 children undergoing deep brain stimulation for dystonia were analysed for the presence of complications. Overall 61 electrodes were implanted. The complication rate was calculated in relation to number of patients and of implanted electrodes.

Results: The mean age of patients at the time of surgery was 11.9 years (3.3-18years). The mean follow up was 17.7 (1-42) months. Infection and/or skin erosions occurred in 4 cases (13% cases, 11% electrodes) requiring total system removal in one case with a cerebral abcess along the electrode track within three weeks of implant and partial system removal in 2 cases followed by replacement 6 months later. Clinically silent microhaemorrhage along the electrode track occurred in 1 patient (3% cases or 1.6% electrodes). System switching off occurred in 5 (16%) cases (11% electrodes) with worsening dystonia corrected by switching on again. Unexpected battery failure occured in 2 patients (6.6% cases, 5% electrodes). There was one case of serohaematoma, one CSF collection at electrode tip and one electrode was re-sited during initial surgery (3 % cases, 1.6% electrodes). A faulty lead (high impedence) occurred in 1 case (3% cases, 1.6% electrodes).

Conclusions: This study confirms the safety of DBS surgery in children. The commonest single complication was infection. Two third of complications were noted within 6 months of surgery. Monitoring complications and technical failures is crucial for optimizing management and delivering best possible care.

Tu-66

Effects of long-term potentiation (LTP)-like and long-term depression (LTD)-like plasticity on subsequent motor learning in healthy subjects and writer's cramp (WC) patients

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Objective: To investigate effects of LTP- and LTD-like plasticity induced by transcranial magnetic stimulation (TMS) on subsequent motor learning in healthy subjects and writer's cramp patients.

Background: Homeostatic metaplasticity is impaired in WC patients when testing the interaction between two subsequent plasticity inducing transcranial brain stimulation protocols (Quartarone et al. 2005, Brain 128: 1943-50). Therefore, homeostatic regulation of motor learning, an LTP-dependent process, may also be impaired in these patients. Here we tested this proposition by examining the interaction between motor learning with one of three different conditioning paired associative stimulation (PAS) protocols, which either induce a LTP-like increase (PAS25), a LTD-like decrease (PAS10) or no change (PAS100, control condition) in motor cortex excitability.

Methods: 8 right-handed WC patients and 8 age- and sex-matched healthy subjects took part in three experiments in randomised order at least one week apart, each consisting of one PAS protocol (PAS25, PAS10, PAS100) directly followed by a motor learning protocol. For learning, fastest possible thumb abduction movements of the right hand were performed for 2x15 min at a rate of 0.25 Hz. Motor learning was quantified by the increase in the first peak acceleration of the trained thumb abduction movement during and after motor practice compared to baseline.

Results: Healthy subjects showed homeostatic modulation of learning (enhancement after PAS10-induced LTD-like plasticity, depression after PAS25-induced LTP-like plasticity) when compared to the control protocol (PAS100). In contrast, WC patients showed enhanced learning when conditioned by LTP-like (PAS25) and LTD-like (PAS10) plasticity, suggesting an impairment of homeostatic metaplasticity in focal hand dystonia at the behavioural level. It is possible that this abnormality contributes to the development of dystonia.

Tu-67

Is "target panic" phenomenon a form of task-specific dystonia in archers?

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Objective: To collect data confirming that the "target panic" phenomenon is a form of task- specific dystonia occurring in archers and not an anxiety disorder.

Background: Dystonia that occurs only during a specific activity is referred to as a task-specific dystonia. Writer's cramp is the most common form of task-specific dystonia. In sport task-specific dystonias were described in golfers (sudden jerks and tremors while putting called "yips"), tennis players (freezing spasms of a shoulder), runners (proximal lower limbs dystonia).

Methods: Out of 120 active archers from two large, local archery associations in central Poland, using a specially created questionnaire and based on the information from coaches, we selected 6 archers who had become unable to shoot properly. They had the sensation of a physical barrier preventing them from releasing an arrow, usually freezing spasms of the shoulder in the last phase of aiming. That occurred when they were moving the aiming point to the center of the target face whose colour is yellow (so called "gold shy" in English and "yolk symptom"- the equivalent of it used by Polish archers). We took a video recording of 5 series of shooting, each of 3 shots to the target and without a target face (distance of 30 meters, all conditions similar to a regular archers' tournament). We compared the time needed for aiming (starting from the moment of anchoring till the releasing) in those having the yolk symptom to the matched archers without the symptom. Psychological studies in all the archers were also performed.

Results: We found the increase of aiming time with the target in archers presenting the yolk symptom compared to the control group. All the affected archers developed their shooting problem after several years of correct shooting. Freezing occurs only when shooting and not only during tournaments but also during stressless regular exercise. The results of psychological tests were similar in both groups.

Conclusions: Our data suggest that so called "target panic" may be a form of task- specific dystonia occurring in archers during aiming.

Tu-68

Repeated sessions of repetitive transcranial magnetic stimulation (rTMS) given during an 'active motor state' in focal hand dystonia (FHD)

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Objective: To evaluate if repeated rTMS during active hand movement effects measures of handwriting, neural activity and/or symptom report in FHD.

Background: Focal hand dystonia (FHD) is an enigmatic disorder that can severely limit hand function and adversely affect quality of life. There is growing evidence that deficient cortical inhibition plays an integral role in the pathophysiology of FHD. Low-frequency rTMS is a neuromodulatory technique that can alter neural activity and reinforce inhibition. Previous work has shown lasting effects of repeated rTMS on handwriting performance, cortical excitability and symptom report in FHD that may be enhanced with repeated stimulation exposure during motor activity with the affected hand.

Methods: A randomized, single-blinded, sham-controlled partial cross-over design was used to investigate the effect of five-consecutive days of low-frequency, subthreshold (90% of resting motor threshold) rTMS (30min) to left dorsal premotor cortex in subjects with FHD. 1Hz rTMS was applied while subjects scribbled holding a pen in their affected right hand. Symptom report and measures of handwriting performance were collected before and after the first and last rTMS session and ten days after intervention completion.

Results: We report preliminary data of 8 FHD patients (7male, age: 55.7±9.9y, duration of symptoms: 10.5±11.4y). Following five-consecutive rTMS sessions, 6 subjects reported clinical symptom improvement (mild:n=4/marked:n=2), lasting for at least ten days in 4 subjects. Reductions in handwriting pressure were observed. There appears to be an association between symptom improvement and changes in pen force during handwriting following rTMS.

Conclusions: These preliminary results build upon our previous research demonstrating lasting improvements in handwriting performance, dystonic symptoms, and cortical inhibition following five consecutive days of rTMS in FHD. These results extend the previous results and further support that behavioral change can be achieved with rTMS in some individuals with FHD. Future experiments should attempt to elucidate the neural mechanisms underlying the beneficial effect of rTMS in FHD. It remains to be clarified whether and how much a change in the motor cortex during rTMS can be used to boost the therapeutic effects of rTMS on dystonia.

Tu-69

The syndrome of deafness-dystonia – A case series of 11 patients

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Objective: To report clinical and genetic data of patients with the syndrome of deafness–dystonia and to highlight different possible causes of this rare syndromic association.

Background: The syndrome of deafness- dystonia is rare. Most cases reported are due to X-linked deafness/dystonia peptide (DDP-1) gene mutation (Mohr-Tranjebaerg syndrome: MTS), although Woodhouse-Sakati syndrome (WSS), mitochondrial diseases, organic acid acidurias, perinatal hypoxic brain injury and kernicterus account for a small percentage of cases with known aetiology.

Methods: We reviewed the medical records of 11patients (6 females, 5 males;mean age 45, range 18-62), diagnosed with syndrome of deafness and dystonia in our movement disorders clinic between 1994 and 2008.

Results: 9 patients were unrelated and 2 patients were siblings. Deafness preceded dystonia in all cases. The mean age of dystonia onset was 22. Distribution of dystonia was generalised in 10 and segmental in 1 patient. 8 patients had bulbar involvement. 6 patients had additional neurological findings, including pyramidal signs, visual impairment and cognitive decline. 1 patient had possible family history (FH) of dystonia and 5 patients had a FH of deafness. 1 patient had a history of postnatal jaundice. Organic acid acidurias were excluded in all patients, along with secondary causes of dystonia. DYT 1 mutation was excluded in all appropriate cases. DDP1 gene mutation screening was done in 6 cases either with negative FH or positive FH with possible X linked inheritance. Common mitochondrial mutations were checked in cases with FH compatible with mitochondrial inheritance (8 patients). Testing for C2orf37 gene mutation was done in a sib pair of Middle Eastern extraction with other systemic features suggestive of WSS. 1 patient was positive for DDP1 mutation. 2 affected siblings were positive for C2orf37 mutation and have been reported recently. None of the patients tested positive for mitochondrial mutations.

Conclusions: The syndrome of deafness dystonia is a rare, genetically heterogeneous disorder. Although MTS is generically referred to as deafness-dystonia syndrome in the literature, this genetic disorder is only occasionally implied as the cause of this phenotype. In most cases, there are yet to be discovered genetic or other causes for the syndrome of deafness and dystonia.

Tu-70

Blepharospasm and the modulation of cortical excitability in primary and secondary motor areas

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Objective: To evaluate the clinical and electrophysiological effects of three different non-invasive brain stimulation techniques over four different brain areas in patients with blepharospasm (BEB).

Background: Traditionally, BEB has been considered a disorder caused by basal ganglia disorders. Electrophysiological and brain imaging studies suggest pathological changes in excitability also in the primary motor cortex (MC), the anterior cingulate (AC) and secondary motor areas, such as pre-and supplementary motor cortex (PMC, SMA).

Methods: In this pilot study in seven patients with BEB, we experimentally reduced the cortical excitability of four areas: MC, PMC, SMA and AC, each with three techniques: repetitive low frequency (lf) transcranial magnetic stimulation (rTMS), continuous theta burst stimulation cTBS and transcranial direct cathodal stimulation (tDCS). Primary outcome was the clinical effects on blepharospasm (blink rate observation by an investigator blinded to the intervention and subjective rating by the patient); secondary outcome was the blink reflex recovery curve (BRR).

Results: Stimulation over the frontal areas was more effective reducing the number of blinks and eye lid spasms than stimulation over MC and PMC. rTMS was more effective than TBS and tDCS. rTMS over the AC was the most effective stimulation technique–brain area combination with significant improvements for each of the three outcome parameters.

Conclusions: This increased susceptibility of the SMA and AC in BEB suggests that the lack of inhibition in the MC is secondary to the hyperactivity of mesial frontal areas. Inhibition of these areas using (lf) rTMS could provide a therapeutic tool of BEB.

Tu-71

Mutation analysis of the GTP cyclohydrolase I (GCH1) and Parkin genes in 76 cervical dystonia patients in Taiwan

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Objective: To evaluate the frequency and characteristics of GTP cyclohydrolase I *(GCH1)* and *parkin* gene mutations in a Taiwanese population presenting with cervical dystonia.

Background: Cervical dystonia is known to be a clinically and genetically heterogeneous group of movement disorders. The *GCH1* and *parkin* genes have been reported as rare pathological mutations in cervical dystonia patients.

Methods: We screened for the *GCH1* and *parkin* mutations in a Taiwanese cohort of 76 non-*DYT1* cervical dystonia patients from unrelated 75 families. All patients have had negative results in our previous screening of GAG deletion in the *DYT1* gene. Mutational analysis was undertaken on all proband by single strand conformation polymorphism analysis and DNA sequencing. In addition, to test for the presence of exon rearrangements in both genes, we performed multiple ligation-dependent probe amplification (MLPA) and quantitative duplex PCR assay.

Results: We evaluated 52 female (mean age of onset: 40.19±13.71) and 24 male (mean age of onset: 35.67±15.46). The etiology of cervical dystonia were 66 idiopathic, 7 drug-induced, and 1 trauma-related. Seven patients from six families have at least one more family member s affected by dystonia. The frequencies of mutations for both genes were 1.31%. By sequencing *GCH1* gene, we identified a novel missense mutation in *GCH1* gene (c. 239 G>A in exon 1 causing Ser 80 Asn substitution) in one patient (a female, age at onset: 31). Using MLPA technique, we detected a large-scale deletion of exon 5 in *parkin* gene in another patient (a male, age at onset: 22). Both mutations were in the heterozygous states. The patient with *parkin* mutation has a sister of early-onset parkinsonism (age of onset: 37). Dopamine scan of brain showed marked deceased of uptake in this family.(Video of the index patients will be shown during presentation.)

Conclusions: By mutation analysis of the *GCH1*and *parkin* genes, we discovered one carrier in each gene. Although the mutation frequency is low but it should not be overlooked. It suggests both genes have to be considered in cervical dystonia, especially those with earlier onset.

Tu-399

Cognitive assessments in children with severe movement disorders who undergo deep brain stimulation (DBS) require multidisciplinary (MDT) involvement

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Objective: To demonstrate that pre- and post-DBS cognitive assessments of children with severe dystonic movement disorders requires active involvement of the MDT, in order to address the environmental access difficulties that this group typically experiences.

Background: Most centres routinely include objective assessment of cognitive function as part of the work up to DBS. Traditionally these assessments are conducted by psychology services in isolation. Our service philosophy, underpinned by the ICF, advocates a joint approach to assessment of cognition in this population. The materials and environment may be adapted using assistive technology, and positioning or therapeutic handling used, to enable access to a range of cognitive tests.

Methods: Two illustrative cases are described. Dystonia was measured using BFMDRS. Wechsler scales of intelligence were used to assess cognition.

Results: Case 1:19-year-old with PKAN, anarthria and total body dystonia provoked by attempts to speak. BFMDRS results suggest short lived positive effects post DBS (+11% at 6 mo, -49% at 9mo, -34% at 2 years). AAC provision and adaptation of test materials improved access to cognitive testing, showing no cognitive decline over 2 year follow up, despite progression of disease. **Case 2:** 14-year-old with secondary dystonia/dyskinesia. BFMDRS remained unchanged 1 year post-DBS, although definite subjective improvement reported, including some access to a communication device. Extensive psychology and occupational therapy co-working enabled a broader range of assessments to be completed at follow-up (compared to 1 subtest pre-DBS with a low scaled score), showing average to high average cognitive abilities.

Conclusions: Cognitive assessments for children with severe movement disorders benefit from close MDT collaboration within the ICF framework. Therapy input ensures that the task and environment is appropriately adapted, in order to enable the child to physically access the test materials and thus optimise their performance. This approach prevents potential biased results, which maybe more likely when assessments with this population are completed by lone professionals working outside of an MDT context.

Tu-400

Efficacy and safety of NT 201, botulinum neurotoxin type A free from complexing proteins) in pre-treated cervical dystonia patients

S. Grafe, C. Comella, J. Jankovic, D. Truong, A. Hanschmann (Frankfurt/Main, Germany)

Objective: To evaluate the safety and efficacy of NT 201 (Botulinum neurotoxin A (BoNT/A) free from complexing proteins, (Merz Pharmaceuticals, Germany compared to placebo in subjects with cervical dystonia (CD) previously exposed to BoNT.

Background: NT 201 has no complexing proteins and has shown non-inferiority to another BoNT/A for the treatment of CD. This is subgroup analysis of a prospective, double-blind, placebo-controlled, multi-center study of two doses of NT 201 compared to placebo.

Methods: CD patients previously treated with another brand of BoNTA were randomized to placebo, 120 U NT 201, or 240 U NT 201. Following injection, patients were evaluated at 4 weeks using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Adverse events (AEs) were also collected up to 20 weeks or until the next injection. The change from Baseline to week 4 for the TWSTRS scores was analyzed using an ANCOVA model.

Results: There were 143 CD patients (65% women, mean age 53.9 years, mean CD duration 83.3 months), Patients were randomized to placebo (N= 46), 120 U NT 201 (N= 47), and 240U NT 201 (N= 50). The change in total TWSTRS from baseline to week 4 was -2.4 ± 8.1 points (placebo group); -8.5 ± 9.7 points (120 U group) and -11.4 ± 13.1 points (240 U group) ($p < 0.002$ compared to placebo). Improvement in TWSTRS-Severity score from baseline to week 4 was -1.9 ± 3.7 points (placebo group); -3.7 ± 4.4 points (120 U group) and -5.6 ± 6.4 points (240 U group). AEs occurred in 34.8% of patients of the placebo group, 55.3% of the 120 U group and 46.0% of the 240 U group. AEs reported most frequently were dysphagia (4.3% vs 8.5% vs 16.0%), neck pain (4.3% vs 8.5%, vs 10.0%), and injection site pain (2.2% vs 8.5% vs 2.0%) for each group, respectively.

Conclusions: NT 201 (BoNT free from complexing proteins) is a safe and effective treatment for patients with CD previously exposed to BoNT/A as shown in the non-inferiority trial.

Tu-401

Efficacy and safety of NT 201; botulinum neurotoxin type A free from complexing proteins) in treatment-naive cervical dystonia patients

S. Grafe, C. Comella, J. Jankovic, D. Truong, A. Hanschmann (Frankfurt, Germany)

Objective: To evaluate the safety and efficacy of NT 201 (Botulinum neurotoxin A (BoNT/A) free from complexing proteins, (Merz Pharmaceuticals, Germany) compared to placebo in BoNT treatment-naïve subjects with cervical dystonia (CD).

Background: NT 201 has no complexing proteins and has shown non-inferiority to another BoNT/A for the treatment of CD. This is a subgroup analysis of a prospective, double-blind, placebo-controlled, multi-center study of two doses of NT 201 compared to placebo.

Methods: CD patients not previously treated with BoNT were randomized to placebo, 120 U NT 201, or 240 U NT 201. Following injection, patients were evaluated at 4 weeks using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Adverse events (AEs) were also collected up to 20 weeks or until the next injection. The change from Baseline to week 4 for the TWSTRS scores was analyzed using an ANCOVA model.

Results: There were 90 CD patients (67.8% women, mean age 51.1 years, mean CD duration 13.5 months), Patients were randomized to placebo (N= 28), 120 U NT 201 (N= 31), and 240U NT 201 (N=31). The change in total TWSTRS from baseline to week 4 was -2.0 ± 6.0 points (placebo group); -11.9 ± 11.1 points (120 U group) and -10.0 ± 9.2 points (240 U group) ($p < 0.001$ compared

to placebo). Improvement in TWSTRS-Severity score from baseline to week 4 was -1.9 ± 4.5 points (placebo group); -4.1 ± 4.3 points (120 U group) and -5.4 ± 5.5 points (240 U group). AEs occurred in 53.6% of patients of the placebo group, in 58.1% of the 120 U group and in 71.0% of the 240 U group. AEs reported most frequently were dysphagia (0% vs 19.4% vs 22.6%), muscular weakness (3.6% vs 6.5% vs 22.6%), and neck pain (3.6% vs 3.2%, vs 22.6%) for each group, respectively.

Conclusions: NT 201 (Botulinum neurotoxin free from complexing proteins) is a safe and effective treatment for treatment-naive patients with CD.

Tu-402

A case of Ear Moving syndrome: Treatment with botulinium toxin injection

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Objective: We aimed to present a case of ear moving syndrome who treated with botulinium toxin injection.

Background: Ear dyskinesia is extremely uncommon among focal dyskinesia. Movements appear spontaneously, following trauma, surgery, or drugs (neuroleptics or selective serotonin reuptake inhibitors(SSRI)).

Methods: A 23 year-old man presented 2 days history of involuntary movements of both ears. He had been given fluoksetine for tension type headache 20 days ago. He had no other medical history. On neurological exam, semi-rhythmic movements in both ears that suppressed partly during speech and laughing were seen symmetrically. Involuntary movements in both ears disappeared during sleep. He could not control them voluntarily. There was no other dyskinesia. The patient had social anxiety because of these involuntary movements.

Results: Blood tests were normal. Brain magnetic resonance imaging was normal. The patient responded well to injection of botulinium toxin type A(Botox) into both auricularis superior, anterior and posterior muscles(50 MU for each ear). After treatment focal dyskinesia in both ears decreased within 7-10 days. He had no involuntary movements in both ears 3 weeks later.

Conclusions: Focal dyskinesia of ear is extremely uncommon and called as moving ear syndrome in the literature. Most probably our case is a SSRI induced ear moving syndrome. Botulinium toxin injection in the ear moving syndrome is a good option for fast recovery.

Tu-403

Treatment of heterogeneous subtypes of cervical dystonia with botulinum toxin A (500 Units Dysport®)– First aspects of a multicentre open study

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Objective: The aim of this study was to analyse effectiveness and safety in the treatment of the most frequent subtypes of cervical dystonia (CD), predominantly rotational torticollis, or predominantly laterocollis, with a standard initial dose of 500 units Dysport® in a large representative group of patients presenting as out-patients in specialized clinics.

Background: Dysport® (botulinum toxin type A) has been used as a first line therapy for CD for many years. Nevertheless, there are only few studies available on dose, efficacy and safety in the treatment of heterogeneous subtypes of CD.

Methods: Between November 2004 and January 2008, 514 *de novo* patients with CD were recruited by 81 study sites in Germany and Austria. Muscle selection for injection was based on clinical assessment taking into account direction of head deviation and occurrence of the additional components shoulder elevation and/or tremor, evaluated using the Tsui rating scale. These ratings on the one hand permitted individual treatment according to the muscles affected and on the other hand provided a structure of twelve CD subgroups for intra-individual treatment comparison.

Results: Results of a first Data Analysis comparing baseline values with the effect of treatment after 4 weeks estimated by means of changes of the TSUI-score and analysing efficacy in dependance on CD-subtype will be presented.

Conclusions: This study with a large patient population will provide valuable insights for optimal initial treatment of heterogeneous subtypes of CD.

Tu-404

Pallidal deep brain stimulation in dystonia restores physiological feeding, toileting, ambulation & allows reduced rate of intrathecal baclofen infusion in severe childhood primary dystonia

M. Kaminska, L. Baker, S. Jupp, R. Mahoney, H. Gimeno, K. Tustin, D.E. Lumsden, R. Selway, J.-P. Lin (London, United Kingdom)

Objective: To describe improved dystonia following deep brain stimulation (DBS), removal of suprapubic catheter & gastrostomy after physiologic routes were restored & return of ambulation.

Background: Childhood onset dystonia may be severe & debilitating. Medical treatment is often unsuccessful though intrathecal baclofen (ITB) infusion may help. DBS is a recognised method of treatment of primary & secondary dystonia.

Methods: A 14 year girl without significant family history had normal development up to 18 months. She was diagnosed with developmental delay & subsequently with learning difficulties from the age of 2. She could walk & ride a bike, but not run. At 9 years she rapidly lost motor function, becoming wheelchair dependent at 11years, stopped supported walking at 12 years, mostly lying prone. She required a suprapubic catheter for urinary toileting & gastrostomy feeding along with nocturnal oxygen for sleep apnoea. Biochemical & genetic tests were normal. Brain MRI initially normal, at 13 years showed mildly decreased cortical volume. Symptoms were moderated by trihexyphenidyl, diazepam & ITB without functional gain. Bilateral pallidal DBS was implanted at 13years.

Results: At 2 months post DBS surgery she started to walk using walking frame, nocturnal apnoea ceased. The suprapubic catheter was removed at 3 months followed by the gastrostomy tube at 6 months. She returned to school. Urinary tract infections ceased. The daily rate of ITB infusion was reduced by 30%. She continues making progress.

Conclusions: Pallidal DBS improved motor performance, restored oral feeding & bladder voiding. Independence & social participation increased with a return to school outdoor activities & trips. DBS appears more effective than ITB for dystonia.

Tu-405

Decline in Soletra® neurostimulator battery voltage associated with decline in response to pallidal deep brain stimulation before complete battery failure has occurred

M. Kaminska, S. Jupp, H. Gimeno, K. Tustin, R. Mahoney, D.E. Lumsden, R. Selway, J.-P. Lin (London, United Kingdom)

Objective: Implanted neurostimulators used in pallidal deep brain stimulation (DBS) have variable battery life, influenced by a number of factors. In July 2008, Medtronic™, the manufacturer of the Soletra® neurostimulator, issued new guidelines regarding Battery Voltage Level as a measure of Battery Status and as an indicator of remaining battery life. In our clinical practice a number of patients have required replacement of Soletra® neurostimulator batteries. We aimed to determine whether these new guidelines would have allowed us to predict imminent battery failure and also whether a decline in response to DBS coincided with a decline in Battery Voltage Level.

Methods: Battery voltage data of three patients requiring replacement neurostimulator batteries were reviewed. In each case, the Battery Voltage Levels were plotted against time, along with the severity of dystonic symptoms as measured by the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). Currently, Medtronic™ guidelines suggest three battery levels for Soletra® stimulators. A Battery Voltage Level > 3.6V: "Okay"; Battery Voltage Level 3.4-3.6V: "Low" and Voltage <3.4V: "End of Life Imminent".

Results: In all three patients, the steady state of maximum neurostimulator voltage was above 3.7V. Battery Voltage Levels began to decline 20-24 months post insertion. A decline in BFMDRS scores preceded absolute battery failure, and was evident at Battery Voltage Levels >3.6V maximum output. Small voltage reductions produced a marked decline in response. Battery changes were followed by improvements in dystonia in all cases.

Conclusions: A decline in response to pallidal deep brain stimulation appears to occur with a decline in Battery Voltage Level prior to absolute battery failure. This may occur with only very small declines in voltage from the steady state. Our results support planning for battery replacement at greater voltage levels than suggested by existing manufacturer guidelines. The abstract was also submitted for BPNA Annual Conference 2009.

Tu-406

Electroacupuncture in movement disorders after peripheral trauma. A Soleus h-reflex study

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Objective: To elucidate whether segmental sensorimotor pathways are involved in abnormal movements of peripheral origin, and whether electroacupuncture in selected patients influences these segmental pathways.

Background: Some patients with a dystonic or segmental myoclonic movement disorder of probable peripheral origin may show a beneficial, albeit temporary, response to electroacupuncture.

Methods: Six patients with a dystonic or segmental myoclonic movement disorder of probable peripheral origin who repeatedly showed a beneficial, albeit temporary, response to electroacupuncture, were examined. Soleus H-reflex tests were performed before and immediately after acupuncture.

Results: Soleus H-reflex tests before acupuncture showed normal H/M ratio, increased late facilitation of the recovery curve and diminished vibratory inhibition. After acupuncture, concurrent with a beneficial response of the movement disorder, late facilitation and vibratory inhibition normalized.

Conclusions: We suggest that abnormal afferent input is involved in the generation of abnormal movements in these patients. Electroacupuncture, by its afferent stimulation, probably alters the modulation of afferent input, allowing polysynaptic spinal and supraspinal pathways involved in motor control to resume normal function.

We-45

Disruption of sensorimotor integration in writer's cramp

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Objective: To study sensorimotor integration processes in patients with writer's cramp.

Background: Several lines of evidence suggest an abnormal processing of sensory information in patients with writer's cramp, potentially leading to a disruption in sensori-motor integration. However, where this phenomenon occurs in the brain remains unclear.

Methods: We used event-related functional magnetic resonance imaging (fMRI; 1.5 T) and quantified electroencephalography (qEEG) to study sensorimotor integration processes when subjects used a sequence of sensory inputs to generate a sequence of motor actions. Proprioceptive informations were randomly delivered through pression rings placed on the last fourth fingers of the right hand defining a sequence of 4 sensory stimulations. Subject had to retain this sequence for a variable delay before reproducing it by pointing on a panel of pression sensors. Two control tasks were performed, one for sensory information and one for motor execution.

Results: Experiments were performed in 14 control subjects and 14 subjects with occupational dystonia matched by sex and age. Activations in a wide network of cortical areas involving bilaterally the sensorimotor cortex, premotor, prefrontal and parietal cortices was observed during the task. When subjects analyzed proprioceptive information, a decrease of metabolic activity was found in the left primary somesthesic area (BA2), left primary motor area (BA4), right and left premotor cortex (lateral BA6), and right supplementary motor area (SMAp) in dystonic versus control patients. During movement execution, a decreased activity was observed in the right SMAp, and in the left temporal cortex (BA21). On the other hand, activation in dystonic patients was greater bilaterally in the parietal lobe (BA39 and 40) and in the right medial frontal gyrus (BA10). Analysis of functional connectivity and qEEG are currently under investigation.

Conclusions: Our preliminary data suggest that, in writer's cramp, motor and premotor cortical areas do not correctly process proprioceptive information. Data of the present study could explain the incorrect adaptation of muscle force necessary to complete complex sensorimotor tasks such as writing in patients with occupational dystonia.

We-46

Dystonia secondary to tetrahydrobiopterin deficiency(BH4); recognition and therapy of the disorder

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Objective: To report the diagnostic studies, clinical variability and therapy in children with dystonia secondary to BH4 deficiency,to delineate this from L-dopa responsive dystonia in childhood.

Background: BH4 deficiency is caused by BH4 synthesis deficits or regeneration deficits. Common form is 6-pyruvyltetrahydropterin synthetase deiciency(PTS). Patients may be identified with newborn screening with hyperphenylalanemia, subtle elevations are under appreciated. Symptoms in infancy and childhood include: hypotonia, parkinsonism, abnormal gait, dystonia. In BH4 deficiency both copies of hyperphenylalanine genes are altered by mutations. No correlation between 33 mutations in PTPS deficieny and clinical phenotype exists. Hyperphenylalinemia due to BH4 is a heterogeneous group of progressive neurologic disorders caused by recessive inherited mutations affecting enzyme synthesis or regeneration of BH4. BH4 presents with neurological signs secondary to impairment in dopamine and serotonin metabolism. Three aromatic aminoacid hydrolases are affected.

Methods: Biochemical evaluation of five patients with BH4 synthesis deficiency was carried out plus CSF neurotransmitter studies. Measurements of plasma amino acids, urine biopterin content, biopterin/neopterin ratio in urine, csf biopterin, neopterin and neurotransmitter levels were obtained. Specific PTPS enzyme assay was perfromed. Neurological evaluation,MRI, biopterin levels, phenylalanine levels obtained. Biopterin and L-dopa was administered in3/5 patients, one patient received amantadine hydrchloride prior to L-dopa therapy.

Results: Serum and plasma levels of phenylalanine, biopterin, were measured prior to and after therapy. Phenylalanine levels normalized rapidly after initiation of therapy with BH4 supplementation(Biopterin). Clinical symptoms did not respond until initiation of L-dopa at which point dystonia improved.

Conclusions: Variability in presentation with childhood dystonia is not well known in BH4 deficiency. Response to therapy is individualized and difficult to quantify compared to adult Parkinson's disease. BH4 patients have a dopamine synthesis /regeneration defect in

the absence of substantia nigra degeneration. Replacement therapy includes 5-OH tryptophan cofactor BH4, and carbidopa/L-dopa. Management includes a multidisciplinary team: genetics, neurology, physical therapy to maximize the outcome.

We-47

Table tennis dystonia

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Objective: To describe four cases of focal task-specific dystonia in table tennis (TT) players.

Background: Focal task-specific dystonia (FTSD) occurs exclusively during a specific activity. Various tasks can be involved and are usually highly skilled activities. The classical FTSD dystonias include writer's cramp, typist dystonia, and musician's dystonia. Only few cases of sport-related dystonias have been reported, including golf, trap shooting, pistol shooting, billiards, darts, snooker, cricket, tennis, running and petanque.

Methods: The patients had a detailed standardized interview, neurological examination and were videotaped by playing TT. In addition, the patient had routine laboratory examination, electromyography and nerve conduction studies, and brain MRI.

Results: Two patients were professional TT players and two amateurs. All were regular player with a weekly training time ranging from 8 to 30 hours (4/4). None of them had personal or familial history of neurological disease (3/3). Age at onset of dystonia ranged from 17 to 65 years (4/4). Neurological examination was normal in all patients except for TT dystonia (4/4). Laboratory studies and brain MRI were normal (3/3) and neurophysiological examination found no feature of peripheral neuropathy or muscular disease. Dystonia resulted in a marked decrease of performance level in all patients. The two professional players mentioned an increased time of training in the months preceding dystonia onset. Reduction of the training time and exclusion of the repetitive exercises improved dystonia but dystonia persisted and they never recover their previous level (2/2).

Conclusions: These observations are in keeping with the findings that the total amount of practice and a recent increase in practice time are associated with writer's cramp. A maladaptive response can occur when motor training in highly skilled movements is pushed to extremes. In such situations, homeostatic mechanisms that regulate cortical plasticity may be overwhelmed, resulting in the consolidation of abnormal motor programs with altered muscle activation patterns. TT training is characterized by highly skilled movement involving the hand and highly repetitive exercises. We propose that these characteristics may account for a higher risk of FTSD in TT as compared with other sports.

We-48

Mechanisms of non-compliance in spasmodic torticollis patients undergoing botulinum toxin treatment

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Objective: Investigating mechanisms for non-compliance in spasmodic torticollis patients undergoing botulinum toxin treatment.

Background: Though not a cure, Botulinum treatment of dystonic symptoms is safe and effective but its efficacy depends on its regular administration. Therefore, the mechanisms of non-compliance were investigated in spasmodic torticollis patients undergoing botulinum toxin therapy.

Methods: Two-hundred and eighty-eight patients were studied with respect to the course of disease, timing of botulinum treatment, subjective symptom intensity, depression, disease-specific anxiety, body image, coping habits, quality of life, personality, and handicap and disability. The perceived course of the disease was assessed by drawings of the development of symptom intensities across years. Patients indicated phases of exacerbation and remission, the beginning of botulinum toxin treatment, and the onset of major life events. Psychological variables and disability and handicap scores were obtained from standardized questionnaires (e.g., HADS-D; Self-Image-Scale; "repressor" vs. "sensitizer"; EQ 5d; "Big Five"; Functional Disability Score"; Cervical Dystonia Questionnaire, etc.).

Results: Despite symptom durations up to decades and persistent disability, about half of the patients underwent botulinum therapy less than twice per year. A substantial minority of patients (about 15%) refused to undergo botulinum treatment or only used a total of 2-3 botulinum treatments throughout the course of the disease. Neither the duration of disease nor symptom intensity were related to compliance. Situation-specific exacerbation was associated with depression and anxiety, respectively. Compliance was strongly related to life events and a large variety of psychological factors.

Conclusions: Results show that sub-clinical states of anxiety and depression are core symptoms of dystonia which strongly influence compliance and, therefore, the course of the disease. Thus, the presentation of medical information should be carefully individualized. Moreover, the effects of botulinum treatment could be further improved if anxiety, depression, coping habits, and body image are carefully assessed and treated by means of psychological short-term interventions.

We-49

Serotonin responsive sleep disturbances in a patient with sepiapterin reductase deficiency

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Objective: To describe serotonin responsive sleep disturbances in a patient with sepiapterin reductase deficiency (SRD).

Background: SRD leads to a combined deficit of serotonin and dopamine. The motor phenotype is mainly characterized by dopa-responsive fluctuating generalized dystonia. Non motor symptoms are poorly recognized in this setting.

Methods: Before and after treatment, the patient had neurological evaluation, sleep interview, wrist actigraphy and sleep log over 7 days, 48-hour long continuous sleep monitoring, and measures of the circadian serum melatonin levels.

Results: A 28 years-old man was evaluated for a fluctuant generalized childhood onset dystonia-parkinsonism. An unusual cause of of dopa-responsive dystonia was searched because of sleep and eating disorders; incomplete although dramatic response of the motor symptoms to L-dopa; history of oculogyric crisis in childhood; absent GTP cyclohydrolase 1 mutation; and consanguinity of the parents. Neurotransmitter and pterins measurement in the CSF were highly suggestive of SRD. Molecular analysis confirmed he had a homozygous mutation of the *SPR* gene. Despite L-dopa treatment, the patient reported sleep symptoms since childhood with excessive daytime sleepiness, irregular night sleep and the need for long naps during daytime. Sleep investigations demonstrated an ultradian sleep-wake rhythm with a mild hypersomnia and a flat melatonin circadian profile. He also had an excessive eating with mild obesity. He received an additional treatment with 5-OH-tryptophan. Sleep and eating behaviour completely normalized.

Conclusions: Our patient has a levodopa responsive generalized dystonia-parkinsonism, as previously reported in SRD. In addition, he has serotonin responsive non-motor symptoms, including an ultradian sleep-wake rhythm, a mild hypersomnia and an eating behavior disorder. The flat melatonin profile parallels the irregular sleep-wake rhythm, suggesting that this observation provides a unique paradigm of melatonin deficiency caused by lack of its substrate, serotonin.

We-50

Characterization of cerebral cortex-specific and Purkinje cell-specific Sgce conditional knockout mice

Y. Li, F. Yokoi, M.T. Dang (Birmingham, Alabama)

Objective: To analyze the contribution of different brain regions in basal ganglia circuit in the pathogenesis of myoclonus-dystonia or DYT11 dystonia.

Background: DYT11 myoclonus-dystonia is a movement disorder characterized by myoclonic jerks and rapid muscle contraction combined with dystonic postures and repetitive movements that often exhibits diverse psychiatric symptoms. Mutation of SGCE gene (coding for ε-sarcoglycan) has been linked to the diseases. In previous studies, we reported the making of Sgce knockout mice to model the DYT11 dystonia. Sgce is the mouse homolog of the human SGCE gene. We reported that *Sgce* knockout mice lacking exon 4 exhibit myoclonus, motor deficits and alterations in emotional responses and striatal monoamine metabolism. We also reported that striatum-specific conditional knockout mice exhibited motor deficits in rotarod and beam-walking tests. Rotarod and beam walking test are excellent tests for motor coordination and balance, which has high relevance to movement disorders including dystonia.

Methods: We produced Purkinje cell- and cerebral cortex-specific *Sgce* conditional knockout mice and performed rotarod and beam-walking tests. Purkinje cell specific knockout was achieved through the use of Pcp2-cre mice that utilize L7 promoter. Emx1-cre knock-in mice were used to achieve cerebral cortex-specific knockout of the Sgce gene. Mice at 4 to 9 months of age were used for motor behavioral tests.

Results: Unlike the striatum-specific Sgce knockout mice, cerebral cortex-specific knockout mice did not exhibit any motor defects in these tests. Overall, mice with epsilon-sarcoglycan specifically inactivated in Purkinje cells were able to perform the beam-walking test, however, the mutant mice showed a specific motor learning defect. Wild type control mice were able to achieve significant improvement of their performance during their second test over the first test. This ability was lost in the Purkinje cell-specific Sgce knockout mice.

Conclusions: The result suggested that ε-sarcoglycan have essential function in Purkinje cells for motor learning. In addition, we were able to localize the motor learning part of the beam walking test to Purkinje cells. Finally, our results are consistent with clinical and animal studies pointing to the role of cerebellum in the pathogenesis of dystonia.

We-51

Bilateral pallidal deep brain stimulation (DBS) for primary and secondary paediatric dystonia improves quality of life (QOL) measured by the caregiver priorities and child health index of life with disabilities (CPCHILD)

D.E. Lumsden, S. Jupp, H. Gimeno, K. Tustin, R. Mahoney, M. Kaminska, R. Selway, J.-P. Lin (London, United Kingdom)

Objective: To determine if bilateral pallidal DBS used in the treatment of paediatric dystonia improved patient quality of life as perceived by caregivers.

Background: Pallidal DBS is an effective treatment for dystonic symptoms in children. Studies have confirmed that quality of life is improved by DBS in adults. Quality of life is difficult to measure in children with chronic neurological conditions. The CPCHILD[1] is a validated scoring system of caregiver's perspectives on health measures, functional limitations, and well being of children with severe cerebral palsy. We have used the CPCHILD as a proxy measure for caregiver's perception of patient QOL. Caregivers report a score in 5 areas: 1 Personal Care, 2. Positioning, Transfer and Mobility, 3. Communication and Social Interaction, 4. Comfort and Emotions and 5. Health. These scores are combined to give a total score.

Methods: 14 children with primary and secondary dystonias for whom baseline pre-operative CPCHILD scores had been prospectively recorded prior to DBS are reported. Following DBS, CPCHILD scores were recorded at three monthly intervals for the first year and 6 monthly thereafter.

Results: Follow-up data spanned the first 6 to 18 months post DBS. The average baseline CPCHILD score was 328, failing to 233 (29% reduction) at 18 months. There was an average 24% reduction in CPCHILD score over the 18 month period for the group. All patient CPCHILD scores improved compared to baseline.

Conclusions: In paediatric patients receiving pallidal DBS for the treatment of dystonia, caregiver perceptions of health measures, functional limitations, and well being improve in the short term as measured using the CPCHILD. References: 1. Narayanan et al Initial development and validation of the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD). Dev. Med. Child Neurol. 2006 Oct;48(10):804-12.

We-52

Paediatric quality of life (QOL) using the caregiver priorities and child health index of life with disabilities (CPCHILD) correlates with changes in the Burke, Fahn, Marsden dystonia rating scale (BFMDRS) following bilateral DBS

D.E. Lumsden, H. Gimeno, S. Jupp, K. Tustin, R. Mahoney, M. Kaminska, R. Selway, J.-P. Lin (London, United Kingdom)

Objective: To compare the BFMDRS measure of dystonia with the CPCHILD following bilateral pallidal DBS in children.

Background: The movement scale of the BFMDRS is used to demonstrate the effectiveness of anti-dystonic therapies but may not reflect changes in the quality of life in chronic paediatric movement disorders. The CPCHILD[1] is a validated scoring system of caregiver's perspectives on health measures, functional limitations, and well being of children with severe motor impairment. Caregivers report a score in 5 areas: 1. Personal Care, 2. Positioning, Transfer and Mobility, 3. Communication and Social Interaction, 4. Comfort/Emotions and 5. Health The CPCHILD is routinely gathered in our institution as a proxy measure of patient QOL. These scores are combined to give a total score which diminishes as care-giver burden is relieved.

Methods: 14 children, 3 primary and 11 secondary dystonias receiving bilateral pallidal DBS treatment, for whom baseline pre-operative BFMDRS & CPCHILD scores were prospectively obtained over one year are reported. Pearson correlation coefficients were calculated between BFMDRS and CPCHILD scores.

Results: The baseline BFMDRS v. CPCHILD Pearson correlation coefficient was weakly positive (0.5), but the coefficients for raw scores (0.76) and percentage change (0.74) at one year respectively indicated strong agreement between the BFMDRS and CPCHILD scores.

Conclusions: 1. The change in BFMDRS and CPCHILD after DBS are well correlated indicating objective changes across a variety of impairment, functional and participation domains. 2. Caregiver perceptions of health, functional limitations and well being vary according to the severity of dystonia following pallidal DBS. References: 1. Narayanan et al Initial development and validation of the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD). Dev. Med. Child Neurol. 2006 Oct;48(10):804-12.

We-53

Pallidal deep brain stimulation improves dystonic symptoms in patients with pre-existing intrathecal baclofen pumps

D.E. Lumsden, S. Jupp, H. Gimeno, K. Tustin, R. Mahoney, M. Kaminska, R. Selway, J.-P. Lin (London, United Kingdom)

Objective: Continuous Intrathecal Baclofen (ITB) infusions have been used in children with dystonia without corticospinal tract impairment. In our service, a number of patients receiving ITB have subsequently received DBS to the Globus Pallidus internus (GPI). We aimed to determine whether these patients experienced an improvement in their dystonic symptoms or quality of life.

Methods: Data of patients receiving continuous ITB was prospectively collected following bilateral GPi DBS. Two patients were positive for the PKAN mutation; 1 was born at 28/40 and 1 had onset primary dystonia at age 9 years (the case presented elsewhere, M. Kaminska et al). The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) score prior to DBS insertion was taken as a baseline for each patient. Changes in these scores over time following DBS inser-

tion, daily dose of intrathecal baclofen delivered and Caregiver priorities and Child Health Index of Life Disabilities (CPCHILD) questionnaire scores when available were then collected for each patient.

Results: The average age at ITB insertion was 8 years 5 months (22 months – 13 years) and average duration of 1 year and 3 months of ITB prior to DBS insertion. Changes in BFMDRS are shown in Table 1.

Table 1 (We-53).

Months post DBS insertion	0	3	6	9	12	18	24
Average BFMDRS score (max 120)	91.1	55	49	60.3	58.1	62.1	70.3
Average BFMDRS improvement (%)	N/A	39.4	46.2	33.8	36.2	31.7	22.8

Prior to DBS, the average dose of ITB was 1697mg/day (range 700-3,700mg/day), falling to an average of 507mg/day (range 0-1200mg/day). In one patient, removal of the ITB pump was performed because of pump erosion through the skin. CPCHILD data was available for one patient, with a pre-DBS score of 429 falling to 236 at 9 months post-DBS.

Conclusions: In patients with pure dystonia pallidal DBS is superior to ITB therapy in improving dystonic symptoms and quality of life allowing reductions of daily ITB dose. This abstract was also submitted for BPNA Annual Conference 2009, Birmingham, UK.

We-54

Cognitive functioning in children with pantothenate kinase-associated neurodegeneration (PKAN) undergoing deep brain stimulation (DBS)

R. Mahoney, H. Gimeno, K. Tustin, S. Jupp, M. Kaminska, D. Lumsden, R. Selway, J.-P. Lin (London, United Kingdom)

Objective: 1. Describe the cognitive profiles of a group of children with PKAN who have undergone DBS. 2. Demonstrate the intellectual decline previously associated with PKAN may have been overinterpreted and apparent cognitive impairments may in fact be related to difficulties accessing cognition due to the dystonia severity.

Background: PKAN is characterised by a progressive generalised dystonia and historically associated with cognitive decline. This observation of intellectual impairment is based on small studies of adults using limited assessment measures. This may reflect the difficulties patients have in accessing test materials due to the dystonia severity. With growing evidence that DBS can improve motor function in adults and children with PKAN, there is now the opportunity to study cognitive profiles of young people with PKAN over time.

Methods: Seven children with PKAN who have undergone DBS are described. All children were assessed pre- and 1 or 2 year post-DBS. Cognitive functioning was assessed using standardised measures where possible. For each child, the tools used depended on their ability to physically access the materials, including subtests from the Perceptual Reasoning and Verbal Comprehension Indices of Wechsler intelligence scales (WISC-IV, WASI, WPPSI-III) and measures of immediate and delayed visual memory (CMS, NEPSY2).

Results: Pre-DBS, it was possible to complete cognitive measures in 6 of the children. One child was unable to access the tests due to status dystonicus. During follow-up, it was possible to complete standardised cognitive measures with all 7 children. Of the 6 children who completed measures pre-DBS, all were able to tolerate longer assessment sessions and completed a greater number of subtests. In addition, no cognitive decline was observed; in fact scores were shown to improve in 5 of the 6 children for whom baseline measures were obtainable.

Conclusions: No cognitive decline was observed in children receiving DBS for management of PKAN-associated dystonia. At follow-up, scores improved in all but 1 child. Whilst this may reflect cognitive improvement, it is more likely to reflect improved access to test materials, evidenced by a larger number of subtests administered at follow-up.

We-55

Cervical dystonia reduces working capacity

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Objective: To assess the effect of cervical dystonia on patients' working capacity.

Background: Cervical dystonia begins typically in working age. Little is known about its effect on working capacity in long term.

Methods: A questionnaire study among working-aged members of the Finnish Dystonia Association (n=433).

Results: Of the 303 patients who participated in the questionnaire study 247 (82%) had cervical dystonia. Their median age was 50 years, the median duration of CD symptoms was 12.3 years. Of the CD patients, 35 (14%) were men and 212 (86%) women. Ninety-seven (39%) had retired because of CD at a median age of 48 years, 96 (39%) were working: 87 full-time and 9 part-time. The remaining participants were on sick leave, unemployed, studying or retired of other reasons. After 50 years of age 25% of CD patients were working, compared to 62% of general Finnish population. Most (78%) subjects were on botulinum toxin treatment. The proportion of subjects without BTX treatment did not differ significantly among employed and retired. Of the participants still in the workforce 30/123 (24%) felt that CD had reduced their working capacity and 54 (44%) had needed days off because of CD during the last year. A multidisciplinary evaluation of working capacity had been made only for 36 (15%) subjects. Adjustments in work such as changed tasks, an easier job or the possibility of extra breaks had been used significantly more often among those subjects who had continued to work for more than five years (63% had some adjustment) compared to those who had retired within one year (9% had some adjustment) from diagnosis.

Conclusions: Cervical dystonia often leads to a premature retirement; retirement occurs more than ten years earlier compared with the general Finnish population.

We-57

Frequency and clinical features of lower limb dystonia in a large Italian series of primary late-onset dystonia

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Objective: To assess frequency and clinical features of lower limb dystonia (LLD) in a large Italian series of patients with primary late-onset dystonia (PLD).

Background: Lower limb involvement is rare in PLD. Previous case collections selected patients with focal LLD, or with lower limb as the site of onset of non-focal forms of PLD, but the frequency of LLD in the general population of patients with PLD has never been estimated.

Methods: We analysed 582 patients with PLD using a common electronic medical records system and a semi-structured clinical interview dedicated to clinical assessment of LLD. All potential secondary causes of LLD (including Wilson's disease and DYT1-dystonia) were excluded.

Results: LLD was identified in 14 of 582 patients (2.4%). The demographic and clinical features of the whole cohort were representative of the general population of patients with PLD. The mean age at onset of LLD was 45.6±18.9 years, and the mean duration of LLD was 10.3±10.3 years. The age at onset of LLD did not differ from that of CD, ULD and primary axial dystonia, whereas it was significantly lower than that of BSP ($p<0.00001$), OMD ($p=0.0002$) and LD ($p=0.015$). Only 4 of the 14 LLD patients had a focal LLD, whereas the other 10 had dystonia in at least another body site (3 in

one, 5 in other 2, and 2 in other 3); 5 of the 14 LLD patients had the lower limb as the site of onset. Ten of 14 patients did not report any precipitant for their LLD, whereas 4 reported pregnancy, emotional stress and orthopaedic problems as possible triggers. LLD was clearly mobile in 12 patients, and associated with pain in 5.

Conclusions: Lower limb involvement in PLD may be more frequent than previously thought. LLD may be heterogeneous in its presentation, and seems more frequent as a site of dystonia spread rather than as site of dystonia onset.

We-58

Brain-derived neurotrophic factor and risk for primary adult-onset cranial-cervical dystonia

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Objective: To explore the effect of the single nucleotide polymorphism (SNP) of the *BDNF* gene, the Val66Met SNP upon the risk of developing common forms of primary adult-onset dystonia.

Background: Adult-onset dystonia may be related, among other factors, to abnormal neuronal plasticity in cortical and subcortical structures. Brain-derived neurotrophic factor is a major modulator of synaptic efficiency and neuronal plasticity. Recent works documented that a SNP of the *BDNF* gene, the Val66Met SNP, modulates short-term plastic changes within motor cortical circuits.

Methods: We explored the influence of the Val66Met single nucleotide polymorphism (SNP) of the *BDNF* gene on the risk of cranial and cervical dystonia in a cohort of 156 Italian patients and 170 age- and gender-matched healthy control subjects drawn from the same population.

Results: The presence of the rare Met allele was not significantly associated with the diagnosis of dystonia (age- and gender-adjusted OR of 1.22, $p=0.38$; study power $> 90\%$). Moreover, there was no relationship between Val66Met SNP and age at dystonia onset or type of dystonia.

Conclusions: Our data do not support the common variant Val66-Met of the *BDNF* gene as an etiologic factor shared by the various forms of primary adult-onset dystonia.

We-59

Central motor conduction time in children with severe dystonia aids assessment for deep brain stimulation (DBS)

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Objective: To report Central Motor Conduction Time (CMCT) & main imaging findings in children with severe dystonia, in order to demonstrate corticospinal tract (CST) integrity before consideration for DBS.

Background: Dystonia in childhood has many causes. Imaging findings may imply CST dysfunction. Transcranial Magnetic Stimulation (TMS) is a non-invasive, painless tool for assessing the CST, and has been used to demonstrate maturation of central motor conduction time (CMCT) in childhood and prolonged CMCT in congenital hemiparesis or stroke. Muller[1] found normal CMCT in 16 children with extrapyramidal disorders, mainly of genetic origin & normal imaging. We report new CMCT data in children with severe dystonia and the use of CMCT in assessment of these patients for DBS.

Methods: Distal motor & F wave latencies were measured in the ulnar &/or posterior tibial nerves in 53 patients (3 – 19 years). TMS was applied over contralateral motor cortex & Motor Evoked Potentials recorded in the activated Abductor Digiti Minimi &/or Abductor Hallucis. CMCT was calculated from the two latencies.

Results: Clinical phenotype: 31 generalised dystonia, 17 dystonia-dyskinesia, 3 hemidystonia, 1 dystonia-myoclonus; 1 mixed dystonia & spasticity. **Aetiology:** 12 primary dystonia (2 DYT1 positive, 1 DYT11 positive); 16 ex-premature, 5 Term Hypoxic Ischaemic Encephalopathy, 9 neurodegenerative/neurometabolic (5 Pantothenate Kinase 2 deficiency; 3 Glutaric Aciduria type 1; 1 Lesch-Nyhan); 2 vascular; 5 misc. **Provisional Diagnostic Imaging:** 13 normal; 11 isolated thalamic/basal ganglia (BG) changes; 7 Periventricular White Matter (PVWM) changes; 9 mixed thalamic/BG &PVWM changes; 4 diffuse term anoxia; 3 malformation, 6 other. **TMS:** CMCT was normal in 44/53 patients; 9 patients showed prolonged CMCT to upper &/or lower limbs (2 normal imaging; 2 isolated basal BG; 5 PVWM changes).

Conclusions: Most of our children with severe primary & secondary dystonia had normal CMCT indicating CST integrity in 44/53 cases with abnormal imaging in 33/44 of these. 2/9 cases with abnormal CMCT had normal imaging. Under 6 years old, prolonged CMCT to lower limbs may reflect immaturity & 3/9 cases with slow CMCT have had a decision regarding DBS deferred, pending reassessment of CMCT in 1 year. [1]Muller et al. Electroenceph. clin. Neurophysiol.1992, 85: 86-94

We-60

Shot put like paroxysmal arm dystonia

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Objective: To describe patients with arm dystonia who remain in the initial position of athletes during shot putting.

Background: shot put is an athletic discipline that requires of the skillful ability of "putting" (tossing) a heavy metal ball (called the shot) as far as possible into the field. When ready to initiate the toss athletes hold the shot with one hand "in close proximity to the neck" below the chin, whilst he/she gains momentum before releasing the shot.

Methods: Retrospective clinical evaluation.

Results: Case I. A 18 year old female patient suffering primary DYT1 generalized dystonia underwent GPi-DBS combined with contralateral pallidotomy at the age of 11 with a remarkable response and total improvement of upper limbs dystonia. Six moths ago coincidentally with DBS battery wore off patient suddenly started with dystonic movement of the right upper limb consistent with finger flexion, wrist hyperextension forearm pronation and flexion and arm rotation, abduction and flexion. Placing the hand in close and tight contact with the neck/chin with elbow pointing upward and forward imitating the initial shot resting position of shot put athletes. Position was not constant but triggered by minimal voluntary movements in a paroxysmal way. EMG recording confirmed co-contraction. After battery replacement described dystonic movement completely disappeared returning to her previous clinical state. Case II. A 23 year old female who at the age of 5 suffered from hemidystonia hemiparesis secondary to brain trauma started in the last year with an increment of her right upper limb dystonia, progressively started with dystonic movement of the right upper limb consistent with finger flexion, wrist hyperextension forearm pronation and flexion and arm rotation, abduction and flexion. Placing the hand in close and tight contact with the neck/chin with elbow pointing upward and forward very similar the initial shot resting position of shot put athletes. Paroxysm of this dystonic movement lasted a few minutes appeared almost every hour. EMG recording confirmed co-contraction. Patient is on trial of anticholinergic with poor response waiting for botulinum toxin treatment.

Conclusions: This report illustrates a paroxistic dystonic arm movement in primary and secondary dystonia patients which remains similar to the unusual position of shot put athletes.

We-61

Neurophysiological and kinematic factors associated to spreading of symptoms in primary late-onset focal dystonia

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Objective: To demonstrate in patients with late-onset focal dystonia with spreading of symptoms, neurophysiological and kinematic alterations in clinically unaffected body parts.

Background: Primary late-onset dystonia is often focal at onset but may spread over time to adjacent body regions, with greater risk of spreading in blepharospasm (BS) in the first 5 years of disease. Neurophysiological mechanisms underlying spreading in focal dystonia are unclear so far.

Methods: We studied 6 patients with writer's cramp (WC), 5 patients with BS who presented spreading of dystonia to the oromandibular district (BS-OMD) and 9 healthy controls. Each subject underwent kinematic analysis of writing, using an inking digitizing pen and a pressure-sensitive digitizing tablet, and kinematic analysis of finger movements, using a sensor-engineered glove. Moreover, electrophysiological testing was carried out by means of transcranial magnetic stimulation (TMS). Recordings were obtained from the affected hand of WC and the dominant hand of BS-OMD and controls, evaluating the following parameters: mean stroke frequency during writing of a sentence and drawing of a circle; touch duration (TD) during finger tapping movements. TMS was used to study motor cortex plasticity by means of the paired associative stimulation protocol (PAS).

Results: In WC mean stroke frequency was significantly reduced during writing of the sentence and drawing of the circle compared to healthy subjects. In patients with BS-OMD mean stroke frequency was reduced as in WC in the drawing of the circle task. TD tested during finger tapping movements was significantly prolonged in both WC e BS-OMD compared to healthy controls. Finally, both WC and BS-OMD showed abnormal plasticity probed in the primary motor area controlling hand muscles.

Conclusions: Our data demonstrate neurophysiological and kinematic alterations in unaffected body regions in dystonic patients who had spreading of dystonia. These subclinical alterations might represent the neurophysiological basis for inducing diffusion of dystonic symptoms to contiguous body regions.

We-62

Psychogenic movement disorders – A Brazilian series of 72 cases

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Objective: To describe psychogenic movement disorders in a Brazilian series of patients.

Background: Identifying psychogenic movement disorders (PMD) is a defying task in neurological practice. Time is wasted in widely investigation for exclusion of organic disorders. Moreover, specific criteria must be met to define the correct diagnosis.

Methods: Seventy two patients were studied. They attended outpatient consultations at the Movement Disorders Unit of Neurology Service, of Hospital de Clínicas of Federal University of Paraná. Analyzed variables were gender, age of onset, treatment, level of symptoms, improvement after treatment and presence of comorbidities. Movement disorders were classified according to basic definitions proposed by Fahn and Marsden. Psychiatric comorbidities such as anxiety and affective disorders, somatoform disorders, factitious disorders, adjustment disorders, personality disorders, schizophrenia and other psychotic disorders that might interfere on the medical condition were classified according to DSM IV criteria. From a total of 72 patients, there were sixty-three females (93.05 %) and five males (6.95 %). Female mean age was 38.95 years old and male mean age was 39.50 years old.

Results: Tremor was the most frequent abnormal involuntary movement, occurring in 40 (55.55 %) of all patients. Predominant limb tremor was present in 31 patients. Of these, cephalic tremor was present in five patients, generalized tremor was seen in three patients, and orthostatic tremor in 1 patient. Dystonia was the second most frequent abnormal movement and was observed in 24 (33.33 %) patients. Of these patients, 15 had segmental dystonia (particularly facial dystonia), 5 had focal dystonia, and one had generalized dystonia. Gait disorders were seen in 12 patients (16.7 %), Blepharospasm and facial movements were found in 12 patients (16.7 %), and myoclonus in other 4 patients. Parkinsonism was seen in 4 patients and 8 patients had mixed or bizarre movement disorders. Tics and Stiff Person syndrome were not found in this series of patients Interestingly, cerebellar ataxia was seen in 3 patients (4.16 %).

Conclusions: In our series, there was female predominance as found in literature. Tremor was the main PMD, and depression the main psychiatric co-morbidity. There was total disappearance of abnormal movements in only 20 % of these patients.

We-63

Additional deep brain stimulation of subthalamic fiber tracts is effective for mobile segmental dystonia

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Objective: To evaluate the effect of deep brain stimulation (DBS) of subthalamic nucleus (STN) or subthalamic fiber tracts in a patient with mobile segmental dystonia.

Background: GPi is a well-defined target of DBS for intractable dystonia. Recently STN is also proposed to be a favorable target. We tried STN DBS to a patient who already had shown marked effect for mobile symptoms by GPi DBS but residual symptoms of postural abnormality still persisted three years after initiation of GPi stimulation.

Methods: A 67-year-old man who had cervical and axial dystonia could not walk more than a few steps ten years after the initial symptoms. GPi DBS was markedly effective for mobile dystonic symptoms and moderately effective for dystonic posture. For residual symptoms, STN DBS was planned.

Results: Stimulation of STN proper caused ballistic movement and it was quite useless. Stimulation of subthalamic fiber tract (Forel's field H2) showed marked improvement of dystonic posture of neck and trunk. The effect continued for more than half a year and gradual improvement made it possible to reduce the drug of D2 antagonist haloperidol and cease olanzapine.

Conclusions: Subthalamic fiber tract (Forel's field H2) contains pallidofugal fibers and its stimulation augmented the inhibitory output from GPi, which resulted in the supplementary effect for dystonic posture. According to the pharmacological change, additional stimulation of subthalamic fiber tract was supposed to be effective through indirect pathway mediated by D2 receptor.

We-64

Long-term effect of repetitive transcranial magnetic stimulation over the premotor cortex for writer's cramp

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Objective: To evaluate the long-term effect of repetitive Transcranial Magnetic Stimulation (rTMS) for patients with writer's cramp who were resistant to the common therapies of botulinum toxin (BTX), lidocaine injection and/or medication.

Background: We already reported the acute effect of rTMS over the premotor cortex for writer's cramp (Murase N et al., 2005). However, it is unknown whether this condition of rTMS can induce long-term effect enough to be considered as an alternative therapy.

Methods: Subthreshold (85% of resting motor threshold) 0.2 Hz rTMS was applied and 250 stimuli were delivered to the premotor cortex contralateral to the affected side. Among 93 patients with idiopathic upper limb dystonia, 23 (25%) were chosen because they were resistant to the therapies of BTX, lidocaine injection and/or medication. Acute effect was seen in 16 (70%) patients (7 female and 9 male, mean age 37.7 years). rTMS was applied once a month (n=9) or twice (n=4) as Group 1 and twice a week (n=3) as Group 2 for 6 months. Long-term effect which continued more than one month was evaluated by BFM scale of handwriting (neurology, 1985).

Results: Ten patients (63%) showed improvement of more than one point in BFM scale. Six months later BFM scale was improved

(before 3.8±1.6, after 2.2±1.9) in Group 1, but no patients showed complete remission. On the contrary, complete remission was seen in 2 patients of Group 2.

Conclusions: Increased sensitivity of premotor cortex to subthreshold rTMS in dystonia has a therapeutic effect of suppressing LTP. Our data suggest 0.2 Hz subthreshold rTMS over the premotor cortex is an alternative therapy for upper limb dystonia.

We-65

Anti-NMDA receptor (NMDAR) encephalitis presenting with psychiatric and extrapyramidal symptoms in a patient without tumor

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Objective: Anti-N-methyl-D-aspartate receptor encephalitis (NMDARE) is a recently described disorder likely mediated by antibodies (AB) to the NR1 subunit of the NMDAR.

Background: The disorder was initially identified in young women with ovarian teratoma who typically developed schizophrenia-like symptoms and dyskinesias. Current studies indicate that this disorder also occurs without tumor association and can affect man.

Methods: Case report: An 18 year old woman was admitted to the Department of Psychiatry for new onset hallucinations with strong sexuall content with the tentative diagnosis "drug induced psychosis". After developing generalized seizure she was transferred to Department of Neurology. At examination she was agitated, with orofacial dyskinesias.

Results: CSF showed a lymphocytic pleocytosis and positiv oligoclonal bands. MRI demonstrated mild bilateral temporal lobe hyperintensity. Antiviral and antibiotic therapy showed no effect. Routine blood tests, extensive viral and autoimmune panels were normal or unrevealing. Levels of 14-3-3 protein in CSF were elevated, and considered a non specific marker for encephalitis. EEG showed delta activity but no triphasic waves. Showing increasing extrapyramidal symptoms with rigidity, oral dyskinisias and choreic movements that affected the entire body, she was transferred to intensive care. There was no response to treatment with benzodiazepines and corticosteroids, L-Dopa and amantadine. Biperiden injections led to a slight improvement. Because of severe dyskinesias and aspiration pneumonia she required intubated. Whole body CT and PET scans did not reveal a tumour. The diagnosis of Encephalitis lethargica (EL) was considered, but basal ganglia AB were absent. The patient was then treated with 5 cycles of plasma exchange with good response. The dyskinesias decreased, her mental status improved and she became interactiv. AB to NMDAR were found positive.

Conclusions: The syndrome associated with AB to the NR1/NR2 heteromers of the NMDAR is notable for prominent psychiatric symptoms, unresponsiveness, and dyskinesias. These clinical features may suggest EL. Detection of AB to the NMDAR establishes the diagnosis of the disorder and reveals an immune mediated mechanism, suggesting an immunotherapeutic approach.

We-66

New and recurrent mutations in the ATP1A3 gene in patients with rapid-onset dystonia parkinsonism (RDP)

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Objective: Determine the molecular basis of mutations that cause RDP.

Background: RDP (DYT12) is an autosomal-dominant disease caused by mutations in the Na/K-ATPase a3 subunit gene (ATP1A3). Na/K-ATPase a3 is a P-type ATPase known to catalyze active transport of cations across neuronal membranes and maintain ionic gradients through hydrolysis of ATP. To date, 8 different mutations (clustered in 4 out of the 23 exons) have been reported to cause RDP in either familial or *de novo* cases. Analysis of protein structure and function suggests that these mutations may impair the enzyme's activity and/or stability. The phenotype associated with ATP1A3 mutation-positive patients includes the abrupt onset of dystonia with features of parkinsonism, a rostrocaudal gradient, and prominent bulbar findings.

Methods: Exons were directly sequenced to identify mutations. Protein molecular models were based on crystal structures of Na/K-ATPase a1 and SERCA1a.

Results: We report the recurrent finding of the T613M mutation in 8 separate cases (3 familial, 4 de novo, 1 unknown origin) as well as the identification of two novel missense mutations, S684F and G893R. The two missense mutations were not seen in at least 100 control individuals, and are both conserved across species. They are not clustered with the other mutations, instead being located in unique exons. Interestingly, T613M and S684F are at critical interfaces between cytoplasmic protein domains, and G893R is at the interface with the Na/K-ATPase β subunit.

Conclusions: The recurrent T613M mutation most likely represents a mutational hotspot related in part to the sequence surrounding the mutation, as it is a transition mutation that occurs within a CG doublet; but also because of its functional significance: previous studies have shown a functionally altered pump with 25% of the activity, reduced Na^+ affinity in competition with K^+, and a preference for one conformation of the enzyme (Rodacker JBC 281:18539-48, 2006). S684F and G893R are predicted to interfere with domain-domain interactions that are part of the conformation changes that catalyze uphill ion transport. Further investigation of these and other mutations is required to elucidate the underlying mechanism of disease in RDP patients. Supported by NIH, NS058949.

We-67

Familial primary blepharospasm

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Objective: To evaluate the proportion of familial BSP cases among the primary blepharospasm patients and to describe other types of primary dystonia within the families.

Background: Blepharospasm (BSP) is a common form of primary torsion dystonia (PTD). Although most cases are sporadic, an increased familial incidence of BSP has been reported. The exact form of inheritance of blepharospasm remains unclear. Other studies provided some evidance of familial clustering but with no precise penetrance pattern.

Methods: We investigated the accumulation of familial primary blepharospasm (FPB) in 43 index cases of primary blepharospasm and their 247 first degree relatives either by direct examination, 97 patients, or by telephone interview,121patients. 39 first degree relatives were deceased.

Results: 7 of the index cases have a first degree relative with either primary blepharospasm or focal dystonia, 16 % of the index patients. 12 relatives of index cases have primary blepharospasm and 11 with focal cervical dystonia and one with writer's cramp. One family have a transmission within three generations that suggests autosomal dominance.

Conclusions: Our data add further evidance of familial accumulation of primary blepharospasm in one fifth of patients that suggests autosomal dominant penetrance but further genetic studies should be performed to confirm the mode of inheritance patterns to make a deduction.

We-68

Impairment of health related quality of life in cervical dystonia: Gender differences

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Objective: The aim of this study is to assess health related quality of life (HRQoL) in a sequential selected sample of CD patients, and

to compare the results with gender- and aged-matched general Spanish population data.

Background: Cervical dystonia (CD) is a chronic disease which is known to impair self esteem and health related quality of life (HRQoL).

Methods: Patients were provided from the neurology clinical department after a following period of more than five years. HRQoL was tested using: the EuroQoL questionnaire and the Short Form Health Survey 36 scale (SF36). CD severity was evaluated using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Comparison between groups was undertaken either by parametric or by non parametric coefficients using SPSS+v14.

Results: Sixty six patients with CD were recruited. Four patients were excluded. There were a total of 31 women (50 %) and 31 males. The mean age of the patients was 49,78 ± 12,86 years (47,61 ± 12,032 years in women, and 51,61 ± 13,6 years in men, p=0,206 Mann-Whitney U). No significant differences were found in TWSTRS among sex groups (mean 19,84 ± 13,43; 19,21 ± 13,02 in women and 20,4 ± 14,036 in men, p=0,760, t Student). CD female patients had significant worse scores in: usual activities (EuroQoL) (p=0,024, Mann-Whitney U), mental health (MH) (p=0,005, Mann-Whitney U) and role-physical scales (RF) (SF36) (p= 0,037 t Student) than men. CD men patients scored significantly worse in: body pain (BP), social functioning (SF), and role emotional (RE) (p<0,05, t Student) compared with gender- and age-matched general population data. CD female patients scored significantly worse in: BP, vitality, SF, RE and MH compared with gender- and age-matched general population data. Age had no significant effect in HRQoL questionnaires scores (p>0, 05, one way ANOVA). Multiple stepwise backward regression analysis revealed that participants' scores on general health had a significant impact on visual analogue scale (VAS) scores (Standardized regression coefficient (SRC) = 0,734, R2=0,528).

Conclusions: CD impairs HRQoL affecting different aspects of it, particularly those related to physical and social functioning. Gender differences in HRQoL and psychological components should be considered and evaluated in patients under treatment.

We-69

Functional imaging of the brain in dystonia

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Objective: The purpose of the present study is to determine the clinical benefit of DBS surgery in 7 patients with dystonia, as well as to evaluate the putative effects of stimulation in brain perfusion, using Single Photon Emission Computed Tomography (SPECT).

Background: Deep brain stimulation (DBS) has been proved to be an effective treatment for medically intractable dystonia. Functional neuroimaging provides well-established means of studying regional cerebral blood flow (rCBF) in humans in vivo. Nevertheless, very few studies have investigated the changes in rCBF after DBS in dystonic patients.

Methods: Seven patients with dystonia, refractory to any conservative treatment, underwent DBS surgery. Six patients presented with secondary dystonia and 1 patient with idiopathic orofasial dystonia (Meige's Syndrome). Clinical assessment of dystonia was performed pre- and post-operatively using the Burke-Fahn-Mardsen Dystonia Rating Scale (BFMDRS). Cosman-Roberts-Wells (CRW) frame, Magnetic Resonance Imaging (MRI) Scan, FrameLink software and microelectrode recordings (MER) have been used for localization of the targets (GPi and Voa). Brain SPECT was performed post-operatively in two separate studies for each patient, one in the "off-DBS" and the other in the "on-DBS" state. The change of rCBF in the 3 following brain regions of interest (ROIs): primary motor mortex, premotor and supplementary motor cortex and prefrontal cortex, was evaluated.

Results: Clinical response to DBS was variable among patients. A mean improvement rate of 54.7% in BFMDRS total scores was found post-operatively. Brain SPECT imaging analysis revealed an overall decrease in rCBF in the investigated ROIs, during the "on-DBS" state. Post-operative improvement in BFMDRS total scores was significantly correlated with the observed decrease in perfusion in the presence of DBS.

Conclusions: When conservative treatment fails to relieve severely disabled patients suffering form dystonia, DBS may be a promising therapeutic alternative. Moreover, our study points out a putative role of brain SPECT as a helpful tool correlating clinical outcomes with changes in rCBF induced by DBS.

We-70

Health-related quality of life in patients with focal dystonia

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Objective: The aim of this study was to examine whether differences in HR-QoL among patients with cervical dystonia, blepharospasm, and writer's cramp could be related with selected clinical, psychosocial and demographic characteristics.

Background: Little is known about the clinical, psychosocial and demographic factors associated with a poor health-related quality of life (HR-QoL) in patients with primary focal dystonia.

Methods: The study comprised 157 consecutive patients with adult-onset primary focal dystonia treated and followed at the Institute of Neurology, Clinical Centre of Serbia, Belgrade. All patients completed SF36 (Serbian translation). In order to measure disease related factors, the Global Severity Scale (GBS) was used. The level of social participation was measured by the Leisure Activity Scale (LAS), and coping behavior by the Acceptance of Illness Scale (AIS) and the Stigma Scale (SS). The Multidimensional Personal Support Scale (MPSS) was used to measure support from partners, friends, and family members. Self esteem and a tendency to self deprecate were measured by two subscales: the Self Esteem Subscale (SES) and Self Deprecation Subscale (SDS). Pearson's correlation coefficient was used to study the association between subscales of the SF36 and GSS, LAS, AIS, SS, MPSS, SES, SDS scores.

Results: Patients with higher GSS, AIS, SS, and SDS values, had significantly ($p<0.01$) lower scores of PF, RP, RE and MH. Significant ($p<0.01$) positive correlation was obtained between the LAS and PF, RP, and RE. When we analyzed each group separately, among patients with torticollis, a significant ($p<0.05$) inverse correlation was observed between each SF-36 domain and the following scales: GSS, AIS, SS and SDS. LAS and SES values inversely correlated with GH (r=-0.249) and VT (r=-0.275). The QoL in patients with blepharospasm was affected in several domains. Significant ($p<0.05$) inverse correlations were registered between RP and all the scores of the used scales except MPSS. In patients with hand dystonia, significant inverse correlation were showed between RE and both AIS (r=-0.516) and SDS (r=-0.525).

Conclusions: We concluded that the dystonic patients present with a wide range of social disabilities and impairments of HR-QoL.

We-71

Characteristics and concordance of mirror dystonia in patients with writer's cramp

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Objective: To study the prevalence, and characteristic features of mirror movements in patients with writer's cramp.

Background: Mirror movements in writer's cramp has been described, but there are very few studies on their characteristics and concordance with the dystonic movements.

Methods: Consecutive WC patients along with age matched controls were studied. All subjects were examined for WC, mirror dystonia (MD) while writing with their non dominant hand and mirror movements during other voluntary repetitive tasks(finger tapping, closing and opening a fist, pronation and supination), using a standardized protocol with videographic recording. Writer's cramp was evaluated and

scored according to the writer's cramp rating scale and MD was assessed using a modification of Woods and Teuber mirror movements scale, which assessed amplitude, onset and distribution of dystonia. Concordance and discordance of MD was evaluated for digits I-III, wrist and elbow movements. Correlation between dystonia severity and MD score was analysed using Pearson's correlation coefficient.

Results: Twenty WC patients with a mean age of 41±15.1 years (17 males), along with 20 controls were included in the study. All were right handed individuals. Mean disease duration in WC patients was 64.4± 60.2 months. Family history was noted in 25%. Mirror dystonia was noted in 13 patients (65%) while 5% of controls had mirror movements in their right hand while writing with their left hand. Discordance of MD for the digits I-III, wrist and elbow were seen in 23.1, 46.2, 57.1, 55.6 and 50% respectively. Maximum discordance of MD was seen with wrist flexion noted in 75% of WC patients. Mean score on writer's cramp rating scale was 8.1± 2.7 and mean MD score was 3.8± 0.4 and Pearson correlation coefficient of 0.46 ($p = 0.04$). Mirror movements during other voluntary repetitive tasks were significantly higher among patients (70%) compared to 15% among controls ($p = 0.007$).

Conclusions: Mirror dystonia and mirror movements were seen frequently in WC patients. Significant discordance was noted in mirror dystonia, emphasizing its role in differentiating dystonic movements from compensatory movements; thus it may help in muscle selection for botulinum toxin injection.

We-394

Tetany as a differential diagnosis of musician's cramps

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Objective: We report a 34-year-old male professional hornist complaining of perioral stiffness impairing his embouchure and rendering him unable to perform. The stiffness was first noticed 10 months ago and worsened subsequently. It is triggered by playing the horn for at least 15min.

Background: Muscle cramps can interfere with a patient's ability to play musical instruments. In most cases they represent focal dystonia. Other aetiologies, however, have to be considered.

Methods: Detailed patient's history, clinical examination, clinical neurophysiology and laboratory tests were performed.

Results: Detailed evaluation of the patient's history revealed perioral dysaesthesias occuring together with the stiffness as well as carpopedal spasms after hyperventilation. On clinical examination 5min hyperventilation elicited reproducible carpal spams. Trousseau and Chvostek signs were negative. Laboratory tests including total and free serum calcium, parathyroid hormone, vitamine D, calcitonin, aldosterone, magnesium and arterial blood gases were normal. Postischemic needle electromyography of the first dorsal interosseus muscle showed typical multiplets of up to 11 serial discharges during a period of 10min. After diagnosing the condition as normocalcaemic tetany triggered by professional hyperventilation oral increase of the serum calcium level to the upper normal range produced reduced the hyperventilation tetany substantially and ameliorated the perioral stiffness to some degree.

Conclusions: Tetany may be a differential diagnosis to focal dystonia in musicians especially when localised periorally or manually. Playing of wind instruments and anxiety during public performances may trigger the attacks. Dysaesthesias, prolonged provocation and provocation by hyperventilation may direct one's attention towards tetany.

We-395

Acute blepharospasm and torticollis associated with an ependymoma of the lateral ventricle

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Objective: We report the case of a young man with bilateral blepharospam revealing an intraventricular ependymoma.

Background: Ependymomas are tumours of the central nervous system (CNS) rarely observed in adults. Secondary focal dystonias, albeit classical, remain rare. In most cases they correspond to vascular lesions of the lenticular nucleus. The extent of clinical signs depends on the lesion s size and its location. A tumoral cause is particularly rare and most frequently corresponds to a vascular lesion (e.g. cavernoma).

Methods: A 23 year-old man, without personal or familial medical history, suddenly presented a bilateral blepharospasm. Computed tomography and magnetic resonance imaging were performed, revealing an intraventricular lesion. Surgical resection of the lesion via an interhemispheric transcallosal approach was proposed with histopathological analysis of the lesion.

Results: Clinical examination showed the existence of a blepharospasm with severe bilateral spasms of orbicularis oculi muscles associated with a spasmodic torticollis. No other neurological deficits were observed. Polygraphic electromyographic recordings indicated a synchroneous activation of the neck and face muscles. Computed tomography and magnetic resonance imaging showed two lesions: the largest was located in the right lateral ventricle reaching the caudate nucleus; another smaller lesion was observed in the right temporal horn. Surgical resection of the intraventricular lesion was performed and histopathological analysis revealed a diagnosis of ependymoma (grade II). A clinical improvement was observed in the following days after surgery. However, several weeks later, a treatment with botulinium toxin was necessary because of the persistence of some blepharospasm but torticollis was no longer observed. The clinical status remained unchanged during the one-year post surgical follow-up with the exception of some residual cephalalgia.

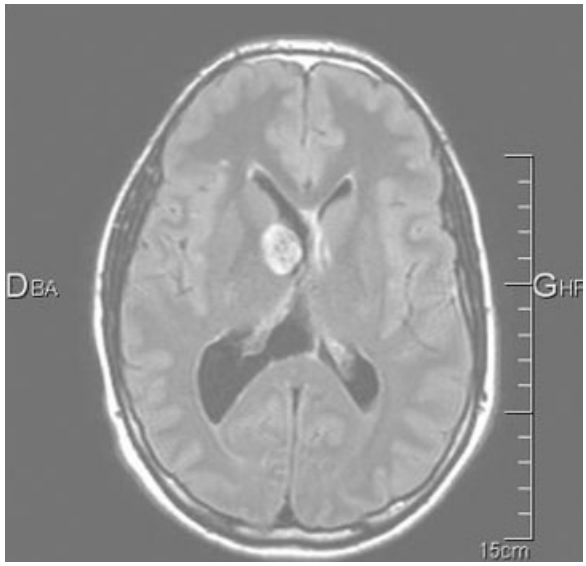

FIG. 1 (We-395). MRI showed that the lesion measuring 21 × 15 mm involved the right lateral ventricle, the head of the right caudate nucleus and a portion of adjacent white matter.

Conclusions: Ependymoma, a rare CNS tumour, is mainly observed in children with a predominant location in the fourth ventricle. Our observation reveals that it can be responsible for focal dystonia in young adults.

We-396

A patient with a novel mutation of ε-sarcoglycan gene responded to anticholinergic treatment and improved spontaneously

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Objective: To report a female patient with myoclonus-dystonia(MD) due to SCGE deletion who showed good response to the anticholinergics and spontaneous improvement.

Background: MD is a familial disorder with autosomal dominant inheritance, and is associated with a mutation of the ε-sarcoglycan (SCGE) gene. About 80% of patients with genetically confirmed MD respond dramatically to alcohol ingestion. But symptomatic drug therapy is usually disappointing. There are several reports of patients benefiting from treatment with L-dopa. Among reported patients with genetically confirmed MD, a marked therapeutic effect to anticholinergics has not been described yet. The clinical courses vary widely and cannot be predicted. Most patients with SCGE mutations show progressive deterioration or static clinical courses, but spontaneous remission occurs rarely.

Methods: A 19-year-old girl was seen in our clinic with 14-year history of involuntary jerky movements. She was extensively followed over 7 years. Genetic studies for the mutation of SCGE gene were performed.

Results: A 19-yr-old girl showed retrocollis and backward and right side tilting of the trunk as well as generalized jerks and dystonia severely affecting the left arm. Her father had a 40 year history of asymptomatic fine jerky postural tremor of both hands. The myoclonus and dystonia improved markedly by the ingestion of small amounts of alcohol. Brain MRI studies were normal. DNA analyses of her and her father showed the same mutation of the SGCE gene [deletion in exon 6 [c.771_772delAT, Cys258X)]. She did not respond to either L-dopa/carbidopa or clonazepam. Both dystonia and myoclonus responded markedly to trihexiphenidyl (2 mg t.i.d) The effects lasted for 7 years and dyskinesia did not recur for 1 year after discontinuation of anticholinergics.

Conclusions: This patient had some clinical features atypical for MD, such as good response to low-dose anticholinergics and spontaneous remission. We suggest that a trial of anticholinergics may be considered in patient with MD. The possibility of spontaneous improvement should be kept in mind in the therapeutic strategy, especially regarding deep brain stimulation.

We-397

Paroxysmal kinesigenic dyskinesia (PKD) and focal epilepsy: Association or coincidence

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Objective: To report a case, along with accompanying video, of a patient who presented with episodes of dystonic posture of her left leg and coexistent epilepsy.

Background: Paroxysmal kinesigenic dyskinesia (PKD) is a rare group of hyperkinetic movement disorders that recur in episodic fashion. The typical clinical characteristics are brief attacks of dystonia, chorea or combinations of different hyperkinesias affecting a limb. The pathophysiology of PKD is unclear although it is thought to be a disorder of the basal ganglia or a form of epilepsy.

Methods: A 35 year-old female patient presented with difficulty walking. She noticed her symptoms since she was 10. Her left leg usually gets spasm and in dystonic posture when she stands up quickly from a sitting position, starts walking or quickly moves of her left leg. She had neither pain nor loss of consciousness during the attack. She usually has paresthesia of her left leg as a premonitory sensation of imminent attack. The attack usually lasts for seconds and occurs up to 100 times per day. She had a history of generalized tonic-clonic seizures and nocturnal seizures when she was 19. Her aunt has a history of epilepsy. General physical and neurological examinations were unremarkable. Her symptom was well control with carbamazepine 800 mg/day and phenytoin 400 mg/day.

Results: Laboratory tests which included CBC, BUN, Creatinine, LFT were normal. The MRI of the brain revealed a focal small non-enhancing lesion at the left middle frontal gyrus. The electroencephalogram (EEG) revealed a normal pattern. Given history and exam findings, her symptom was concordant with the diagnosis of PKD. History of recurrent seizures and gliotic lesion at the left cerebral cortex support the diagnosis of focal epilepsy. According to the literature, there were about 8% who had both PKD and epilepsy. However its relationship is still questioning. Absent of epileptogenicity and the normal MRI finding in the right cerebral cortex may not exclude the functional abnormality.

Conclusions: This case may support the relationship between PKD and epilepsy in view of its paroxysmal nature, the stereotype, the response to anticonvulsants, the sensory aura and the association of epilepsy in her history. However, PKD can not be considered as a simple focal cortical epilepsy or a disorder of extrapyramidal system but it appears to be a circuit disorder between cortex and the basal ganglia.

We-398

Use of botulinum toxin type B (neurobloc) for segmental dystonia in a regional neurology centre

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Objective: To report indication, clinical response, tolerability, and injection interval in patients prescribed BoNT-B for segmental dystonia, where Dysport is first-line treatment and BoNT-B is second or third-line.

Background: Segmental dystonia is the commonest application for botulinum toxin (BoNT) injection therapy, but requires repeated injections to maintain therapeutic response. Two main subtypes (BoNT-A as Dysport, Botox, and Xeomin, and BoNT-B as Neurobloc) are commercially available; there are indications Neurobloc may have a longer duration of benefit.

Methods: Data for 539 patients receiving BoNT treatment from 2005 was analysed, with a focus in patients in whom there was current or prior use of BoNT-B.

Results: Of 539 patients, 162 had hemifacial spasm or blepharospasm, leaving 377 with segmental dystonia. 40 of those (10.6%) (15 male) had received BoNT-B. Mean age 57.9 years (SD 12.2) and time since diagnosis 9.6 years (6.4). Cervical spine imaging, performed in 21 (52.5%), normal in 7 (33.3%) but showed some degenerative change in 14 (66.7%). 20 (50%) had head and/or limb tremor and 4 (10%) had positive family history of dystonia. All had previously been treated with BoNT-A: 26 (65%) tried 1 preparation, 13 (32.5%) tried 2, and one (2.5%) tried all 3. Mean duration on previous BoNT-A was 51.9 months (64.4), and injection interval 12.8 weeks (5.4). The reason for switch to BoNT-B was reducing effect of BoNT-A in 29 (72.5%) and side effects (swallowing/speech difficulties) in 11 (27.5%). Mean BoNT-B treatment duration 20.8 months (24.8) and mean injection interval greater than for BoNT-A at 15.6 weeks (1.5) ($p<0.05$). Good clinical response was reported in 8 (20%). 30 (75%) had no/poor response – 9 of whom (22.5%) experienced side effects. 2 (5%) yet to be reviewed. 12 (30%) remained on BoNT-B long-term (good response 8, improvement 4). 28 (70%) discontinued BoNT-B (22 (78.6%) restarted BoNT-A and 6 (21.4%) stopped BoNT). The mean injection interval was not different for patients continuing BoNT-B long-term compared with those who stopped (15.3 weeks (SD 2.2) v 15.7 (0.8), $p=0.50$).

Conclusions: BoNT-B shows some efficacy in patients with segmental dystonia who have a reducing response to BoNT-A, with a significantly longer injection interval in patients continuing on BoNT-B than for BoNT-A preparations.

We-399

The phenomenology of the geste antagoniste in blepharospasm and cervical dystonia

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Objective: To assess the phenomenology of the geste antagoniste (GA) in patients with primary blepharospasm (BSP) and primary cervical dystonia (CD).

Background: The GA is a voluntary action performed by patients with dystonia which alleviates the severity of dystonic postures or movements. It is a well-recognized clinical feature of primary cranial and CD, and its presence may give support to the diagnosis. Whereas the clinical phenomenology of the GA in CD has been already described, little information is available on the main features of the GA in patients with BSP.

Methods: Forty-three patients with primary BSP (74.5% women, mean age at onset 57.2 years, mean disease duration 8.5 years) and 27 patients with primary CD (70.4% women, mean age at onset 44.8 years, disease duration 9.9 years) underwent a standardized investigation including a semi-structured interview and semiquantitative clinical rating of their GA.

Results: Test-retest analysis on a sub-sample of patients showed substantial reliability in reporting presence or absence of GA ($k=0.79$; $Z=5.47$; $p<0.00001$). Thirty-two BSP patients (74.4%) and 26 CD patients (96.3%) reported to have (or have had) an effective GA; 10/32 (31.2%) of BSP patients and 14/26 (53.8%) of CD patients reported more than one GA. The phenomenology of GA was influenced by the clinical form of dystonia associated with the GA: a "forced" type of GA (i.e. a geste characterized by voluntary forceful opposition to the dystonic movement), and a GA performed in the same anatomical site affected by dystonia were significantly associated with a diagnosis of BSP ($OR=4.2$, $p=0.04$, and $OR=$, $p<0.0001$, respectively). Age, age at disease onset, disease duration, spread of dystonia and effect of botulinum toxin did not significantly impact upon quality and efficacy of the GA in both BSP and CD patients.

Conclusions: The GA is a relatively stable feature of both BSP and CD, although there are differences in phenomenology and frequency of the GA between patients with BSP and patients with CD.

We-400

A novel, easier and safer botulinum toxin injection technique for the treatment of epiphora

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Objective: We present two patients with epiphora treated with a novel BTX injection technique with a significant improvement of the lacrimal drainage and symptoms recovery.

Background: Several clinical reports showed an improvement on the epiphora by injecting BTA through the lacrimal gland. This technique is not exempt of adverse events.

Methods: 2,5 UI BTX A were injected into the medial part of the lacrimal common canaliculi, medial to the upper and lower canaliculi junction.

Results: A reduction in the tear secretion after the BTX A injection was reported. The patients had been receiving continuously periodic botulinum toxin injections every 3 or 3 and half months for 5-6 years. They denied any adverse.

Conclusions: Our novel injection technique for the treatment of epiphora is easy to perform, effective and with a safer profile of adverse events than the previous one. The mechanism of the BTX A effects on the lacrimal drainage need to be established as the mechanism of tear outflow.

We-401

Pseudoathetotic movements due to cervical stenosis mimicking a thalamic hand syndrome

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Objective: To describe hyperkinetic involuntary movements mimicking a thalamic hand syndrome in a patient with cervical stenosis.

Background: Focal lesions in the thalamus have been frequently associated with dystonia and athetosis. Rarely, spinal cord disease can present with isolated involuntary movements.

Methods: Case report of a 69-year-old man developing paresthesias, athetosis and dystonia in the left hand, that progressed to the right side after 18 months of disease duration. Cranial MRI and ^{99m}Tc-HMPAO cerebral SPECT scans were performed.

Results: A 69-year-old-man was referred to our Unit because of sensitive disturbances and involuntary movements in the left hand. One year ago, he noted onset of sensory loss and dysesthesias limited to the left hand, followed by progressive impairment, severe sensitive deficits and involuntary movements. Examination revealed dystonia, athetosis, and loss of all sensory modalities in the left hand (Video). No rigid-akinetic syndrome, or abnormal movements involving the oro-facial-buccal region were observed. Cognition was intact. No history of exposure to neuroleptic medications or severe head trauma existed. Brain MRI and SPECT did not disclosed focal lesions in thalamus, basal ganglia, or cortical structures. Eighteen months after the onset of involuntary movements, similar but milder symptoms appeared in the contralateral hand, with progressive sensory loss, dystonia and athetosis. Diagnosis of corticobasal degeneration was initially given. However, bibrachial symptoms, sensory loss involving all modalities, and no imaging alterations led to the performance of cervical MRI showing cervicoarthosis with spinal stenosis and myelopathy at C3-C6 level. Laminectomy was perfromed, with recovery of sensory loss but persistence of hyperkinetic movements.

Conclusions: Movement disorders due to cervical pathology have been scarcely reported. Cases reported described sensory disturbances and a stereotyped pattern of movement disorders combining hand dystonia and athetosis, similar to so-called thalamic hand. Our case report describes unilateral involuntary movements usually associated with thalamic lesions. A delay in the diagnosis of cervical stenosis probably accounted for persitent sequelae. Cervical pathology should be ruled out in the presence of abnormal movements resembling a thalamic hand syndrome.

Th-45

Impaired lateral inhibition in focal dystonia

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Objective: To explore if sensory information is processed and integrated during sensory-motor plasticity phenomena by using lateral inhibition mechanisms in normal humans and in patients with focal hand dystonia.

Background: Several evidences suggest that lateral inhibition is a powerful operational system within sensory-motor cortex where it could aid the selective execution of desired movements. It can also be hypothesized that such a mechanism is operating during motor learning in order to select the appropriate muscle sequence to be stored within the final motor engram.

Methods: We have used transcranial magnetic stimulation to explore lateral inhibition during sensory-motor plasticity in 8 dystonic patients and in 8 healthy subjects. In particular we looked at motor evoked potential (MEP) facilitation obtained after 5 Hz repetitive paired associative stimulation after median (PAS M), ulnar nerve stimulation (PAS U) and median+ulnar nerve (PAS MU) stimulation. In this way we could compare the amount of MEP facilitation in the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) obtained after PAS MU with the arithmetic sum of MEP

facilitation obtained after stimulation of the individual nerves (PAS M + PAS U).

Results: In healthy subjects we have demonstrated that the amount of APB MEP facilitation obtained in the condition PAS MU was about 60% of the algebraic sum of PAS M + PAS U. This parameter can be defined as lateral inhibition index (LI index). In dystonic patients the amount of facilitation in the condition PAS MU was around 85%.

Conclusions: These data suggest that lateral inhibition is deficient during sensory-plasticity and this could contribute to the formation of motor memories with redundant information, which could culminate in overt dystonia.

Th-46

Painful legs moving toes treated with botulinum toxin as a dystonic syndrome

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Objective: To demostrate the use of botulinum toxin as a potential therapeutic option for the treatment of PLMT.

Background: The syndrome of painful legs moving toes (PLMT) is a rare disorder characterized by painful sensation in the legs associated with involuntary movement of the toes. The treatment of this condition can be challenging and often has a poor response to pharmacotherapy. We present a case of a patient with PLMT who obtained substantial and sustained benefit in both pain and severity of involuntary movement when treated as a dystonic syndrome with Botulinum toxin type A injections.

Methods: Case Report.

Results: A 43 year old man presented with a complaint of constant burning pain for two years that was located in the right lower extremity, and was most severe in the right large toe, associated with spasms in the RLE. He was a recreational marathoner and the pain was preventing his participation in athletic events. He had no history of trauma or surgery to the leg or foot, other than the exertional stress from running. Treatment with acetaminophen, naproxen, pregabalin, clonazepam and ropinirole were ineffective. MRI, NCS and EMG were unremarkable. Physical examination revealed constant abduction/adduction with intermittent flexion/extension oscillations of the toes. There was no discoloration or allodynia. Distraction did not alter the involuntary movement. A diagnosis of PLMT was made and given the severity of the symptoms, their resemblance to a dystonic phenomenon, and the refractory nature of his problem, we decided to initiate a trial with botulinum toxin type A in the flexor hallucis brevis, adductor hallucis and flexor digitorium brevis. Significant reduction of the involuntary toe movements and pain to a "minimal" level was reported by patient. No weakness or other side effects were noted. The benefit was documented for 11 weeks. Repeat injection every three months for 24 months have provided similar benefit. He was able to resume his exercise program after treatment.

Conclusions: The clinical presentation of PLMT could resemble a dystonic phenomenon and can be poorly responsive to conventional pharmacotherapy. Given the potential for substantial and sustained improvement in both pain and abnormal involuntary movement, botulinum toxin should be considered as a treatment option for these cases.

Th-47

Clinical spectrum of dopa-responsive dystonia in the Polish families

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Objective: To present the clinical features of DRD patients from the Polish population.

Background: Dopa-responsive dystonia (DRD) is an autosomal dominant disease caused by mutations in the *GCH1*, characterized clinically by progressive foot dystonia and gait disorder, with marked diurnal fluctuation and sustained response to low dose levodopa therapy. In the last few years, some additional clinical features, including adult-onset parkinsonism, oro-mandibular dystonia, focal cervical dystonia and depression, were described.

Methods: Clinical course and symptomatology of 12 patients (all women) from 5 families with genetically proven DRD were analyzed.

Results: In 10 of 12 patients the onset was between 4 and 12 years of age. In two others, DRD symptoms started in adulthood (28 and 44 years). The first symptom was foot dystonia. In one case the food dystonia promptly progressed to hemidystonia, and in the other cervical dystonia developed a few years later. In 6 patients some other involuntary movements (myoclonic jerks, hemifacial spasms) or parkinsonian syndrome additionally developed. Depression was diagnosed in one case. Five patients from one family presented clinically significant shortening (1.5—4 cm) of a dystonic leg. The dystonia was progressive, except in one patient with spontaneous remissions. The typical diurnal fluctuations of dystonia severity was observed in all foot dystonia and hemidystonia patients. Administration of low dose of lewodopa (50—300 mg) resulted in relieve of foot dystonia, but in 2 cases dyskinesias appeared thereafter. Coincidence of parkin mutations was excluded. Of five *GCH1* mutations identified in these families, three were novel, c.453+1G>A, c.509+5delG, c.539A>C (Q180P), c.680C>A (Thr227Asn), while one, c.614T>G (V205G), was reported previously.

Conclusions: In the course of the disease, many DRD patients develop symptoms other than foot dystonia. Even carriers of the same mutation demonstrated variable combinations of additional clinical features.

Th-48

Longitudinal effects of deep brain stimulation in the globus pallidus on intracortical GABAergic inhibition and LTP-like plasticity in dystonia

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Objective: To study longitudinal effects of GPi-deep brain stimulation (DBS) on motor cortex excitability in dystonia.

Background: Deep brain stimulation (DBS) in the internal globus pallidus (GPi) is an effective treatment in patients with dystonia, particularly in primary generalized dystonias. Compared with rapid improvement in symptoms seen in Parkinson's disease, maximum clinical effect in dystonia often occurs only 3-6 months after starting stimulation.

Methods: To understand more about underlying mechanisms of long term DBS effects in dystonia we studied responses to transcranial magnetic stimulation protocols in patients with different types of dystonia before, and at various time-points after GPi-DBS-surgery. Two main paramenters in our design were short latency intracortical inhibition (SICI) as a measure of GABAergic excitability of cortico-cortical connections and paired associative stimulation (PAS) which reflects LTP-like synaptic plasticity. The latter was increased compared with normal before implantation of DBS, whereas SICI was reduced.

Results: The results show that in primary dystonias DBS gradually normalizes SICI and that the time course of this change correlates with clinical improvement. In contrast the pathologically exaggerated LTP-like plasticity was completely abolished in the early phase after the onset of DBS treatment and then gradually increased to the levels observed in healthy individuals.

Conclusions: The cortico-basal ganglia-cortex circuitry is thought to play an important role in motor learning and in automatisation of sequential movement. Our hypothesis is that prior to DBS, abnormal basal ganglia output shifts the control of synaptic plasticity towards

increased levels, with the result that inappropriate associations are made between inputs and outputs, thereby causing excessive dystonic muscle contraction. Removing the abnormal basal signal after DBS causes the control of plasticity to swing below normal levels. This reduces excitability in the abnormal, dystonic connections and allows the remainder of the motor system to relearn normal movement patterns.

Th-49

Clinical and genetic description of a family with paroxysmal exercise-induced dystonia

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Objective: To describe a new family with paroxysmal exercise-induced dystonia (PED).

Background: PED is a rare paroxysmal dyskinesia manifesting as episodes of dystonia following physical exercise. PED may occur spontaneously or as an autosomal dominant hereditary disorder. Fewer than 20 families have been described so far.

Methods: A family with three affected female patients has been assessed. Family members have been interviewed by telephone and all volunteering persons, including the three patients have been examined. Genetic analyses for known possible causes of paroxysmal dyskinesia have been performed (myofibrillogenesis regulator 1 [MR1], calcium-sensitive K+ channel [KCNMA1], glucose transporter type 1 [GLUT1]).

Results: The index patient and two of her children were found to have mild PED. The physical exam in the interval was unremarkable in two patients; the third had a very mild right sided spastic syndrome after a car accident with a cerebral haemorrhage from which she had otherwise fully recovered. PED attacks were infrequent, involved the legs and/or arms and lasted a few minutes up to 1 hour. Consciousness was not impaired during an attack, and dystonia rapidly abated during rest. Episodes were typically triggered by physical exercise involving the affected limb. Treatment with valproic acid efficiently prevented attacks. The first PED episodes occurred during childhood in one and at age 22 and 18 in the other patients. Migraine (2 patients) and generalized epilepsy (1 patient) were the only comorbidities known to be associated with PED found in our patients. Sequencing of GLUT1 exon 4, KCNMA1 exon 1, and MR1 exon 1 in the three affected family members showed normal sequences.

Conclusions: We describe a new family with PED compatible with autosomal transmission. The clinical manifestations are in line with previous descriptions of PED. None of the known mutations studied so far has been detected in this family suggesting a novel change.

Th-52

Target point optimization in pallidal deep brain stimulation in cervical dystonia

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Objective: To evaluate the effect of deep brain stimulation on motor impairment in patients with cervical dystonia (CD) at different localizations in the globus pallidus (GPi).

Background: Pallidal deep brain stimulation has been shown to improve cervical dystonia. Presumably, the therapeutic effect critically depends on electrode localization, however optimal target point remains controversial in the absence of quantitative assessment of clinical benefit at different sites within GPi.

Methods: Post-operative magnetic resonance imaging (MRI) data of 21 patients with CD (median age 59; 11 male) and treated by bilateral DBS were assessed to derive lead contact coordinates after normalisation into the standard Montreal Neurological Institute (MNI) stereotactic space. Motor performance of patients was assessed pre- and post-operatively using Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Relative improvement from baseline to post-operative TWSTRS severity score at different active contact settings was mapped to corresponding MNI coordinates. This three-dimensional functional distribution was analyzed with k-means cluster analysis to identify subsets of contacts with similar amelioration of CD severity. Centroids as geometrical centers of clusters were calculated to assess spatial variance of contacts.

Results: 120 combinations of pre-operative TWSTRS severity score (mean 19.3) to post-operative scores (mean 13.5) assigned to single contact-positions were assessed, resulting in one cluster with higher TWSTRS improvements (HTI; mean 58.8 %; n=44) and one with lower TWSTRS improvements (LTI; mean 13.9 %; n=76). Distances from contacts to their associated centroids differed significantly ($p<0.001$; t-test) between HTI (1.76 ± 0.91 mm [$\mu \pm \sigma$]) and LTI (2.83 ± 1.68 mm), indicating increased dispersion of LTI-contacts. The centroid of HTI was located to MNI X:-20.15 mm, Y:-6.82 mm, Z:-5.22 mm. Spatial distance of stimulating contacts with respect to HTI-centroid correlates with TWSTRS severity score ($p<0.01$; Spearman's rho = -0.483).

Conclusions: Amelioration of CD severity negatively correlates with distance to a sub-region of GPi, which can be described in normalized MNI-coordinates. Further analysis should address the shape and extents of this clinically responsive sub-region.

Th-53

GLUT1 gene mutations cause sporadic paroxysmal exercise-induced dyskinesias

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Objective: To report novel mutations in the glucose transporter 1 (*GLUT1)* gene which cause paroxysmal exercise-induced dyskinesias (PED) in sporadics

Background: Paroxysmal exercise-induced dyskinesias (PED) are involuntary intermittent movements triggered by prolonged physical exertion. Autosomal dominant inheritance may occur. Recently, mutations in the glucose transporter 1 *GLUT1* gene (chr. 1p35-p31.3) have been identified as a cause in some patients with autosomal dominant PED. Mutations in this gene have previously been associated with the GLUT1 deficiency syndrome.

Methods: We performed mutational analysis in ten patients with apparently sporadic PED.

Results: We identified two novel *GLUT1* mutations, at least one likely to be de-novo, in two of our patients. Onset was in early childhood. One of our patients had a predating history of childhood absence epilepsy and a current history of hemiplegic migraine as well as a family history of migraine. The other patient had no other symptoms apart from PED. Brain MRI showed cerebellar atrophy in one case.

Conclusions: Mutations in *GLUT1* are one cause of apparently sporadic PED. The detection of this has important implications for treatment as ketogenic diet has been reported to be beneficial.

Th-54

Long-term follow-up of DYT-1 dystonia

C.S. Schwarz, D. Raymond, N. Lubarr, M. Tagliati, R. Saunders-Pullman, S. Bressman (New York, New York)

Objective: To evaluate the naturalistic course of older (>age 39 years) patients with DYT-1 dystonia.

Background: Little is known about later-life clinical outcome in patients with DYT1 dystonia, which renders counseling with respect to long-term disease progression difficult. A systematic investigation of older individuals with DYT1 dystonia will provide important information in this regard.

Methods: Subjects were first ascertained in the clinical setting because of symptoms of dystonia and then were identified genetically as DYT1 mutation carriers. We identified 10 patients who were under current care, age >39 years at last exam and had childhood or adolescent–onset dystonia (age at onset <20 years). We obtained Burke-Fahn-Marsden Rating Scale (BFMRS) scores and evaluated history based on clinical records.

Results: The mean age was 49.8 ±10 years and the mean disease duration was 40.4 ± 10.4 years. The mean age of onset was 9.4 ±1.8 years; mean Burke-Fahn-Marsden Rating Scale (BFMRS) score at last exam was 17.4 ± 7.2 and distribution was generalized in all patients. Based on the review of clinical records, functional status had not changed significantly after midlife except for one patient who developed mild new signs in a leg and another patient who improved. None became wheelchair-bound. Mean degree of disability was 2.85 ± 1.1. All patients finished college, 60% were employed, 60% married, and 40% had children. Two patients who were younger than the mean, including one with more severe scores, decided to undergo DBS.

Conclusions: Our data suggest that dystonia symptoms in DYT-1 patients stabilize in midlife. Despite a generalized distribution in all, severity and disability in most was only moderate. The two youngest patients subsequently underwent DBS.

Th-55

Gait analysis in a dystonic patient pre and post pallidal deep brain stimulation

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Objective: To study influence of DBS in a patient with multisegmental dystonia referred to gait spatio-temporal and kinematic parameters of lower limbs.

Background: Deep brain stimulation (DBS) of the internal globus pallidus has been shown to be effective in primary dystonia. Although quantitative gait analysis is largely used to study kinematic deviations and movement disorder analysis was applied to study upper limb in focal and generalized dystonia, gait analysis of more complex movement disorders are less described.

Methods: Case report The patient's described is a 52 yrs old female with a cranio cervico-brachial dystonia not responsive to medical therapy.and inejections of botulin toxin. Was videotape-assessed preoperatively and postoperatively (at 6 months and every year) by Burke-Fahn-Marsden Dystonia Rating Scale(BFMDRS). She was followed for 4 years after surgery. • Gait Analysis: Kinematic spatial and temporal gait measurements preoperatively and 12- 24 months following surgery. Patients were assessed by means of the Vicon system during gait using Plug in Gait protocol (PIG) sharing common spherical, retroreflective markers placed bilaterally on anatomically well-defined points to define different segments of the pelvis and legs. The 3-dimensional trajectories of pelvis, hip, knee and ankle in the frontal, sagittal and axial planes were recorded by 6 infrared cameras and analyzed with Polygon software.

Results: Clinical results: the long term follw up confirmed the remarkable improvement after six months that remained stable after 4 years (around 70%). Gait results: Kinematic, spatiotemporal parameters are reported. In this patient was documented a significant improvement in Kinematic spatial and temporal gait measurements in all districts examined (pelvis, hip, knee and ankle and legs) with a normalization of the speed in the gait analysis.

Conclusions: This is the first report of a gait analysis of a patient with multisegmental dystonia pre and post GPi DBS. These data demonstrate that the efficacy of DBS is noteworthy not only in affected segments of dystonia but also could influence and spread to the non affected districts with an evident improvement also in posture and gait.

Th-56

Feedback influences the function of head neural integrator

A.G. Shaikh, H.A. Jinnah, D.S. Zee (Baltimore, Maryland)

Objective: To investigate the role of feedback in stable head holding.

Background: Mathematical integration by central neurons can convert velocity commands for movement to position commands that hold posture. A neural integrator to maintain head posture (hNI) has been identified in the midbrain. We hypothesize that hNI is inherently 'leaky' (i.e., its output is characterized by exponentially decaying drifts of the head toward a null position). The brain likely uses neck proprioceptive feedback or an efference copy of head movement commands to improve the function of the 'leaky' hNI. In certain circumstances, surrogate error signals including visual, vestibular or eye movement information might aid head stabilization.

Methods: We measured head holding in primary (straight ahead) and eccentric positions in 11 healthy subjects; with and without an imposed visual reference (head fixed laser) which the subject was instructed to align with an LED on the wall. Similar experiments were repeated with a vibrator stimulating the neck to distort proprioceptive feedback.

Results: With the head-fixed laser, subjects held their head steady (Figure 1A). When neck vibration was added, their heads drifted centripetally which was followed by rapid corrections (Figure 1B). The

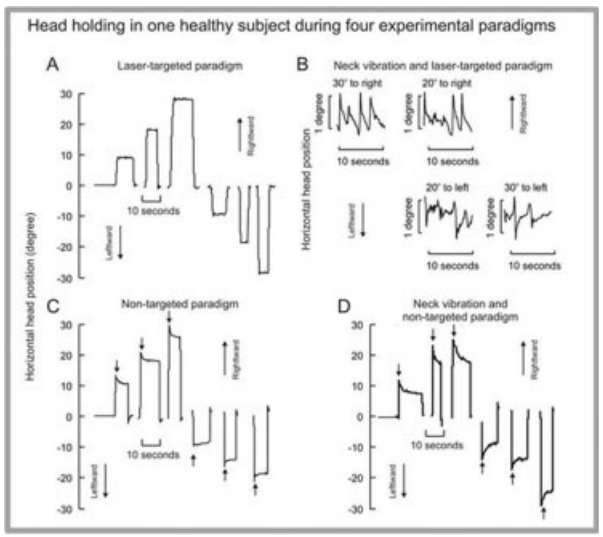


FIG. 1 (Th-56). (A) Epochs of central and eccentric head positions during the laser-targeted paradigm are illustrated. Horizontal head position (ordinate) is plotted versus time (abscissa). Stable head position is seen at central and eccentric positions. (B) An example of epochs of head holding at 20° and 30° on to the right and left side by the same subject when neck vibration was added to the laser-targeted paradigm. During this paradigm, leftward drift in the head position were present during attempted rightward head holding and rightward drifts in the head positions were seen during leftward holding. The drifts in the head position were followed by rapid corrective movements turning the head back to the desired orientation. (C) This panel illustrates an example of head holding by the same subject during non-targeted paradigm. As the LED turned off (arrow), the head position began to drift towards the center. The leftward drifts were present during attempted head holding to the right, while rightward drifts were present while attempting to hold the head to the left. Qualitatively similar phenomenon was also seen when neck vibration was added to the non-targeted paradigm (D).

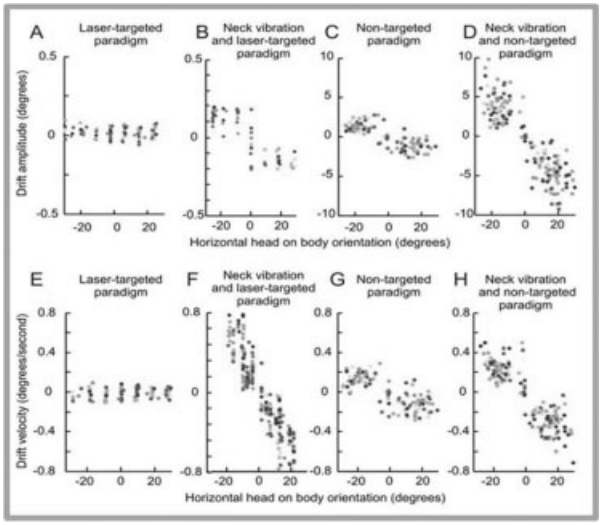


FIG. 2 (Th-56). Dependence of drift amplitude (A-D; ordinate) and velocity (E-H; ordinate) on the eccentric horizontal head position (abscissa). Each data point represents one drift, while each color depicts one subject. Drift amplitude and velocity increase systematically as horizontal head position rotates farther away from the central position. There is no drift at the central position–null position. The drift direction reverses as the subjects turn head on the other side of the null orientation (change in the sign of drift amplitude and velocity in panels A-H). Slope of the linear fit of the amplitude (and velocity) to eccentric horizontal head position dependence increases when neck vibration was added to the non-targeted paradigm. This suggests that the amplitude and velocity of the drifts is increases in presence of neck vibration.

head drifted, without corrections, when there was no visual reference (Figure 1C,D). In all subjects, the amplitudes and velocities of the drifts was dependent upon the head eccentricity (Figure 2). Initially the drifts were absent at primary gaze (null position); during eccentric head holding the drifts were centripetal and their velocity increased proportionately as the desired head position moved farther away from the null. Rebound drifts were seen when the subjects returned their head to the null position after sustaining an eccentric position.

Conclusions: These results suggest: (1) hNI is inherently 'leaky'. (2) The feedback from neck proprioceptive systems improves the function of 'leaky' hNI, since a perturbation of neck proprioceptive afferents impaired head holding. (3) Providing a visual reference with a head-fixed laser improves head holding; thus under certain circumstances surrogate error signals can improve head stabilization. These results may have implications for understanding the the head drifts in patients with idiopathic cervical dystonia.

Th-57

Effects of botulinum toxin on the oscillatory head movements in cervical dystonia

A.G. Shaikh, D.S. Zee, H.A. Jinnah (Baltimore, Maryland)

Objective: To investigate the effects of botulinum toxin (BTX) on kinematic properties of oscillatory head movements (OHM) in idiopathic cervical dystonia (CD).

Background: We showed two types of OHM in CD; large OHM is jerky and appears like 'head nystagmus'; and small OHM is sinusoidal and resembles essential tremor. A possible role of an impaired head neural integrator (hNI) was proposed. We also showed in healthy subjects that altered neck proprioceptive feedback impairs stable head holding and manifests as head drifts that resemble large OHM in CD. Subsequently, neck proprioception was proposed as an important feedback source to hNI. Here we hypothesize that in addition to changing neck muscle tone in CD, BTX also improves the neck proprioceptive feedback to the neural integrator.

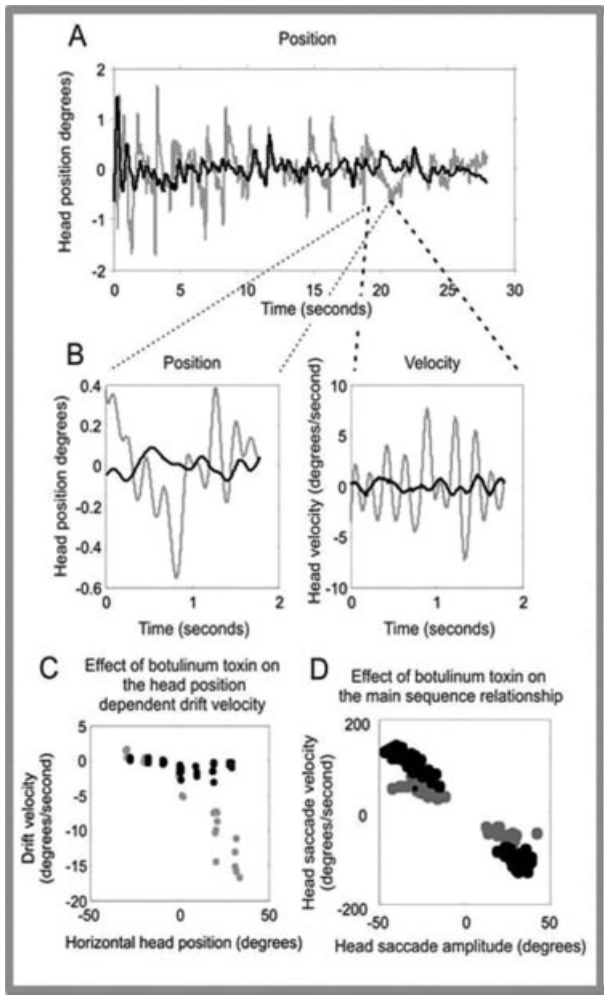


FIG. 1 (Th-57). Effects of botulinum toxin (BTX) therapy on oscillatory head movements in a patient with idiopathic cervical dystonia (CD). (A) Horizontal head position is plotted versus time. Grey trace depicts the head position (characterized by the mixture of jerky and sinusoidal oscillatory head movements) before BTX; while the black trace represents the head position after the therapy. Robust reduction in the both types of oscillatory head movements were noticed (A,B). (C) Slow phase velocity of the drifts in the head positions that comprises the jerky head oscillations are plotted versus corresponding head on torso orientation. Grey data points depict observations before BTX therapy, while the black data points are after. A systematic change in the drift velocity, nullposition (where drift velocity is zero), and drift directed towards the null (sign reversal of the drift velocity after null) before BTX are consistent with the head neural integrator dysfunction in CD. As a response to BTX therapy, not only drift velocity but also its head position dependence was reduced. (D) In a plot depicting the velocity amplitude relationship of ballistic head movements (head saccades), BTX did not reduce the head velocity for the given amplitude (before BTX:grey symbols and after BTX:black symbols).

Methods: Three dimensional head positions were recorded in 8 CD patients when the head was oriented straight ahead or turned to the right or left. Measurements were performed before, and six weeks after BTX therapy.

Results: Figure 1A is an example of large and small OHM before BTX (grey trace). BTX reduced the amplitude and velocity of the both types of OHM (black trace; Figure 1A). At least two mechanisms explain these effects: 1) Altered neck muscle tone; and 2) The change in the neck proprioceptive feedback to the hNI. Presence of null position is commonly seen in CD. Existence of null is also the signature of impaired hNI. In addition, like CD, when hNI is 'leaky' the head drifts towards the null, and there is a systematic increase in the drift velocity as the desired head position shifts farther away from the null. If BTX improved the function of hNI, the head position dependence of the drift velocity should be reduced. Figure 1C illustrates this phenomenon in a CD patient, before (grey symbols) and six weeks after (black symbols) BTX. The effects of BTX were not exclusively due to the reduction in the neck muscle pulling. The velocity of rapid head movements (head saccades) increased after BTX. These results were consistently seen in all CD patients.

Conclusions: Inappropriate neck proprioceptive feedback could impair hNI function to cause head drifts in CD. BTX may affect the neck muscle tone to alter the proprioceptive feedback. The head holding function of the hNI is thus improved. Computational simulations (Figure 2) supported this hypothesis.

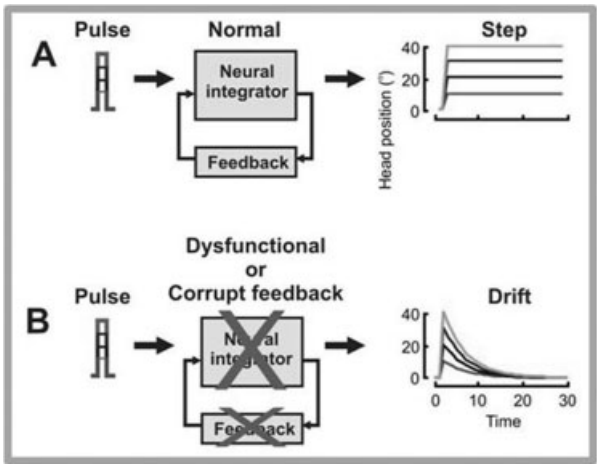


FIG. 2 (Th-57). Head neural integrator hypothesis: (A) Neural integration is a computational process by which the network of neurons (neural integrators) convert pulse of the signal (velocity) to the step (position). We had shown that neural integrator for maintaining head posture is inherently "leaky" (i.e. its output is characterized by drifts). Current simulations underscore the importance of the feedbacks for the optimal function of the neural integrator. In a different set of experiments, we have shown that neck proprioceptive feedback has a critical role in improving the function of head neural integrator. (B) Here we simulated that suboptimal feedback can make neural integrator "leaky" whose output is characterized by exponential drifts. These drifts have kinematic properties of the drifts in the head position that are seen in CD. Therefore it is possible that head drifts in CD could be secondary to the abnormal feedback to the neural integrator. We further propose that BTX therapy reduces the head drifts by changing the feedback to the neural integrator. It is possible that altered tone of the neck muscle after BTX may change the feedback to the neural integrators from the neck proprioceptors.

Th-58

Oscillatory head movements in cervical dystonia: Essential tremor, dystonic tremor, or head nystagmus?

A.G. Shaikh, D.S. Zee, H.A. Jinnah (Baltimore, Maryland)

Objective: To understand the nature and pathogenesis of jerky oscillatory head movements (OHM) in idiopathic cervical dystonia (CD).

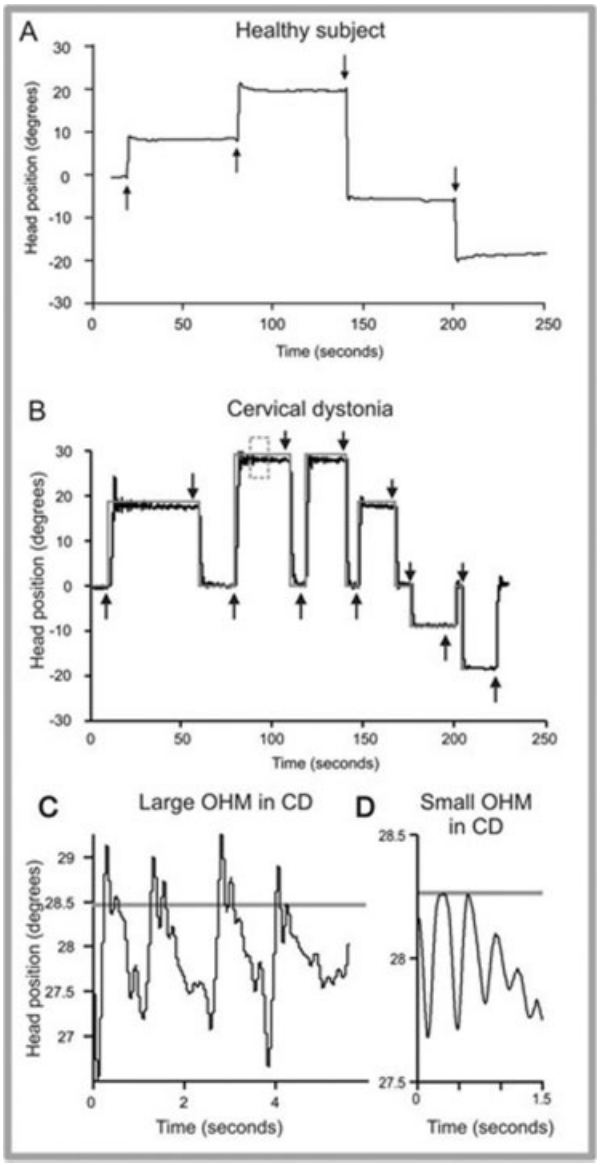
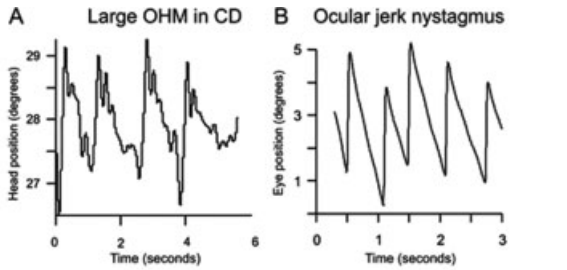


FIG. 1 (Th-58). An example of head movements in a healthy subject (A) and a patient with cervical dystonia (B). The healthy subject can promptly turn the head to either side (black arrow indicates a command to turn the head), and keep it steady in the new orientation. When the CD patient attempts to turn the head, it does not remain stable in a new orientation, but slowly drifts away from the desired target. The grey arrow drawn parallel to the trace indicates the drift direction. Magnification of the boxed zone in panel B shows small amplitude oscillations superimposed upon larger amplitude oscillations (C). Further magnification of the part of trace in panel C reveals a sinusoidal waveform pattern (D) compared to the non-sinusoidal waveform of the larger oscillations (C).

Background: The characteristics of OHM vary among CD patients. One type has a relatively small amplitude and regular frequency. The other type is larger amplitude, jerky, and often depends on head position – traditionally called "dystonic tremor". Both types frequently coexist in the same patient.

Methods: To understand better the nature of larger OHM ("dystonic tremor"), head position was recorded in three planes with a magnetic search coil system in 14 CD patients and 11 healthy subjects when the head was oriented straight ahead or turned to the right or left.

Results: Figure 1A illustrates recordings from a healthy subject. The subject attempted to stabilize the head in the center, and then turn and maintain it towards LED targets to the right or left. Figure 1B illustrates similar head movements in a CD patient. Small sinusoidal OHM were superimposed upon larger non-sinusoidal OHM (Figure 1C,D). The larger OHM, typically identified as "dystonic tremor" were characterized by slow turning of the head away from the target followed by a jerky return movement. The drift-return cycle had kinematic properties strikingly similar to jerk nystagmus of the eyes, with a null position, drifts always directed towards the null, and drift velocity increased with increasing distance from null. The jerky returning movements had kinematic properties of normal head saccades. Table summarizes the comparison of the kinematic properties of the "dystonic head tremor" and jerk nystagmus of the eyes. These results were consistently seen in all CD patients.



Table

Criteria defining jerk nystagmus due to neural integrator dysfunction	Large OHM in CD	Ocular jerk nystagmus
A slow drift in the eye or head position away from its desired orientation.	Present	Present
Drifts are followed by relatively fast corrective movements back to the desired orientation.	Present	Present
Presence of null-position where the drifts are minimal.	Present	Present
Dependence of the drift velocity on the angle of eye or head position relative to the null-orientation.	Present	Present
Velocity decreasing waveform of the eye or head drift.	Present	Present
Decay time constant of the drift in the eye or head position does not change with alteration in the eye-in-orbit or head -on-trunk orientation	Present	Present
Reversal of the drift directions as the eye or head orientation changes from one side of the null-orientation to the other.	Present	Present
Similar kinematic properties of quick phase of eye or head nystagmus and eye or head saccades.	Present	Present

FIG. 2 (Th-58).

Conclusions: 1) These results raise the provocative suggestion that the larger OHM, traditionally called "dystonic tremor" should be considered a form of head nystagmus. 2) Impaired neural integration is a known functional correlate of gaze evoked eye nystagmus. In principle this integrator processes information based upon intended and current eye position, and computes changes needed to keep the eye on target. Analogous integrators are likely to control head movements. These results suggest a possible role of impaired head neural integrator in the pathogenesis of CD.

Th-59

Sinusoidal head oscillations in idiopathic cervical dystonia

A.G. Shaikh, H.A. Jinnah, L.M. Optican, D.S. Zee
(Baltimore, Maryland)

Objective: To investigate the effects of ballistic head movements (head saccades) on sinusoidal head oscillations (SHO) in idiopathic cervical dystonia (CD).

Background: The characteristics of head oscillations in CD vary among patients. We described two waveforms of head oscillations in CD -- small amplitude, regular, and sinusoidal (SHO); and larger amplitude, irregular, and jerky ("head nystagmus"). The quantitative characteristics of sinusoidal oscillations are often altered during and after ballistic movements, for example re-emergent tremor. Here we investigated the effects of head saccades on the quantitative characteristics of SHO.

Methods: We measured 3D head movements in 8 CD patients who made head saccades. We compared the frequency and phase relationships of the SHO before and after the head saccades.

Results: Figure 1 is an example of the effects of head saccade on SHO in a CD patient. Blue trace represents horizontal head position, red trace is the corresponding head velocity, and grey trace is the reference sine wave fitted to head velocity. Dashed vertical line depicts the onset of the head saccade. There was a 90° phase shift in horizontal SHO after 12° horizontal head saccade. Such phase shift was noticed during all trials of head saccades in all patients. Mean phase shift in the horizontal SHO after horizontal saccades was 86.1°. The horizontal saccade also caused a phase shift in torsional and vertical SHO (mean: 69.6° 75° and, respectively). Polar histograms show the distribution of the number of trials of head saccades (radial axis) binned into the range of induced phase shift of SHO (Figure 2). Dis-

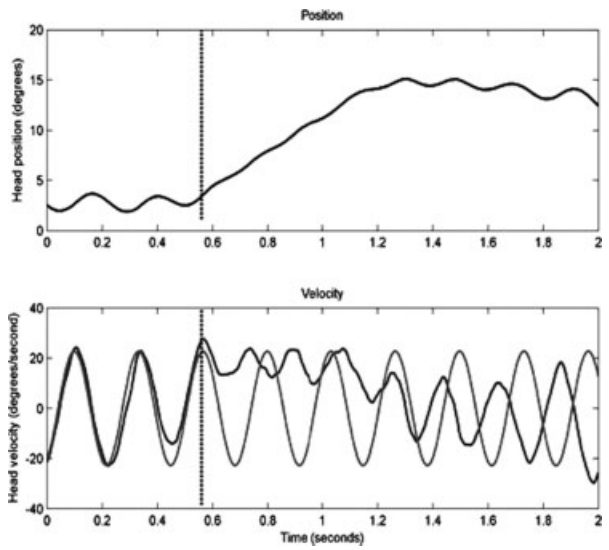


FIG. 1 (Th-59).

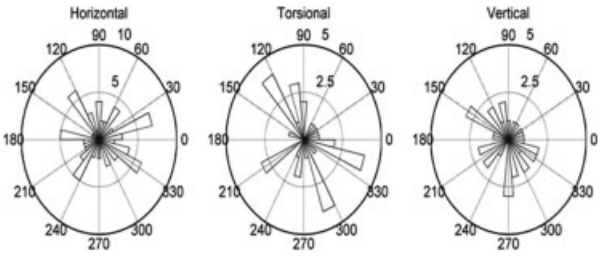


FIG. 2 (Th-59).

tributions of the phase shifts of the horizontal, torsional, and vertical SHO after horizontal saccade are shown. Neither horizontal head saccade, nor a change in head-on-trunk orientation altered the frequency of SHO (4.5 ± 0.6 Hz). Therefore the phase shifts in SHO should be attributed to the resetting of the oscillations. Unlike the re-emergent tremor, we did not notice a delay in appearance of SHO after the head saccade.

Conclusions: Head saccades affect the phase of SHO in CD. Such phase shift can be attributed to the resetting of the oscillations. Previous studies had attributed the eye saccade induced phase reset of sinusoidal eye oscillations to the instability in the neural integrator and presence of an abnormal feedback to the integrator.

Th-60

Novel GCH1 mutation and clinical study Chinese patients with dopa-responsive dystonia

S. Zhang, X. Liu, X. Hu, H.F. Shang (Chengdu, China)

Objective: To investigate the clinical feature and screen mutation of *GCH1* gene of Chinese DRD patients.

Background: Dopa-responsive dystonia (DRD) was a rare primary childhood-onset dystonia.

Methods: We analyzed a cohort of Chinese DRD patients' clinical data. Mutation of the *GCH1* gene was screened by direct sequencing.

Results: Ten sporadic DRD patients and a three-patient pedigree were included in the study. The onset age ranged from 3 to 13 years old. All initial symptoms presented walking problems due to dystonia of the lower limbs. The delay between onset and diagnosis ranged from 4 to 42 year. The patients with long delay between onset and diagnosis developed parkinsonism symptoms with the disease progression. The symptoms were completely or near-completely abolished with low dose levodopa treatment (rang from 62.5mg-500mg/day). Twelve patients were screened for mutation of the *GCH1* gene by after informed consent was given. Two known mutations (Gly203Arg in exon5 in four patients and Met102Lys in exon1 in one patient) and one new mutation (Thr186Ile mutation in exon5 in the three-patient pedigree) were detected. No mutations were found in four sporadic patients.

Conclusions: Our clinical findings were consistent with other studies. The *GCH1* gene mutations are quite common in Chinese patients with DRD.

Th-61

Writer's cramp rehabilitation approaches

O.A. Shavlovskaya, O.R. Orlova (Moscow, Russian Federation)

Objective: To determine the effect writer's cramp rehabilitation approaches.

Background: Writer's cramp (WC) is a focal hand dystonia, task-specific disorder of movement, characterized by excessive co-contraction of agonistic and antagonistic muscles during writing only (simple WC) and non-rarely during several activities other than writing (complex WC).

Methods: We studied WC patients since 1995 to 2008. Eighty one WC patients were included, 22 men and 59 women, with a mean age of 36.4 years; they made one's début before 20 years 25,6% and 20-30 years 25,6%, too. Twenty one patients (25,9%) had simple WC, sixty patients (74,1%) had complex WC. All cases were examined with Complex clinical inventory for WC patients and gave informed written consent.

Results: WC therapeutic approaches base on the brain plasticity mechanisms. Paradoxical kinesis (PK) phenomenon, exerting a beneficial influence on dystonia, was found in all WC patients. The most frequent writing maneuvers were as follows: hand printed (100%), proximal arm muscles writing (82.5%), individual selected writing instrument (80%), unaccustomed writing ways (75%), writing imitation with non-pen subjects (70%), marked papers (52.5%). Daily exercise with PK phenomenon as rehabilitation approaches such as hand printed with proximal arm muscles and marked papers was use. Pen with a setting-ball of palm-size was used also. Executing task-writing recorded in home exercise book and then evaluated. To alter the visual-motor coordination during writing digitizer tablet (Volito2 Wacom) nine cases used. Positive changes were observed three month ago after initiation of therapy. All except two patients (3.1%) in different degree were improvement there hand movements control during writing. Ten patients (15.4%) after therapy course not tried writing difficult.

Conclusions: Thus, the beneficial influence paradoxical kinesis phenomenon on dystonia expression may be considered as one of the directions of writer's cramp rehabilitation.

Th-62

Striatal dopaminergic function in spasmodic dysphonia

K. Simonyan, P. Herscovitch (Bethesda, Maryland)

Objective: To examine striatal dopaminergic function during rest and symptomatic speech production in patients with adductor spasmodic dysphonia (ADSD) using PET with [^{11}C]raclopride (RAC).

Background: SD is a primary focal dystonia characterized by involuntary spasms in the laryngeal muscles during speech production. The pathophysiology of this disorder is unknown. Recent neuroimaging studies have found structural and functional abnormalities within the basal ganglia-thalamo-cortical circuitry in SD patients; however, the underlying neurochemical correlates have not been fully investigated.

Methods: Eleven ADSD patients (mean 49.5 y.o., 6F/5M) and 11 controls (mean 54.8 y.o., 5F/6M) underwent a dynamic 100-min RAC PET scan, which included 50-min rest and 50-min speech production. RAC was administered as a 1-min bolus followed by a constant infusion. Volumes of interest were defined on each induvidual's MRI and transferred to the co-registered PET images. RAC binding potential (BP) was determined as a ratio of concentrations in the regions with (putamen and caudate nucleus) and without (cerebellum) specific binding during rest and speech. The speech-induced effects on dopamine release were estimated as the percentage change from resting baseline of the RAC BP values during speech production. Statistical significance of RAC BP changes between conditions and between groups was assessed using *t*-test ($p \leq 0.05$, corrected).

Results: At rest, RAC BP values were similar in patients and controls (ADSD vs. control: R putamen 2.26±0.29 vs. 2.16±0.39; L putamen 2.25±0.33 vs. 2.30±0.35; R caudate 1.48±0.36 vs. 1.53±0.38; L caudate 1.61±0.34 vs. 1.50±0.42). During speech production, RAC BP was significantly reduced in controls by 9.9% in right and 11.6% in left putamen and by 12.7% in right and 13.5% in left caudate nucleus (all $p < 0.001$). However, this decrease was less prominent in ADSD patients with significant between-group changes found in the right putamen (4.6%, $p = 0.003$), left putamen (5%, $p = 0.006$) and left caudate nucleus (5.3%, $p = 0.006$).

Conclusions: We found normal levels of striatal BP at rest and significantly decreased dopamine release during speech production in ADSD patients compared to controls. Selective abnormality of en-

dogenous striatal dopamine release during symptomatic speech production is consistent with task-specificity of SD and may underlie the pathophysiology of this disorder.

Th-63

The phenomenology of cervical dystonia. Proposed new treatment strategy with botulinum toxin

G. Reichel, A. Stenner, A. Jahn (Zwickau, Germany)

Objective: Cervical dystonia is the most common form of focal dystonia. Most cases of cervical dystonia are idiopathic and generally it is a life-long disorder. In recent years, Botulinum toxin has become the first line therapy.

Background: However, some patients are resistant to it. This problem led us to study the clinical forms of cervical dystonias with the help of CCT and MRI.

Methods: 78 patients with diagnosed cervical dystonia were examined. All underwent CT of the soft tissues of the neck with the aid of slices at the level of cervical vertebra 3 and 7. The cervical spine and the soft tissues of the neck were examined using magnetic resonance tomography in T1 and T2 with a slice thickness of 2 mm and in T1 tilted towards the deep neck muscles. For comparison the MRT image data of 50 patients who had no cervical dystonia was analysed. The largest diameters were measured and the shape of all muscles captured in the neck region was described.

Results: It was shown that in lateral flexion and in rotation, in 1/5 of patients the disorder affected only muscles which work on atlanto-occipital joints (latero- or torticaput), and in a further 1/5 it affected only muscles which work on the cervical spine (latero- or torticollis). 3/5 showed both disorders, but with a different degree of caput and collis involvement. Thus a ration of 1:1:3 was obtained in relation to this.

Conclusions: 1. In lateral tilt, differentiation between laterocaput and laterocollis is clinically possible. 2. Lateral shift always occurs when laterocollis is present on one side and laterocaput on the other. 3. In rotation, clinical differentiation between torticollis and torticaput is not always possible. In this case CT sections at levels C3 and C7 are recommended. By comparing the vertebral position at the two levels it is possible to differentiate reliably between torticollis and torticaput. 4. Anteflexion–differentiation between anterocollis and anterocaput – is analysed by lateral inspection of the angle between the cervical spine and the thoracic spine or between the cervical spine and the base of the skull. The same applies for the analysis of retroflexion, the differentiation between retrocollis and retrocaput. 5. A posteroanterior sagittal shift requires no further diagnosis: it is always caused by bilateral dystonic activity of the sternocleidomastoid muscles.

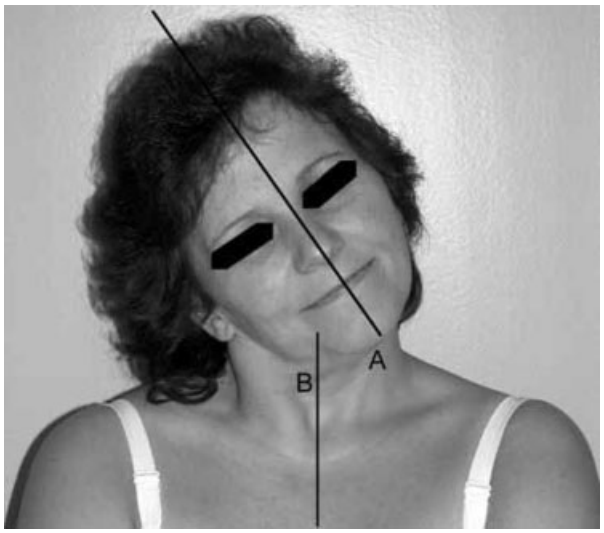


FIG. 1 (Th-63).

FIG. 2 (Th-63).

Th-64

Novel compound heterozygous mutations in the PANK2 gene in a Korea patient with atypical pantothenate kinase associated neurodegeneration

Y.H. Sung, S.H. Kim, G. Kim (Incheon, Republic of Korea)

Objective: We report a patient with atypical pantothenate kinase associated neurodegeneration (PKAN) who carries novel compound heterozygous mutations in the PANK2 gene.

Background: PKAN is autosomal recessive disorder characterized by mutations in the pantothenate kinase 2 (PANK2) gene and typical MRI finding. Mutaions in this gene were found in patients with the typical syndrome and in those with variable phenotypes, such as later age onset.

Methods: A 40-year-old man was admitted with dystonia of right hand and left foot. Progressive crossed focal dystonia and gait disturbance have started at age 35 and there were no family history. Laboratory tests and slit lamp examination revealed no remarkable abnormality. There was typical finding, the 'eye-of-the-tiger' sign, in magnetic resonance imaging of brain.

Results: Automated DNA sequence analyses revealed two single-base variants in exon 3 and exon 4. Both pathological variants alter conserved amino acids in *PANK2*, Asp268àGly (D268G) and Arg330àPrp (R330P). To our knowledge, our patient is the first case identified carrying mutation R330P and second case to show the mutation D268G.

Conclusions: We report the first case that compound heterozygous PANK2 missense mutations (D268G, R330P) caused atypical PKAN.

Th-65

Rapid onset Dystonia-parkinsonism: Symptoms in a mouse deficient in Na,K-ATPase α3

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Objective: To determine whether haploinsufficiency in *Atp1A3* makes mice vulnerable to stress-invoked dystonia.

Background: Na,K-ATPase is the major ion pump of the brain and consumes a large fraction of the energy used. The α3 isoform of its catalytic subunit is abundant in neurons in the CNS. Mutations in *ATP1A3*, the human gene encoding α3, were found in patients with a motor disorder, rapid-onset dystonia-parkinsonism (RDP) (de Carvalho Aguiar, Sweadner, Penniston, Zaremba, Liu, Caton, Linazasoro, Borg, Tijssen, Bressman, Dobyns, Brashear, and Ozelius. *Neuron* 43:169-175, 2004). RDP is triggered by stressful events.

Methods: An *Atp1a3* heterozygous knock-out mouse strain was evaluated for baseline motor skills, and subjected to stresses similar to events known to trigger dystonia in RDP patients. Two stresses are described here: swimming, and repeated ethanol intoxication.

Results: Protein expression levels for α3 were 65% of WT regardless of age. Relative to littermate controls, heterozygote mice showed normal gait parameters except for lower stride frequency and longer stride length at an imposed running rate (DigiGait apparatus). They were apparently normal in tests such as beam walk, wire grip, pole climb, and elevated chickenwire walk. On voluntary running wheels, they showed reduced average speed and reduced total running time. When filmed on wheels in the dark, they showed shorter bouts of running. During initial swim stress, heterozygotes were indistinguishable from littermate controls. However when retested in water, the youngest mice showed variable and sometimes dramatic rigidity and discoordinated movements, which disappeared after 2 or more months. During ethanol exposure heterozygotes variably showed myoclonus, incoordination at lower dose, and deeper anesthesia at high dose. Upon recovery, however, they were indistinguishable. Several stressed heterozygotes were found prematurely dead.

Conclusions: Haploinsufficiency for the α3 subunit of Na,K-ATPase increases the vulnerability of mice to motor abnormalities after stress, but lasting dystonia was not observed. Incomplete penetrance and occasional prodromal symptoms also characterize humans with mutations in the gene.

Th-66

Botulinum toxin treatment for oromandibular dystonia (OMD): Clinical features and treatment response of series of 20 patients

R. Taipa, M. Magalhaes (Porto, Portugal)

Objective: Characterize clinical features and treatment response of OMD patients treated with BTX.

Background: Oromandibular dystonia (OMD) refers to spasms of the mastigatory, facial and lingual muscles, resulting in repetitive and/or sustained jaw movements. OMD is most often idiopathic and it may interfere with chewing, swallowing, speaking, and cause considerable psychosocial disability. Botulinum toxin (BTX) has been used with success to treat various forms of focal and segmental dystonia, being OMD the most challenging dystonia to treat. Drug therapies are generally only moderately effective, surgical options are usually no useful and there is no formal recommendation consensus for BTX in OMD. Delay in appropriate treatment can induce sequelae.

Methods: Retrospective analysis of the OMD patients followed in our outpatient clinic treated with BTX.

Results: Twenty patients were identified, with an average age onset of the dystonia of 29.7 years (minimum 1 and maximum 71 years). Twelve were classified as early-onset and 8 as late-onset dystonias, with 7 patients beginning OMD in pediatric age (<18 years). Regarding the distribution pattern, 4 were focal, 5 segmental and 11 generalized. There was a variable etiology. The patterns of OMD were usually a combination of jaw and lingual movements (9) or jaw and perioral movements (8). The latency between the beginning of OMD and BTX treatment ranged from 6 months to 52 years. The muscles selected for BTX application were masseter (12), temporalis (9), pterigoid (12), submentalis complex (7) and perioral muscles (4). Clinical response was considered good in 19 patients, with loss of efficacy in one due to disease progression (Hallervorden-Spatz disease patient). In 5 patients there was transient and not disabling dysphagia, one had transient mastigatory weakness and one had non complicated facial hematoma. The follow-up period ranged from 4 weeks to 7 years.

Conclusions: Our experience suggests that the use of BTX in the symptomatic treatment of selected OMD cases is safe and have good clinical efficacy. The latency between symptoms and treatment lead us to think that BTX should be considered in pediatric patients to avoid future OMD complications (articulation or dental problems, weight loss due to eating difficulties, speaking and social disability).

Th-67

Quality of life in patients with various forms of dystonia

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Objective: The purpose of study was to evaluate the quality of life (QoL) in patients with different forms of dystonia (DYT) and to analyze the factors that predict QoL.

Background: DYT is a movement disorder with the involuntary, sustained muscle contractions causing repetitive movements or abnormal postures with a big influence to QoL in the most of patients.

Methods: Patients and methods: 78 patients with dystonia were included into the study. According to the body distribution patients were categorized as focal, multifocal, segmental, hemidystona and generalized dystonia. According to type of focal DYT they were separated in groups with cervical dystonia (CD), blepharospasmus (BS), hemifacial spasm (HFS) and graphospasums (GS). Age, gender, disease duration and duration of DYT therapy were also analyzed. All patients had completed various questionnaires (Croatian translation): Craniocervical Dystonia Questionnaire (CDQ-24), 36-Item Short Form Health Survey Instrument (SF-36), Rosenberg's Self-Esteem Scale and Beck Depression Inventory (BDI). The examiner had completed Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) for patients with CD and Global Dystonia Scale (GDS) (by Cintia Comella) for all patients.

Results: The mean age of patients (F= 57, M= 21) was 52.5 ±2.7 yrs. The mean duration of DYT was 8.2±3.4 yrs. The mean duration of DYT therapy was 6.1±4.2 yrs. There were 51 patients with focal DYT (66%), 12 with segmental (15%), 7 with multifocal (9%), 5 with hemidystonia (6%) and 3 with generalized DYT (4%). The most of focal DYT patients had CD- 37, then BS- 7, HFS- 5 and GS- 2. Analyzes of the questionnaire scores had shown impairment of QoL in all types of DYT and in all age groups, similar in both genders. Compared to the focal DYT group patients with multifocal, segmental, hemidystonia and generalized DYT scored significantly ($p<0.05$) worse on all measures. Duration of DYT had no significant influence to the scores. Moderate to severe depression was reported by 36 % patients. Depression in DYT patients was important predictor for QoL.

Conclusions: To most of patients dystonia significantly reduces quality of life, especially in those with depression.

Th-68

Movement related potentials recorded from the human internal globus pallidus during voluntary movements

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Objective: We examined the role of the human internal globus pallidus (GPi) in movement preparation by recording movement related potentials (MRPs) while patients performed wrist movement.

Background: The role of the human GPi in movement preparation is currently unclear.

Methods: Thirteen patients (three men and ten women) with dystonia and deep brain stimulation (DBS) electrodes implanted unilaterally or bilaterally at the GPi were studied 3-6 days after electrode implantations when the leads were externalized. The subjects performed wrist extension movements in two paradigms: (1) self-paced (internally triggered, INT) once every 10 sec. (2) triggered by an external cue (EXT) presented in an interval from 7 to 8 sec. Each

paradigm was studied for 10-15 min. Local field potentials (LFPs) were recorded from the DBS contacts (Medtronic 3387, contacts numbered 0 to 3) in the GPi and scalp EEG was recorded using Fz, Cz, C3, and C4 electrodes. MRPs of the GPi were examined using bipolar montages (0-1, 1-2, and 2-3) whereas scalp EEG were studied using a monopolar montage. MRPs were examined from 4 sec before movement onset to 1 sec after movement. Potentials were considered as MRP if the amplitudes were above mean+3SD of the baseline (-4 to -3 sec) with a duration of at least 500 msec. Maximum amplitude of the MRP was calculated by comparing the mean of a 50 ms window from that of the baseline.

Results: All patients showed MRPs from EEG and GPi in both paradigms. The MRP latencies and amplitudes for EEG were -2.3 s, 17μV for EXT and -2 s, 16 μV for INT. In the ipsilateral GPi, the latencies and amplitudes were -2.1 s, 3μV for EXT and -1.8 s, 4 μV for INT. In the contralateral GPi, the latencies and amplitudes were -2.4 s, 5μV for EXT and -2.3 s, 4 μV for INT. GPi phase reversals were observed in 23 of 34 studies.

Conclusions: MRP phase reversals indicate potentials originated at the GPi. Our findings suggest that the human GPi is active during preparation of both ipsilateral and contralateral wrist movements.

Th-69

Differential diagnostics of facial dyskinesia using the 'gesture antagonistic'

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Objective: To devise methods of evaluating of hyperkinesis of miotic musculature, to work out ways of differentiation of blepharospasm and hemifacial spasm.

Background: 61 patients with benign essential blepharospasm (BEB) and 31 patients with hemifacial spasm (HFS) were examined. The mean interval between the appearance of involuntary more frequent blinking and blepharospasm was 15±3,98 months. The first symptoms were unilateral in 18% of BEB cases (11 patients), while the period of involving another side was 6,4±1,3 weeks. In 36% of cases (22 patients) the predominance of clinical symptoms on one of the sides took place. On the other hand, some patients with HFS complained of involuntary blinking of both eyes in the beginning of disease. The average period of progression of hyperkinesis on the one half of face was 18±5,5 months (from 2 months up to 10 years). Besides, 29% of patients, as well as those with dystonia, applied special methods so that to decrease hyperkinesis. Summarizing these facts, a special method of differential diagnosis of BEB and HFS applying laser technologies has been devised.

Methods: 30 patients with BEB and 22 patients with HFS have been examined. Parameters of the orbicularis oculi muscle were evaluated by means of specl-optical method. A patient was laid on the couch. The sensors of laser apparatus were placed by the external angle of an eye, then that zone was irradiated by helium-neon laser. Registration of the parameters was conducted in the range of 1-16 hertz. One analyzed the range of maximum amplitude of a spectrum F_0. Then a test was carried out using distant synergia, it was called the gesture antagonistic. It lied in moving aside ipsilateral upper extremity without leaning on a certain surface. The parameters were registered in that position once more.

Results: While carrying out the test, F0 characteristics of 80% of patients with BEB replaced from 1,6-4,5 hertz range up to 6,0-12 hertz. 59% of patients with HFS had no substantial changes of F_0, 32% of patients resulted in moving to 4,6-7,0 hertz.

Conclusions: The abovementioned test is informative and may be applied for quantative evaluation of facial hyperkinesis as well as additional objective information while conducting defferential diagnostics of BEB and HFS.

Th-70

Temporal discrimination thresholds in AOPTD – Voxel based morphometry in unaffected relatives validates a new endophenotype

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Objective: To validate the significance of abnormal Temporal Discrimination Thresholds (TDTs) in familial and sporadic AOPTD patients and unaffected relatives using Voxel based Morphometry (VBM).

Background: Familial adult onset primary torsion dystonia (AOPTD) is an autosomal dominant disorder with markedly reduced penetrance. Most AOPTD patients are sporadic cases. Sensory processing abnormalities in unaffected relatives of AOPTD patients may indicate non-manifesting gene carriage. We have found abnormal TDTs in AOPTD patients and relatives. Voxel-based morphometry (VBM) is an MRI technique used to demonstrate microstructural grey-matter change.

Methods: TDTs were examined in 32 AOPTD patients, 40 unaffected first degree relatives, 17 unaffected second degree relatives and 43 control subjects using visual and tactile stimuli. In 33 unaffected relatives VBM was used to compare putaminal volumes between relatives with abnormal and normal TDTs. VBM scans (0.9mm isotropic voxels) were obtained at 1.5T.

Results: The mean TDT in 26 control subjects <50 years of age was 22.85ms and in 17 control subjects >50 years was 30.87ms. The upper limit of normal was defined as control mean +2.5 SD. 27/32 (85%) AOPTD patients had abnormal TDTs. 20/40 (50%) unaffected first degree relatives and 7/17 (41%) second degree relatives had abnormal TDTs. VBM analysis compared 13 unaffected relatives with abnormal TDTs (mean age 38.1) and 20 with normal TDTs (mean age 41.7); age difference was not significant ($t(21) = 1.11$, $p > 0.05$). The mean TDT Z-score in the normal TDT group was 0.51 (range -1.83 to 2.40) and in abnormal TDT group was 5.9 (range 3.39 to 12.68). Relatives with abnormal TDTs had significantly greater putaminal gray matter volume compared to relatives with normal TDT (Talairach x, y, z coordinates in parentheses) in the left putamen (Z = 3.75, -26, 14, 2) and right putamen (Z = 3.00, 24, 16, -4).

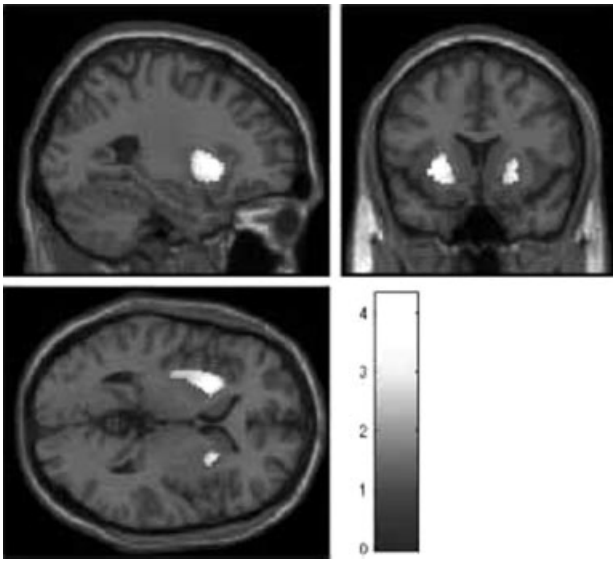

FIG. 1 (Th-70).

Conclusions: The prevalence of abnormal TDTs in AOPTD patients and relatives follows the rules for a useful endophenotype. A structural correlate of abnormal TDTs in unaffected relatives was demonstrated using voxel based morphometry. VBM findings indicate that putaminal enlargement in AOPTD is a primary phenomenon. TDT may be an effective tool in AOPTD research.

Th-71

Mutations in ATP7B explain Wilson's disease but not the whispering dysphonia and dystonia in the original DYT4 family

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Objective: To clinically re-evaluate the Australian DYT4 family and to elucidate the genetic cause.

Background: In 1985, a large four-generational Australian family was described with at least twenty members affected with dominantly inherited dystonia and prominent whispering (spasmodic) dysphonia, later designated as DYT4. In addition to the dystonia, two deceased siblings in the pedigree also had Wilson's disease (WND), which is usually transmitted in an autosomal recessive fashion and associated with mutations in the ATP7B gene.

Methods: DNA samples were obtained from 7 affected (5 women; 2 men; age range: 39-66 yrs; age at onset range: 23-29 yrs.) and 7 unaffected (2 women; 5 men; age range: 35-54 yrs.) family members. Linkage analysis in the DYT1, DYT6, DYT7, DYT13, and the ATP7B (WND gene) region was performed with microsatellite markers. Two of the affected members were tested for the GAG deletion in DYT1. We also sequenced the ATP7B in two family members and investigated segregation of the two detected mutations.

Results: Re-evaluation of affected DYT4 family members revealed variable phenotypic expression ranging from mild cranio-cervical dystonia with spasmodic dysphonia to severe generalized dystonia, combined with ataxia, cognitive decline, and neuropsychiatric features. Linkage analysis excluded the DYT1, DYT6, DYT7, and DYT13 loci; the GAG-deletion in DYT1 was also absent. Haplotype analysis of the ATP7B region resulted in three different haplotype combinations in the living siblings of the two WND patients, indicating that the fourth combination with two mutated alleles occurred only in the affected and deceased WND patients. On these two haplotypes, we identified a novel missense mutation in exon 8 (c.2297C>G, p.T766R) and a splice-site mutation in intron 5 (IVS5+1G>T). The mutation in exon 8 was detected in three affected and four unaffected, the mutation in intron 5 in one affected and one unaffected family member. Three DYT4 patients carried neither ATP7B mutation.

Conclusions: We have retrospectively identified the likely genetic cause of WND in this family and excluded involvement of known primary dystonia gene loci. The ATP7B mutations do not segregate with the dystonia phenotype; thus, two different genetic diseases appear to be present in this family.

Th-72

A 10 year retrospective audit of epileptic seizures post deep brain stimulation for dystonia

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Objective: To document the frequency and types of seizures occurring in patients with dystonia who underwent deep brain stimulation (DBS) at Charing Cross Hospital from 1998 to 2008. To analyse the demographic details and electrode settings of this cohort, and to compare it to post-DBS dystonia patients who have no documented seizure activity.

Background: DBS is a potential treatment for various forms of refractory dystonia, with the preferred surgical target being the Globus Pallidus internus (GPi). Although a known post-operative complication, seizures occurring post GPi stimulation for dystonia have rarely been documented in published literature.

Methods: The case records of all the dystonia patients who had undergone implantation of GPi electrodes at Charing Cross Hospital during this 10 year period were examined. The demographic details, seizure activities and most recent stimulation parameters of each patient were documented on a standard proforma. The patients were then divided into those who had pre and post-operative seizures and those who did not. The two groups were compared to look for any significance in parameter settings.

Results: Twenty dystonia patients (15F, 5M) ranging from 27 to 66 years old underwent DBS between 1998 and 2008. Six patients suffered post-operative seizures, three of whom had a history of epilepsy prior to DBS. Two of these three patients' epileptic seizures changed character post-DBS. Of the 6 patients with post-operative seizures, two developed seizures within one week of surgery and the remaining four patients developed seizures from 4 months to 5 years post-GPi implantation. Of the fourteen patients who did not suffer post-operative epilepsy, one had a previous history of childhood epilepsy. There was no significant difference in demographic details or electrode settings between patients who had epilepsy post-DBS and those who did not.

Conclusions: Our retrospective 10 year audit showed a seizure frequency of 30% (6 out of 20) and a de novo rate of 15% (3 out of 20) after bilateral GPi stimulation for dystonia. This information is important for the pre-operative counselling of dystonia patients and is valuable to driving licence authorities deliberating on the capacity of dystonic patients to drive after DBS.

Th-73

Comparison of dystonia between Parkinson's disease and atypical parkinsonism

W.T. Yoon, W.Y. Lee, S.H. Jeon, J. Ahn, J. Cho
(Seoul, Republic of Korea)

Objective: To analyze the clinical characteristics of dystonia associated with parkinsonism and to compare them among the various types of parkinsonism.

Background: Dystonia can occasionally be found in Parkinson's disease (PD) and atypical parkinsonism such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). However, systematic analysis of clinical features of dystonia associated with parkinsonism has seldom been reported.

Methods: We prospectively enrolled 176 patients presenting dystonia combined with parkinsonism out of 1,278 patients with parkinsonism (1,045 PD, 191 MSA, 27 PSP and 15 CBD). We analyzed the clinical features of dystonia and parkinsonism including demography, temporal profile of symptoms, distribution and characteristics of dystonia, clinical diagnosis of parkinsonism and relationship with levodopa treatment.

Results: In 176 dystonic patients with parkinsonism, 115 patients were clinically diagnosed as PD, 40 patients were probable MSA, 11 patients were probable PSP and 10 patients were probable CBD. The frequency of dystonia was 11.0% in PD, 20.9% in MSA, 40.7% in PSP and 66.7% in CBD. According to the distribution of dystonia, craniofacial and cervical dystonia were more frequently observed in non medicated atypical parkinsonism than in non medicated PD (10/115, 8.7% vs. 45/61, 73.8%). In contrast, limb dystonia was frequently observed in both non medicated and medicated PD patients (28/115, 24.3% and 39/115, 33.9%). In CBD, only limb dystonia was observed (10/10, 100%). Truncal dystonia including camptocormia was detected only in non medicated PD and MSA (27/115, 17.4% and 5/40, 12.5%), and medicated PD (7/115, 6.1%). In terms of relationship with levodopa treatment, medication related dystonia was markedly more frequent in PD than in atypical parkinsonism (48/115, 41.7% vs. 4/61, 6.6%).

Conclusions: In our study, we concluded that limb or truncal dystonia was more frequently observed in PD than in atypical parkinsonism except CBD for limb dystonia. Contrarily, craniofacial or cervical dystonia was more frequently observed in MSA and PSP. Medication related dystonia might be representative of PD rather than atypical parkinsonism.

Th-74

Task-specific versus non-task-specific retraining after immobilization – A one year follow-up in writer's cramp patients

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Objective: To evaluate the long-term effect of a new treatment strategy in patients with writer's cramp.

Background: Recently, we reported that forearm immobilization followed by retraining of the affected hand improved writer's cramp after 8 weeks of training. Task-specific re-training and non-task-specific retraining were equally effective. Here, we prospectively followed and reassessed 18 patients after 6 and 12 months and present long-term results.

Methods: After 4 weeks of limb immobilisation group 1 performed task-specific training consisting of drawing and writing exercises with a pen attached to the bottom of a finger splint. Group 2 learned non-task-specific training and practiced finger movements with therapeutic putty without writing movements. While 5 patients discontinued after 8 weeks (group 3), 13 patients continued for at least four more weeks (group 1: task-specific-training: n =7; mean training duration 6.3 ± 2.9 weeks, group 2: non-task-specific-training: n=6; mean training duration 8.3 ± 4.9 weeks). At 6 months all patients stopped practicing. The Writer's Cramp Rating Scale (WCRS) served as primary outcome measure. The scale is based on blinded assessment of video tapes obtained during a standardized handwriting task. Patients were assessed at baseline, after 8 weeks of continuous training (week 12), 6 and 12 months.

Results: Patients, who continued to train, improved consistently after 6 months. The effect was still present at 12 months in group 2 (baseline: 11.6 ± 6.8; 6 months: 6.1 ± 5.0; 12 months: 6.8 ± 5.2 at 12 months), but not in group 1 (12.0 ± 6.1 at baseline; 9.1 ± 6.3 at 6 months; 12.7 ± 6.0 at 12 months). In that group, dystonia had worsened after 12 months. Patients, who stopped training (group 3), deteriorated after 6 months compared to those continued with either training method. However, differences between groups 1 and 2 or those who discontinued were not significant due to considerable inter-individual variations.

Conclusions: The data confirm that task-specific-training is not superior to non-task-specific training. If training is continued, the clinical effect apperars to remain constant. Although differences were not significant, training with therapeutic putty seems to show a more stable long term effect than task-specific-training.

Th-400

A primary torsion dystonia phenotype with substantia nigra hyperechogenicity: A case report

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Objective: To report a clinical case presenting as primary torsion dystonia with neurosonographic hallmarks of substantia nigra hyperechogenicity.

Background: Primary torsion dystonia is a movement disorder characterized by involuntary abnormal postures and movements. Transcranial sonography in dystonic disorders was reported to found hyperechogenic lesions of the lenticular nucleus mainly on the side opposite to clinical symptoms.

Methods: Neurological evaluation, blood tests, neuroimaging (cranial MRI) and transcranial ultrasound.

Results: A 18-year-old young man presented with involuntary movements (irregular, jerky dystonic tremor of the head) and writing difficulties (dystonic posture of the right hand during writing). The disease had its onset at the age of eight with writing troubles with a slowly progressive course and involvement of other body parts. On clinical examination he showed dystonic neck and trunk posture, writer's cramp and dystonic foot posture during walking. The rest of the neurological examination was normal, without evidence of bradykinesia, rigidity, mental, pyramidal, cerebellar or sensory disturbances. There was no family history of neurological disorders and the early development was unremarkable. The main diagnostic consideration as Wilson's disease was excluded by normal blood tests (serum ceruloplasmine level, 24-h urinary cooper level, liver tests), absence of corneal Kayser-Flecher ring and normal brain MRI. On acute levodopa challenge there were no clinical changes. Examination by transcranial sonography revealed hyperechogenic lesions of the substantia nigra, more pronounced on the left side and reduction of mean velocity in both posterior cerebral arteries. The patient was started on low dose anticholinergics with a slow titration up to 12 mg.

Conclusions: In this report we observed a patient with a clinical phenotype of idiopathic generalized dystonia presenting also with substantia nigra hyperechogenicity. This feature is associated with a subclinical functional impairment of the nigrostriatal dopaminergic system and may be in this clinical context a risk factor for subsequent development of a neurodegenerative disorder.

Th-401

The X-ray symptoms of spasmodic torticollis

Y. Rushkevich, S. Likhachev, T. Charnukha, A. Avlasevich (Minsk, Belarus)

Objective: To study the degree of degenerative changes of the cervical spine in the patients with spasmodic torticollis (ST).

Methods: X-ray investigations were performed for 68 patients with ST (sex ratio 1:1, mean age 41,7±1,4) and a control group of 31 persons (mean age 42,1±1,2) with local cervical syndrome. Degenerative changes were assessed and rated as absent, minimal, moderate, or severe. They were analyzed by a neuroradiologist for loss of lordosis, widening of atlanto-occipital joints, narrowing of disk space, number and position of osteophytes, arthritis of uncovertebral joints, scoliosis, and anomalies of the development.

Results: 56 (82,3%) out of 68 patients with ST had degenerative changes, 40 (58,8%) of them had moderate and severe. There was no significant difference in the degree of degeneration of the cervical spine between ST patients and the control group. Scoliosis was revealed in 51(75%) patients with ST and in the majority of cases (60,3%) the direction of scoliosis observed was to the side opposite to the forced turning of the head. While in the control group not a single case of scoliosis has been determined ($p<0,001$).

Conclusions: The X-rays analyses of patients with ST showed the scoliosis directed to the side opposite to the forced turning of the head. ($p<0,001$). Probably, the changes revealed are due to the asymmetrically increased tension of the cervical muscles, involuntary, sustained, patterned muscle contractions of opposing muscles, which cause neck twisting or its abnormal postures.

Th-402

Quantitative EEG analysis in assessment of blepharospasm treatment efficiency by botulotoxin type A

V. Rybakova, S. Likhachev, E. Veevnik (Minsk, Belarus)

Objective: To estimate by means of quantitative electroencephalography (EEG) influence of Dysport injections on the brain bioelectrical activity in patients with blepharospasm.

Background: Objective estimation of blepharospasm treatment efficiency is a topic for research.

Methods: Clinical and EEG investigations were performed 22 patients (mean age 54,5± 4,1) with blepharospasm. EEG was regis-

tered prior to the beginning of treatment and in a month after Dysport injection. The control group included 23 healthy individuals. Dynamics of the EEG basic rhythms spectral characteristics (delta, theta, alpha, beta 1, beta2, beta 3) 16 brain areas was analyzed.

Results: Screening of the EEG changes before treatment and in a month after treatment by Dysport injection has shown, that statistically significant dynamics was found out in alpha rhythm parameters. Quantitative EEG analysis has revealed distinctions of alpha rhythm parameters in patients with blepharospasm in contrast to healthy control on an index (channel O1-A1: 22,70±10,91 % and 48,60±5,10 %). Alpha rhythm index increase (channel O1-A1: 22,70±10,91 % and 31,80±17,37 %, $P<0,05$) and muscular artefacts reduction was revealed in patients with blepharospasm in one month after the Dysport injection in comparison with parameters before treatment.

Conclusions: Blepharospasm patients treatment by Dysport injections is accompanied by brain bioelectrical activity normalization (alpha rhythm index increase) that probably reflects functioning improvement of the reticulo-thalamo-cortical system.

Th-403

Improvement of primary blepharospasm after needle orbicularis oculi muscle puncture: Report of one case

F. Alarcon, R. Salinas (Quito, Ecuador)

Objective: Reporting the effectiveness of stimulating the orbicularis oculi muscles with muscle puncture in the blepharospasm.

Background: Blepharospasm is a focal dystonia whose physiopathology has not been clearly explained. It is a motor phenomenon where a sensory deficit has been recognized. In blepharospasm a deficit in tactile temporal discrimination has been demonstrated, related to the loss of cortical inhibition and increase of neural plasticity. The MRI identified structural changes in the putamen, the caudate cerebellum and the lower left parietal lobe, which are directly related to functional changes in brain activity. The administration of botulinum toxin is a safe and effective treatment, as oral drugs have not proven to be effective.

Methods: We present a 41-year-old female patient without any personal or family pathological background of dystonia or movement disorders. Onset of the patient's blepharospasm started intermittently six months earlier, triggered by exposure to sunlight and other intense light stimuli. It got progressively worse with continuous blinking and closure of the eyes, preventing her from doing almost any daily activity. The brain RMN and blood tests were normal. We performed puncture of the orbicularis oculi for 30 minutes with acupuncture needles twice a week for three consecutive weeks.

Results: As of the first muscle puncture, the patient presented dramatic and progressive improvement with complete opening of the eyes and decrease of the blinking. This significant improvement has remained unchanged up to one month after the last muscle puncture.

Conclusions: Our result suggests that an intense, prolonged and repeated peripheral stimulus of the orbicularis oculi muscles of the eyelids can significantly improve blepharospasm, persisting over time. This response could probably be explained by a change of the afferent sensory impulse and the cortical sensory-motor integration. Clinical studies with a larger number of patients should be conducted to confirm our finding. Evidence based on neurophysiological and imaging studies is needed to demonstrate that a prolonged and intense peripheral sensory stimulus might change the motor response and improve the dystonia.

Th-404

Visual evoke potentials in pallidal surgery

M.S. Sankhe (Mumbai, Maharashtra, India)

Objective: Introduction: Visual Evoke Potentials in Pallidal Surgery have been used during pallidal surgery under general anesthesia for locating the optic tracts. Various methods have been used to elecit Visual Evoke Potentials in Pallidal Surgery. The results of these method have been variable and standarisation not established. 1. To study visual evoke potentials during pallidal surgery under general anesthesia. 2. To try and establish a standardised procedure for intraoperative Visual Evoke potentials during pallidal surgery.

Methods: Two methods to elicit Visual Evoke Potentials in Pallidal Surgery were used. Flash visual evoke potentials were used and potentials altered intracranially using macroelectrode. In the other method progressive direct macroelectrode stimulation with occipital recordings was done as the electrode advanced ventrally to locate the optic tracts.

Results: Recordings were obtained in all cases even with the patients under general anesthesia. Using the flash Visual Evoke Potentials in Pallidal Surgery with intracranial macroelectrode interruption of the signal did not produce consistent results in all cases. Using the direct macroelectrode stimulation to localize the optic tract produced consistent results.

Conclusions: We conclude that visual evoke potentials are producible and useful during pallidal surgery to decide the ventrality of the electrode. Direct macrostimulation is probably a better method to locate the optic tracts during pallidal surgery.

Th-405

The observation of patients with dystonia at the clinical diagnostic center

L.P. Shperling, V.V. Vardosanidze (Novosibirsk, Russian Federation)

Objective: To study the forms of dystonia at outpatient clinic.

Background: Dystonia was considered a rare disease because there were no common specific clinical criteria and its diagnostics was difficult. The new classification of dystonia by aetiology, distribution and the age of onset was adopted in the last decade. L. Geyer and S. Bressman have established some additional clinical criteria for the correct diagnostics of dystonia in 2006.

Methods: The disease was diagnosed according to the new classification, additional clinical criteria (L. Geyer, S. Bressman, 2006) and video-monitoring.

Results: There were 86 patients with dystonia under observation. 64 women (74,4 %) predominated 22 men (25,6%). The following types of dystonia were found out:1. Focal dystonia- 68 (79,0 %): blepharospasm 8 (11,8%), oro-facial dystonia 15 (22,1%), cervical dystonia 41 (60,3%), spasmodic dysphonia -2 (2,9%), writer's cramp -2 (2,9%). 2. Segmental dystonia- 4 (4,7%). 3. Multifocal dystonia- 3 (3,5%). 4. Generalized dystonia 11(12,8%). The average age of patients was 52,8 years. The average disease duration was 8,8 years. The average of disease onset was 44 years. There are 9 (60%) with Jaw closing dystonia and 6 (40%) patients with Jaw opening dystonia in the group with oro-facial dystonia. There are rotatory torticollis to the right side- 9 (22%), rotatory torticollis to the left side- 7(17,1%), retrocollis- 3 (7,3%), anterocollis- 3 (7,3%), laterocollis to the right side- 1 (2,4%), laterocollis to left the side- 7 (17,1%) in the cervical dystonia group. There is a combination of rotatory torticollis and laterocollis in the complex forms of the cervical dystonia. We have registered the predominance simple forms of the cervical dystonia above complex forms and the most frequent types were deviation head to the right side or flexion head to the left side. The segmental form is in 4 patients (combination of blepharospasm and oro-facial dystonia). 3 patients have the multifocal form (oro-facial dystonia plus writer's spasm).

Conclusions: Thus dystonia is not rare disease. Early diagnostics of dystonia in its correct form allows to help forecast the disease course and improve the life quality of a patient in the right time. This work will be continued.

Th-406

Zerviton: A new tool to measure head position in patients with cervical dystonia: Preliminary results

S. Sommer, R. Viga, H. Petersen, E. Koletzki, W. Jost (Wiesbaden, Germany)

Objective: Patients with cervical dystonia before and after therapy with botulinum toxin type-A (BTX-A) were examined by a motion

analysis system, consisting of the 'Zerviton-helmet' and PC software (university of Duisburg-Essen).

Background: Cervical dystonia is the most common focal dystonia. It is characterized by abnormal head and neck posture due to tonic involuntary contractions in a certain set of muscels often superimposed by dystonic tremor. Diagnosis is based on identification of typical clinical signs and symptoms such as turning of the head, lateroflexion or ante-/ retroflexion. The first line treament in cervical dystonia is intramuscular injection of botulinum toxin. Until now there is no valid test available to measure abnormal head movements and postures due to cervical dystonia. Diagnosis is based on clinical impression only.

Methods: Patients with cervical dystonia were examined by a motion analysis system, consisting of the 'Zerviton-helmet' and PC software, a tool to measure head position at rest (university of Duisburg-Essen). We performed measurements of abnormal head movements and postures in 5 female non-selected patients with cervical dystonia. Movements, defined as turning, tilting and nodding of the head (measured in degree), were recorded during a one minute period. The patients were tested before and after treatment with botulinum toxin type-A (BTX-A).

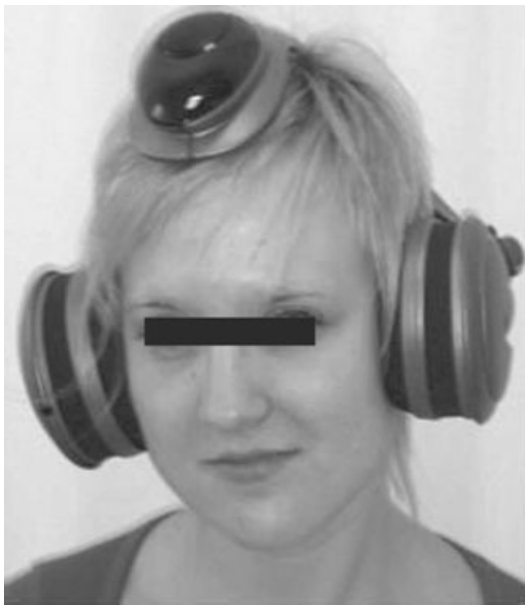

FIG. 1 (Th-406).

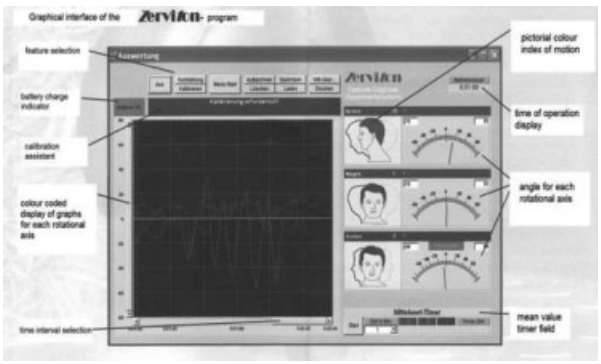

FIG. 2 (Th-406).

Results: The analysis of involuntary movements and postures at rest in patients with cervical dystonia after treatment with BTX-A compared to baseline exhibited decrease in turning of the head in 3 patients and decrease in nodding of the head in 5 patients; decrease in tilting of the head was noticed in 3 patients. Enhanced turning of the head after treament with BTX-A occurred in 2 patients; enhanced tilting of the head was noticed in 2 patients.

Table (Th-406). Results of motion analysis

Movement direction	Before treament with BTX-A [°]	After treatment with BTX-A [°]	Change in movement [°]
Patient A (cervical dystonia)			
Turning of the head	To the right: 34	To the right: 14	−20
Tilting of the head	To the right: 1,1	To the right: 5,5	+4,4
Nodding of the head	Forwards: 7,6	Forwards: 4,3	−3,3
Patient B (torticollis)			
Turning of the head	To the left: >90	To the right: 5,3	−95,3
Tilting of the head	To the right: 3,5	To the left: 2	−5,5
Nodding the head	Backwards: 11,2	Forwards: 1,1	−12,3
Patient C (cervical dystonia)			
Turning of the head	To the right: 10,1	To the right: 17	+6,9
Tilting of the head	To the right: 7,3	To the right: 9	+1,7
Nodding of the heaf	Forwards: 29	Forwards: 23	−6
Patient D (torticollis)			
Turning of the head	To the left: 26,1	To the left: 1,8	−24,3
Tilting of the head	To the right: 7,5	To the left: 0,6	−8,1
Nodding of the heaf	Backwards: 11,3	Forwards: 2,1	−13,4
Patient E (torticollis)			
Turning of the head	To the right: 1,4	To the right: 11	+9,6
Tilting of the head	To the left: 6	To the right: 1	−7
Nodding of the head	Forwards: 5,9	Forwards: 4,3	−1,6

− = decrease; + = increase [°].

Conclusions: The 'Zerviton-helmet' provides objective quantificable information of the patient's head position during the measuring period. Therefore the Zerviton system could be a useful tool in diagnosis and monitoring of patients with cervical dystonia and may consequently improve the treatment management of this disease. Further studies with a sufficient number of patients are planned.

Th-407

Displacement of deep brain stimulation electrode causing epileptic seizures in a dystonic patient

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Objective: To describe the experience of seizure activity as an indicator of an electrode displacement following revision of a pulse generator and extension leads in a dystonic patient treated by deep brain stimulation (DBS).

Background: DBS is a useful surgical tool for the treatment of refractory dystonia. Epilepsy is a known but rarely documented complication following DBS. There is currently no documented case report of DBS electrode malpositioning inducing epilepsy.

Methods: A 38 years old female with DYT1 positive dystonia underwent implantation of GPi electrodes at the age of 31 at Charing Cross Hospital. Although enjoying good clinical effects from DBS, she developed new onset epilepsy 6 days post-operatively that required treatment with a combination of anti-epileptics for two years, after which she remained seizure free. In July 2008, she underwent a routine operation to change the implantable pulse generator (IPG) and insert new extension leads to allow repositioning of the IPG from her chest to her abdomen. Her dystonia was found to be worse immediately post-operatively and she experienced 5 to 6 absence seizures per day. She suffered a generalised tonic-clonic seizure 10 days post-operation.

Results: A skull radiograph showed gross displacement of the right DBS electrode. As there was an impedance fault in the left electrode, both electrodes were revised, and were confirmed to be correctly positioned by Magnetic Resonance imaging. The patient's

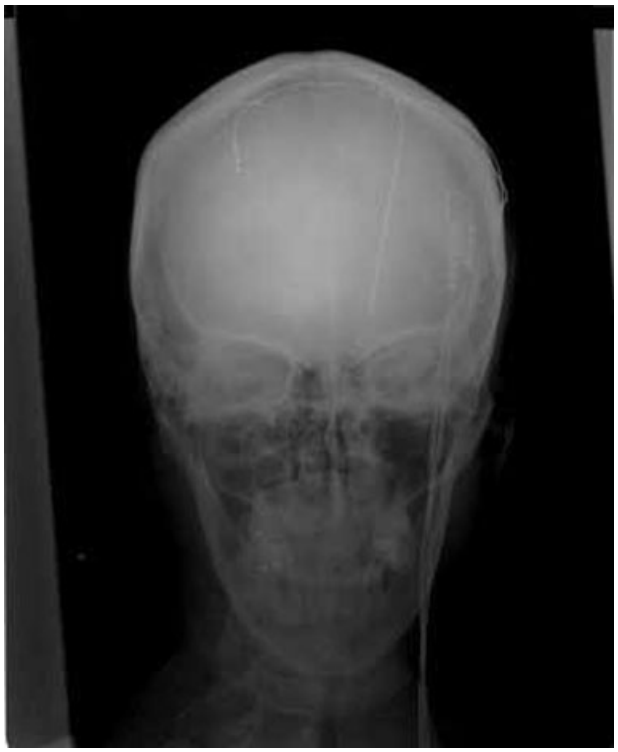

FIG. 1 (Th-407).

dystonia improved with the use of DBS post revision, and she did not suffer seizures subsequently.

Conclusions: Our patient illustrates the significance of epileptic seizure activity as a manifestation of an electrode misplacement. Patients should be advised of this potential risk prior to undergoing revision of DBS extension leads.

Th-408

Late onset dystonia secondary to static encephalopathy in the newborns: Physiopathological mechanisms and surgical treatment
F. Vivancos Matellano, I. Ybot Gorrín, E. Díez Tejedor (Madrid, Madrid, Spain)

Objective: To present two patients treated with deep brain stimulation (DBS) and discuss possible physiopathological mechanisms for late onset dystonia.

Background: There are not many clinical cases related to DBS of the globus pallidus (GP) for generalized dystonia, and the monitoring period is not very long because the work experience at present is short. We present here two more cases treated with DBS of the GP.

Methods: Two patients, 18 and 19 years old, who presented late onset generalized dystonia, secondary to post-anoxic injury in the newborn period, were treated with conventional therapies without satisfactory results, so they were offered DBS treatment of GP.

Results: After taking anticholinergic drugs, benzodiacepines, tetrabenazine and botulinum toxin, both patients experienced barely any improvement, but responded satisfactorily to DBS of internal GP.

Conclusions: In spite of its relatively short experience, DBS of internal GP should be considered as a good choice also for those patients with secondary generalized dystonia who hardly respond to conventional medical therapies.

EDUCATION IN MOVEMENT DISORDERS

Mo-74

Botulinum toxin type B may alleviate pain and movements in Painful Legs Moving Toes
M.V. Alvarez, V.G. Evidente (Lackland AFB, Texas)

Objective: To report the benefit of Botulinum toxin type B (BoNT-B) in the treatment of pain in patients with Painful Legs and Moving Toes (PLMT).

Background: In 1971, Painful Legs and Moving Toes syndrome (PLMT) was first coined. In due course the syndrome expanded to include hand movements, called Painful Hands Moving Fingers (PHMF), and the painless variants had been identified which includes Painless Legs Moving Toes (P-LMT) and Painless Hands Moving Finger (P-HMF). The most common causes reported in case reports/series are peripheral nervous system lesions such as radiculopathy, neuropathy, and/or trauma. Less commonly, PLMT may have central nervous system disorders, such as Wilson's disease, cerebral infection such as HIV/AIDS, or systemic disorders such as sarcoidosis and Hashimoto's. Drug-induced PLMT may also occur (e.g., neuroleptics). Some cases are idiopathic. The involuntary movements typically described as fanning or clawing of toes can be stopped with mental concentration but reemerge with mental distraction and may continue during light stages of sleep. The biggest challenge is the treatment of pain. Most common agents prescribed are anti-epileptics (gabapentin, baclofen, benzodiazepines, or carbamezapine) and antidepressants (SSRIs/ TCAs). Local anesthetic nerve blocks, epidural blocks, symphatectomy/symphatetic blockade, neurectomies, TENS, vibratory stimulation, and epidural spinal cord stimulation have been reported to be of little or limited benefit.

Methods: Case Report of 2 patients.

Results: Patient #1 is a 61 y.o. woman with PLMT for 18 months and a diagnosis of sarcoidosis since 5 years ago. Patient #2 is a 38 y.o. man with PLMT for 24 months and AIDP 30 months ago. Both presented with burning pain in the legs, and with curling/fanning of toes bilaterally. Patient #1 failed all oral medications tried, while patient #2 had minimal relief with pregabalin (20% pain reduction). Both opted for a trial of BoNT-B (Myobloc). Both reported significant relief of pain and PLMT that lasted 3 months. No adverse effects were reported.

Conclusions: BoNT-B may be an effective alternative for relief of pain and movements in PLMT patients who have a poor response to oral medications. BoNT-B may be effective in treating pain perhaps due to previous suggestion that BoNT may reduce peripheral and central sensitization to pain. References available upon request.

Mo-75

Parkinson's disease on the internet: An evaluation of the readability, quality, and content of patient-accessible information
B.R. Barton (Chicago, Illinois)

Objective: To evaluate the most readily available information on the internet about Parkinson's disease (PD), as discovered through popular search engines.

Background: As the use of the internet to access medical information becomes increasingly more popular and common, online patient-accessible health information requires critical evaluation. While there are no standardized tools for this purpose, general quality standards have been previously proposed. Evaluation of PD websites has not been performed.

Methods: The term "Parkinson's disease" was entered in the most popular internet search engines (Google, Yahoo, AOL, MSN, Ask Jeeves). The first 20 non-sponsored links from each engine were compiled, resulting in 35 unique websites; of those, 27 provided original educational content. Websites were rated by one reviewer using

the following pre-determined criteria: readability (Flesch-Kincaid Grade Level Score, ideally 8th grade or lower), overall website quality (Sandvik adaptation of the Health on the Net (HON) Foundation Code), and quality of technical information (adapted PD-specific scale). A composite score was determined for each site (range 0-46).

Results: Searches overall yielded an average of $10.5x10^6$ (SD $13.4x10^6$) website references. Of the 27 evaluated websites, identifiable sponsors included 9 biomedical information companies (33%), 8 PD organizations (30%), 3 general information companies (11%), 3 hospital systems (11%), and 2 commercial sponsors (7.4%). Average composite score was 33.3 (range 17-41, SD 6.5). Sites scored highest in accuracy and detailed summaries of symptoms and treatments. The lowest scores occured with readability (average grade 12.6, range 9.3-19.3, SD 2.4) and documentation of authorship/source material. PD organizations were less likely to reference authorship and currency of source material compared to biomedical sites ($p=0.01$). Neither HON-certification or absence of advertising predicted higher scores.

Conclusions: Readability levels of easily located PD websites are too advanced for education of the general public. While largely accurate and detailed in technical content, compliance with proposed quality measures was less stringent. Online resources for PD require re-evaluation and revision for compliance with ideal standards of health information quality.

Mo-407

Ancient walking to primal rhythms: therapeutic "continuum of movement" rituals employed to alleviate symptoms of movement disorder

R. Eady (Boca Raton, Florida)

Objective: Stress floods the brain with certain hormones (glucocorticoids) known to suppress neurogenesis, (especially in the hippocampus). It is reasonable to consider that an integrative lifestyle that engages music, rhythm and physical movement reduces stress and would be beneficial to stimulating "time-keeper" brain function (to assist with development/cognition and neuromuscular integration).

Background: Research has shown bio-molecular benefits of ambient sound that mimics maternal heartbeat. Additionally, studies are affirming hormone enhancing activities that help release serotonin and Atriol Neuriatic Factor (ANF) strengthen the immune system and new brain cell growth. This neurogenesis appears prevalent in the hippocampus--a region of the brain associated with learning, memory and stress-related emotions and appears to benefit those at early and late life stage. Vibration, music, rhythm -- said to be the first language in sensate form in the body -- is a key homeostasis factor. This discussion explores the social effect of ambient energy (as music) in specialized settings. Elaborates on how music has been used for thousands of years in concert with movement mediations such as labyrinth walks, tai chi and other poly-rhythm activity to serve as a culturally responsive avenue to wellness.

Methods: Biomimicry of components in neonatal development that initiate a "calming reflex" are employed around the three vegetative balance centers. Focusing on movement and rhythm protocols that correspond with proximal heart contact/womb biomimicry, our research demonstrates how the *basal ganglia* (in the cerebellum's critical *body-rhythm and time-keeper function*) continues to serves as a prime "neural-network orchestrator" to regulate precise shifts of brain activity. Using a Doppler-aided, steady percussion of 60 beats per minute, participants within 15 cm of each other restored natural rhythms of the body (breathing) and brought about synchronized heart rates that corresponded with a mood calming effect.

Results: Understanding the anthropology of neurological development in social bonding brought about a biological wellness effect on communal gatherings in specialized living settings.

Conclusions: Ongoing research indicates movement meditation that also mimics heartbeat synchronization may serve as a calming activity that boosts serotonin and perhaps neurogenesis.

Tu-72

Unified Wilson's disease rating scale (UWDRS) training and evaluation DVD – A new training tool for evaluation of neurological symptoms of patients with Wilson's disease

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Objective: Introducing UWRDS and training how to evaluate neurological syptoms of Wilson's disease patients with new UWDRS scale.

Background: Wilson's disease (WD) is a rare autosomal recessive disease resulting in copper toxicity, primarily in liver and brain, causing initial hepatic (40%) or neurological (40%) symptoms. Neurological symptoms are diverse, but mainly result from basal ganglia, pontine and cerebellum lesions. What is important is that these signs are rarely isolated. Usually patients present a combination of signs from different brain structures. That is why, previously known rating scales dedicated for evaluation of severity of single symptoms like dystonia (e.g. RSD), ataxia (e.g. ICARS) or parkinsonism (e.g. UPDRS) used alone seem to be insufficient for WD patients.

Methods: In 2004, on behalf of the EuroWilson Consortium and GeNeMove, clinicians from Poland, Germany and France prepared a new neurological scale, naming it the Unified Wilson's Disease Rating Scale (UWDRS). It stems from mentioned above scales and also from the Barthel index. UWDRS consists of 3 parts, including: evaluation of consciousness level; depth of functional impairment based mainly on the Barthel scale and neurological examination.

Results: For teaching and evaluation purposes, a special UWRDS training and evaluation DVD was prepared including films presenting patiens with neurological signs of Wilson's disease. It consists of 3 modules: educational (UWDRS -learning), training (UWRDS–verification), and practical (UWRDS–test). During educational module the user gets acquainted with UWDRS scale thanks to films clearly showing symptoms characteristic for each point on the scale. In the training phase a user can verify his knowledge by possibility to evaluate 5 patients on videos according to the full UWRDS scale. Practical module has been designed to be helpful in practice while examining WD patients–presenting the scale as easy to use electronic version of scale with printable option.

Conclusions: Authors hope, that this user friendly presentation will appear a very useful tool making more easer usage of UWDRS.

We-73

Final results from a Canada-wide survey to assess regional differences in the diagnosis and management of movement disorders responsive to botulinum toxin type-A (Botox®)

M. Jog, Canadian Movement Disorder Survey Group, S. Simonyi (London, Ontario, Canada)

Objective: To understand the diagnostic and treatment paths of patients with movement disorders responsive to Botox® by geographic region in Canada and to review their relative frequency.

Background: Many people affected with movement disorders remain undiagnosed or misdiagnosed. The time to diagnosis from onset of symptoms is considerable, resulting in patients visiting numerous healthcare practitioners in the interim.

Methods: Patients with Botox®-responsive movement disorders completed a 19-question survey developed by the Canadian Movement Disorder Survey Group in 14 Canadian botulinum toxin treatment centres. The survey included demographics, time to diagnosis, number of physicians seen and wait times.

Results: Over 6,000 patients were treated for movement disorders in 2008 by the 14 centres participating in the survey, of which over 85% have Botox®-responsive movement disorders. This final analysis includes 879 patients that completed the survey. 72% of those patients were female. The average age of patients was 57 yrs, with 28% being over 65. The average distance traveled to a clinic was 69 kms one-way, ranging from 43 (Quebec) to 111 kms (Saskatchewan).

Common diagnoses of patients included cervical dystonia (42%), hemifacial spasm (20%), and blepharospasm (9%). The average number of physicians seen prior to diagnosis was 3.1, ranging from 2.9 (Ontario) to 3.3 (Eastern provinces). The average time from onset of symptoms to diagnosis was 5.1 yrs, ranging from 4.0 (Western provinces) to 5.9 yrs (Ontario). 95% of all patients were treated with BoNTA following diagnosis. The average waiting time to Botox® treatment from diagnosis was 2.9 months, and common reasons for delay were physician waiting lists (54%) or insurance paper work (18%).

Conclusions: The number of physicians seen and length of time from onset to movement disorder diagnoses are considerable. Geographic location, expert injector availability, variability in provincial and private insurance access for patients across Canada may account for regional differences in travel and wait times.

We-74

Recommendations for optimal organization of care in Parkinson's disease

S.H.J. Keus, T. van Laar, J.A. Vriezen, S. Flikweert, M. Hulscher, M. Munneke, B.R. Bloem (Leiden, Netherlands)

Objective: To develop recommendations to optimize the organization of integrated multidisciplinary care for patients with Parkinson's disease (PD).

Background: Because of the complex and progressive nature of PD, many patients require multidisciplinary care. However, guidelines for the optimal organization of such a multidisciplinary care were not available. A national multidisciplinary guideline for PD has been developed in the Netherlands (2006-2008). This guideline was partially an update and extension of the NICE clinical guideline on Parkinson's disease (UK, 2006), supplemented with newly developed recommendations to optimize the organization of multidisciplinary care for patients with PD.

Methods: Using focus group interviews, PD patients and health care professionals (representing all disciplines involved in the care of patients with PD) identified barriers in the current organization of care. A literature search was performed to identify additional barriers. The identified barriers were subsequently transformed into requirements for optimal care. This was combined with recommendations provided by the NICE-guideline. An integrated model and recommendations for the organization of care were then developed based on consensus among patients and health care professionals.

Results: Sixteen requirements for optimal PD care were identified, covering four important aspects of care organization: (1) expertise; (2) communication and cooperation; (3) coordination of care; and (4) finances. To address these issues, 48 specific recommendations were developed. Some recommendations concern a specific health care professional or the relationship between two professionals, other recommendations are generally applicable to the entire health care network. We combined these recommendations in an integrated health care model with a central role for the patient, the neurologist, the Parkinson's disease nurse specialist, the rehabilitation specialist and the nursing home doctor.

Conclusions: Recommendations for optimal organization of PD care have been developed as part of a multidisciplinary evidence-based clinical practice guideline. These recommendations apply to all health care professionals involved in the care of patients with PD.

Th-75

Use of Parkinson's disease research as a model for teaching aspiring young scientists

R.B. Rosenbaum, J.T. Rosenbaum, K.H. Farris, T. Martin, E.A. Neuwelt (Portland, Oregon)

Objective: The history of Parkinson's disease is a paradigm of scientific progress. We use examples of Parkinson's research to teach high school students about research and to inspire them to pursue careers in science.

Background: We need our best students to pursue scientific careers, but high school science teaching can be dull and uninspiring. We want to teach the excitement of scientific exploration.

Methods: Annually since 1997 we have offered a free elective course on research to Oregon high school students. The course meets weekly during spring semester. Students receive high school credit and grades for their work. The students participate in a weekly interactive lecture on varied approaches to research on Parkinson's disease, such as clinical evaluation, pathology, epidemiology, clinical and molecular genetics, cell biology, animal models, toxicology, pharmacology, clinical trials, surgery, or ethics. A textbook *Understanding Parkinson's disease. A Personal and Professional View* (Rosenbaum, RB Praeger, 2006) parallels the lecture material. The course teaches how an illness can be studied in many ways by researchers with diverse interests and talents and illustrates the excitement of a research career. The students present journal clubs, develop research proposals, and pursue research projects with mentors from the Oregon Health & Sciences University, often exploring topics other than Parkinson's disease.

Results: Between 1997 and 2008 our enrollment has grown steadily; 51 students completed the class in 2008. The course is taught with minimal expense by more than 35 volunteer faculty and mentors. Students have completed varied research projects written papers, presented abstracts at major meetings like the American College of Cardiology, and won the Neurosciences Creativity Prize of the American Academy of Neurology. When we surveyed our graduates, 73% planned careers in health or science and most found our class more influential than their traditional high school classes on their career choice (FASEB J **21**(9): 1954-7 (2007)).

Conclusions: Recent developments in Parkinson's research exemplify biomedical or scientific research. By exposing high school students to this burgeoning field, we encourage them to join us in research. We challenge other medical schools and research centers to offer similar courses.

EPIDEMIOLOGY

Mo-76

Parkinson's disease registry in Thailand launched: The first pilot project

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Objective: The initial goal is to generate a confidential database containing basic information about individual cases of PD in various regions of Thailand. Chulalongkorn Comprehensive Movement Disorders centre (www.chula-parkinsons.org) as a representation of the Thai Red Cross society and the Ministry of Public Health of Thailand implement this work.

Background: Little is known about the epidemiology of PD in Thailand. Therefore, a nationwide PD registry in Thailand is established in 2008 to determine the number of PD patients (pts) and to identify the trends of PD rates in Thailand.

Methods: Project staff will be contacting physicians, healthcare facilities as well as directly promoting the campaign to Thai residents through different sources of media, including public radio, television and newspaper. Based on the interest expressed by disease advocates, a means of PD pts who voluntarily register their own clinical information (age at onset, disease duration, symptoms, social stigmata) will be created.

Results: The project commenced in July 2008 and will last two yrs. As of January 2009, a total of 15190 (23.02% of target PD population) pts voluntarily registered and 3511 pts completed the 7-item questionnaire containing basic clinical information. There were 1819 males (51.8%) and 1692 females. 1522 (43.5%) patients were >

70 yrs old and 377 pts (11.0%) represent a young-onset PD. 2160 pts (74.3%) had tremor as their initial symptom, followed by bradykinesia (57.9%). In contrast, 1992 pts (68.52%) reported bradykinesia as their major troublesome symptom. Above 40% of pts reported symptoms of motor fluctuations with wearing-off being the most common (56.16%). 2206 pts (75.89%) take levodopa while only 27% and 22% of pts utilize dopamine agonist and entacapone respectively. 76.92% of pts denied history of smoking.

Conclusions: Due to the complexity of the project, the registry will be developed in several stages. 6 months after the launch of the project, a total of 15,190 pts have been recruited and a nationwide database using state-of-the-art procedures and technology is being created. Collecting the information in a whole nation will provide important clues about the causes of the disease as well as help make sure that adequate health resources are available to most if not all PD pts.

Mo-77

An observatory study of primary and secondary hemifacial spasm

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Objective: To investigate possible differences in the demographic and clinical features between primary and secondary hemifacial spasm.

Background: Hemifacial spasm (HFS) is a peripherally induced movement disorder. Although HFS is believed to be more common in Asia, there is few published data available on the similarities or differences in the demographic and clinical features between primary and secondary HFS.

Methods: We did a prospective observatory study on patients diagnosed with HFS in Neurology outpatient clinic of Kaohsiung Medical University hospital from Oct.2008 to Dec.2008.

Results: The study sample comprised 50 patients with HFS, 34 women and 16 men, having a mean ± SD age of 59.3± 13.5 years. 40 patients were classified as having primary HFS and 10 patients were classified as having secondary HFS. Patients with primary HFS and those with secondary HFS had similar age at onset (50.6 ± 14.8 vs. 55.1 ± 11.6 years), male-female ratio (14:26 vs. 2:8), right-sided-left-sided HFS (24:16 VS. 5:5). Most patients with primary HFS(70%) and those with secondary HFS (80%) had similar initial symptoms of periocular muscle contraction and subsequent involvement of lower face muscles. Initial symptom of simultaneous periocular and lower face muscle contraction was not found in patients with secondary HFS. Signs of synkinesis were present in primary (82.5%) and secondary (90%) HFS.

Conclusions: Patients with primary and those with secondary HFS share common demographic and clinical features in our limited study. The higher prevalence of secondary HFS and right-sided predominance in primary HFS in the study may be attributed to small sample size within limited time in tertiary medical center. Further study of larger scale and longer time may disclose more significant and useful data of HFS in Taiwan.

Mo-78

Prevalence and incidence study of Parkinson's disease in the metropolitan city of Kolkata, India – A community based study

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Objective: To determine the prevalence and incidence rates of idiopathic Parkinson's disease (IPD) in a stratified heterogeneous population in the city of Kolkata.

Background: Though there are few cross-sectional studies on parkinsonism (PD) from India, incidence study has not been reported.

Methods: This was a prospective study carried over 5 years from 2003 to 2007 in two phases with a validated screening questionnaire. The sample population was selected on the basis of randomly chosen national sample survey organization blocks (NSSO). The trained non-professional workers screened the cases and the field doctor examined them and recorded the clinical details. The information was verified by a group of senior neurologists including one movement disorders specialist. The crude prevalence (CPR) and annual incidents rates (AIR) were age adjusted (AAR) to World Standard Population (WSP).

Results: Out of 282 randomly selected blocks, 100802 subjects were screened and prospectively studied. Based on UK Parkinson's disease Brain bank Criteria, 41 subjects were prevalent cases of IPD (CPR- 40.67/100,000; AAR- 52.69). The CPR of parkinsonism plus syndrome was 10.91/100,000. A total of 22 cases of IPD were detected over 5 yrs (AIR–4.36/100,000/year; AAR- 5.44). Sex specific prevalence was higher among women. There was no difference in sex specific incidence rates. Both age specific prevalence and incidence rates showed increase with advancement of age.

Conclusions: The prevalence and incidence rates of IPD from India are lower than the Caucasian population.

Mo-79

Long-term mortality of Parkinson's disease and other types of parkinsonism. Data from a populational study

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Objective: To report the risk of mortality in patients with Parkinson's disease (PD) and in patients with other types of parkinsonism (PK) using data from the Neurological Disorders in Central Spain (NEDICES) study.

Background: Population-based studies analyzing long-time mortality in PD and PK are scarce. In general, data estimate that PD increases mortality slightly.

Methods: NEDICES is a prospective, population-based study in which 5,278 participants, 65 years of age or older, taken from the census, were evaluated for neurologic illnesses at baseline (1994-1995), using a door-to-door approach. PD and PK were diagnosed based on specified criteria and reviewed to increase reliability across neurologists at follow-up 3 years later. The status living/dead were determined by means of the Mortality National Register and the mortality analysis was fulfilled 10 years later of the baseline. The hazard ratio (HR) for mortality (PD or PK vs non-PD/non-PK) was estimated using Cox proportional hazards models that adjusted for baseline age, gender, educational level, comorbidity and prevalent dementia.

Results: The cohort consisted of 5,236 subjects (mean age 74.3, 95% CI = 74.1-74.5): 81 subjects affected by PD (mean age 77, 95% CI = 75.8-78.2), 36 with PK (26 drug-induced parkinsonism, 6 parkinsonism in dementia, 3 vascular parkinsonism, and 1 unspecified parkinsonism) (mean age 78,9, 95% CI = 76,0-81,8) and 5,119 non-PD/non-PK (mean age 74,2, 95% CI = 74,0-74,4). There were 53 deaths (65.4%) among PD cases, 19 (52.8%) PK and 1,718 (33.6%) among non-PD/non-PK subjects. In an adjusted Cox model for PD, HR = 1.56, 95% CI = 1.18-2.06, $p < 0.005$; for PK, HR = 1.32, 95% CI = 0.83-2.11, n.s.

Conclusions: In this longitudinal, prospective and adjusted study, the risk of mortality was increased in patients with Parkinson's disease, in accordance with previous data. By contrast, it was not increased in subjects with other types of parkinsonism.

Mo-80

Patients' perception of premotor symptoms before motor manifestation of Parkinson's disease – Occurrence according to Braaks' staging

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Objective: To evaluate the time span from first (pre-motor) symptom onset to diagnosis as well as the order of occurring premotor symptoms.

Background: Before Parkinson's disease (PD) is recognized as such by patients and clinicians, more than 50% of the dopaminergic neurons of the substantia nigra have degenerated (Fearnley and Lees,

1991). This time span between onset of neurodegeneration and manifestation of motor symptoms is referred to as premotor period of PD. It is estimated to last 5 to more than 30 years. (Fearnley and Lees, 1991; Scherman et al., 1989).

Methods: Retrospective interview of 100 patients with PD without dementia by a standardized questionnaire.

Results: 94.4% of all patients reported premotor symptoms before the diagnosis of PD. The patients noticed in mean 5,4 (range 0-15, SD 3,7) different non motoric signs before the diagnosis of PD was made. The symptom with longest time span until motor manifestation was constipation with a mean duration of 15,8 years, followed by sleeping disturbances (involuntarily crying/talking in sleep, nightmare, vivid dreams, involuntarily limbs moving in sleep) with a duration of 12-13 years before diagnosis. Smell deficits were realized in mean 11,8 years earlier than the diagnosis was made. Bad mood was noticed by affected patients 10,9 years beforehand, depression was diagnosed 9,3 years, increased salivation occurred 7,6 years and reduced voice volume 4,5 years before the diagnosis of PD. There was a clear association of the course of premotor sign onset and the pathological staging according to Braak as well as the clinical modification of this staging according to Przuntek et al., (Braak et al., 2003; Przuntek et al., 2004).

Conclusions: These retrospective data confirm a long premotor period in PD mirroring the pathological staging. Standardised questionnaires on these symptoms may be helpful in the premotor and early clinical diagnosis.

Mo-81

Alternative therapies and Parkinson's disease in Portugal

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Objective: The aim of this study was to determine the frequency and the spectrum of AM use in a sample of Portuguese patients with Parkinson's disease, as well as to establish the factors (demographic, social, philosophical and disease-specific) involved in such choice.

Background: According to World Health Organization, Alternative Medicine (AM) is "a broad set of health care practices that are not part of that country's own tradition and are not integrated into the dominant health care system". Data from the literature reports a high prevalence of the use of such practices. This number has been increasing despites the insufficient evidence of its efficacy and safety.

Methods: A structured questionnaire was sent by mail for the patients members of the Portuguese Association of Parkinson's Disease Patients. Logistic regression analysis was used to determine which covariates were associated with AM use.

Results: We included 412 questionnaires corresponding to a response rate of 51.5%. The mean age of patients was 67.1 years with a mean age at onset of 55.6±12.5 years. AM was used by 49.6% of patients. The most used were natural products, supplements and vitamins (18.6%), acupuncture (24.8%) and massage therapy (20.3%). Number of adverse reaction in conventional Medicine (2.7 *vs* 2.6, $p=0.001$), devaluation of a symptom by a health professional posteriorly associated with a malign situation (31% *vs* 17%, $p=0.001$), congruence with a holistic philosophy (87% *vs* 79%, $p=0.03$) and believes and attitudes towards religion and spirituality (2.7 *vs* 2.2, $p=0.002$) were the factors associated with the use of AM.

Conclusions: The high prevalence of use of AM and the high subjective perception of efficacy justify a critical approach of the variables involved in such choice as well as of its efficacy and safety.

Mo-82

Mild parkinsonian signs are associated with cognitive impairment without dementia in a door-to-door study of an elderly Arab population

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Objective: To examine whether mild parkinsonian signs (MPS) are associated with cognitive impairment without dementia (CIND).

Background: MPS are more common in older people and linked to functional disability, increased mortality and incident dementia. It is unclear whether MPS are more common in mild cognitive impairment and which MPS are associated with CIND.

Methods: All consenting residents aged ≥65 years in Wadi Ara villages, Northern Israel were assessed by medical history, full neurological examination, motor UPDRS (mUPDRS), Minimental State Examination and Brookdale Cognitive Screening Test by an Arabic speaking medical team. CIND was defined as memory or cognitive impairment in one domain without functional disability. Presence of MPS was defined as mUPDRS score ≥2. We categorized mUPDRS by 4 item-clusters: Axial (items 18,19,27-31), Tremor (20-21), Rigidity (item 22), and Bradykinesia (23-26). Chi-square comparing CIND to normals was performed for each item-cluster and 3 age groups (I: 65-69, II: 70-79 and III: ≥80 years).

Results: Of 472 approached subjects, 395 (226 normal, 169 CIND) were included. Examination was declined by 21 (4.4%). 56 were excluded: prior stroke 27, comorbidity 8, drug induced tremor 4, incomplete data 17. Mean age(SD) of normals was 72(5) and CIND 73(6) years ($p>0.1$). Mean mUPDRS score was 0.3(1.2) for normals and 1.29(4.4) for CIND. MPS were more frequent in CIND vs. normals: 12% vs. 4% ($p=0.04$), 13% vs. 8% ($p>0.1$) and 20% vs. 13% ($p>0.1$) for groups I-III respectively. The frequency of abnormal Axial Score in CIND vs. normals was 10% vs. 0 ($p=0.002$), 11% vs. 2% ($p=0.009$) and 7% vs. 15% ($p>0.1$) for group I-III respectively. A similar trend was observed for limb bradykinesia: 5% vs. 0 ($p=0.02$), 9% vs. 3% ($p=0.05$), and 15% vs. 0 ($p>0.1$). No significant difference for tremor or rigidity was found between CIND and normals.

Conclusions: MPS frequency increases with aging in both groups. In CIND patients, MPS are more frequent than in controls at ages <70 years. Axial and bradykinesia scores are significantly higher in CIND than cognitively normal controls. The CIND-MPS co-occurrence might represent an early presentation of Lewy body dementia.

Mo-83

Asymmetry of symptoms and signs in multiple system atrophy

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Objective: To asses the prevalence of assymetric presentation in symptom and signs in large population of multiple system atrophy (MSA) patients.

Background: MSA is a sporadic neurodegenerative disease characterized by cerebellar ataxia, parkinsonism, and autonomic dysfunction. The disease affects both sexes and is more prevalent in males. It has been recognized that some of the symptoms and signs of MSA emerge with asymmetry, and small-scale case reports that have been published thus far suggest that asymmetry in MSA is a rather rare finding.

Methods: In order to examine the prevalence and characteristics of asymmetry in multiple system atrophy (MSA), we retrospectively investigated the records of 155 patients who satisfied the criteria of probable and definite MSA according to the Consensus statement on the diagnosis of MSA.

Results: There were 110 MSA-C and 46 MSA-P patients. The overall male to female ratio was 1.46, and the mean age of onset was 56.2 ± 7.9 years. Among them, 39% had episodes such as clumsiness in limb movement, tremors, or a tendency to lean or fall to a certain side during walking that suggested the presence of asymmetry in their illness history. MSA-P patients presented with more episodes of asymmetry than MSA-C patients (75% vs. 23.6%). Among the episodes, asymmetry was more frequent in parkinsonism than for cerebellar symptoms (56% vs. 33%). Interestingly, these symptoms were more prevalent at the left side of the body (64% for parkinsonism and 83% for cerebellum symptoms). Next, we surveyed the neurological signs examined by multiple neurologists during the admission, which was considered consistent if more than three neurologists agreed whether there were any predominance in the side of the signs.

Asymmetry in the cerebellar signs was present in 63% of the MSA-C patients and asymmetry in parkinsonism was exhibited by 64% of the MSA-P patients. Interestingly, cerebellar signs, parkinsonism, and Horner's sign were all observed predominantly at the left side (cerebellar signs: left, 52%; right, 12%; and bilateral, 36%; parkinsonism: left, 35%; right, 18%; and bilateral, 47; and Horner's sign: left, 62%, and right, 38%). Pyramidal signs were observed without any asymmetry.

Conclusions: We concluded that a significant number of MSA patients present with asymmetry in both symptoms and signs and that more interestingly, these are predominantly observed at the left side.

Mo-84

Urate and the risk of Parkinson's disease in a community-based population in the United States (Cardiovascular Health study)

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Objective: To determine if serum urate concentration is associated with the risk of Parkinson's disease (PD) in a community-based American population.

Background: Although studies have found higher urate concentrations associated with lower risk of PD, this has yet to be reported in the general U.S. population. We investigated this using the Cardiovascular Health Study (CHS), a U.S. community-based longitudinal study of cardiovascular disease in 5,888 adults ≥65 years at baseline with follow-up into very old age.

Methods: PD cases were identified with a tiered algorithm: (Tier 1: anti-parkinsonian medication (APM) & ICD-9 code & self-report; Tier 2: (APM & ICD-9 or APM & self-report or ICD-9 & self-report); Tier 3 (ICD-9 or self-report); and Tier 4 (only APM). Diagnosis date was the earliest data source. All PD cases at or within 1 year of baseline were excluded. Using all cases without prevalent PD at baseline, we evaluated the association of urate and risk of incident PD over 10 years using serum urate concentration both in quintiles and as a continuous variable. Hazard ratios (HR's) of developing PD according to urate concentration were estimated with Cox's regression model adjusting for age, sex and smoking.

Results: Serum urate concentrations (μmol/L) were determined in 5808 participants of whom 189 developed PD. Incident PD rates were lower in women than men, 2.7% vs 4.1% ($p=0.003$). Women had significantly lower urate concentrations than men (316.7 (sd=87.9) vs 371.2(sd=88.2), $p<0.0001$) and urate concentration was not associated with rates of incident PD in women. Loess smoothed curves in men demonstrated lower PD risk for higher concentrations of urate from 300-500 μmol/L. Very high levels of urate (>500 μmol/L, 38% of 5th quintile) were associated with higher risk of PD, HR=2.28 (1.23, 4.22) when compared to lower levels (300-500 μmol/L). Fitting linear ($p=0.017$) and quadratic ($p=0.016$) urate terms suggested PD risk is higher at both the low and high ends of the urate level range.

Conclusions: Our findings suggest that in men, there is a range (300-500 μmol/L) for which higher urate concentration is associated with lower PD risk, but PD risk increases at >500 μmol/L.

Mo-408

Pharmacogenetic determinants for discontinuation of non-ergoline dopamine agonists in Parkinson's disease

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Objective: To identify genetic determinants for discontinuation of non-ergoline dopamine agonist (DA) treatment in patients with Parkinson's disease (PD).

Background: Of all patients put on the non-ergoline DA's ropinirole and pramipexole, approximately 50-60% discontinue this medication within three years due to lack of efficacy or side effects. Determinants for discontinuation of non-ergoline DA therapy are largely unknown. Polymorphisms in DRD2 and DRD3 could be important determinants, because the non-ergoline DA have high binding characteristics for the DRD2 and DRD3 subgroup.

Methods: The setting of this cohort study was the neurology department of Medisch Spectrum Twente, Enschede, The Netherlands. First time users of the non-ergoline DA ropinirole or pramipexole diagnosed with PD before 2005 were included. Treatment discontinuation was defined as a gap of 180 days or more between two pharmacy refills of the DA. Genetic determinants for non-ergoline DA treatment discontinuation were the following polymorphisms: DRD2 141C Ins/Del, DRD2 $(CA)_n$ STR, DRD2 *Taq*IA, DRD3 *Msc*I SNP and DRD3 *Msp*I SNP. Cox proportional hazard analysis was used to estimate the hazard ratios (HR) for discontinuation of non-ergoline DA treatment.

Results: The population consisted of 38 patients. The mean age of the patients was 63.4 years with a mean duration of PD of 52.6 months. The proportion of patients using levodopa at the index date was 50%. Absence of a 15x DRD2 CA repeat allele was significantly related to a decreased risk of discontinuation of DA treatment (HR: 0.23; 95%CI: 0.07-0.81). There were no significant relations between other polymorphisms studied and discontinuation of DA treatment. There was a non-significant allele dose effect with the DRD3 *Msp*I polymorphism.

Conclusions: This study identified the 15x DRD2 CA repeat allele as a genetic determinant for discontinuation of DA treatment in patients with PD. The DRD3 *Msp*I polymorphism needs further study, because of existence of an allele dose effect. The consequences of these polymorphisms on the DRD2 and DRD3 protein function are still unravelled. More research is needed to replicate these findings and to elucidate the consequences of these polymorphisms.

Tu-73

Drug interaction with genes in early Parkinson's disease

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Objective: To evaluate the feasibility of a cohort study of PD patients to investigate the interaction between drugs and genes for the occurrence of motor and non-motor complications.

Background: The course of Parkinson's disease (PD) is hampered by motor complications (e.g., fluctuations, dyskinesias) and non-motor complications (e.g., cognitive decline, depression). The factors affecting these complications are still largely unknown although there is some evidence that clinical factors, drug exposure and genetic background may play a role. Our goal is to identify gene polymorphisms associated with the occurrence of motor and non-motor complications in PD and their interaction with clinical factors and drug exposure.

Methods: Methods: A feasibility study of the consecutive inclusion in a cohort of PD patients with a disease course of 5 years or less was performed between January 2007 and November 2008 at the Pitie-Salpetriere hospital (Paris). Patients received a comprehensive structured clinical evaluation including assessment of disease history and severity, motor and non motor complications, quality of life and social function, drug use history, smoking, alcohol drinking, and pesticides use. We report the results from the baseline analysis.

Results: Among 120 PD patients fulfilling the inclusion criteria, 91 were enrolled, 22 refused to participate and 5 lived to fare to participate. Sex ratio (m:f) was 1.46, mean age 59.4 +/- 13.7 years, age at PD onset 56.5 +/- 15,3 years, disease duration 35.5 +/- 17.3 months, UPDRS III score 18.8 +/- 10.3. The daily equivalent L-DOPA dose was 435 +/- 247 mg/day. The non motor score was 8.0 +/- 4.6. Forty six (51%) patients had motor fluctuations and 12 (13%) had dyskinesias. Patients with motor fluctuations had longer

disease duration, younger age at onset and higher doses of treatment, although differences between groups were not significant.

Conclusions: Following this feasibility study, we plan to recruit a larger cohort of 600 PD consecutive patients in 8 French centres. Patients will be followed annually during 5 years in order to assess the occurrence of motor and non-motor symptoms. The findings of this study may contribute to improve our understanding of the complex relationships between gene-drugs interactions and PD prognosis.

Tu-74

Movement disorders post stroke

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Objective: Study purposed to assess the prevalence, clinical features and MRI correlates of post stroke movement disorders.

Background: Poststroke movement disorders including vascular parkinsonism, chorea, hemidystonia are well known sequels of stroke. They have a negative effect on the recovery of motor functions, social activity and life quality of stroke survivors. Establishing the risk factors, clinical features and radiological correlates of post stroke movement disorders might be helpful in improving the patients rehabilitation.

Methods: 348 stroke patients were prospectively studed. Initial stroke severity assessed by NIHSS. Type, side and size of stroke lesion was evaluated by conventional MRI. Movement disorder type was recorded in acute stage and 3 month later using the Unified Parkinson's Disease Rating Scale, Tremor and Dystonia Scale, Pain Visual Analog Scale. Risk factors, clinical, demographic and radiological variables were set to multiple linear regression and binary logistic regression analysis to find the independent correlates of poststroke movement disorders.

Results: Post stroke parkinsonism found in 16(4,59%), is the most common movement disorder represented by brady-hypokinesia and muscles tonus rigidity, which is not depending on stroke side. Tremor, mostly in affected side, occurs in 5(1,43%) patients. Hemidystonia with intractable pain has been recorded in 1(0,28%)case correlating with anterior fronto -temporal and basal ganglia stroke in the right hemisphere. Multiple linear regression analysis revealed a significant share of hypertension, hemorrhagic stroke and large vessel diseases in the development of post stroke movement disorders. The follow-up NIHSS scale found to be worse in patients with post stroke movement disorders.

Conclusions: According to the present study the most common movement disorder found to be the vascular parkinsonism that is not depending on stroke side and size.

Tu-75

Study of the prevalence of Parkinson's disease using dopamine transporter imaging

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Objective: To investigate the prevalence of Parkinson's disease (PD) among community-dwelling elderly persons in Korea, using a symptom-based questionnaire and dopamine transporter (DAT) imaging.

Methods: A community-based epidemiological study. **Patients:** Korean elders aged 65 years old or over randomly selected from Seongnam city, Korea. **Main Outcome Measures:** Phase-1: Standardized interviews were performed in a random sample of elderly aged 65 years or older using the questionnaire. Phase-2: Neurological examinations were performed to clinically diagnose PD. Phase-3: DAT imaging was performed using [^{123}I]-FP-CIT SPECT to support the clinical diagnosis. After the 3-phase study, longitudinal clinical observation was performed.

Results: A total of 714 subjects participated in the phase-1 interview. 221 subjects, scored more than 2 points, were referred to the movement disorder specialist. Eighteen of these subjects showed overt or equivocal parkinsonian features. Three subjects were clinically diagnosed with possible PD: five with essential tremor with equivocal extrapyramidal signs, eight with frontal-subcortical gait disorder, and two with drug-induced parkinsonism. All 18 subjects were evaluated with [^{123}I]-FP-CIT SPECT. The three subjects with possible PD showed a typical pattern of reduced DAT density in PD. DAT density was normal in the other 15 subjects. Results of long-term follow-up supported the initial clinical diagnoses. The crude prevalence of PD was 0.42 per 100 persons in the population aged 65 years or older.

Conclusions: During the clinical evaluation, we encountered a very large proportion of subjects with equivocal parkinsonian features, who posed a diagnostic challenge to correct diagnosis and a substantial risk of misestimating the prevalence of PD. The combination of specific DAT imaging and longitudinal clinical observation of equivocal cases enabled us to differentiate PD from other conditions posing a diagnostic challenge. The prevalence of PD in our study is lower than that reported in other studies performed in industrialized countries. We suspect that one of the factors in the variation in estimates of the prevalence of PD may be attributable to a considerable proportion of subjects with equivocal parkinsonian features and how they are evaluated.

Tu-76

Cholesterol and apolipoproteins in patients with Parkinson's disease: A case-control study

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Objective: To evaluate the association of serum cholesterol and apolipoproteins with the risk of Parkinson's disease (PD).

Background: Cholesterol has an important role in brain development and neuronal function. However, little is known about the association between serum cholesterol levels and risk of PD. Furthermore, the role of apolipoproteins in the pathogenesis of PD has been unknown.

Methods: Our samples of case-control study included 82 patients with PD aged more than 55 years and 246 sex- and age-matched normal controls between October 1, 2006 and June 30, 2007. We compared the serum levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, and apolipoprotein A-I/B (ApoA-I/B) ratio between PD patients and controls. Body mass index (BMI), history of hypertension, smoking, and type-2 diabetes were also compared between cases and controls.

Results: The serum levels of total cholesterol ($p=0.035$), LDL-C ($p=0.001$), HDL-C ($p=0.002$), triglyceride ($p=0.035$), ApoB ($p=0.007$), ApoA-I/B ratio ($p=0.002$) were significantly lower in patients with PD than in normal controls. There was no difference in BMI or serum ApoA-I level between cases and controls. History of hypertension was inversely correlated with PD, whereas history of smoking or type-2 diabetes was not associated with PD.

Conclusions: Results of this case-control study suggest that low levels of serum cholesterol and apoliproteins are associated with PD. Further studies are needed to clarify the role of lipids in the pathogenesis of PD.

Tu-77

Non-uniformity of movement disorders care across the world – More is needed

H. Kumar, M.S. Jog (London, Ontario, Canada)

Objective: Determine the ratio of movement disorders experts to population as an approximate measure to showcase the disparity of movement disorders care across the world.

Background: Since its inception, The *Movement* Disorder Society has spread it wings world-wide and brought the sub-specialty of

Movement disorders in the fore-front of neurological sciences. Through its visiting Professor and Ambassador programs, the society has tried to further extend its outreach. In this study, we have made an attempt to analyze the membership demography of the society and its relation with population of the area.

Methods: Countries were listed from official UN websites. Population data of each country were obtained through the most recent and authorized online documents. Demographic data of members of MDS were pulled out from "members-only" section of MDS website. Key variables studied were: 1) Absolute number of MDS members from each country and continent, 2) ratio of MDS member to population of individual country and continent, 3) Population of countries having no representation in MDS.

Results: Ten countries accounted for 70% of MDS membership and served only 12 % of world population. Ratios of number of MDS members to population in Africa and Asia were 75 and 16 times higher than that in North America, respectively. Using published prevalence data for Parkinson's disease (PD), India and China which account for 38% of world population, have approximately one MDS member per 28000 patients with PD, as compared to 1/452 in the USA. These two most populous countries have only 3.4% share in MDS membership as compared to USA that serves 4.5% of world population but has 32.3% share in membership.

Conclusions: Huge segments of world population are either underrepresented or unrepresented in the MDS This study clearly shows these inadequacies. Aiming to achieve a world-wide uniform movement disorder representation and care will truly make the society global. The non-uniformity of movement disorders experts to population distribution of the world is enormous which means that more needs to be done.

Tu-78

Trends in mortality from Parkinson's disease in Chile

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Objective: To evaluate characteristics and trends of mortality from Parkinson's disease (PD) in Chilean population between 1990 and 2004.

Background: Mortality as an indicator of the public health burden associated with diseases and higher mortality rates have been reported in PD. However, no data are available about trends of mortality associated with PD in Chile.

Methods: Data were obtained from the Database of the Department of Statistics and Information of Health (DEIS) of Chile. Cause of death was identified using the International Classification of Disease (CIE), CIE9 (code 332.0) and CIE10 (code G20-21). The evolution of mortality rates for PD and general population, adjusted by age and gender, were compared.

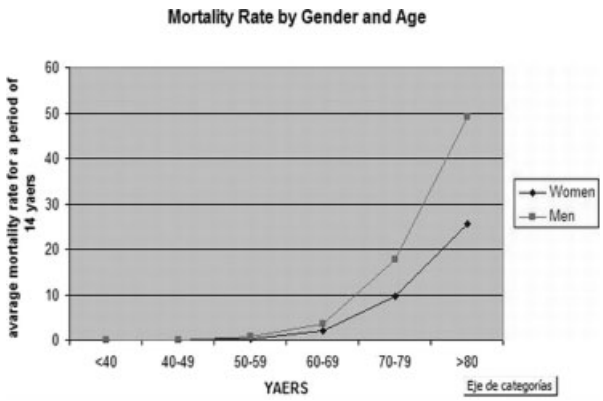

FIG. 1 (Tu-78).

Results: There were 2561 deaths associated with PD registered during the study. Mortality rates due to PD have an increased variation of 0.35 to 2.07/per 100.000 inhabitants from 1990 to 2004. The rates were greater in men than in women during the entire study period, particularly in those over 80 years. The mean age (mean +/- SD) of death, during the analyzed years, was 77.1+/-8.8 and 78.9±8.5 years for males and females ($p<0.001$. T= -5.45).

Conclusions: Our data suggest an increased mortality associated with PD as compared to general population, especially in males. Even more, mortality rate of PD was increasing over time. Prospective epidemiological studies about deaths associated with PD are warranted in our population, to establish the determinants of these findings.

Tu-79

NSAID use and the risk of Parkinson's disease: The influence of comorbidity

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Objective: To evaluate the influence of comorbidities on the relationship between Parkinson's disease (PD) and prior use of non-steroidal anti-inflammatory drugs (NSAIDs) in a large prospective cohort of men.

Background: Prior analyses of regular NSAID use and the risk of PD may not have controlled adequately for the influence of comorbidity.

Methods: Case-control analysis nested in the Physicians' Health Study, a prospective cohort of 22,007 U.S. male physicians aged 40-84 years (y) without indications/contraindications to regular NSAID use and free of PD at baseline. PD was self-reported on yearly questionnaires, as was the number of days of aspirin and non-aspirin NSAID use in the preceding 12 months. Regular use was defined as >60 days/y. Case control sets were matched by 1) age; 2) age and PD risk factors (RF): smoking, alcohol use, exercise and BMI; and 3) age, Charlson comorbidity score and scores for indications for or against NSAID use. We estimated odds ratios (OR) and 95% confidence intervals by conditional logistic regression.

Results: We matched 639 PD cases to 639 controls by age, 629 cases to 629 controls by age and RF, and 578 cases to 578 controls by age and comorbidity scores. Age and RF matched cases had substantially more comorbidity than their controls. In the age-matched cohort, PD cases had an OR of 2.06 (1.56-2.73) for regular NSAID use. The OR decreased to 1.66 in the RF matched group and 1.41 in the comorbidity matched. When we excluded NSAID use within 5y of the matching date, the association in the comorbidity matched group disappeared (OR=1.03; 0.75-1.42). Cases had an OR of 5.9 for long-term (≥5y) NSAID use in the age-matched group vs. 1.0 in the comorbidity matched. In contrast, aspirin appeared protective among ever-regular users (OR=0.47; 0.28-0.77), but this association also disappeared with comorbidity matching (OR=1.21). In a stratified analysis, level of comorbidity significantly modified the relationship between NSAID use and PD (p=0.01), and longer-term aspirin use and PD (p=0.01).

Conclusions: In this prospective case-control study of initially healthy men, we did not find strong evidence that NSAID or aspirin use reduces the risk of PD. We demonstrate the importance of adequately adjusting for the influence of comorbidity and the utility of comorbidity matching for this purpose.

Tu-80

Co-occurrence of substantia nigra hyperechogenicity and putative premotor signs as well as risk factors of PD in a large cohort older than 50 years

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Objective: To define the occurence of different risk and premotor markers in a large cross-sectional population over 50 years, with no

diagnosis of PD and to evaluate their relation to the echostatus of the SN.

Background: Neuroprotective treatment of Parkinson's disease (PD) is supposed to be most effective in the premotor phase of the disease, in which less neurons of the substantia nigra (SN) have degenerated compared to the motor stage. Therefore, much effort has been put in the identification of risk and premotor makers of the disease. To date, however, prevalence of these markers singularly or in combination is not known in subjects in the typical age for the development of PD. SN hyperechogenicity (SN+) assessed by transcranial sonography (TCS) is a typical finding in PD, which has also been found in a small percentage of healthy subjects. Several studies indicate that this echofeature constitutes a marker for nigrostriatal vulnerability.

Methods: In two centers (Tübingen and Homburg, Germany) 1204 individuals > 50years without the diagnosis of PD were investigated. Putative risk and premotor makers were assessed. All subjects were investigated by TCS to define those, in whom SN+ was present.

Results: More than 10% of the participants reported a positive family history for PD. Concerning premotor markers hyposmia (25.4%) was the most frequent sign in the cohort, followed by the occurrence of motor performance alteration (9.7% had single parkinsonian features, 11.6% showed reduced arm swing), depression (11.4%), and constipation (6 %). In 16% of the participants SN+ could be detected. Risk markers and premotor markers were associated with SN+, with a subgroup showing several markers, which was larger ($p<0.001$) than the group of SN- subjects.

Conclusions: Risk and premotor markers are highly prevalent in subjects >50 years, and therefore unspecific when regarded singularly. We hypothesize that a combination of markers in a subgroup, here predefined by the echostatus of the SN, could be a good predictor for the future development of PD, which has to be verified in further longitudinal studies.

Tu-81

Movement disorder among the new Parkinson diseases patients in China

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Objective: The present study present the PD's clinical epidemiology, focus on the signs among the new diagnosed PD patients.

Background: PD is becoming known recently in China as Chinese lives longer. BUT PD epidemiology is not clear yet.

Methods: Subjects comprised 88 Parkinson's disease patients (88 men, 84 women; mean (±SD) age, 64.3 ±9.6 years) who had been patients for <3 years, and sex- and age-matched (<2years old) controls with no Parkinson's disease, but with headache, dizziness etc. attending the inpatient clinic of No. 1 People's Hospital in Xiangfan and Jingmen, Hubei, China. All clinical examination data was input a database and statistical analyzed with SPSS 13.0.

Results: The authors found that all the PD patients due to the thrill and /or movement difficult of the four limbs on the chief complaint. Among these patients, there were only 32 persons (36.4 %) seek clinical aids within one year since they had medical problems, 19 persons(21.6 %), 19 persons (21.6 %), 18 persons (21.5%) go to hospital in 1-, 2- and longer than 3 years, respectively. The authors also found that 16 PD patients (18.2%) had thrill of limbs, and there are 13 (81.3%) patients had hemi-thrill, only 3 PD (8.7%) patients had bilateral thrills. Concerning the thrill ranges of these PD patients, 10 (62.5%) subjects limit on the arms, 4 subjects (25%) thrill on all of the four limbs, only 2 subjects had a body's thrills. There were 18 subjects showed an increase muscular tension, one showed decrease muscular tension. There were 15 patients had orofacial dyskinesia, and 15 patients appeared body movement difficult.

Conclusions: PD should be pay more attention both on clinical doctors and citizens.

Tu-82

Prevalence of gait disorders in elderly men and women aged 58-97 years (Bruneck study cohort): A population-based study

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Objective: Our aim was to assess the prevalence of gait disorders in a population, accounting for sex differences and age trends.

Background: There is emerging awareness that gait disorders are common in the elderly population. However, the overall burden of these disorders in the general community is not well defined.

Methods: As part of an ongoing prospective population-based study of carotid atherosclerosis and stroke risk (the Bruneck Study), nearly 500 men and women aged 58-97 years underwent a thorough neurological assessment (door-to-door visits of the study participants). Gait disorders were classified according to a recent classification system based on clinical signs and symptoms (Snijders *et al*., *Lancet Neurol* 2007, 6: 63–74). This is an interim analysis of most of the subjects available for the study (n=460).

Results: One third of the population complained of gait problems, of whom one quarter had a completely normal gait. Overall, the prevalence of all gait disorders was 25% [21-29] in the population. Proportions in men were significantly lower than in women (19% [13-23] vs 31% [26-37]) and increased significantly with age (from 11% [7-15] in 58-69-years old to 30% [23-38] in 70-79-year olds and to 53% [43-63] in 80-97-years old). At the age of 90 years or older 80% [52-96] of the subjects had some form of gait disorder. Over one third had multiple causes for their gait impairment. 60% [51-69] of the subjects with gait disorders were classified as neurological gait disorders of which hypokinetic-rigid gait, ataxic gait and higher-level gait disorders were the most common. Overall one quarter of the subjects with gait disorders suffered from recurrent falls.

Conclusions: There is a high prevalence of gait disorders in the general community. In the very elderly population (80 years or older) only half of the population has a normal gait.

Tu-407

Influence of vascular risk factors on the prevalence and progression of sporadic amyotrophic lateral sclerosis: An 85-case study

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Objective: We focused on hypertension, hypercholesterolemia, triglyceridaemia, tobacco use, diabetes, obesity and sleep apnoea syndrome (SAS) at the time of diagnosis and during the course of the disease. We compared the impact of these factors on disease severity in terms of (i) age at disease onset, (ii) total disease duration (in months) and (iii) slow vital capacity at the time of the diagnosis.

Background: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder characterised by the progressive loss of upper and lower motor neurons and, ultimately, terminal respiratory failure. Chronic and/or intermittent episodes of hypoxaemia are closely related to disease progression. Vascular risk factors (VRFs) in general and chronic arterial hypertension (AHT) in particular may be associated with an increased risk of cellular hypoxemia. We decided to study the influence of VRFs on the occurrence and progression of ALS.

Methods: Our retrospective cohort was composed of 85 sporadic ALS patients, (22 bulbar and 63 spinal forms; gender ratio: 1.3). The median age at disease was 63 and the median disease duration was 29 months. The median ALS Functional Rating Scale score at the time of diagnosis was 34.

Results: We found a high prevalence of AHT (46%), tobacco use (42%) and hypercholesterolemia (24%) in ALS patients but these factors were not associated with disease severity. Hypertension and hypercholesterolemia were associated with later disease onset

(p=0.002 and 0.04, respectively). We also found a high prevalence of SAS (19%) at the time of diagnosis.

Conclusions: Hypertension at the time of diagnosis does not seem to accelerate ALS progression**.** Indeed, it may act to compensate for the repeated hypoxemic episodes and thus restore good vascular perfusion of the motor neurons. Likewise, hypercholesterolemia may compensate for the hypercatabolism observed in the early stages of the disease. Tobacco use and obesity seem to be deleterious, whereas diabetes and hypertriglyceridaemia have only a weak influence on disease progression.

We-75

Evaluation of types and distribution of movement disorders in adults with cerebral palsy

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Objective: Cerebral palsy (CP) is a disability that affects individuals throughout their lifespan. This study was conducted to evaluate the movement disorders in adults with cerebral palsy.

Background: Although CP was well studied in Europe and USA, little is known about movement diorders in this condition specially in the Middle East.

Methods: In cross-sectional study carried out during the period of February 2001 through to June 2007, in Baghdad-Iraq, 100 adults with cerebral palsy were evaluated by reviewing their prior medical records and present clinical status.

Results: Maternal medical problems during pregnancy recorded in 34% of cases. Kernicterus was the most common possible cause occurred in 28 (28%) cases. Movement disorders were the only neurological manifestation in 7 patients (7%). Dystonia reported in 5 patients (5%) and chorioathetosis in 2 patients (2%). Various forms of combination occurred in 18 patients (18%). Spastic quadriplegia & Dyskinesia in 7 patients, spastic heiplegia & dyskinesia in 6 patients and spastic diplegia & dyskinesia in 5 patients. Dysartheria was reported in 60 patients (60%) and mental retardation in 30 patients (30%). Relationship of movement disorders to the development of mental retardation was statistically significant (P value 0.0001).

Conclusions: Movement disorders are relatively common in adult patients with cerebral palsy in Iraq, which is mostly due to a preventable cause e.g. RH incompatibility (kernicterus), and causes significant loss of function and deterioration in quality of life.

We-76

Prevalence of Parkinson's disease in five French districts and its relation with type of farming

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Objective: To estimate the prevalence of Parkinson's disease (PD) among affiliates to the Mutualité Sociale Agricole (MSA, health insurance system for persons working in the agricultural world) in 5 French districts and to investigate the relation between the risk of PD and type of farming.

Background: Several studies have shown that farming increases the risk of PD, possibly through exposure to pesticides. However, farming is very heterogeneous in terms of types of pesticides used and it is unknown whether some farming activities are more particularly associated with PD.

Methods: The population study included all MSA affiliates (≥18 years) in five French districts (Charente-Maritime, Gironde, Haute-Vienne, Mayenne, Côte d'Or) in 2007. PD cases were defined as: 1) persons who benefited from free heath care coverage for PD at the prevalence date (April 1, 2007) and/or 2) persons who had at least one prescription of levodopa before and after April 1, 2007. Standardized prevalence rates were computed using the US 2001 population. We used the agricultural census (1988) to estimate at a small area level (French cantons) the proportion of farms according to their main farming activity categorized by 18 variables (cereals, livestock, etc) (not available for Côte d'Or). Socio-economic status was defined based on the median household income at the canton level (2005). We used logistic regression to estimate OR (95%CI).

Results: We identified 1,647 PD cases among 242,472 MSA affiliates, yielding a crude PD prevalence of 6.79 per 1,000; the age- and sex-standardized PD prevalence was 2.91 per 1,000. PD prevalence increased with age and was significantly higher in men than women (p<0.001). A difference across districts was also observed (p=0.015). The risk of PD increased with the proportion of fruit farms (p=0.003) and a significant association with the highest tertile of the proportion of fruit farms was observed (OR=1.25 [1.08-1.45], p=0.003) (adj for age sex district). This relation remained significant (p=0.004) in a model that included median household income.

Conclusions: We describe the prevalence of PD in five French districts among MSA affiliates. PD prevalence increased with the proportion of fruit farms which rank among the farming activities with highest pesticide use.

We-77

Risk factors for psychosis in patients with Parkinson's disease: Regional perfusion change on SPECT study in pre-psychotic state

T. Oeda, K. Yamamoto, H. Sawada (Kyoto, Japan)

Objective: To clarify which neural background mechanism participates in psychosis in PD, we evaluated regional perfusion changes in pre-psychotic state of patients with PD who experienced psychosis in the study period of two years.

Background: Psychotic symptoms in Parkinson's disease (PD) are relatively common and, in addition to disturbing patients' daily lives, have consistently been shown to be associated with poor outcome.

Methods: Methods: We enrolled 325 consecutive patients without psychosis at the entry of the study period (2years). The endpoint was defined as the use of antipsychotics or end of the study period. We performed a nested case-control study, in which, subjects who needed antipsychotics were classified as case-patients and remains were designated as controls. We examined age, sex-ratio, Hoehn and Yahr stages (H&Y), disease duration, mini-mental state examination (MMSE) and ^{123}I-IMP SPECT at the entry and investigated the differences of these values between cases and controls.

Results: Of the 325 patients, 142 patients were excluded by dropping out and 183 patients were analyzed. Fifty-eight patients were assigned as cases and the remaining 125 patients as controls. In the results of multivariable logistic regression analyses, male-sex and higher H&Y stages significantly increased the risk of psychosis (P=0.001, 95%CI 1.73-9.13, Odds ratio 4.0 and P=0.005, 95%CI 1.27-4.00, Odds ratio 2.3/stage, respectively). ^{123}I-IMP SPECT were performed in 37 patients of cases and 68 of controls at the entry. In the analyses of brain perfusion image of ^{123}I-IMP SPECT using 3D-SSP analysis, left lateral frontal lobe perfusion were significantly decreased in cases compared to controls.

Conclusions: The reduced IMP uptake in the left lateral frontal lobe may be risk for developing psychosis in patients with PD.

We-78

Atypical parkinsonisms in a rural Japan

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Objective: We conducted an epidemiological study and searched medical treatment and local care service in AP to facilitate diagnosis, treatment and local care system in a rural Japan.

Background: In atypical parkinsonism (AP), there were a few prevalence studies reported, and patients' daily life was rarely reported.

Methods: We collaborated with all the medical institutions including hospitals, nursing homes, or Japanese long-term care insurance system facilities in the KOBAN district, Kochi, Japan, to pick up all patients who had a diagnosis or a suspicion of AP or Parkinson's disease (PD). Under information from the collaborators, we captured patients for screening who were seen by the specialized neurologists later. According to the conditions, UPDRS I, II, III, UMSARS, PSP-QoL or MSA-QoL was used appropriately. At the time of diagnostic visit, all patients were given disease specific QOL questionnaire.

Results: We screened 184 patients out of a total population of 66465, where the elderly population aged 65 or over was 32%. Result with PD was separately reported. We captured 12 patients with PSP, eleven patients with MSA (six MSA-C and five MSA-P) and six patients with CBD. The crude prevalence was 18 for PSP, 17 for MSA and 9 for CBD. The average onset age and age at visit were, 76 and 81 for PSP, 63 and 68 for MSA, and 71 and 75 for CBD. Other results included UPDRS II (average: 28 for MSA, 30 for CBD), UPDRS III (50 for PSP, 57 for CBD), UMSARS I (25), UMSARS II (26), UMSARS IV (3), PSP-QoL score (44, n=9), and MSA-QoL score (41, n=9). Average L-dopa equivalent dose were 83mg, 215mg and 170mg for each. In total AP, 18% of the patients live in home with long-term care insurance system service and 52% were institutionalized.

Conclusions: The crude prevalence of PSP and MSA were approximately one-tenth of that for PD, which were higher than reported. Patients age was also higher than these reported in other countries. As expected, patients with AP suffered more severe disability and lower ADL level than those with PD.

We-79

Parkinson's disease in a rural Japan

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(Nankoku, Kochi, Japan)

Objective: We conducted an epidemiological study and searched medical treatment and local care service in PD to facilitate a diagnosis, treatment and local care system in a rural Japan.

Background: In Parkinson's disease (PD), a number of community-based prevalence and QOL assessment studies were reported to longstandingly improve patients' QOL.

Methods: We collaborated with all the medical institutions including hospitals, nursing homes, or Japanese long-term care insurance system facilities in the KOBAN district, Kochi, Japan, to pick up all patients who had a diagnosis or a suspicion of PD. Under information from the collaborators, we captured patients for screening who were seen by the specialised neurologists later. UPDRS I, II, III, PDQ-39 were used appropriately. The presence of depression or dementia was defined by UPDRS I or the diagnostic criteria for DLB, respectively. At the time of diagnostic visit, all patients were given PDQ-39 questionnaire.

Results: We screened 184 patients out of a total population of 66465, where the elderly population aged 65 or over was 32%. We captured 116 patients with PD (43 men and 73 women), and 29 of them had dementia. The crude prevalence for PD was 175. There were 39 hospitals, 890 in-hospital beds and no full-time specilaised neurologists in the district. The average onset age and age at visit was 67 and 75, respectively. Other results included HY stage (average: 2.9), UPDRS II (16), UPDRS III (33), L-dopa equivalent dose (LEDD) (267mg), depression (17%), patients live in home with long-term care insurance system (15%) and institutionalization (31%). The average PDQ-39 score was 44, to which UPDRS II, LEDD, postural instability, UPDRS III and presence of dementia significantly contributed.

Conclusions: The crude prevalence of PD was higher than previously reported, which probably due to its elderly population. Disability, ADL, LEDD and dementia contributed patients' QOL. Future plans should include these points.

We-80

Anti-Parkinson drugs consumption. A pharmaco-epidemiological study

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Objective: Pharmaco-epidemiological studies are very important to determine the correct use of different drugs and to detect misuse. Also, these studies are tools to calculate cost of medicaments for the population and to estimate prevalence of chronic diseases.

Methods: We evaluated consumption of anti-Parkinson drugs in a Buenos Aires population, being cared by the National Health Program (n = 13236), between January and December 2008. We present consumption data as Daily Definite Dose (DDD) per one thousand inhabitants per day (DHD).

Results: The total consumption of anti-Parkinson drugs was 7,56 DHD. Considering pharmacological groups, the consumption was: Levodopa + Peripheral Decarboxylase Inhibitor (3,24 DHD); Anticholinergics (2,44 DHD); MAOI (0,65 DHD); Adamantanes (0,59 DHD), Dopaminergic Antagonists (0,54 DHD) and COMT Inhibitor (0,10 DHD). Considering drugs separately, the consumption was: Biperidene (2,06 DHD), Levodopa/Carbidopa (1,9 DHD), Levodopa/Benserazide (1,31 DHD), Amantadine (0,59 DHD), Selegiline (0,55), Pramipexole (0,45) and Trihexyphenidyl (0,38).

Conclusions: The pharmaco-epidemiological studies about anti-Parkinson drugs are very rare. We found consumption to be slightly higher than the one reported in the international bibliography. The relative consumption of Biperidene is higher than the one reported in other studies.

We-81

Statin use and the risk of developing Parkinson's disease in Denmark

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(Los Angeles, California)

Objective: To investigate whether statin use is positively or negatively associated with the occurrence of PD in Denmark.

Background: It has been suggested that widely used cholesterol-lowering drugs known as statins (3-hxydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) may be neuroprotective for Parkinson's disease (PD) because of their anti-oxidants and possibly anti-inflammatory properties. However, since statins inhibit the hydroxylmethyl-glutaryl Co-A reductase (HMGCoA) enzyme that participates in both cholesterol and Co-enzyme Q10 synthesis pathways, some hypothesized that statins might instead be harmful to the dopaminergic system due to lowering of Co-enzyme Q10 levels.

Methods: Between 2001- 2006, we identified 1,931 patients with a first time primary diagnosis of PD reported in hospital or outpatient clinic records and density matched them by birth year and sex to 9,651 controls selected from the Danish population register. We linked subjects' records to a pharmacy database that covers prescription medication use for all Danish residents since 1995.

Results: Employing logistic regression analysis adjusting for age, sex, diagnosis of COPD (chronic pulmonary obstructive disorder), and Charlson co-morbidity score our data suggested that cases were prescribed statins somewhat less frequently than population controls between 1995 and a two-year period prior to their PD diagnosis dates (Odds ratio (OR) 0.90; 95% CI 0.72 to 1.12). While the risk of developing PD seemed more than 30% reduced at the highest statin use intensity (OR 0.69; 95% CI 0.46-1.05), the results were consistent with no association due to the small number of regular statin users in Denmark in the 1990s (less than 6% of the population) that rendered our moderate size associations imprecise. We also found no difference by sex, age, or type of statins used (lipohylic/hydrophilic) or with duration of use in our data.

Conclusions: A potential neuroprotective role for statins in PD should be further investigated; preferably in studies that have data to

evaluate long treatment periods and latency intervals for a sufficient number of regular users.

We-82

L-Type calcium channel blockers and the risk of developing Parkinson's disease in Denmark

B. Ritz, L. Qian, E. Schernhammer, J. Olsen, S. Friis
(Los Angeles, California)

Objective: To investigate whether L-type Ca21 channel antagonists used to treat hypertension are associated with the occurrence of Parkinson's disease (PD) in Denmark.

Background: Adult substantia nigra pars compacta dopaminergic (DA) neurons are Ca21-dependent autonomous pacemakers that in the absence of synaptic input generate action potentials at a clock-like 2–4 Hz rhythm. DA neurons can be returned to 'juvenile' ionic mechanisms of pacemaking by the L-type Ca21 channel antagonist isradipine in-vitro and in-vivo, and these channel blockers protect animals against cell loss and motor deficits after the administration of MPTP.

Methods: Between 2001- 2006, we identified 1,931 patients with a first time diagnosis and/or treatment for PD reported in a nationwide hospital and outpatient clinic record system and a pharmacy database and density matched them by birth year and sex to 9,651 controls selected from the Danish population register. This pharmacy database covers prescription medication use for all Danish residents since 1995.

Results: Employing logistic regression analysis adjusting for age, sex, diagnosis of chronic pulmonary obstructive disorder, and Charlson co-morbidity score we found that cases were prescribed calcium channel blockers of the hydropyridine class (excluding amlodipine, a blocker that mainly acts peripherally rather than centrally) less frequently than population controls between 1995 and a two year period prior to the diagnosis date of PD cases; specifically risk of receiving a PD diagnosis was about 27% lower when treated with hydropyridine class calcium channel blockers (Odds Ratio (OR) 0.73; 95% CI 0.55 to 0.97); the estimated risk reduction did not differ with the intensity or length of treatment (low-high intensity OR range: 0.64-0.85; low-high duration OR range: 0.72-0.77). For other types of calcium channel blockers and anti-hypertensive drugs we did not find protective associations with PD in our study.

Conclusions: Our data suggests a potential neuroprotective role for L-type calcium channel blockers of the hydropyridine class in PD that should be further investigated, preferably in studies that can evaluate longer latency periods than our study.

We-83

Occurrence and treatment of depression and anxiety prior to Parkinson's disease

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(Los Angeles, California)

Objective: To assess the relation of depression and anxiety diagnosis and treatment to PD diagnosis.

Background: Many people with Parkinson's disease (PD) suffer from depression and anxiety prior to the onset of motor symptoms. Studies suggest these psychiatric conditions may represent risk factors for PD or may be prodromal non-motor symptoms.

Methods: Using a population-based approach in three rural California counties, we recruited 371 incident PD cases, 402 population and 115 unaffected sibling controls. During a baseline interview, we recorded self-reports of lifetime depression/anxiety diagnoses and use of psychotropic medications. Diagnoses and medication use first occurring at or after PD diagnosis (cases) or at time of interview (controls) were excluded. We employed the history of a depression/anxiety diagnosis and medication use. All analyses were adjusted for age, race, sex, pack-years of smoking, and education, and we conducted analyses after excluding (lagging) both diagnoses and medication use first occurring within 2, 5, 10, and 20 years of the index/diagnosis date.

Results: We found that cases compared to population controls were more likely to have received a diagnosis of depression and/or anxiety at any time in their life prior to index date (OR 1.42, 95% CI 1.01, 2.00), but were not more likely to have been both diagnosed and treated (OR 1.11, 95% CI 0.77, 1.60). However, male PD patients received diagnoses combined with treatment more often than population controls within 5 years prior to PD diagnosis (OR 2.21, 95% CI 1.21, 4.04; 2 year lag: OR 2.44, 95% CI 1.29, 4.61; 5 year lag: OR 1.67, 95% CI 0.80, 3.49). We did not see any differences for females. Results for cases compared to sibling controls were similar to those obtained for population controls.

Conclusions: Depression and/or anxiety diagnoses were more common in cases prior to their PD diagnosis, and male cases received both a diagnosis and treatment more often during the 5 years before a PD diagnosis was made. This suggests that non-motor behavioral symptoms of depression and/or anxiety may be early symptoms during the prodromal phase of PD rather than etiologic risk factors.

We-84

Psychogenic movement disorders in children and adolescents

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Objective: To describe the clinical spectrum of psychogenic movement disorders (PMDs) in the pediatric and adolescent population.

Background: PMDs are difficult to diagnose and may respond well to correct and timely intervention. Childhood-onset PMDs have not been studied extensively.

Methods: We conducted a retrospective review of the medical records of 19 patients diagnosed with PMD starting before the age 20 years who were evaluated at a university-affiliated specialty movement disorders center between 2002 and 2008.

Results: Of the 19 children identified, 7 were boys and 12 were girls. The mean age at symptom onset was 15 years, ranging from 8 to 19 years. According to Fahn and Williams' criteria for level of diagnostic confidence, 9 fulfilled criteria for documented PMD, 9 were clinically established and one was probable. The most common movement disorder was tremor, occurring in 68.4% of children, followed by dystonia (47.3%), tics (21%), myoclonus (15.7%), Balance and gait difficulties (15.7%) and chorea (5%). More than half of the children exhibited multiple symptoms. 63% of children reported an abrupt onset of symptoms and in 21% an identifiable trigger was identified. 52.6% of children had paroxysmal episodes as part of their clinical manifestation. 52.6% of children had a history of psychologic or psychiatric conditions. The time from the onset of symptoms until the diagnosis of PMD was variable, ranging from 1 month to 18 years. Alternative diagnoses given prior to the diagnosis of PMD included organic dystonia and tremor, seizures, Sydenham's chorea, paroxysmal kinesigenic dyskinesia and restless leg syndrome. Prior to diagnosis, most of the children had undergone extensive investigation, including brain imaging, EEG, EMG, and numerous blood tests. Various medications as well as botulinum toxin injections had been tried, and 2 children were referred to our center for evaluation for possible deep brain stimulation surgery. Of 11 children in whom follow up was available, 9 showed significant improvement after treatment with combinations of psychotherapy, physical therapy and pharmacotherapy.

Conclusions: Childhood-onset psychogenic movement disorders are a cause of significant morbidity in children, resulting in extensive investigation and delayed diagnosis. Children who are diagnosed and treated accordingly may have a good prognosis.

Th-76

Risk for Parkinson's disease after hospitalisation for a head injury: A population-based case-control study

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Objective: To determine whether a hospital contact for a head injury increases the risk of subsequently developing Parkinson's disease.

Background: Injuries to the head have been suspected of causing Parkinson's disease since 1817. Epidemiological studies mostly supported this hypothesis.

Methods: We conducted a population-based case-control study including 13 695 patients with a primary diagnosis of Parkinson's disease (ICD-8 code 342, ICD-10 code G20) in the Danish National Hospital Register during the period 1986-2006. Each case was matched on year of birth and gender to five population controls selected at random from inhabitants in Denmark alive at the date of the patient's diagnosis. Hospital contacts for head injuries (*International Classifications of Diseases,* 8th revision (ICD-8): 800, 801, 803, 850-854; ICD-10: S02.0, S02.1, S02.7-S02.9, S06.0-S06.9, S07.0, S07.1) were ascertained from electronic files of the Hospital Register, and the frequency of a history of head injury was recorded.

Results: We observed an overall 50% increased prevalence of hospital contacts for head injury prior to the first registration of Parkinson's disease in this population (odds ratio (OR), 1.5; 95% confidence interval (CI), 1.4 to 1.7). The observed association was, however, due almost entirely to injuries that occurred during the 3 months period before the first record of Parkinson's disease (OR, 8.0; 95% CI, 5.6 to 11.6), and no association was observed between the two events when they occurred 10 or more years apart (1.1; 0.9 to 1.3).

Conclusions: We conclude that the steeply increased frequency of hospital contacts for a head injury during the months preceding the date at which Parkinson's disease was first recorded is a consequence of the evolving movement disorder rather than its cause.

Th-77

Cross-sectional analysis of parkinsonian features in the Einstein aging study

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Objective: To cross-sectionally study the prevalence of parkinsonian features and their relation to age, gender and cognitive impairment in a selected cohort from the Einstein Aging Study (EAS).

Background: Parkinsonian features are common in the non-Parkinson's disease elderly. Population studies show a marked increase with age of these features. Risk of death is increased in elderly individuals with such features and may be related to gait disturbance. Parkinsonian features have also been associated with lower scores in neuropsychological testing. Signs of parkinsonism frequently accompany dementias and neurological gait disturbance has been associated with higher dementia risk.

Methods: In a longitudinal ambulatory elderly cohort, age-estimates of UPDRS-III scores, prevalences of different parkinsonian signs and p-for linear trend were determined. Multivariate linear regression models were applied.

Results: Complete UPDRS-III scores were available for 301 subjects. Mean age was 81.4 (SD 5.3), 61.8% women (n=186), 72.8% Caucasian, 20.7% African-American, mean education years 14 (SD 3.6), 9 subjects were demented (3%). The median UPDRS-III score was 6 (IQR 4). Age-estimates of UPDRS-III scores increased significantly with age (table 1) validating the parkinsonian sign score. Age and CDR (clinical dementia rating) were independent predictors of UPDRS when controlled for gender, ethnicity and education.

Table (Th-77). Age and gender specific estimates of UPDRS

Age groups	All subjects	P for trend	Men	P for trend	Women	P for trend
UPDRS (median, IQR)						
Less than 75	4 (7.5)	0.000	4 (5)	0.005	3.5 (7)	0.000
75 to 79	5 (6)		5.5 (5)		4 (6)	
80 to 84	5 (6)		6 (8)		5 (6)	
85 to 89	8 (8)		6 (6)		9 (10)	
90 and older	10.5 (5)		11 (6)		9 (8)	

n=301.

Information on parkinsonian signs was available for 378 subjects. The prevalences of all 4 signs (bradykinesia, rest tremor, rigidity, gait/posture) increased with age and it was statistically significant except for rigidity. The prevalence of parkinsonism (at least two signs) was 17.1% (SE 4.3) in subjects older than 85 and 40% of subjects older than 85 had at least one sign on exam. A higher prevalence of gait/posture abnormalities and presence of any parkinsonian sign in women 85-90 was seen (35.7% vs. 11.76%, p=0.02; 50% vs. 26.5%, p=0.03).

Conclusions: Our study is consistent with prior reports in which parkinsonian features are common in the elderly and are strongly associated with age and cognitive decline. Whether the presence of parkinsonism reflects age-related striatonigral degeneration, Lewy body or Alzheimer's disease pathology or vascular changes in the basal ganglia circuitry is a matter of debate.

Th-78

Environmental risk factors in a population based incidence study of Parkinson's disease. Differential effect of alcohol and smoking on akinetic rigid and tremor dominant Parkinson's disease

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Objective: We have examined environmental risk factors such as occupation, smoking habits, alcohol and coffee consumption, in a Norwegian population of incident PD patients and controls, the Norwegian ParkWest study.

Background: Both environmental and genetic factors are shown to contribute to the development of Parkinson's disease (PD).

Methods: A 4-step diagnostic procedure was used to establish a representative cohort of patients with incident PD at a high level of diagnostic accuracy. 217 incident PD patients and 175 age and gender matched controls were included. At the baseline visit PD patients and controls was asked for information on occupation, education, exposure to pesticides, tobacco, alcohol and caffeine consumption, earlier medical history and family history.

Results: Agricultural work was associated with a higher risk of PD (OR 1.75 1,03-3,0), p= 0.009). Surprisingly, a history of exposure to pesticides was not a risk factor in our material. Smoking (OR 0,63 (0,42-0,95), p=0,016) and alcohol consumption (OR 0,55, p=0.008) was associated with a lower risk for PD. These inverse associations were however only seen in akinetic rigid (AR) PD, (p= 0.012 for smoking, p=0.07 for alcohol consumption), not tremor dominant (TD) PD. Consumption of coffee was lower in PD patients (3,3±1,8 cups pr day vs. 3,8±2.0 in controls p=0,02). PD patients had a higher frequency of depression and anxiety disorders at or before baseline. They tended to have a higher frequency of diabetes (p=0,09) and had a higher frequency of prior stroke or TIA (p=0.004).

Conclusions: Agricultural work increases the risk of PD, while using alcohol, tobacco and caffeine give some protection. Smoking and alcohol did only lower the risk for AR PD, not TD PD, strengthening the hypothesis of differences in pathophysiology between AR PD and TD PD.

Th-79

Microelement change of the Parkinson diseases movement disorder patients in China

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Objective: The present study examined the relationship between serum levels of heavy metals and MD Parkinson's disease in China.

Background: Heavy metals poisoning is well known to have an association in parkinsonian symptoms.

Methods: Subjects comprised 50 Parkinson's disease patients (40 men, 10 women; mean (±SD) age, 65.3 ±9.7 years) who had been patients for <3 years, and sex- and age-matched (<2years old) controls with no Parkinson's disease, but with headache, dizziness etc. attending the outpatient clinic of Xiangfan No. 1 People's Hospital in Hubei, China. Intake of metals was computed from a nutritional survey by ingestion frequency per week before diagnosis of Parkinson's disease. Morning blood samples were collected before breakfast. Serum was used to measure concentrations of manganese, iron, copper and zinc. Informed consent was obtained from all subjects, and the study protocol was approved by the ethics committee of the hospital.

Results: Fasting serum levels of manganese, iron, copper and zinc in Parkinson's disease patients were 0.035±0.021 mg/ml, 1.52±0.87 mg/ml, 1.23±0.31 mg/ml and 0.95±0.27 mg/ml, respectively. Levels in controls were 0.015±0.007 mg/ml, 0.95±0.54 mg/ml, 0.97±0.15 mg/ml and 0.65±0.21 mg/ml, respectively. Serum manganese and iron levels were significantly higher in MD Parkinson's disease patients than in controls. No differences were seen in intake of each metal between groups, but water and tea intakes were significantly lower in Parkinson's disease patients.

Conclusions: In China, accumulation of manganese and iron in blood might be involved in the etiology of Parkinson's disease.

Th-80

Parkinson's disease and nutritional survey

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Objective: This study explored the relationship between development levels and its nutritional status among Parkinson's disease patients.

Background: many studies showed that there is some links between the starting of Parkinson's disease (PD) and its nutritional intake.

Methods: Based on a hospital out-patient section, 40 Parkinson's disease patients whom was identified as pure PD were enrolled for this study among 2005-2006. 37 control subjects were selected from the in-patient section of the Dept. of neurology of the same hospital. The questionnaire included one week diet interview (food frequency survey), living environment, and general social economic status. Fast vein blood was got for the determination of Vit B_2, Vit E, Cu, Mn, Fe, Ze. Comparison statistical analysis was used between PD patients and control subjects.

Results: The control subject ate more vegetable, milk than that of the PD patients, ($P<0.05$) from the one-week food frequency questionnaire survey, calcium, and Vit B2 from the nutritional intake analysis of control subjects were significant higher than that of the PD patients($P<005$). But Fe, Mn of PD patients was higher than that of the control subjects ($P<005$). Logistic analysis presents such a result: high animal fat acid intake, depress, Vit E levels were hazard factors of PD development, OR: 1.98 (95%CI: 1.06-1.35), 39.12 (95%CI: 1.90-8.26), 1.74 (95%CI: 1.23-2.46), respectively. High social class and more milk intake were protective factors of PD development: OR: 0.06 (95%CI:0.002-0.25), 0.86 (95%CI: 0.75-0.99), respectively.

Conclusions: Development of Parkinson's disease were highly relative with nutritional status, depress, further study should focus on it.

Th-81

A 15-year population-based longitudinal study of incidence of Parkinson's disease (PD) and parkinsonian syndromes (PS) in an elderly French population (PAQUID)

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Objective: To study the incidence of PD and PS in a population-based cohort of elderly subjects.

Background: Although several prevalence studies on PD and PS are available in the elderly, there is less data on the incidence of such diseases. Long-term population-based longitudinal incidence studies involving a large at-risk elderly population and based on accurate case ascertainment of PD and PS are particularly lacking.

Methods: We screened, identified and classified the incident cases of PD and PS during a 15-year follow-up of the population-based PAQUID elderly cohort in South-western France (Bordeaux).

Results: Of 3726 subjects aged over 65 years without PD and PS at baseline (T0), 144 new cases of parkinsonism were identified during the 15-year follow-up period. Among these, 44 had PD (UKPDSBB criteria), 24 possible PD, 13 had probable and 16 possible dementia with Lewy bodies (DLB, new McKeith criteria), 23 vascular parkinsonism, 15 drug–induced parkinsonism, and 9 Alzheimer's disease with secondary parkinsonism. The incidence of all causes of parkinsonism was 558 per 100,000 per year, the incidence of PD was 170 per 100,000 per year and the incidence of dementia with DLB was 112 per 100,000 per year. In subjects >90 years old, incidence of PD decreased while that of DLB increased.

Conclusions: We provide new data on PD and PS incidence in the long-term follow-up of a large elderly cohort. In contrast to recent incidences studies, we found a decrease in PD incidence in the very old, while DLB increased notably.

Th-82

Long-term outcome of patients with Wilson's disease in Serbia

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Objective: To investigate survival rates, prognostic factors and causes of patients death in a large database of national study on Wilson's disease (WD).

Background: WD is inherited autosomal recessive disorder of copper metabolism, leading to its accumulation in various organs including liver, brain, cornea, kidneys and heart, with resulting chronic degenerative changes.

Methods: We performed a retrospective analysis of 142 patients with clinically verified WD from several specialized institutions in Belgrade and Novi Sad. The data collection process scroll off continuously from 1980 to 2008. All data were calculated by life table method, Cox proportional hazard model and Standardized Mortality ratio.

Results: The average age at onset of our patients was 23.5±9.0 years, while the average duration of the treatment was 10.2±8.6 years. The cumulative probability of survival in a fifteen-year' period for whole group was 76.7±4.9 %. WD patients who treated more than 11 years had statistically significantly better survival than those who treated 10 years and shorter (49.4±13.6 % vs. 92.3±4.3 %). The univariant Cox regression analysis also confirmed that significantly poorer outcome of WD in our population was related to duration of treatment (HR=0.1, 95%CI 0.01-0.2, p=0.001) The most frequent reasons of death in our patient's population were liver cirrhosis (five patients, 16.6%), haemorrhage due to oesophageal varices (four patients, 13.3%) and suicide (four patients, 13.3%), while in three cases cause of death was unknown.

Conclusions: Better prognosis of WD was associated with male sex, younger age at onset, neurological clinical profile, and treatment continuity.

Th-83

Survey of presentation and natural history of Wilson's disease (WD) in childhood

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Objective: To survey the presentation and treated neurological natural history of paediatric WD patients. In adults presenting with WD, treatment with chelation can worsen neurological symptoms. The objective of our study was to determine if this is demonstrable in a paediatric population.

Background: Chelation treatment for WD, using pencillamine and trientine, increases copper excretion in urine. Toxic side effects include bone marrow failure, a lupus like syndrome and hepatotoxicity. In addition, in adults, initiation of treatment using penicillamine may worsen neurological symptoms (Brewer, 1987). Our patients presented with liver symptoms and were treated mainly with penicillamine. We wished to survey their neuropsychiatric natural history on treatment.

Methods: Data were collated on all patients over a 32 year period (1975-2007) in a large tertiary hospital with regional neurosciences and hepatology units. Retrospective case note review was performed for all children treated with pencillamine (n=96). All were<16yr old.

Results: Neurological symptoms such as lethargy, motor disorder including tremor and in-coordination, and psychiatric problems were found in 47. Excluding lethargy, 18/47 showed neurological features at some point during treatment. In 3/ 18 pre-existing neurological symptoms resolved after pencillamine was commenced. Nine of the 18 patients had symptoms both prior to and following pencillamine treatment with no definite change. Six of the 18 developed neurological symptoms and signs only after penicillamine was administered, and in these children there was an improvement when the treatment was stopped/altered.

Conclusions: Non-specific neuropsychiatric symptoms (eg lethargy) are very common in paediatric WD. Excluding this, more specific neurological manifestations occurred in 19% in our cohort who presented hepatologically. In 33%, neurological symptoms worsened after initiation with penicillamine, in 50% there was no significant change (despite improvement in liver disease) and in 16%, there was neurological improvement. Our study is limited by its retrospective nature and in the extent of neurological notes information recorded. Further prospective neurological study pre and post treatment in paediatric WD is required to verify these findings.

Th-84

Distinct motor features of young onset Parkinson's disease – A community based case control study

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Objective: To describe the clinical motor features of Young Onset Parkinson's disease (YOPD) compared with Late Onset Parkinson's disease (LOPD) in a community based study.

Background: Parkinson's disease (PD) is an age dependant condition. A proportion of patients develop the condition at an earlier then expected age termed Young Onset PD (YOPD).

Methods: We have carried out a community based study to determine whether YOPD has different clinical features to later onset PD (LOPD).

Results: We studied 358 PD patients, selected by age at onset (126 cases from primary care in Cardiff, 323 from secondary care in South Wales). Of these 173 were YOPD patients (onset before age 55 (70 of which had onset before age 45) and 185 were LOPD patients (onset after 55). The mean age at onset was 45 and 66 years, and disease duration 11 and 7 years respectively. YOPD is significantly more likely to present with symptoms related to akinesia and rigidity than LOPD (61% vs 29%, $p<0.001$) and less likely to present with tremor (36% vs. 61%,$p<0.001$). YOPD is significantly more likely to involve dystonia (55% vs19%,$p<0.001$). There was no difference in practically defined "on" period UPDRS motor scores, despite differences in disease duration (UPDRS III 27/108 vs.30/108,$p=0.015$). YOPD patients appear to have a greater rate of motor complications (35% vs 11% at time of assessment, $p<0.001$) with a greater impact on daily activities (mean Lang and Fahn Dyskinesia scale 10 vs 6.8, $p<0.017$). This was still the case when adjusted for disease duration.

Conclusions: YOPD has a distinct clinical presentation, progression and impact on daily life. It is uncertain whether this relates to disease heterogeneity but specific genetic diagnoses may explain some disease features. It is also possible that the differences reflect genetic/pathological heterogeneity, or are due to biological age related factors and co-morbidity.

Th-85

Interaction of pesticide exposure and glutathione transferase poymorphisn with the risk of the development of Parkinson's disease

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Objective: To examine the association of pesticide exposure and genetic polymorphism of glutathione transferase (GST)with the individual susceptibility of developing Parkinson's disease. Moreover, interaction between pesticide exposure and GST's polymorphisms with the PD risk was elucidated.

Background: Pesticide exposure has been shown to increase risk of Parkinson's disease in many epidemiology study. Genetic polymorphisms of glutathione transferases (GSTs) may potentially modify the susceptibility of PD to pesticide exposure by preventing oxidative stress caused through pesticides metabolic pathways.

Methods: Genomic DNA was collected from 125 sporadic idiopathic PD patients and 162 age-and gender-matched controls in a Taiwanese population from rural area of southern Taiwan. We genotyped four GST classes, including GSTM1, GSTP1, GSTT1 and GSTZ1 genes using the allelic-specific polymerase chain reaction and PCR-based restriction fragment length polymorphism methods. The modified effect of pesticide usage on PD risk was estimated simultaneously.

Results: Pesticide exposure was an independent risk factor for PD. GSTP1 *Val105* polymorphism was the most significant determinant in association with PD development, exhibiting of an increasing risk of 2.23-fold ($p=0.004$) in univariate analysis. However, no association was found with any of the other GST polymorphisms. The elevated PD risk was modified by pesticide exposure in GSTP1 carriers ($p=0.0007$). In addition, the increasing trend of PD risk appeared to be stronger and more significant in pesticide-exposed patients who carried one additional number of putative high-risk GST genotypes ($p=0.007$).

Conclusions: The current study unravels the genetic traits that individual susceptibility of Parkinson's disease may be independently modulated by GSTP1 polymorphism, and the combination of the other GSTs polymorphisms involved in oxidative stress response with environmental pesticide may provide the important insights in PD development.

Th-86

Risk factors for psychosis in Parkinson's disease: Cohort study using Cox proportional hazards models

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Objective: To identify predictive risk factors to develop psychosis in patients with PD.

Background: Psychiatric complications such as delusion and hallucination are serious problems in treating patients with Parkinson's disease (PD). Most of the studies examining clinical features associ-

ated with PD psychosis are cross-sectional, and longitudinal studies are required to determine the risk factors for PD psychosis.

Methods: We enrolled 343 consecutive patients with PD which were without psychosis at the entry of study period (2 years). The endpoint was defined as the use of antipsychotics or end of the study period. Cox proportional hazards models were used to estimate hazard ratios (HR) of reaching endpoint for analyzing the association of the development of psychosis and the following factors, such as age, gender, disease duration, Hoehn-Yahr stage at the study entry.

Results: Anti-psychotic medications were required in 56 out of 343 patients during the 2 years. 248 patients including censored participants had no history of psychosis. 39 patients were excluded due to missing values. During study period, HR was significantly higher for male than for female (2.135, 95% confidence interval (CI) =1.268-3.595), but not significantly different as for age (1.017, 95% CI 0.986-1.049). Longer disease duration (1.044, 95% CI 1.004-1.086) and higher Hoehn-Yahr stage (3.887, 95% CI 1.357-11.129) also significantly shortened the period to the development of PD psychosis.

Conclusions: Disease duration, male gender and the severity of the disease were significant risk factors for earlier development of psychosis in PD.

GENETICS

Mo-85

Clinical findings and molecular characterization of perlecan gene in 4 Jordanian children with Schwartz Jampel syndrome

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Objective: To describe the clinical and pathogentic findings in 4 Jordanian children with Schwartz-Jampel syndrome (SJS).

Background: SJS is a rare autosomal recessive skeleteal dysplasia associated with myotonia. Children with SJS have myotonia induced distinctive facial features, limb stiffness, weakness and skeletal abnormalities. Several mutations in the perlecan gene (HSPG2) have been described.

Methods: In 4 Jordanian patients with SJS from 3 different families, clinical data including response to botulinum toxin injections were collected. HSPG2 mutations were analyzed by genomic DNA sequencing.

Results: All four children presented with the distinctive facial features of SJS. Three children were identified as having SJS1A, and one had SJS1B. Botulinum toxin injections for the facial myotonia resulted in subjective improvement in one of the patients. Eleven different polymorphisms were identified, 3 of which were silent polymorphisms, and 8 resulted in the following missense mutations: Asparagine765Serine, Methionine638Valine, Glutamic Acid1898 Lysine, Histidine3256Tyrosine, Serine4331Asparagine, Serine4362Leucine, Proline4369Serine.

Conclusions: The clinical findings and management of these patients including the use of botulinum toxin for the facial myotonia is discussed. The functional significance of the newly identified mutations is currently under investigation.

Mo-86

Motor phenotype of LRRK2 G2019S carriers in early onset PD

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Objective: To compare demographic and clinical features between carriers and non-carriers of *LRRK2* G2019S mutations in early onset Parkinson's disease (EOPD).

Background: Clinical features of *LRRK2* G2019S mutation carriers have not been systematically described in EOPD.

Methods: Demographic information, family history, and the Unified Parkinson Disease Rating Scale (UPDRS) were collected on 925 EOPD cases defined as age at onset (AAO) $\leq$ 50 at 13 centers. Cases were classified as tremor-dominant (TD) or postural instability gait disorder (PIGD). DNA samples were genotyped for *LRRK2* mutations (G2019S, I2020T, R1441C and Y1699C). Logistic regression was used to examine associations of G2019S with disease duration, Jewish ancestry, levodopa daily dose, family history of PD in a first-degree relative (FHPD) and motor phenotype.

Results: 34 cases (3.7%) (14 previously reported) were G2019S carriers. No other LRRK2 mutations were found. Carriers and non-carriers did not significantly differ in mean AAO (41.8yrs vs. 41.4yrs), current age (53.3yrs vs. 52.3yrs), disease duration (11.4yrs vs. 10.9yrs), gender (50.0% vs. 37.9% females), FHPD (17.6% vs. 14.3%), levodopa dose (580mg vs. 509mg) or UPDRS-III score (18.4 vs. 20.3). Carriers were more often of Jewish ancestry (50.0% vs. 12.3% $p<0.001$), had a lower mean tremor score (mean of eight tremor items on the UPDRS, $p=0.031$) and were more likely to have a PIGD phenotype (92.3% vs. 58.9% $p=0.003$). The association of the G2019S variant with PIGD phenotype persisted after controlling for disease duration and Jewish ancestry (OR= 16.0, $p< 0.001$).

Conclusions: EOPD G2019S *LRRK2* carriers are more likely to manifest the PIGD phenotype, which may have implications for disease course.

Mo-87

GBA gene variants are associated with PD in France

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Objective: To compare the frequency of heterozygous variants in the *GBA* gene which encodes b-glucocerebrosidase, in patients with Parkinson's disease (PD) and in controls. To compare the clinical features of PD patients carrying *GBA* variants with PD patients without any mutations.

Background: Homozygous mutations of *GBA* are responsible for Gaucher's disease (GD) which is a lysosomal disorder comprising 3 distinct types. GD type 1 is the most frequent and is a adult-onset polymorphic and gradual disease including hepatosplenomegaly, osteonecrosis, osteopenia, anemia, thrombocytopenia and optional symmetrical parkinsonism with poor levodopa response. It has been previously reported that heterozygous mutations of *GBA* was a risk factor for PD, especially in Ashkenazi Jews.

Methods: *GBA* sequencing was performed in 293 mostly (87%) French PD patients and 252 age matched controls.

Results: Mean age at examination was 57.7± 11.5 years (33-85) for PD and 57.8± 11.9 years (31-85) for controls. Mean age at onset and mean disease duration were 47.5±10.0 years (30-70) and 10.3±6.6 years (1-30). *GBA* variants were more frequent in PD patients compared to controls (11% versus 0.4%, $p<0.0001$). We detected the following variants which are considered of severe (S), intermediate (I) or unknown (U) severity: N370S (I, n=7), L444P (S, n=2), D409H (S, n=1), R131C (S, n=1), E10V (U, n=2), Y212N (U, n=2), D282N (U, n=1), A292P (U, n=1), the combination of E326K (homozygous) + D410H (S, n=1), the combination of L444P + A456P + V460V (S, n=1) and the following single nucleotide polymorphisms which are modifier and neutral, respectively: E326K (n=11) T369M (n=3). Four variants (U) were newly described. The overall phenotype of GBA-PD was similar to PD without GBA variants. Interestingly, GBA-PD had significantly delayed onset of fluctuations due to treatment (186± 229 months versus 52± 42 months, $p=0.013$) and more often increased reflexes in lower limbs (25% versus 10%, $p=0.026$).

Conclusions: *GBA* heterozygous variants are significantly associated with PD in the French population and influence the phenotype.

Mo-88

Ataxia with oculomotor apraxia type 2 (AOA2): Clinical and molecular delineation, genotype to phenotype correlations and strategy for diagnosis

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Objective: To describe the clinical and molecular findings of a large series of AOA2 patients, to report genotype to phenotype correlations and to propose recommendations for the *SETX* sequencing based on the alpha-foetoprotein (AFP) serum value.

Background: AOA2 is a recently described progressive autosomal recessive cerebellar ataxia related to mutations in *SETX* characterized by polyneuropathy, cerebellar atrophy, oculomotor apraxia and elevated AFP serum level.

Methods: We review the clinical and molecular data of a cohort of 125 ataxic patients with suspected AOA2 who were tested for *SETX* mutation in our laboratory. AOA2 patients (AOA2+) were compared to non-AOA2 patients (AOA2-). Correlations between the type of the mutations and the location of the mutations in *SETX* and the corresponding phenotype were investigated. AFP distribution in AOA2+, AOA2- and control patients have been studied.

Results: Ninety AOA2+ patients including 22 new mutations are reported. AFP serum level was higher in AOA2+ patients than in AOA2- ($p<0.001$). The probability to miss an AOA2 diagnosis in case of sequencing *SETX* only in non-Friedreich ataxic patient with AFP $>$ 7μg/L is 0.0023. Deletion and nonsense mutations were correlated to more severe phenotype than missense mutations ($p<0.01$). Pyramidal signs were more frequent with missense mutations in the helicase domain of *SETX* ($p=0.001$) and were associated to less severe phenotypes ($p=0.01$).

Conclusions: It appears that lack of pyramidal signs may correlate with severity, possibly as a result of the masking of the pyramidal signs by the severe motor neuropathy. The results could be consistent with the existence of one or more additional functional domains in senataxin. The selection of patients with an AFP level value above 7 μg/L for *SETX* sequencing is a good strategy for AOA2 diagnosis.

Mo-89

Complex I deficiency and dopaminergic neuronal cell loss in parkin-deficient zebrafish (Danio rerio)

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Objective: Currently, only symptomatic therapy is available for Parkinson's disease (PD). The zebrafish (*Danio rerio*) is a new vertebrate animal model ideally suited for high throughput compound screening to identify disease-modifying compounds for PD. The aim of our study was to develop a zebrafish model for early onset Parkinson's disease (EOPD).

Background: Zebrafish embryos develop externally, can readily be manipulated genetically and are transparent. The dopaminergic (DA) system is well characterised in both embryos and the adult zebrafish.

Methods: Micro-injection of morpholino (MO) antisense oligonucleotides into zebrafish embryos at the single cell stage was used to suppress the translation of the *parkin* gene.

Results: The zebrafish parkin protein is 62% identical to its human counterpart with 78% identity in functionally relevant regions. The *parkin* gene is expressed throughout zebrafish development and ubiquitously in adult zebrafish tissue. Abrogation of parkin activity leads to a significant decrease in the number of ascending dopaminergic neurons in the posterior tuberculum (homologous to the substantia nigra in humans), an effect enhanced by exposure to MPP+. Both light microscopic analysis and staining with the pan-neuronal marker HuC confirmed that this loss of dopaminergic neurons is not due to general impairment of brain development. Neither serotonergic nor motor neurons were affected, further emphasizing that the effect of *parkin* knockdown (k/d) appears to be specific for dopaminergic neurons. Notably, *parkin*-k/d zebrafish embryos also develop specific reduction in the activity of the mitochondrial respiratory chain complex I.

Conclusions: We have developed a zebrafish model for early onset PD (EOPD) using antisense oligonucleotide mediated knockdown of the most commonly mutated EOPD gene, *parkin*. Our *parkin* k/d zebrafish are the first vertebrate animal model to share both important biochemical (complex I deficiency) and morphological (loss of dopaminergic neurons) characteristics with *parkin* mutant patients. The zebrafish model is thus ideally suited for future drug screens and other studies investigating the functional mechanisms underlying neuronal cell death in EOPD.

Mo-90

α-synuclein gene dosage study in individuals with parkinsonian syndromes and other neurodegenerative disorders

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Objective: To identify potential α-synuclein (*SNCA*) whole gene duplications or triplications in individuals with various parkinsonian syndromes and other neurodegenerative disorders.

Background: Gene dosage aberrations of *SNCA* have been shown to be disease-causing in familial as well as sporadic cases of parkinsonism with and without associated atypical symptoms such as pyramidal signs, autonomic dysfunction and dementia. Increased *SNCA* dosage results in overexpression of the wild-type α-synuclein protein which appears to be toxic at levels above normal in neurons. The severity of the phenotype correlates with *SNCA* gene dosage, hence a duplication results in clinical features indistinguishable from idiopathic Parkinson's disease, including age-of-onset and good levodopa response, whereas triplications tend to produce associated atypical features and result in earlier disease-onset and more rapid progression of the disease.

Methods: Patients (n=200) with different parkinsonian syndromes (IPD, MSA, PSP, CBD, DLB), dystonias, cerebellar ataxias, and dementias with and without a family history were included. Patients with atypical parkinsonian syndromes had previously been screened for mutations in *MAPT*, *GRN*, *FMR1*, and *SCA1, 2, 3, 6,* and *17*. In patients with dystonia, cerebellar ataxia and/or dementia, known genetic causes of these phenotypes had also been excluded. The p.G1920S mutation in the *LRRK2* gene had been excluded in all patients. *SNCA* gene dosage was determined by one of two methods: 1) quantitative, real-time PCR dosage assay; data analyzed by the $2^{-\Delta\Delta Ct}$ method; or 2) multiplex ligand-dependent probe amplification (MLPA) assay using the commercially available Parkinson's disease kit (SALSA MLPA kit P051-B1/P052-B Parkinson) by MCR-Holland; raw data analyzed using the GeneMarker software (Softgenetics) and generated peak area data imported into an Excel spreadsheet for calculation of relative copynumbers of each genetic location amplified.

Results: No *SNCA* duplication or triplication carriers were identified among the included patients.

Conclusions: Whole gene *SNCA* multiplications are not found in our heterogenous cohort, but should be kept in mind when searching for underlying genetic causes of parkinsonian syndromes.

Mo-91

CTCF depletion in the FXN gene constitutes an epigenetic switch in Friedreich ataxia

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Objective: To decipher the mechanism of frataxin deficiency in Friedreich ataxia.

Background: Friedreich ataxia patients are homozygous for an abnormally expanded GAA triplet-repeat sequence in intron 1 of the FXN gene. The expanded GAA triplet-repeat results in a severe deficiency of FXN gene transcription, but the exact mechanism of the gene silencing is not clear. Reversal of FXN transcriptional deficiency is achieved via administration of HDAC inhibitors, indicating that the primary defect in Friedreich ataxia is an epigenetic abnormality. Others have identified heterochromatin formation in the vicinity of the expanded GAA repeat, but the exact cause of transcriptional silencing is not clear.

Methods: ChIP assays in Fibroblast cell lines from normal controls and patients were performed to analyze in vivo CTCF binding in the FXN gene. ChIP assays were also performed to detect evidence of heterochromatin formation. siRNA mediated knockdown followed by quantitative real-time RT-PCR was performed to detect the effect of CTCF displacement on FXN gene expression.

Results: We found a severe depletion of the chromatin insulator CTCF in the 5'UTR of the FXN gene in Friedreich ataxia. Patients showed enrichment of H3K9me3, H3K27me3, and HP1 in the vicinity of the transcription start site of the FXN gene indicative of heterochromatin formation. Deficiency of FXN transcript was reproduced via siRNA mediated knockdown of CTCF in normal cells.

Conclusions: CTCF depletion in Friedreich ataxia constitutes an epigenetic switch that allows heterochromatin formation near the transcription start site and FXN transcriptional deficiency. These data have important implications for the design of specific therapies for Friedreich ataxia.

Mo-92

Two types of neurological manifestion in Woodhouse-Sakati syndrome

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Objective: To study the neurological manifestation, imaging and genetic findings in Woodhouse-Sakati Syndrome (WSS).

Background: Woodhouse-Sakati Syndrome (WSS) [MIN 241080] is a rare autosomal-recessive syndrome with alopecia or sparse hair, hypogonadism, diabetes mellitus, extrapyramidal disorder, brain white matter or basal gaglia disease and low IGF1. Recently mutation in C2orf37 gene encoding nuclear protein found to be the underlying gene responsible for WSS and that the nuclei of patients lymphoblasts displayed and enhanced sensitivity to transcriptional blockade (Alazami 2008).

Methods: We studied the neurological manifestation in 31 patients with WSS (13 male and 18 female) belonging to 8 families from Saudi Arabia. Patient clinically divided in two types. Type 1: fourteen (14) patients affected, the onset of focal dystonia noted around 12 years of age followed by relentlessly progression to generalized dystonia with anarrthria, severe disability and loss of ambulation within 4 to 10 years (average 5y±3) with mild mental subnormality. MRI brain showed progressive putaminal, caudate and substantia nigra lesions with ion accumulations and diffuse non-enhancing white matter lesions. Three patients died over observational period of 5 to 27 years. Type 2: 17 patients were studied the disease course was much milder with only focal dystonic posturing noted in 6 patients (Unilateral arm dystonia in 4 patients and craniocervital in 2 patients, one patient should a mild parkinsonial, nonLdopa responsive syndrome. The onset of dystonia was at older age, around 16 years (average 14 to 21y). The rest of this group showed no other movement disorder over observational period of 5 to 16 years, activity of daily living and school performance were minimally affected. MRI brain showed scattered white matter lesions in all members. Intrafamilial variability was noted in two families.

Results: Mutations analysis in the C2orf37 gene revealed a common founder mutation 1bp deletion (c.436delC) that fully segregate with all families studied.

Conclusions: We conclude that this peliotropic syndrome have two distinct phenotypes with variable prognosis, the presence of a single mutation in the two groups is enigma will need further clarification on the functions of C2orf37 gene.

Mo-93

Decreased expression of alpha-synuclein isoforms in peripheral blood cells of sporadic parkinsonian patients

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Objective: To compare the level of expression of alpha-synuclein (SNCA) gene isoforms in peripheral blood cells from parkinsonian patients and healthy controls.

Background: The major component of Lewy body is SNCA and its aggregation represents a key event in the pathogenesis of Parkinson's disease (PD). Variations of expression level of SNCA have been shown to contribute to the disease process.

Methods: Total RNA was extracted from peripheral blood mononuclear cells (PBMC) of 20 sporadic PD cases and 18 controls. We designed primers for real-time quantitative PCR of SNCA 140, SNCA 126, SNCA 112 and SNCA 98 splicing variants. Real-time PCR were carried out on a 7500 Fast Real-Time PCR System (Applied Biosystems). The amount of the product of interest was normalised to that of ribosomal protein S18 and compared to controls in order to define the relative gene expression derived from the $2^{-\Delta\Delta C}{}_{T}$ method. Differences in abundance were determined using a Mann & Whitney test. Moreover, we conducted whole human genome expression micro-arrays experiments (Agilent 44K) on 18 sporadic PD cases and 18 controls.

Results: We observed a significant decrease in expression of the 4 isoforms ranging from 58 to 64% between PD patients and controls. These data are in agreement with the decreased expression of total SNCA gene product (41%) observed on microarray analysis in PD patients.

Conclusions: While overexpression of SNCA in brain tissue and PBMC has been linked to familial parkinsonism with SNCA multiplications, our data suggest that its underexpression might also be considered as a potential peripheral marker of the disease.

Mo-94

Analysis of lysosomal storage disorder genes in Lewy body disorders

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Objective: To determine the relationship of lysosomal storage disease (LSD) gene mutations to Lewy Body (LB) and Alzheimer's disease (AD) pathology.

Background: Mutations in the LSD gene, glucocerebrosidase (GBA), are associated with LB disorders. We hypothesized that other LSD genes in the same biochemical pathway may also represent susceptibility genes for LB.

Methods: Brain tissue from 187 autopsies (87, 46.8% female) from the New York Brain Bank at Columbia University included: 95 brains with primary neuropathological diagnoses of LB disorders with or without AD changes, 60 brains with AD without significant LB pathology, and 32 control brains with neither LB or AD pathologies. Four LSD genes were completely sequenced, including hexosaminidase A (HEXA), sphingomyelin phosphodiesterase 1 (SMPD1), mucolipin 1(MCOLN1) and GBA.

Results: We found non-GBA variants in 72 (38.7%) brains (HEXA 34 (18.3%), SMPD 11 (5.9%), MCOLN1 27 (14.5%), of

which 11/72 (15.3%) brains had variants in two of the genes. Several of the variants that we identified including, c.1278insTATC (HEXA), c.672+30T>G (HEXA), S3S (HEXA), P330R (SMPD1) and E515V (SMPD1) have been reported previously as mutations in patients with lysosomal storage disorders. GBA, as previously reported was in 34 (18.3%) brains (23 without and 11 with non-GBA variants). We showed an association of GBA mutations with presence of cortical LB: OR=6.48, 95%CI, 2.45-47, $p<0.001$ adjusting for sex, death age, and ApoE4 status. Mutation status for each non-GBA gene individually did not show significant association with LB or AD pathology. But the presence of any non-GBA gene variant was associated with brainstem LB pathology and 8/13 (62%) of these brains had variants compared with 53/120 (44.0%) of those with cortical LB, AD, or controls ($\chi 2$ p = .03; OR 1.32 95%CI 1.04 -13.6, p = 0.04, adjusting for age and sex).

Conclusions: This work suggests that other mutations in the lysosomal pathway may be associated with LB pathology, perhaps due to defects in a-synuclein processing. It extends earlier work by us and others that GBA mutations are associated with presence of LB, particularly cortical. Further work should ascertain whether variants in different LSD genes might predispose to differing LB involvement.

Mo-95

Twenty novel mutations in SPG11/spatacsin identified using both direct sequencing and MLPA

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Objective: Our objectives were to extend the *SPG11* mutation spectrum and establish the frequency of genomic rearrangements in this gene using a newly developed Multiplex Ligation-dependent probe Amplification (MLPA) kit.

Background: Truncating point mutations in *SPG11*/spatacsin are the major cause of autosomal recessive spastic paraplegia with thin *corpus callosum.* Recently a large genomic rearrangement was also involved in this clinical and genetic entity.

Methods: Forty-five unrelated patients were selected on the basis that they had spastic paraplegia associated with thin corpus callosum, with or without mental retardation or cognitive delay. Most of them were isolated cases. Genomic DNAs extracted from blood samples were screened using both direct sequencing and MLPA.

Results: A total of 25 different *SPG11* point mutations, 18 of which were novel, were identified in 16 patients (36%). All mutations but one introduced premature termination codon in the protein sequence and were compatible with a degradation of the corresponding mRNA by the nonsense-mediated mRNA decay surveillance system of the cell. The remaining mutation was a missense variant which alters a highly conserved amino-acid of the protein and was found associated with a truncating mutation. In addition, MLPA analysis detected a heterozygous *SPG11* micro-rearrangement of one or several exons in two patients who already had a single heterozygous point mutation. Analysis of the affected relatives and parents when possible showed that the mutations segregated with the disease and that heterozygous compound mutations were inherited each from a healthy parent. Only two patients out of 16 had homozygous mutations; the remaining 14 patients had heterozygous compound mutations. Finally, we identified new missense polymorphisms that did not segregated with the disease.

Conclusions: Altogether, these findings expand the *SPG11* mutation spectrum and highlight the importance of screening the whole coding region with both direct sequencing and a quantitative method. The identification of rare missense mutations in *SPG11* could help defining the functional domains of the protein. However, rare missense polymorphisms are frequent in *SPG11*, complicating interpretation of diagnosis.

Mo-96

Clinical features and natural history of neuroferritinopathy caused by the 458dupA FTL mutation

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Objective: To describe the clinical features and natural history of neuroferritinopathy caused by a new mutation (458dupA) in the gene ferritin light polypeptide (FTL) in a French family.

Background: The clinical features and natural history of neuroferritinopathy caused by the classical 460dupA mutation have been defined in 38 patients by a familial history of progressive generalised dystonia (Chinnery et al., 2007). Brain MRI showed iron accumulation of the basal ganglia. The genetic analysis demonstrated the presence of *Eco*N1 restriction digestion site in exon 4 of FTL.

Methods: The overall phenotype of the four patients alive (3 males and 1 female) with 458dupA and the three deceased ones was broadly similar to the 38 cases with 460dupA, with a progressive generalized dystonia appearing between 24 and 44 years of age affecting first one limb, then involving orofacial area, pharynx and larynx.

Results: However, the 458dupA mutation differed from the 460dupA by a higher severity and a rapid progression within mean time of 10 years concerning the (i) dystonia leading to anarthria and severe dysphagia in all cases, (ii) the akineto-rigid syndrome in the three males, (iii) the cerebellar ataxia with hypotonia in the female and three deceased members and (iv) the subcortico-frontal dementia with apathy in all cases. Structural MR imaging revealed iron deposition and cystic cavitation of the basal ganglia. Serum ferritin levels were below the normal range, despite normal haemoglobin and serum iron levels. The patients had a different mutation, 458dupA, which segregated with the phenotype and was not found in 300 European controls. This mutation creates the same *Eco*N1 restriction site as 460dupA (Curtis et al., 2001).

Conclusions: Our observations in the French family with 458dupA support the view that subtle differences in a critical region of the ferritin protein sequence could modulate the phenotype of neuroferritinopathy.

Mo-97

Autosomal-recessive gene mutation frequencies in Turkish patients with Parkinson's disease

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Objective: To evaluate the frequency of mutations in genes implicated in Autosomal Recessive Parkinson's disease (ARPD) in PD patients in Turkey.

Background: Although the most common form of PD is sporadic, 10-15% of patients have a positive family history compatible with a mendelian inheritance. PRKN, PINK1, DJ-1 and ATP13A2 genes have been shown to be related to ARPD. To date, PRKN gene mutations have been described to be the most frequent cause of early-onset parkinsonism (50%). Incidence of parental consanguinity in Turkey is high and was the starting point for our genetic study.

Methods: 71 patients from 68 PD families, including 32 patients with sporadic PD and 28 families with parental consanguinity, participated in the study. 65 families were originating from Turkey, two families form Greece and one family from Bulgaria. Age at onset ranged from 4 to 83 years (46.5 ± 15.3 years). Haplotype analysis was performed in all families and 23 unaffected relatives, in order to assess segregation patterns of genetic variation. PRKN, PINK1 and DJ1 genes were sequenced and dosage analysis was performed by MLPA (Multiplex Ligation-dependent Probe Amplification).

Results: Eight PD patients from 7 families (10.3%, age at onset ranging from 26 to 40 years) were found to carry homozygous (four with and two patients without familial PD) or compound heterozy-

gous (two patients with sporadic PD) PRKN mutations, while three patients (2.7%, age at onset: 22, 37 and 83 years, all of them with familial PD) were found to be heterozygous for PRKN mutations. We identified only exon rearrangements except one new point mutation in exon 2 (p.lys27del). No pathogenic mutations were found in DJ1 and PINK1 genes.

Conclusions: Our data suggest that PRKN gene mutations are the most frequent form associated with ARPD in Turkey. The prevalence rate with regard to the age of onset in our population is comparable to those previously described.

Mo-98

Phenotypic and genotypic characteristics of patients with early-onset Parkinson's disease: A pilot study in the Czech Republic

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Objective: To determine the frequency of genetic alterations and phenotypic characteristics in Czech early-onset Parkinson's disease (EOPD) patients.

Background: Parkinson's disease (PD) is a sporadic disorder with the onset in most cases between 50–60 years. However, about 15% of cases start before the age of 45. The clinical phenotype of EOPD differs from classic-onset PD in several features such as more frequent occurrence of dystonia, excellent treatment response and early development of levodopa-induced dyskinesias. Genetic mutations in several recessively inherited genes as in *parkin*, *PINK1* or *DJ-1*, can be detected in up to 20% of patients with EOPD.

Methods: A total of 45 EOPD individuals (36 males, 9 females) were phenotyped and screened for mutations by multiplex ligation-dependent probe amplification (MLPA). Mutation screening of the 12 exons of *parkin* was performed using direct sequencing.

Results: Average age of PD onset was 35.6 years (20-45). Dystonia was present in 29 cases (64%). An excellent response to dopaminergic therapy was reported by 38 (84%) of patients. Dyskinesias had developed after a mean interval of 9.1 years (1-18). Positive family history was present in 8 (18%) cases. In total, 12 patients (27%) were carriers of previously described genetic alterations. All alterations occurred in the heterozygous state. Mutations in the *parkin* gene (Ex2del, A82E, R402C) were identified in 3 (7%) cases, *parkin* polymorphisms (2x S167N, 3x V380L, 3x D394N) were found in 8 (18%) individuals. In addition, a point mutation (G2019S) in the *LRRK2* gene was found in 1 (2%) subject. No patients had mutations of *PINK1* or *DJ-1*.

Conclusions: 1. The clinical characteristics of our EOPD patients correspond to previous descriptions of EOPD phenotype. 2. This is the first report of PD-associated mutations and polymorphisms among Czech patients with EOPD. Our results support the hypothesis that single heterozygous *parkin* mutations and polymorphisms may act as risk factors for EOPD. Study support: IGA NR9215.

Mo-99

Complete screening for glucocerebrosidase mutations in Parkinson's disease patients from Greece

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Objective: To examine the association of mutations in the glucocerebrosidase gene (*GBA)* and Parkinson's disease (PD), in a Greek cohort, a population that has not previously been screened for *GBA* mutations among PD patients.

Background: PD is a common neurodegenerative disorder affecting approximately 1% of the population over 60 years of age. Although significant progress has been documented in the understanding of this devastating disease, the pathogenic network of PD currently remains basically unacknowledged. Mutations in *GBA* have recently been implicated in PD, providing an interesting approach regarding PD pathogenesis.

Methods: Complete sequence analysis of the *GBA* exon-coding regions was carried out in 172 PD patients and 132 controls.

Results: *GBA* mutations were overrepresented in PD patients with early disease onset compared with controls ($p=0.019$). The most common *GBA* mutation found among the examined Greek PD patients was p.H255Q, whereas the severe p.L444P and p.D409H *GBA* mutations were also detected in our PD patients. Novel and already reported mutations were found in the present Greek cohort.

Conclusions: This study provides for the first time data regarding the frequency of *GBA* mutations among PD patients, in the Greek population, suggesting that *GBA* mutations may modify age of onset for PD.

Mo-100

The interaction between GSK3β and MAPT genes modify the risk of Parkinson's disease

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Objective: Our objective is to analyze in a case-control association study whether MAPT and GSK3β genotypes or haplotypes have an individual or interacting effect on the risk of Parkinson's disease (PD) in our population.

Background: Tau gene haplotypes (MAPT H1/H2) have been associated with the risk of PD. GSK3β phosphorilates tau and two functional polymorphisms (rs334558 and rs6438552) regulate this process.

Methods: 244 patients with PD and 200 controls. MAPT H1/H2 haplotypes were detemined analyzing the SNP rs9468. Two functional SNPs of GSK3β were genotyped. Taqman probes were used for the genotyping of all the SNPs. The association between each genotype and the risk of PD was analyzed with OR and 95% Confidence Interval. Haplotype frequencies were estimated with the program Hplus. Association between haplotypes and disease, adjusted by sex and age, was calculated by logistic regression.

Results: MAPT and GSK3β genotypes or haplotypes did not show an independent effect on the risk of PD. Stratified analysis showed a significant gene-gene interaction between GSK3β (rs6438552) T/T genotype and MAPT H2/H2 haplotype, increasing the risk of PD six fold (OR 6.03; p=0.02). The haplotype conformed by the two frequent alleles of the GSK3β polymorphisms increased the risk of PD in individuals also carrying at least one copy of the H2 haplotype of MAPT (GSK3β T-T/MAPT H1/H2+ H2/H2: OR 1.75; p=0.01).

Conclusions: Interaction between GSK3β and MAPT haplotypes modify the risk of PD.

Mo-101

De novo interstitial duplication 4q associated with sporadic young-onset dopa-responsive parkinsonism

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Objective: To present clinical, neuroimaging and genetic data of a patient who developed parkinsonian features at age 30 although her neurological family history was unremarkable.

Background: A genetic cause is generally considered in individuals developing young-onset familial or sporadic Parkinson's disease (PD). To date, at least 12 different genetic loci have been identified to be linked to PD.

Results: The patient was first seen in our clinic at age 31 because of a 1-year history of progressive loss of function of her left arm accompanied with a left hand rest tremor and left foot torsion during walking. Her past medical history was mainly characterized by moderate psychomotor retardation. At initial motor exam, we mainly observed a slightly ataxic gait and moderate, left-dominant, akinetorigid and tremulous parkinsonism. The clinical diagnosis was supported by a PET study showing decreased striatal uptake of ^{18}F-DOPA predominant on the posterior putamen, bilaterally. Brain MRI showed significant hydrocephalus. L-DOPA was very successful in

improving parkinsonian features. After 8 years of follow up, the beneficial effects of the dopaminergic therapy are maintained despite development of motor complications that appeared a few weeks after L-DOPA was started. A cytogenetic study performed at age 2 had revealed a lengthening of the long arm of chromosome 4. Fluorescence in situ hybridization (FISH) with a painting probe 4-specific (WCP4) later confirmed an interstitial duplication of chromosome 4q. A cytogenetic study performed in her parents and her 2 younger brothers was normal. Given the overall picture, we conducted a quantitative multiplex ligation-dependent probe amplification (MLPA) analysis that demonstrated a duplication of the α-synuclein gene (SNCA) (OMIM 163890–gene map locus 4q21-23). Further characterization of genomic rearrangements is in progress.

Conclusions: To our knowledge, this is the first report of sporadic young-onset dopa-responsive parkinsonism linked to a de novo interstitial duplication 4q, including the SNCA gene, which has been previously identified as a causative mutation in hereditary Parkinson's disease.

Mo-102

Novel mutations in the PANK2 gene in an Argentinean patient with pantothenate kinase-associated neurodegeneration

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Objective: to report two novel mutations in the PANK2 gene in an Argentinean patient with a phenotype not strictly falling within either classic or atypical categories.

Background: Pantothenate kinase-associated neurodegeneration (PKAN) is an autosomal recessive disorder caused by defective iron metabolism associated with mutations in the PANK2 gene. Two main phenotypes have been identified so far, "classic" PKAN characterized by early onset, dysarthria, pigmentary retinopathy, severe extrapyramidal signs and rapid progression and "atypical" phenotype with late- onset, neurobehavioral signs, speech difficulties, anarthria, aphonia, less severe extrapyramidal signs, and a more variable and slower progression.

Methods: this 27-year-old female was born to a healthy, non consanguineous couple. The family history showed a paternal grandfather uncle with involuntary movements and cognitive impairment beginning at the age of 28 years. Her history was relevant because of preeclampsia and prematurity requiring incubator and enteral feeding. At the age of 3 years she noticed loss of visual acuity and a diagnosis of retinitis pigmentosa was performed two years latter. At the age of 6 years, she developed gait impairment, postural instability, recurrent falls and progressive behavioral and obsessive disorders. At age 12 years a psychotic crisis and two suicidal intents were reported. On the last four years she developed progressive anarthria, echolalia, palilalia, dysphagia, oftalmoparesis, ataxia, severe pyramidal and extrapyramidal symptoms and cognitive impairment. In the past year she suffered two episodes of complex partial seizure with secondary generalization. T_2-weighted brain MRI shows the typical "eye-of-the-tiger" sign.

Results: After informed consent, genomic DNA was extracted from peripheral blood. Sequence analysis of the PANK2 gene revealed that the proband was heterozygous for two novel mutations, a missense mutation c.325G>A (p.109G>S) and a premature Stop codon mutation c.308G>A(p.103W-Stop).

Conclusions: This patient carries two novel mutations in the PANK2 gene illustrating the wide genetic and clinical spectrum of PKAN.

Mo-103

Search for pre-motor signs and symptoms of Parkinson's disease in first degree relatives of PD patients who are LRRK2 G2019S mutation carriers. A pilot study

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Objective: To characterize the healthy asymptomatic first degree relatives of Ashkenazi Parkinson's disease (PD) patients who carry the LRRK2 G2019S mutation.

Background: The autosomal dominant G2019S mutation in LRRK2 gene has specifically been associated with increased frequencies, as high as 40% in familial PD. The healthy asymptomatic first degree relatives of Ashkenazi PD patients who carry the LRRK2 G2019S mutation represent a population at increased risk for developing PD.

Methods: 25 first degree relatives (80% Females) of PD patients, who are carriers of the LRRK2 G2019S mutation and were over the age of 45 with no clinical signs of motor parkinsonism, participated in this study. Subjects were evaluated in one session which included DNA collection, a clinical and neurological exam and questionnaires, smell identification test (UPSIT), autonomic function and sleep questionnaire (Scopa-Aut and RBDSQ), computerized cognitive assessment battery (NeuroTrax Mindstreams), life style questionnaire and gait evaluation. Subjects and researchers were blinded to the LRRK2 mutation status.

Results: 12 subjects were identified as carriers of the G2019S mutation (54.6±9.1 yrs, 45-71, 92% Females) and 13 were Non-Carriers (NC) (59.7±13.3 yrs, range 46-78, 67% Females). Subjects in both groups did not differ in social-demographic background, exposure to toxins, medical history or dietary habits. No differences were observed between the groups in cognitive function, smell or gait parameters. The G2019S mutation carriers' group scored significantly lower ($p=0.02$) on the Geriatric Depression Scale (4.1±3.2) than the NC group (10.4±7.2). In addition, 59% of the mutation carriers reported more episodes of incontinence and urinary urgency ($p=0.06$) as well as constipation ($p=0.07$) than the NC group.

Conclusions: In this pilot study, carriers of the G2019S mutation in the LRRK2 gene tended to suffer from more frequent autonomic disturbances and were less depressed than the mutation free group. Given the small sample size, additional investigation is necessary to validate these results and to further determine the contribution of G2019S mutation in the LRRK2 gene to any pre-motor symptoms of PD.

Mo-104

Anticipation of disease onset in Brazilian patients with early-onset Parkinson's disease, PINK1 polymorphisms and exposure to environmental risk factors

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Objective: We investigated Brazilian early-onset PD (EOPD) patients with PINK1 polymorphisms (SNPs) in order to find possible correlations between SNPs, environmental exposure, and disease age of onset.

Background: Parkinson's disease (PD) etiology has been attributed both to genetic and environmental factors, although the exact mechanisms of its pathogenesis remains elusive.

Methods: We enrolled 48 patients and 61 healthy controls. PINK1 SNPs and environmental exposure (living in rural areas, well water drinking, exposure to pesticides, herbicides and organic solvents and smoking) were investigated in both groups

Results: We found 18 patients (37.5%) and 28 controls (45.9%) with seven known PINK1 SNPs ($p=0.90$). We determined the presence of positive exposition to environmental factors in a total of 26 patients (54.2% out of 48) and in 30 controls (49.2% out of 61), $p=0.6$. We divided our group of patients into four subgroups, according to the presence/absence of PINK1 SNP IVS1 -7 A->G and the presence/absence of environmental factors exposure (EFE). We found a significant decrease of age at disease onset in those patients that had PINK1 SNP and were exposed to environmental factors: SNP+ and EFE+ 30.1+10.8 vs. SNP+ and EFE- 41.2+5.8 vs. SNP- and EFE+ 38.4+5.7 vs. SNP- and EFE- 38.7+6.2, ANOVA test $p = 0.02$. Each patient with SNP had at least one of these risk factors: rural living, well-water drinking or exposure to other agents (pesticides, herbicides, or organic solvents). Well water drinking habit was presented in all.

Conclusions: PINK1 SNP IVS1 -7 A->G and environmental risk factors may play together an important role in the occurrence of EOPD. We believe that each of them individually has a minor influence, whereas their interaction is associated with a significant effect in anticipating the disease clinical onset.

Mo-409

A novel mutation of ε-Sarcoglycan in a Taiwanese family of myoclonus-dystonia

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Objective: To present the clinical and genetic results on studying a family with myoclonus-dystonia.

Background: Myoclonus-dystonia (M-D, DYT11; MIM 159900) is a rare autosomal dominant disorder characterized by involuntary jerks and dystonic muscle contractions that are often responsive to alcohol. Changes in personality as well as obsessive compulsive disorder, panic syndrome, alcoholism, and other psychiatric disorders may be associated with M-D. The mutations of the ε-sarcoglycan gene (SGCE, MIM 604149) are proved to be associated with 30-40% of M-D families. More than 50 mutations have been identified so far reviewed recently by Kinugawa et al. including reports from Korea and China, but no genetic-identified M-D family reported from Taiwan. Here we report the results of the clinical and genetic studies in one family with M-D.

Methods: The proband was a woman who presented with intermittent jerks in the neck and trunk in associated with multiple dystonias progressively since 11 year-old. Her trunk was tilting to the right and neck was tilting backward and to the right. Her elder brother also showed jerks in the trunk and multiple dystonias involving the both upper arms and trunk since 20 year-old. Her younger brother, however, presented initially with writing tremor and mild multifocal dystonias since 7 year-old. Progressively, he developed dominant obsessive-compulsive behaviors and mild jerks in trunk. The video records were obtained. Her parents were normal. The related laboratory tests, advanced neurological and electrophysiological investigations were arranged. Molecular genetic analyses for SGCE including quantitative (multiplex ligation-dependent probe amplification, MLPA) and qualitative mutational screenings (genomic sequencing) were done. Healthy subjects were also tested genetically.

Results: The clinical manifestations of all 3 sibs fulfilled the diagnostic criteria of typical M-D. The laboratory data, brain MRI, EEG, evoked potentials and neurophysiologic study were essentially normal. A novel heterozygous deletion (842 del T) in exon 7 of SGCE gene was found in all 3 sibs and in father but not in mother. The genetic analysis verified an autosomal dominant inheritance and maternal imprinting in this familial M-D.

Conclusions: This is a typical M-D family caused by a novel SGCE mutation firstly reported in Taiwan.

Tu-83

PINK 1 mutations in a Brazilian cohort of early-onset Parkinson's disease patients

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Objective: The aim of this report was to investigate mutations of the *PINK1* gene in a cohort of Brazilian patients with EOPD.

Background: Data on the frequency of *PINK1* mutations in Brazilian patients with early-onset Parkinson's disease (EOPD) are lacking.

Methods: Sixty consecutive familial or sporadic EOPD patients were included. All eight *PINK1* exons and exon-intron boundaries were analyzed.

Results: We did not find any pathogenic mutation of *PINK1* in our cohort. Single Nucleotide Polymorphisms (SNP) were identified in 46.7% of the patients and in 45.9% of controls ($p=0.9$). The SNPs identified in our patients had already been described in previous reports.

Table 1 (Tu-83). Polymorphisms in PINK1 gene*

Exon	Nucleotide Change	Aminoacid Change	PD patients (N=60)	Controls (N=61)	p Value
2	IVS1 −7 A−>G		20	24	0.5
4	C879A(Hom)	V293V	1	2	0.56
5	IVS4 −5G−>A		2	1	0.55
6	IVS6+43 C−>T		1	0	0.32
6	C1230T(Hom)	A410A	1	0	0.32
8	A1562T(Het)	N521T	2	1	0.55
8	3' +36 A−>T		1	0	0.32

*Nucleotide and protein changes are in accordance with the nomenclature guidelines available from the Human Genome Variation Society (HGVS). The A of the translation initiation codon ATG is designated base 1. Het, heterozygous; Hom, homozygous.

Conclusions: The results of our study support the hypothesis that mutations in *PINK1* may not be a relevant cause of EOPD in Brazil.

Tu-84

Neurocognitive and psychiatric profile of patients with type 1 Gaucher disease presenting with a movement disorder

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Objective: To determine the profiles of neurocognitive function in patients with Gaucher disease (GD) referred with parkinsonian manifestations, and to correlate specific cognitive deficits with motor function, and other psychiatric symptoms.

Background: Clinical, pathologic and genetic studies suggest that mutations in glucocerebrosidase, the gene implicated in GD, is associated with a phenotype characterized by parkinsonism and adult-onset progressive neurologic deterioration.

Methods: A consecutive series of 9 patients with GD presenting with parkinsonian manifestations underwent a comprehensive neuropsychological assessment to test psychomotor speed, attention, language, memory, executive and visuospatial functions. Five were tested more than once over 36 months. Subjects received quantitative ratings of motor deficits and functional status. Depression or other psychiatric disorders were diagnosed according to DSM-IV criteria.

Results: The mean age at diagnosis of GD diagnosis 30 (5-61), and onset of parkinsonian manifestations was 50. Unilateral tremor was the most common presentation. Six subjects were diagnosed with PD, and one each had Lewy Body Dementia, a Parkinson plus and psychogenic movement disorder. GD subjects with normal cognition showed discrepancies between verbal and performance scores, with better verbal skills and weaknesses in processing speed, visual-spatial testing and perceptual organization. In two cognitively impaired subjects, verbal abilities, including word knowledge and recognition were spared. Decline was observed in areas of immediate memory and visuospatial function in 3 subjects on sequential testing, without correlation with motor deficits. Major depression, often accompanied by anxiety was diagnosed in 7 GD subjects, and the diagnosis of a psychiatric disorder correlated with a family history of PD or dementia.

Conclusions: GD subjects with parkinsonism demonstrate a neurocognitive profile resembling to that observed in neuronopathic forms of Gaucher disease. While a co-existing psychiatric diagnosis may impede overall cognitive performance, the preservation of verbal skills could mask the decline in other cognitive areas, complicating the evaluation of dementia in GD patients with PD and related disorders.

Tu-86

Mutation analysis of Parkin, PINK1 and DJ-1 genes in Chinese patients with early-onset parkinsonism

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Objective: To study the prevalence rate of *Parkin*, *PINK1*, and *DJ-1* genes mutations in 127 Chinese unrelated patients with early-onset parkinsonism.

Background: Early-onset parkinsonism (AREP) has been associated with mutations in the *parkin*, *PINK1* and *DJ-1* genes. There are some reports about mutations in Ethnic background of the patients affects the mutation rate with frequencies of gene mutations. To our knowledge, there are limited data regarding the prevalence rate of *Parkin*, *PINK1*, and *DJ-1* genes mutations in Chinese patients with EOP.

Methods: To detect small sequence alterations in *parkin*, *PINK1* and *DJ-1 genes*, we performed direct sequencing analysis of all coding exons of these genes. To test for the presence of exon rearrangements in *parkin*, *PINK1*, and *DJ-1*, we established a real-time quantitative PCR analysis assay.

Results: We found sixteen patients (12.6%) carried with *parkin* gene mutations. All patients were found carried with exon deletions, four of which carried small sequence alterations. Two heterozygous point mutations in *PINK1* gene, c.C832G in exon 4 (p.Leu278Val) and c.G1220A in exon 7 (p.Arg407Gln), and a heterozygous rearrangement mutation (exon3-8del) were found in four patients (3.1%) respectively. Three patients (2.4%) were found carried with exon deletions in *DJ-1* gene, in which two carried the homozygous deletion of exon 2, and one carried with heterozygous deletion of exon 2. Five mutations, IVS1-39G→T, c.813delT and IVS9+18C→T in *parkin* gene, c.C832G and exon3-8del mutations in *PINK1* gene, have not been reported previously.

Conclusions: In conclusion, *Parkin* gene mutation is the most common pathogenic factor in Chinese patients with EOP. Mutations of *DJ-1* and *PINK1* gene are also found in Chinese patients with EOP.

Tu-87

Mutations in the LRRK2 (G2019S) and the glucocerebrosidase genes can influence the clinical course and pre-morbid behavior of patients with Parkinson's disease

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Objective: To assess the potential effect of mutations in the LRRK2 and GBA genes on behavior and clinical course of patients with Parkinson's disease (PD).

Background: Mutations in the LRRK2 and GBA genes have been associated with the development of PD among the Ashkenazi population. Incomplete penetrance and phenotypic variability suggest the existence of additional confounding factors.

Methods: 117 Ashkenazi PD patients participated in this study. 36 were carriers of the G2019S LRRK2 mutation, 40 had heterozygote's mutation in the GBA gene and 41 had no known mutations (NC). Groups were matched for age and disease duration. Clinical and environmental information was obtained through a structured phone interview by a researcher blinded to the genetic background. Several domains were assessed: consumption, behavioral, occupational histories and PD clinical features.

Results: Carriers of GBA mutation had significantly ($p=0.005$) more adverse effects to dopaminergic medications compared to those with G2019S mutation and NC patients. More carriers of GBA mutation reported reduced sense of smell ($p=0.004$) then the LRRK2 and NC groups. Patients in the LRRK2 group reported more falls over the past year then patients in the other groups ($p= 0.042$). Significant differences were found in the number of people who consumed alcohol ($p=0.03$) and smoked cigarettes ($p=0.02$). In both cases the LRRK2 mutation carriers reported higher percentages of exposure then the other groups. Average pack years was higher for the LRRK2 group (13.1 ± 29.5 p/yrs) then that of the GBA and NC groups (5.5 ± 14.7; 5.4 ± 15 p/yrs) but was not significant ($p=0.15$) The groups were similar in age of onset of smoking, cessation and average years from quitting until onset of PD symptoms. No differences were observed in dietary habits, toxin exposure or cognitive function.

Conclusions: Mutations in the LRRK2 (G2019S) and the GBA genes seem to influence the clinical course of PD, and raise some interesting observations on the connection between genotype and behavioral or personal choices and their effect on the phenotype-genotype relations. Further investigation is on its way to confirm and continue to probe these findings.

Tu-88

LRRK2 Exon 41 mutations are not common in Turkey

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Objective: To determine the frequency of the leucine-rich repeat kinase (LRRK2) exon 41 mutations in Parkinson's disease (PD) patients from Turkey.

Background: Mutations in the LRRK2 gene, particularly the G2019S mutation in exon 41, are the most common cause of familial and sporadic PD described, but their prevalence varies markedly between populations. While the frequency of LRRK2 mutations have been well-studied in Europe, North Africa, Japan and North America, data is not available from Turkey.

Methods: A total of 99 families originating from Turkey, including 74 patients with sporadic PD and 28 patients with familial PD, were recruited to the study. Age at onset was ranging from 3 to 83 years (53 ± 14.9 years). In 23 families first degree parental consanguinity was known. We analyzed the entire exon 41 of LRRK2 gene using Polymerase Chain Reaction (PCR) protocol followed by direct sequencing of the exon 41.

Results: No pathogenic mutations were found in exon 41 of LRRK2 gene, including G2019S and I2020T.

Conclusions: The common mutations in exon 41 of LRRK2 gene are not a frequent cause of PD in Turkish population. Sequencing of LRRK2 gene in these patients is ongoing.

Tu-89

The phenotype of the 202A deletion in the Parkin gene in two large Muslim Israeli-Arab kindreds

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Objective: To describe the phenotype of the 202A deletion in the *parkin* gene in residents of Muslim Israeli-Arab villages.

Background: Among the numerous *parkin* mutations, no clustering in ethnic populations has been observed. Consanguineous marriages were a common cultural phenomenon in Arabic villages in Israel until the previous generation.

Methods: PD patients of Arabic origin with onset <40 years and family members were examined by a movement disorders specialist. DNA was extracted from blood leukocytes. All exons of the *parkin* gene were screened by direct sequencing of the PCR products on both strands.

Results: 11 PD patients and 15 family members consented to genetic testing. In all patients, the same *parkin* mutation was found: a homozygous single basepair deletion of adenine at nucleotide 202 (exon 2) causing an out-frame mutation with an early-stop codon. All 11 patients [7 men, mean age 51(10) years (36-63)] belong to 2 large Muslim-Arab kindreds called "Hamulas". Each Hamula can trace their ancestry to a few founders about 8 generations ago. Mean PD onset was at 25(8) years (15-37), disease duration 9-35 years.

Rest tremor, bradykinesia and rigidity were present in all, 9/11 had postural hand tremor. Axial features were present in 9/11: gait disturbance (n=1), scoliosis (n=1), camptocormia (n=1), falls (n=1), low back pain (n=5). Response to L-Dopa was excellent with early motor fluctuations. Three patients underwent deep brain stimulation (14, 26, 30 years after PD onset) with a modest benefit. Axial features, especially postural instability and gait disorders, did not improve. None of the patients had autonomic dysfunction, cognitive or psychiatric symptoms. Two heterozygous carriers presented (onset 49 and 60 years) with a mild phenotype with very slow progession.

Conclusions: The 202A deletion of the *parkin* gene causes early-onset PD with marked treatment resistant axial features in 2 large inbred kindreds. The homozygous phenotype is characterized by postural tremor, axial features, low back pain and preserved cognition. Heterozygous carriers may be symptomatic with a mild phenotype. Carrier frequencies amongst Muslim Israeli-Arabs may be high. Due to high consanguinity rates, prenuptial and prenatal screening is necessary for counselling and reduction of disease incidence in this ethnic group.

Tu-90

Analysis of the GRN 3'UTR+78 C>T polymorphism as a risk factor for Parkinson's disease

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Objective: To investigate the association of a single nucleotide polymorphism in the 3'–untranslated region of the progranulin gene (*GRN*; 3'UTR+78C>T; rs5848) and a risk of Parkinson's disease.

Background: Parkinsonism is a feature of several neurodegenerative disorders such as frontotemporal lobar degeneration (FTLD) and Parkinson's disease (PD), suggesting a clinical, pathological and molecular overlap. The *GRN* 3'UTR+78C>T was reported to alter the risk for frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD–U). rs5848 is located within a micro–RNA binding site and affects the expression of *GRN*.

Methods: We investigated the effect of *GRN* rs5848 on risk of PD by genotyping two Caucasian patient-control series (n=1,413) from the US and Poland. Genotyping of rs5848 was performed using TaqMan chemistry. Differences in allele and genotype frequencies between patients and controls were analyzed using Pearson's chi-square test and p-values $<.05$ were considered statistically significant.

Results: The frequency of the rs5848 TT genotype was similar in patients with PD compared with control individuals (10% vs. 8% in the US, 13% vs. 15% in the Polish and 11% vs.10% in the combined series). No association was observed between rs5848 and susceptibility to PD (in the individual series and combined analysis).

Conclusions: This finding shows that *GRN* rs5848 does not affect the risk of PD in the US and Polish populations.

Tu-91

Tetracycline-regulated stable expression of wild type and mutant parkin proteins in HeLa cells

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Objective: We sought to create a cell line that expresses either wild type or mutant parkin protein under the control of tetracycline promoter.

Background: Cell lines stably expressing proteins under the control of tight promoters are in demand because the controlled expression of protein of interests may minimize the toxic effects of the protein and allow researchers to control the amount of protein being made by the cells. Knowing that parkin is a ubiquitin ligase with apparent role in protein degradation and tumor formation.

Methods: We used immunofluoresence staining using monoclonal parkin antibody, western blotting and reverse transcriptase PCR.

Results: Controlled expression of both proteins was achieved in HeLa cells as demonstrated.

Conclusions: Expression of both wild type and mutant parkin proteins did not alter growth parameters and morphological properties of the cells as confirmed by direct immunofluoreescence staining of the cell organelles (Endoplasmic reticulum, Golgi and mitochondria) before and after induction.

Tu-92

DNA methylation pattern in the human IGF-2 imprinted region of Parkinson's disease patients is not altered by the dosage of L-dopa treatment comparing high versus low L-dopa administration

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Objective: To evaluate the methylation of the imprinted region of IGF-2 (human insulin-like growth factor) of Parkinson's disease patients treated with (1) high dosage of L-dopa, (2) low dosage of L-dopa, in particular a predominantly agonist treatment and (3) of healthy individuals, we used bisulfite sequencing PCR (BSP).

Background: IGF-2 is one of the imprinted genes in humans. Loss of imprinting (LOI) of IGF-2 causes human cancers, especially the Beckwith-Wiedemann syndrome. If loss of imprinting or aberrant imprinting is also associated with the onset of Parkinson's disease (PD) has not yet been investigated.

Methods: DNA extracted from human blood leukocytes was first treated with bisulfite. Then PCR amplification was performed and PCR products of IGF-2 exon 8-9 region were subcloned into a TOPO vector. Plasmid DNA was isolated from at least ten clones per individual and sequenced. Each group (high dopa load, low dopa load, controls) consisted of 5 individuals. The methylation profiles of the samples were finally investigated with the Big Analyzer (BiQ).

Results: IGF-2 imprinted region of Parkinson's disease patients with high and low dopa load, as well as of healthy individuals showed an almost total methylation of all CpG islands analyzed. No difference of methylation status between any of the three groups was detectable.

Conclusions: Our observation of a high percentage of methylated CpG islands of IGF-2 in healthy humans is consistent with previous studies in mice and humans. Furthermore the methylation profiles of the imprinted gene regions exon 8-9 of IGF-2 in PD are neither influenced by the dosage of L-dopa treatment nor by the disease itself. In fact methylation of IGF-2 of Parkinson's disease patients is as stable as that of unaffected individuals. Thus loss or disruption of imprinting seems not to exist in Parkinson's disease and therefore seems to be irrelevant for the pathogenesis of PD.

Tu-93

Molecular analysis PARK2 mutations in the group of Polish patients with early onset Parkinson's disease

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Objective: The aim of our study was to characterize Polish EO-PD (frequency and the type of mutations in the PARK2 gene) also as a first step in set up of the molecular diagnostic algorithm.

Background: Majority of PD cases are sporadic but the monogenic form of PD has also has been described. Mutations in the PARK2 gene result in autosomal recessive form of PD. The Parkin type PD is characterized by typical PD features (slower progression, better response to levodopa, often severe dopa-induced complication) and earlier disease onset (EO-PD). The frequency of PARK2 mutations is still not known, but it has been established in Europe as 50% in EO-PD families with recessive inheritance and as18% in isolated patient. Various types of mutations are found at variable frequency, depending on the ethnic background. There is no information about

the PARK2 mutations contribution in EO-PD among the Polish patients.

Methods: We performed an analysis for EO-PD patients group of Polish origin (79 unrelated subjects) with onset of PD $\leq$ 40. Analysis of the coding part of the PARK2 gene was performed by direct sequencing of all 12 exons and exon/intron boundaries. Exons copy number analysis by multiple ligation-dependent probe amplification technique (MLPA).

Results: Two patients with sporadic cases of EO-PD (2.5%) had two mutations in the PARK2 gene; homozygous point mutation (genotype c.203_204 del AG p.34Q > 38X/ c.203_204 del AG p.34Q > 38X) or compound heterozygous point mutation/exons deletion (genotype c.203_204 del AG p.34Q > 38X/ EX4_7 del). The single exon duplication (genotype -/Ex2 dup) was found in one subject (1.3%) of familial history of PD.

Conclusions: The frequency of exon rearrangements and point mutations in PARK2 gene may be less in Polish population than in other described previously groups. Genotype-phenotype correlation revealed that parkin carriers had features similar to those of non-carrier early onset Parkinson's disease patients.

Tu-94

Transcription factor PITX3 in Parkinson's disease

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Objective: To determine whether variants in *PITX3* are associated with Parkinson's disease (PD).

Background: *PITX3* is a transcription factor important for the differentiation and survival of midbrain dopaminergic neurons. Two recent reports from Germany (Fuchs et al, Neurobiology of Aging. 2007; Bergman et al, Neurobiology of Aging. 2008) suggest that single nucleotide polymorphisms (SNP) in the *PITX3* gene may be associated with PD. This preliminary observation requires verification in different population and to examine the nature of the association in a subset of familial PD (fPD) and sporadic PD (sPD) patients.

Methods: We have analyzed two *PITX3* SNPs (rs2281983 and rs4919621) in 265 PD patients and compared them with 210 age-matched healthy controls. PD samples were subcategorized into early-onset PD(EOPD) with a mean age at onset $\leq$ 50 years (n = 81, mean age 44.91 $\pm$ 9.08 years), late-onset PD (LOPD) with a mean age at onset >50 years (n = 184, mean age 64.86 $\pm$ 14.17 years), fPD (n = 98, mean age 54.74 $\pm$ 15.92 years), and sPD (n = 167, mean age 62.24 $\pm$ 12.80 years). Genomic DNA was extracted from peripheral blood using standard protocols. The PCR products of *PITX3* were amplified with the primers targeting rs2281983 and rs4919621 and then sequenced using the 454 GS-FLX and ABI SOLiD systems. Pearson's $\chi 2$ tests were applied to test for significance in differences of gene frequencies.

Results: Our data show that the substitutions of C/T in SNP1 and A/T in SNP2 are significantly higher in PD, and this finding is even more robust in EOPD ($p<0.01$-$p<0.02$) and fPD ($p<0.002$-$p<0.01$) as compared with age-matched healthy controls.

Conclusions: Our findings indicate that rs2281983 and rs4919621variants in *PITX3* are risk factors for PD, particularly EOPD and fPD, and defects in *PITX3* may play a role in the pathogenesis of PD.

Tu-95

SCA17 mutation for ataxia and chorea in Korea

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Objective: To investigate the frequency of SCA17 among Korean patients with ataxia or chorea as a main phenotype.

Background: Spinocerebellar ataxia type 17 (SCA17) is a rare disorder with CAG repeat expansions in the TATA-binding protein (TBP) gene. SCA17 may show ataxia, Huntington-like symptoms, dystonia, parkinsonism, dementia, and pyramidal tract signs. Previously we showed that SCA17 is not rare (0.9%) in our parkinsonian patients.

Methods: Korean patients with ataxia or chorea who visited Movement Disorder Center of Seoul National University Hospital were recruited in the study. Patients with positive gene test for SCA1, 2, 3, 6, 7, DRPLA, and HD were excluded. The gene study for SCA17 was performed using a DNA isolation kit, ABI3100 Genetic Analyzer, and GeneMapper version 3.7 software.

Results: The abnormal expansions of CAG/CAA repeats in TBP gene were detected in 2 (0.3%) of 661 ataxia patients, and 1 (1.0%) of 98 chorea patients. One SCA17-positive patient (Patient 1) had both ataxia and chorea. The repeat sizes of Patient 1 and Patient 2 were 45/38 and 44/40, respectively.

Conclusions: The frequency of SCA17 in our ataxic and choreic patients is low.

Tu-96

Different origins and demographic histories of the LRRK2 G2019S mutation in Parkinson's disease

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Objective: To assess natural histories of the G2019S mutation in a large multi-ethnic population.

Background: Mutations in the Leucine Rich-Repeat Kinase 2 (LRRK2) gene have been identified in families with autosomal dominant Parkinson's disease (PD) and in sporadic cases, with G2019S, as the commonest mutation. Its frequency varies according to ethnicity, accounting for <0.1% in Japan, 1-7% in Europe and 20-40% in PD Ashkenazi Jews and North Africa. Previous studies reported that patients from these populations shared at least 3 haplotypes.

Methods: We genotyped 74 STR and SNP markers spanning 16 Mb in 126 families with G2019S. Of them, 70 were from North Africa, 20 from Europe, 1 from Turkey, 1 from Japan, 34 were of Jewish origin, mostly from Eastern Europe. The haplotypes were reconstructed using Phase v.2.1.1. The age of G2019S was estimated by 2 different maximum-likelihood methods. The network analyses were performed using NETWORK v.4.5.

Results: We identified 3 different haplotypes: Haplotype 1 shared by 95% of G2019S carriers, Haplotype 2, initially identified in 3 European-American families, was found in 2 French families; and Haplotype 3, primarily observed in Japanese PD patients, was shared by a Turkish family. NETWORK analyses showed that Haplotype 1 and Haplotypes 2 and 3 were placed at each edge of the network. Population distribution of the intra-allelic diversity of the common Haplotype 1 showed 25, 33 and 67% of recombining haplotypes in North-Africans, Europeans and Ashkenazi Jews, respectively. Our G2019S age estimations indicated that the LRRK2 mutation initially arose among Near-Easterners ~6-20,000 years ago.

Conclusions: We have shown using a large multi-ethnic population panel that PD-related G2019S mutation has independently appeared in humans at least twice, one of these events having occurred most likely in the Near-East, at least 6000 years ago.

Tu-97

A novel GTP cyclohydrolase 1 mutation identified in a British kindred with variable phenotypes ranging from Parkinson's disease to dopa-responsive dystonia

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Objective: To present and discuss the results from molecular genetic studies in a dominant kindred with variable phenotypes ranging from Parkinson's disease to Dopa-Responsive Dystonia.

Background: We previously presented clinical and functional imaging data on a kindred in which affected individuals demonstrate phenotypes ranging from Parkinson's disease (PD) to dopa-responsive dystonia (DRD), at the MDS 11th International Congress in 2007. Whilst functional imaging provided some support to the clinical diagnosis, we now report on the outcome of molecular genetic screening.

Methods: Each affected participant had detailed clinical assessment, and had Dopamine Transporter scans (DaTSCANs) performed. Affected and unaffected family members were subsequently screened for mutations by sequencing, and for copy number variation by multiple ligation-dependent probe amplification (MLPA) in PD genes: *alpha-synuclein, parkin*, *DJ-1*, *PINK1* and *LRRK2* and in the GTP cyclohyrolase 1 gene (*GCH1*), the most common cause of DRD.

Results: 2 individuals have clinical features consistent with slowly progressive PD, 1 with benign parkinsonism and 2 with DRD. Median age of disease onset is 50 with a median duration of 20 years. DaTSCAN scan images on 5 affected individuals and 1 unaffected sibling are summarised with clinical details below.

Table 1 (Tu-97). Summary of the clinical, functional neuro-imaging and molecular genetic data on subjects from study family

Subject	Age at evaluation	Gender	Clinical diagnosis	Age at symptom onset	DaTSCAN	GCH1 mutation p.E2G
III:1	82	Male	PD	58	Abnormal	Detected
III:2	80	Male	Unaffected	N/A	Normal	Absent
III:3	78	Male	Parkinsonism	75	1st Abnormal 2nd Normal	Absent
III:4	68	Male	PD	50	1st Abnormal 2nd Abnormal	Detected
III:5	66	Male	DRD	44	Normal	Detected
IV:1	26	Female	DRD	6	Normal	Detected
IV:2	59	Female	Unaffected	N/A	N/A	Absent
IV;3	55	Female	Unaffected	N/A	N/A	Absent
IV;4	44	Female	Unaffected	N/A	N/A	Absent

GCH1= GTP Cyclohydrolase 1; PD= Parkinson's disease; DRD= Dopa-responsive dystonia; N/A= Not applicable or not done.

The whole coding sequence of *alpha-synuclein*, *parkin*, *DJ-1*, *PINK1*, and *LRRK2* were sequenced and no mutations found. However, a novel heterozygous missense mutation p.E2G, predicted to result in c.A5G amino acid substitution in GCH1 protein, was detected in 4 out of 5 affected family members, whose clinical features range from PD to DRD. MLPA did not reveal copy number variation in any of the PD genes screened, or *GCH1*.

Conclusions: Accurate clinical diagnosis in affected subjects from this unique family has been challenging for over 20 years. We suggest that variable expression of this novel *GCH1* missense mutation at last provides an explanation for diverse clinical presentations observed in this family. The association of a *GCH1* mutation with such wide ranging phenotypes furthers our understanding of how late onset DRD can present, and suggests a potential role for this gene in PD, requiring further investigation.

Tu-98

Comprehensive molecular genetic analysis of the LRRK2 gene in a UK familial Parkinson's disease cohort

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Objective: To determine the frequency of *LRRK2* mutations in familial PD patients in the UK.

Background: The study of familial PD has led to the identification of a number of PD genes, including *LRRK2*. This is a large gene with 51 exons and putative protein kinase function. Importantly a single *LRRK2* mutation G2019S appears to account for up to 5-6% of familial and 1-2% of sporadic PD cases, although the frequency of this mutation appears to be much higher in North African familial PD cases. We previously presented early data on the known pathogenic mutations from our comprehensive screen of *LRRK2* in UK subjects with familial PD, at the MDS 11th International Congress in 2007. We can now report on the outcome of our completed molecular genetic screening of the gene in this cohort.

Methods: We recruited 46 subjects with PD from around the UK with a history of at least 1 other affected family member, and apparently autosomal dominant inheritance. Each affected participant had detailed clinical assessment of their parkinsonian features. We subsequently screened the whole coding sequence of *LRRK2* in this cohort by sequencing.

Results: In total we identified 61 LRRK2 sequence variations. Heterozygous G2019S mutations were identified in 3 probands (6.5%), similar to mutation frequencies identified in previous studies. In addition we also identified 3 novel heterozygous mutations: c.4364delAT, c.6187delCTCTA, and c.7187insGT. These novel mutations were identified in 1 proband each, associated with phenotypes typical for idiopathic PD, but were not detected in control chromosomes. All three mutations cause a shift in the reading frame and are predicated to lead to the introduction of a premature termination codon. Early *in vitro* studies suggest that for c.6187delCTCTA and c.7187insGT, mutant mRNA is degraded by nonsense-mediated decay (NMD).

Conclusions: In this large cohort of UK PD families we performed a comprehensive screen of the coding sequence of *LRRK2,* and identified the G2019S mutation at the expected frequency. However, we also identified three novel frameshift mutations, with *in vitro* evidence to suggest that mutant mRNA undergoes NMD, in at least two of these mutations. Thus we propose a novel pathogenic mechanism in *LRRK2*-related PD of haploinsufficiency.

Tu-99

Recurrent expansion of a 700kb deletion on chromosome 14 in a family with dopa-responsive dystonia

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Objective: To identify the cause of a recurrent deletion expansion on chromosome 14q.

Background: Dopa-responsive dystonia (DRD) is a childhood-onset movement disorder with an excellent response to levodopa. Most DRD is autosomal dominantly inherited with reduced penetrance and associated with mutations in the GTP cyclohydrolase I (*GCHI*) gene on chromosome 14q22.

Methods: We have identified a three-generation family with four DRD patients and six unaffected individuals. All four affected and one unaffected individual carried a heterozygous deletion of all six exons of *GCH1*. Surprisingly, one obligate carrier (II.3), whose sister and son were both affected, did not carry this deletion, despite confirmed paternity. To elucidate the cause of this apparent inconsistency, we performed haplotype analysis, quantitative PCR, fluorescent in-situ hybridization (FISH) and array comparative genomic hybridization (aCGH).

Results: Haplotype analysis of the *GCH1* region revealed several incompatibilities that could be explained by a smaller deletion localized downstream of *GCHI* in II.3. His mother carried the same deletion of about 700kb. This deletion expanded twice independently in this family to a deletion of about 3600kb involving about 20 genes including *GCH1*. Interestingly, all carriers of the larger deletion also presented with ptosis. We narrowed the breakpoints and identified an

additional small duplication in the carriers of the small deletion by aCGH.

Conclusions: To elucidate the genetic mechanism leading to recurrent expansion of a deletion twice in this family will contribute to a better understanding of the origin of large deletions, an important type of mutation. We will identify the deletion breakpoints by high resolution SNP genotyping. Co-occurrence of apparently unrelated disorders (DRD and ptosis) may be considered a clinical red flag pointing to a deletion involving different genes.

Tu-408

Polymorphism of CYP2D6 alleles in Parkinson's disease

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Objective: In population genetics, allele frequencies are used to show the amount of genetic diversity at the individual, population, or species level. The aim of this study was to determinate the frequency and genotype distribution of non-functional alleles CYP2D6*3, CYP2D6*4, associated with poor metabolism, CYP2D6*6 and the wild type allele CYP2D6-wt, all linked with Parkinson's disease (PD).

Background: Diminished metabolic activity of CYP2D6 enzyme could be associated with increased risk for PD. Although CYP2D6 polymorphism has been studied comprehensively in association with PD, no reliable results have been found.

Methods: Multiplex allele-specific polymerase chain reaction (PCR) was performed in a group of healthy volunteers (n=145) and in a group of PD patients (n=41), matched on age and gender. Allele frequency was calculated as a measure of the relative frequency of an allele at a genetic place (locus) in a population. It is expressed as a proportion or a percentage.

Results: In a group of healthy volunteers the frequency of CYP2D6 alleles was: CYP2D6*3=1.4%, CYP2D6*4=11.0%, CYP2D6*6=1.0%, CYP2D6-wt=86.6%. In a group of PD patients the frequency of CYP2D6 alleles was: CYP2D6*3=1.2%, CYP2D6*4=20.7%, CYP2D6*6=1.2% and CYP2D6-wt=76.8%. Statistically significant difference was found only for allele CYP2D6*4 (RR=2.10; 95% CI: 1.113-3.994). The relation of genotype distribution in healthy volunteers was: *3/wt=2.8%, *4/wt=18.6%, *4/*4=1.4%, *6/wt=1.4%, *4/*6=0.7%, Wt/wt=75.2%. The relation of genotype distribution in PD patients was: *3/wt=2.4%, *4/wt=26.8%, *4/*4=7.3%, *6/wt=2.4%, *4/*6=0.0%, Wt/wt=61.0%. There was no statistically significant difference between these distributions.

Conclusions: Results of this study indicate that the allele CYP2D6*4 could be considered as a fragile risk factor for PD, but similar study should be carried out on larger sample group.

Tu-409

The Jackson Laboratory mouse repository: A genetic resource available to the scientific community for Friedreich's ataxia and other movement related disorders

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Objective: The Mouse Repository at The Jackson Laboratory (TJL) is dedicated to making Mouse Models available to the Scientific Community for use in drug discovery and translational Research. TJL's recent partnership with the Friedreich's Ataxia Research Alliance (FARA) represents an exciting mechanism for making models available to the scientific community and facilitates progress in disease research.

Background: TJL has an extensive reputation as a Repository for mouse models of human disease, with an emphasis on neurodegenerative disorders such as AD, Huntington's Disease, Parkinson's and Spinal muscular atrophy (SMA) and ALS. The Friedreich's ataxia (FA) models promise to be a unique and important component of the neurodegenerative models at Jax.

Methods: Mouse models relevant to disease research are sought by or donated to TJL by the scientific community. Mice are rederived into an SPF facility and cryopreserved as security against the loss of mouse colonies due to breeding declines, disease, genetic contamination, or natural disasters. Allele specific assays are designed for each strain and proper genetic quality control defined and administered. In cases of triplet repeat diseases, such as Friedreich's Ataxia and Huntington's, repeat expansions as well as phenotypes are closely are monitored to prevent drift. Data sheets on phenotype, animal husbandry and relevant publications are available for each mouse strain from our web site and a Technical Support Team is available to assist with questions on model use. Animals can be ordered, shipped and received expeditiously world wide as well as made available through Charles River Lab in designated countries.

Results: FARA grants and activities provide support for basic and translational FA research, pharmaceutical/ biotech drug development, clinical trials, and scientific conferences. The partnership between Jax and FARA recognizes the need to effectively distribute animal models to the scientific community to keep research moving forward.

Conclusions: The Friedreich's ataxia animal models that TJL houses, distributes and improves for scientists will be invaluable in helping determine which of the drugs show the most promise of moving into clinical trials and toward our objective of treatments and a cure.

We-86

Variation in the 3' region of the alpha-synuclein gene modifies risk for Parkinson's disease

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Objective: To determine whether common variation within the alpha-synuclein (*SNCA*) gene, independent of the REP1 polymorphism, is associated with Parkinson's disease (PD).

Background: Our group and others have demonstrated that a putative functional repeat polymorphism in the promoter region of *SNCA* modifies susceptibility for PD. However, it is unclear whether common variation elsewhere in the gene also impacts risk for the disease.

Methods: We performed a two-tiered study of a large case-control sample of white individuals from the NeuroGenetics Research Consortium. In Tier 1 (n=692 cases and 692 controls), we genotyped a comprehensive set of 13 tagging single nucleotide polymorphisms (tagSNPs) selected from the International HapMap Project CEU panel. SNPs associated with PD under an additive model ($\alpha=0.05$) in Tier 1 were then validated in Tier 2 (n=1,277 cases and 1,422 controls). Stepwise logistic regression was used to assess the relative contribution of each SNP (and REP1) to PD risk. Haplotype analyses were performed using HAPSTAT 3.0.

Results: Five tagSNPs were associated with PD in Tier 1 and were genotyped for replication in Tier 2. After adjustment for age and sex, four SNPs (rs2737029, rs2572324, rs356219, and rs2619364) were highly associated with PD in Tier 2, with p values under an additive model ranging from 1.2×10^{-4} to 2.4×10^{-8}. Rs356219, located 9 kb downstream from *SNCA*, had the largest effect (odds ratio, 1.42; 95% confidence interval, 1.29-1.56). A regression model that included only rs356219 best fit the data and was not improved with addition of REP1. Finally, only haplotypes that included the "C" allele of rs356219 were significantly associated with PD.

Conclusions: Our findings suggest that common variation within the 3' region of *SNCA* modifies risk for PD, and that the effect is largely independent of REP1. This further underscores the importance of alpha-synuclein in the etiopathogenesis of the disease. The

mechanism by which variants in this region alter susceptibility is not yet clear and will require further study.

We-87

DLB locus on chromosome 2q35-q36 represents a separate genetic entity

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Objective: To refine the DLB locus on chromosome 2, using new polymorphic markers and haplotype reconstruction, and the exclusion of selected candidate genes. We also choose to investigate the role of the nominated PARK11 gene *GIGYF2*.

Background: We previously mapped a novel locus for dementia with Lewy bodies (DLB) to chromosome 2q35-q36 in a large Belgian family with prominent dementia and parkinsonism (Bogaerts *et al* 2007). The diagnosis was consistent with DLB and is autopsy confirmed for the index patient. This novel locus on chromosome 2 resides in a 9.2 Mb interval neighboring the PARK11 locus and the recently suggested PARK11 gene *GIGYF2*.

Methods: We genotyped STR markers in all 24 available members of family DR246. We performed an extensive mutation analysis of selected candidate genes on gDNA of two patients and two unaffected individuals not carrying the disease haplotype of family DR246 by direct sequencing of all coding and non-coding exons, as well as exon-intron boundaries and 5' and 3' regulatory regions.

Results: To determine the possible contribution of *GIGYF2* mutations in the Belgian DLB family we sequenced all 32 exons of *GIGYF2* (Meeus *et al* 2009) and did not observe mutations that cosegregated with disease. Moreover, genotyping 22 STR markers spanning the 9.2 Mb disease locus in 2 additional asymptomatic family members of DR246 enabled a reduction of the candidate region of 5.2 Mb. Based on 3 additional STR markers, flanking the site of recombination, we were able to further reduce this region and define a minimal candidate region of 3.3 Mb containing 42 genes. So far, extensive sequence analysis of 21 of these candidate genes within the 2q35-q36 region has not revealed a disease-causing mutation.

Conclusions: Taken together, these data rule out *GIFYF2* as the DLB gene in the Belgian-Flanders family DR246. Moreover, our data firmly established the DLB locus at 2q35-q36 as a separate genetic entity of the PARK11 locus.

We-88

The role of ALA746THR variant in the ATP13A2 gene among Hong Kong Chinese Parkinson's disease patients

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Objective: We evaluated this ALA746THR mutation among 80 Hong Kong Chinese PD and 320 Chinese community elderly controls.

Background: Parkinson's disease (PD) is a complex neurodegenerative disease in which there is a strong genetic influence. Previous genetic studies identified various predisposition genes. ATP13A2 (also known as PARK9), which encodes for P5 family of ATPase involved in cation transport, was first identified in patients with Kufor-Rakeb syndrome. Recently, rare mutations were found in patients with PD. A G405R mutation was found in Brazilian patient. ALA746THR was found in Chinese patients (Taiwan and Singapore) and other mutations were found in Caucasians.

Methods: Genomic DNA was extracted from peripheral blood. ALA746THR was genotyped by mismatched PCR-RFLP. Primers CTCCAGGGACACTGTGGAAG and ATTGTACCTGTCgCCATGACGG produce a PCR product of 138 bp and it is then digested by BgII. Wild type was cleaved to give a 122bp fragment.

Results: The mean age of disease onset for the 80 patients was 54.1±9.3 years. 26% of them had disease onset < 50 years. 62.5% of them were male and 10% had family history of PD. We identified 1 patient who was homozygote for THR allele, while one heterozygote was found among 320 elderly controls. Under both dominant and codominant models, the association was not significant (P=0.36 Fisher Exact test). This patient had disease onset at 44 years old with no family history of PD. The carrier in the healthy control was a 70 year old man.

Conclusions: ALA746THR is likely an uncommon polymorphism among Hong Kong Chinese PD patients, especially among early onset cases. A larger study is needed to define its exact prevalence among early onset, familial, and older sporadic cases of Chinese PD in Hong Kong.

We-89

Prevalence of LRRK2, synuclein and parkin mutations in Parkinson's disease patients from Extremadure (southern Spain)

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Objective: To determine LRRK2 (G2019S and R1441G/C/H), synuclein (A53T) and parkin (D394N) mutations frequency in a well characterized cohort of familial and sporadic Parkinson's disease patients from southern Spain and to describe phenotypic characteristics among carriers.

Background: Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting approximately 2% of the population over 60 years of age. Although, the etiology of PD is still unknown, the genetic background of the disease has been documented. LRRK2 (G2019S and R1441G/C/H), synuclein (A53T) and parkin (D394N) mutations have been previously reported in PD. Althought the indicated LRRK2 and synuclein mutations have been well characterized and associated to the development of PD several reports have highlighted that association between D394N mutation and the development of PD is questionable.

Methods: We have genotyped four previously reported LRRK2 mutations (G2019S, R1441C, R1441G and R1441H,) one previously reported synuclein mutation (A53T) and one previously reported parkin mutation (D394N) in 75 cases with PD and 158 controls enrolled in the Genetic Epidemiology of PD Study. Cases and controls were recruited without knowledge of family history of PD.

Results: G2019S mutation was present in two of 75 cases (2,6%) and none of 158 control individuals. Synuclein A53T and LRRK2 R1441C/H/G mutations were not found neither cases nor controls. Parkin D394N mutation was present in six of 75 cases (8.0%) and in two of 158 controls (1,2%). Our results indicate that there is an association between D394N parkin mutation and the development of PD ($p<0,05$).

Conclusions: The frequency of studied LRKK2 mutations and synuclein mutation are similar as previously reported in our area. Our results indicate that there might be an association between Parkinson's disease and parkin's D394N mutation. The true prevalence of these mutations in idiopathic and familial disease, their penetrance, and the phenotypic heterogeneity of associated cases have important implications for genetic screening in the clinical field.

We-90

Genetic and familial study of young onset Parkinson's disease in Wales

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Objective: To investigate the familial and genetic characteristics of Young Onset Parkinson's disease (YOPD) in South Wales, UK.

Background: Although YOPD is rare, our recent community based study showed that1/3 of PD patients develop disease before

the age of 65, and about 5% before the age of 45. Four genes have been identified in YOPD but in most patients the cause of the disease is unknown.

Methods: We carried out a community based study of familial and genetic factors in YOPD and LOPD using a detailed family history and ethnicity questionnaire and analysis of the PARK2 locus. The sample collection includes Welsh patients as defined by birthplace and self-reported ethnicity, and a community based series resident in Cardiff, UK.

Results: We have identified 127 Caucasian YOPD probands defined by an age at disease onset of less than 45 (54 born in Wales, including 10 prevalent cases resident in Cardiff). 1% of siblings and parents, uncles and aunts of YOPD cases have PD, compared with no relatives of age matched younger controls. 4/441 (1.3%) young and late onset PD cases report parental consanguinity compared with no parental consanguinity reported among controls. Analysis of the PARK2 locus identified heterozygous and compound heterozygous parkin mutations in 9/127 (7%) of cases including 10% of Welsh patients analysed, defined by birthplace and self-reported ethnicity. Homozygous parkin mutations have not been identified to date in this sample.

Conclusions: The rate of homozygous autosomal recessive YOPD in outbred populations is likely to be low, nevertheless evidence is emerging to suggest that further Mendelian factors are likely to be important in this group.

We-91

Influence of apolipoprotein E alleles on cognitive status and motor complications in Parkinson's disease

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Objective: To determine the relationship between APOE alleles and cognitive and motor evolution in PD.

Background: The Apolipoprotein E (APOE) e4 allele is associated with an increased susceptibility to Alzheimer's disease. However literature remains uncertain about the relationship between APOE genotype and cognitive decline in Parkinson's disease (PD) and its possible influence on the evolution of motor symptoms has not been properly evaluated.

Methods: The study included 58 patients with PD (34 women and 24 men, mean age 66 years, SD ± 8.3). The APOE genotype was determined in all of them. UPDRS scale and retrospective clinical data were registered. A neuropsychological evaluation was done in 45 patients (FAS test, NPI, Clock drawing test, MMSE, test Barcelona). Parametric and non-parametric tests, linear and logistic regression were used for statistical analysis.

Results: The e3-allele was the most widely represented (e3e3: 66%; e3e4: 17%). PD age onset was not related to APOE alleles. The time from onset to wearing off was significantly longer in patients with an e4 allele versus non e4 (6.9/4.6 years; $p<0.02$) and so was for dyskinesias appearance (9.5/6.9 years; $p=0.037$). There was no relationship between APOE alleles and behavioural alterations or with the scores obtained in the neuropsychological tests. However the NPI score was lower in the carriers of an e2 allele (31/21), but this was not statistically significant ($p>0.05$). Among carriers of an e4 allele, men scored worse than women in cognitive tests, although without statistical significance ($p>0,05$).

Conclusions: Being carrier of e4 allele seems to imply a lower possibility of developing motor complications in PD. APOE genotype is not related to age of onset, behavioural alterations or cognitive performance; nevertheless, being male and carrier of e4 allele might facilitate the appearance of cognitive decline. Studies involving a greater number of patients are necessary to investigate this possibility.

We-92

Assessment of frequencies of simple mutations and copy number variations in five PD genes in Belgian Parkinson's disease patients

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Objective: To obtain an accurate estimation of the relative role of simple mutations versus copy number variations (CNVs) in the five major PD genes in a large patient-control group.

Background: Recent studies have provided evidence that the spectrum of mutations causing complex neurodegenerative disorders extends beyond simple missense mutations. Particularly in Parkinson's disease (PD), the role of gene dosage has been well-established. Four of five genes in which missense mutations lead to familial PD, have also been reported to be susceptible for PD associated dosage mutations (SNCA, PARK2, DJ-1 and PINK1). It is conceivable that CNVs in these genes are currently underestimated since most mutation analyses did not include an extensive search for CNVs.

Methods: We determined the frequency of both simple mutations and CNVs in five familial PD genes, SNCA, PARK2, DJ-1, PINK1 and LRRK2 in 310 Belgian PD patients. We performed mutation analysis of all coding exons by direct genomic sequencing. Using a combination of multiplex amplicon quantification (MAQ) and TaqMan-MGB real-time PCR assays we screened SNCA and LRRK2 for the presence of whole gene multiplications and PARK2, PINK1 and DJ-1 for single/multiple exon CNVs.

Results: We identified heterozygous missense mutations in LRRK2, PARK2, DJ-1 and PINK1 and CNVs in SNCA and PARK2. We also compared the relative frequency of heterozygous mutations (both simple mutations and CNVs) in Belgian PD patients versus control individuals for PARK2 to clarify the biological relevance of these variants in the pathogenesis of PD.

Conclusions: We concluded from this study that CNV analyses should be included in standard mutation analyses of known and novel PD genes to obtain correct estimates on their contribution to PD etiology. Moreover, further genetic and functional analysis of these CNVs are mandatory to estimate their biological relevance in PD pathogenesis.

We-93

Differential expression of mitochondrial and proteasomal genes in Parkinson's disease patients with severe GBA mutations

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Objective: To study the role of severe and mild *GBA* mutations in Parkinson's disease (PD).

Background: Studies in different populations worldwide demonstrated an association between mutations in the *GBA* gene and Parkinson's disease. We recently described (Neurology, June 2008) a genotype-phenotype correlation between mild (N370S, R496H) and severe (84GG, IVS2+1, V394L, D409H, L444P, RecTL) *GBA* mutations and PD risk and age at motor symptoms onset (AAO).

Methods: An extended cohort of 600 PD patients and 353 elderly controls was scanned for eight *GBA* mutations and for the *LRRK2* G2019S mutation. In order to detect genes and genetic pathways that might be involved in the differential effects of severe vs. mild *GBA* mutations, we initiated a global gene expression analysis of peripheral blood leukocytes (PBLs) from PD patients. Samples from patients carrying mild (n=22) and severe (n=7) *GBA* mutations were analyzed using the Affymetrix GeneChip Human Exon 1.0 ST Array.

Results: The frequency of *GBA* carriers was 19.5% in PD patients compared to 4.0% in the elderly controls ($p<0.0001$). The proportion of severe mutation carriers among PD patients-*GBA* carriers was 25% compared to 7% among average risk controls ($p<0.0001$). Severe and mild *GBA* mutations significantly increased the risk for developing PD by 11.4 and 2.3-

fold, and significantly affected the AAO of PD: 55.0 and 58.6 years, compared to 61.0 years in patients without known *GBA* or *LRRK2* mutations ($p=0.003$, One-way ANOVA). Analysis of the "core" exon-expression data (21,980 genes and 232,448 exons) revealed a differential expression of 921 and 135 genes ($p<0.05$ and $p<0.01$, ANOVA), when comparing PBLs from severe and mild *GBA* mutations carriers. Genes from the mitochondrial electron transport pathway and from the proteasome core were over-represented among the 921 differentially expressed genes ($p<1E-07$).

Conclusions: Our results demonstrated the differential effects of severe vs mild *GBA* mutations on PD risk and AAO. We also demonstrated differential gene-expression profiles in PBLs of these two different genotypic groups of patients, suggesting a possible role for the mitochondrial and proteasomal pathways in these effects. This work was partially presented in the ASHG and SfN meetings, November 2008, USA.

We-94

A comprehensive genome-wide genomic and transcriptomic analysis of Parkinson's disease in Ashkenazim

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Objective: To define novel genes and genetic pathways associated with PD by comprehensive genome-wide analyses of transcription-, single nucleotide polymorphism (SNP)-, and copy number variation (CNV).

Background: The genetic background of PD is complex, but surprisingly high proportion of disease-associated mutations were detected in third of the Ashkenazi patients in *LRRK2* and *GBA* genes, render this population valuable for genetic studies aimed to understand PD pathogenesis in the world population-at-large.

Methods: Four different study groups were analyzed: Ashkenazi patients with *LRRK2* G2019S or *GBA* mutations, non-carrier patients and age- and sex-matched controls. The transcriptome analysis included 118 RNAs derived from peripheral blood leukocytes (PBLs) using the Affymetrix Exon Array. The genome-wide association and CNV analyses were performed on 428 samples using the Affymetrix SNP6.0 array, featuring more than 1.8 million probes.

Results: Analysis of the exon-array "core data" (21,980 genes and 232,448 exons) revealed 40 genes with significant expression changes between the 4 study groups (FDR corrected $P<0.1$). Exon-level analysis detected 173 differentially expressed exons between all PD patient and controls ($P<0.01$ and $FC>1.5$). These exons incorporated into 80 genes, some also showed differential splicing. Importantly, the differentially expressed genes were enriched with genes involved in particular cellular pathways, including the PD-related mitochondrial and proteosomal pathways. Analysis of the genome-wide SNP6.0 arrays demonstrated high quality of data, with call rates above 97.86%. Identity by Descent analysis showed up to 4% sharing in our study subjects. Preliminary association analysis confirmed *LRRK2* and *GBA* as major loci associated with PD in Ashkenazi Jews, and identified potential novel PD-associated SNPs on chromosomes 10 and 11. In addition, CNVs distinctive to the Ashkenazi population were detected.

Conclusions: Our results demonstrate the importance of the Ashkenazi PD-patients population for studying the complex genetic basis of PD. The results of the expression studies support PBL a relevant surrogate tissue to identify transcriptional changes involved in PD pathogenesis, and the genome-wide SNP and CNV data will help characterize genes and genetic pathways associated with PD.

We-95

Molecular study and response to levodopa therapy in eight children with tyrosine hydroxylase deficiency

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Objective: To report our experience in a relatively large series of TH deficiency patients.

Background: Tyrosine hydroxylase (TH) is the rate-limiting step in the biosynthesis of catecholamines. Early onset forms of TH deficiency disclose encephalopathy with infantile parkinsonism. Late forms (even adult patients) tend to manifest dopa-responsive dystonia, mimicking Segawa disease. Biogenic amine metabolites in cerebrospinal fluid (CSF) and molecular analysis lead to the diagnosis. L-dopa is the treatment of choice. There are near 40 cases described in the literature.

Methods: CSF samples were collected early in the morning and stored following a previously reported protocol. Biogenic amines and pterins were analysed by HPLC with electrochemical and fluorescence detection procedures. Confirmed diagnosis was performed by molecular analysis of the TH gene.

Results: We describe clinical, biochemical and molecular findings of 8 pediatric patients (from 5 months to 3 years of age) from Spain and Greece. Main features were developmental delay, parkinsonism, and oculogyric crises of different severity. Reduced CSF homovanillic acid and normal pterins were constant. Some patients showed a good response to L-dopa leading to a remarkable improvement of the whole clinical picture, but some others exhibited severe drug-induced dyskinesias and poor outcome. Three Greek unrelated patients presented the same mutation (p.L236P) in homozygosis supporting the hypothesis of a founder effect. Two Spanish patients presented mutations in the same promoter region. Severity of clinical manifestations as well as L-dopa response had no relation with CSF HVA levels or molecular findings.

Conclusions: TH deficiency should be investigated in any child with encephalopathy associated with oculogyric crises and/or parkinsonism. Although this is a rare disease it is potentially treatable. In children, TH deficiency is a heterogeneous disease regarding both clinical severity and response to treatment. However, factors related to this diversity are still not known. Genetic studies should include the promoter region of the TH gene. In Greek patients the p.L236P mutation is highly prevalent.

We-96

Tremor in Parkinson's disease – Endophenotype defined by the DRD3 Ser9Gly polymorphism?

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Objective: To test if tremor in Parkinson's disease (PD) is influenced by the *Ser9Gly* polymorphism of the dopamine D3 receptor gene (*DRD3*) in a large scale genetic association study.

Background: PD is a multisystem disorder of considerable variability, suggesting the existence of subgroups with distinct clinical patterns, and, eventually, varying pathogenesis. Subtypes of young disease onset, rapid progression, isolated motor symptoms, motor plus cognitive symptoms, and bradykinesia plus gait difficulty were identified. With regard to motor symptoms, tremor dominance had the most reliable discriminative value. The hypothesis of a distinct PD tremor subtype is strengthened by pathological, imaging and therapeutic observations, and there is ongoing discussion concerning an overlap of PD and essential tremor (ET). Recently, an association of *DRD3 Ser9Gly* to ET was reported.

Methods: We analysed clinical information of 591 PD patients in German *Kompetenznetz Parkinson*, including motor predominance (equivalent, hypokinetic, and tremor), and tremor symptoms (resting, postural, and action), and genotyped for *DRD3 Ser9Gly*.

Results: Most patients were hypokinetic (47 %), followed by equivalent (33 %), and tremor subtypes (20 %). 63 % had resting tremor, 39 % had postural tremor, and 20 % had action tremor. Any tremor was found in 73 % patients. There were no significant differences in *Ser9Gly* genotype and allele frequencies in motor predominance or tremor symptom subgroups. Various comparisons, including subgroup combinations of predominance (tremor vs hypokinetic, tremor vs hypokinetic plus equivalent, tremor plus equivalent vs hypokinetic), and tremor (resting tremor yes vs no, postural tremor

yes vs no, action tremor yes vs no, any tremor vs no tremor, postural or action tremor vs resting tremor or no tremor) were included. With exception of total dopaminergic load, clinical parameters did not differ significantly between the subgroups.

Conclusions: Or study did not identify any impact of *DRD3 Ser9Gly* on tremor in PD. To avoid missing a weak effect, we included various symptom combinations. We conclude that tremor as endophenotype of PD is not defined by *DRD3 Ser9Gly*. Nevertheless, genetic dissection of this clinically complex disease will help to elucidate PD aetiology.

We-97

Mutation screening of ATP13A2 in patients with early-onset Parkinson's disease and familial Parkinson's disease from mainland China

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Objective: To determine whether mutations of exon19 and 20 in *ATP13A2* associated with early-onset Parkinson's disease and familial Parkinson's disease in mainland China.

Background: *ATP13A2* gene, also assigned *PARK9*, had been found significant association between *ATP13A2* and early-onset Parkinson's disease (EOPD) and familial Parkinson's disease (FPD) by mutation screening and linkage analysis. Up to now, six mutations (c.3057delC, c.1306+5G-A, c.G1510C, c.C35T, c.G1597A, c.C546A) were identified on the patients from Chile, Brazil, Italy and Japan. Especially in Taiwan and Singapore, a novel missense variant on exon20, c.2236G>A (Ala746Thr) has been reported to be an increased risk of Parkinson's disease in the local Han Chinese. Here we sequenced exon19 and 20 and exon-intron boundaries of *ATP13A2* at first to explore whether any mutations could appear in EOPD and FPD in mainland China.

Methods: A total of 220 patients from department of Neurology in West China Hospital of Sichuan university enrolled our study, including 173 with EOPD and 47 with FPD. 101 controls were recruited from the same ethnic group, matched by age and gender. Exon19 and 20 and intron-exon boundaries of the *ATP13A2* were amplified using polymerase chain reaction (PCR), followed by direct sequencing in forward and reverse directions.

Results: No pathogenic mutations were found in coding regions. However, a novel nucleotide variant (IVS19+56C>T) was identified in one patient with EOPD, but was absent in healthy controls. And eight known single nucleotide polymorphisms (SNPs) (IVS19+83T>C, rs57809155) were detected in intron19, too, which was observed in only one normal control. The frequency of the SNP in all patients was 3.6% (8 of 220), and 1% (1 of 101) in normal individuals, and no significant associations between the patients and controls($P=0.332$). Considering different groups, the frequency was 2.9% (5/173) in EOPD and 6.4% (3/47) in FPD. Neither the patients with EOPD ($P=0.543$) nor the patients with FPD ($P=0.181$) were statistically different from healthy controls.

Conclusions: A novel nucleotide variant (IVS19+56C>T) was observed in one patient with EOPD, but the function remained unclear. No pathogenic mutations were found in our patients with EOPD and FPD in mainland China. And the SNP rs57809155 has no significant association with EOPD and FPD, either.

We-98

Genetic analysis of GIGYF2 in Parkinson's disease

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Objective: To conduct a genetic analysis of the GIGYF2 gene in Parkinson's disease (PD).

Background: Mutations in the GIGYF2 (Grb10-Interacting GYF Protein-2) (TNRC15) gene, located within the PARK11 locus have been reported to associate with PD in Italian and French populations. There is limited information regarding these mutations in other populations.

Methods: Consecutive PD patients and controls were recruited from tertiary centers in Singapore. The 27 coding exons of the GIGYF2 gene were sequenced in familial and early onset PD patients. In addition, analysis of any variants/mutations was carried out in our healthy control population and late onset PD patients.

Results: A total of 500 subjects were included. Analysis of familial and early onset cases revealed a total of seven different GIGYF2 variants/mutations resulting in single amino acid substitutions. These variants/mutations were located in exons 2, 8, 10, 23. Further analysis in 200 PD and 200 controls revealed that 4 variants were present in PD but not in controls. Those variants that were detected in controls most likely represent polymorphisms. Clinically, patients with putative mutations do not differ from the general PD population.

Conclusions: We detected several putative mutations and polymorphisms of the GIGYF2 gene in our PD population. Further functional and segregation analysis of the putative mutations would be needed to determine if they are causative.

We-99

Parkinsonism and early cortical involvement in a Swedish family with alpha-synuclein Ala53Thr mutation

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Objective: We report a southern Swedish family with parkinsonism and alpha-synuclein A53T (p.Ala53Thr; c.209G>A) mutation.

Background: Two patients (a female proband and her father) had tremor, rigidity, and bradykinesia. The age at onset was relatively early, with manifestation before age 41 and 30 years, respectively, and the symptoms responded to L-dopa initially. Language and speech difficulties were a characteristic feature relatively early in the disease's course. Cognitive decline indicative of general cortical and subcortical dysfunction as well as myoclonic jerks were documented. Genetic analysis of the index patient showed a c.209G>A mutation in the alpha-synuclein gene (*SNCA*), resulting in an Ala53Thr mutation.

Methods: The two patients were followed longitudinally at our institution for five and ten years.

Results: Extensive clinical, imaging and cerebrospinal fluid biomarker examinations revealed an underlying encephalopathy with cortical dysfunction and neurochemical signs of spreading neuronal damage: Magnetic resonance tomography showed no certain abnormalities. Presynaptic dopamine reuptake was decreased in the basal ganglia in ^{123}I-FP- CIT SPECT. Cortical blood flow assessed by ^{99m}Tc-HMPAO SPECT was reduced, most markedly in the left parietal lobe. Data were available from a previous research study on 16 lumbar punctures performed in the index patient's father, and cerebrospinal fluid (CSF) samples from two lumbar punctures of the index patient were analysed. CSF-protein or albumin concentration was determined, and was increased in each of the 18 samples to values 2-4 fold above the reference range. Neurofilament light chain level was normal in the first CSF-sample from the index patient, but was increased in a sample obtained 1,5 years later. Analysis of tau, phospho-tau, beta-amyloid(1-42) and glial fibrillary acidic protein in CSF was normal.

Conclusions: Our results suggest that, similar to other *SNCA* mutations, this *SNCA* mutation is associated with a neurodegenerative disease with parkinsonism and early cortical involvement.

We-100

Gene-gene interaction of iron-related genes variants on Parkinson's disease in the PEG study

S.L. Rhodes, J.M. Bronstein, K.D. Taylor, B. Ritz (Los Angeles, California)

Objective: To evaluate the possible gene-gene interaction effects of iron related genes on PD occurrence in 357 PD cases and 360

population-based controls from the Parkinsons Environment and Genes (PEG) study.

Background: Excess iron accumulation has been observed in histological studies of PD affected brains when compared to age-matched non-affected brains. MRI studies have observed abnormalities suggesting increased iron content in the substantia nigra of PD subjects. We previously reported main effects associations with PD for 17 iron-related genes.

Methods: All 90 successfully genotyped SNPs were included in a single run of the program Multifactor Dimensionality Reduction (v.2.0 alpha; MDR). The resulting two- and three-SNP interaction models were investigated in logistic regression adjusted for gender, age (at diagnosis for cases, at enrollment for controls), and smoking status (current, former, never).

Results: MDR analysis suggested interactions between FRRS1 (rs7522921) and FECH (rs1790619), between TFRC (rs13072608) and HFE (rs4529296), and among TF (rs1525892), SLC11A2 (rs224575), and FRRS1 (rs12961441). Main effects were observed for FRRS1 (rs7522921 minor allele carriers vs wildtype homozygotes: OR=0.70, 0.51-0.96); TF (rs1525892 minor allele homozygotes vs wildtype allele carriers: OR=1.61, 0.99-2.63); and FRRS1 (rs12961441 minor allele carriers vs wildtype homozygotes: OR=0.66, 0.49-0.90). Logistic regression analysis suggested interactions between FRRS1 and FECH (p-value=0.036), TFRC and HFE (p-value=0.039), SLC11A1 and FRRS1 (p-value=0.014), TF and FRRS1 (p-value=0.044), and possibly among SLC11A1, TF, and FRRS1 (p-value 0.056).

Conclusions: These analyses suggest that possessing one gene variant in a pathway might not impact risk of PD, but that multiple gene variants in a common pathway might adequately impact the biological redundancy or compensatory mechanisms so as to affect PD risk. These results also support the multiple hit hypothesis of PD; in addition to environmental exposure(s), it is likely that multiple genetic variants, particularly when those variants are in the same biological pathway, are necessary for disease.

We-101

Cumulative effect of multiple risk and protective iron-related genes variants on Parkinson's disease in the PEG study

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Objective: To evaluate the cumulative effect of multiple risk or protective genotypes on PD occurrence in 357 PD cases and 360 population-based controls from the Parkinsons Environment and Genes (PEG) study.

Background: In addition to death of dopaminergic neurons and presence of Lewy bodies, iron accumulation, beyond that of normal aging, has been observed in histological studies of post-mortem PD affected brains. Imagining studies have observed abnormalities consistent with increased iron content in the substantia nigra. We previously reported risk and protective associations for iron-related genes.

Methods: Each subject was assigned a cumulative risk score from 0-4 based on the number of risk genotypes present (AA or AG of rs7596205 in SLC40A1, CC or CG of rs4145237 in SLC40A1, GG or AG of rs4434553 in TFR2, TT or CT of rs2015356 in CYB561); and assigned a cumulative protective score from 0-3 based on the number of protective genotypes present (AA or GA of rs953019 in FRRS1, CC or CT of rs16840812 in TF, AA or GA of rs1880669 in TF). Odds ratios and 95% confidence intervals were estimated by logistic regression adjusted for gender, age (at diagnosis for cases, at enrollment for controls), and smoking status (current, former, never).

Results: For the risk genotypes, we observed an increased risk for increasing number of genotypes (p-trend 0.0086): 0 risk genotypes as reference group; 1 risk genotype OR=1.13 (0.61-2.07); 2 risk genotypes OR=1.47 (0.81-2.67); 3 risk genotypes OR=2.34 (1.23-4.45); 4 risk genotypes OR=2.0 (0.83-4.79). For the protective genotypes, we observed an increased protective effect for increasing number of protective genotypes (p-trend 0.0388): 0 protective genotypes as reference group; 1 protective genotype OR=0.72 (0.46-1.12); 2 protective genotypes OR=0.62 (0.40-0.97); protective genotypes OR=0.48 (0.29-0.81). These trends remained present when both factors were included in a regression model together.

Conclusions: If these gene variants impact protein structure so as to affect brain iron homeostasis, then our results suggest that subjects with more risk (or protective) genotypes might be at increased (or decreased) risk of PD, possibly as a result of increased (or decreased) iron concentrations or modified distributions in the brain.

We-102

Adult onset Alexander's disease with cognitive impairment and autosomal dominant transmission associated with a novel mutation in the GFAP gene

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Objective: We report a sibling pair with adult-onset Alexander's disease (AOAD) of presumed autosomal dominant inheritance, associated with a previously unreported mutation in the GFAP gene.

Background: The phenotype of AOAD associated with various GFAP gene mutations includes progressive bulbar, oculomotor and gait abnormalities, but has not been reported to involve cognitive impairment.

Methods: The first patient (38y, F) presented at age 34 with dysarthria, developed a 3Hz palatal and laryngeal tremor, dysphagia and mild cognitive impairment within 1 year, and on examination demonstrated oculomotor abnormalities, limb ataxia, pyramidal signs and specific cognitive deficits on neuropsychological testing, which have remained stable over 3 years. Past history included sleep apnoea proven on a formal sleep study. MRI showed extensive confluent bifrontal white matter signal change and marked atrophy of the medulla and upper spinal cord. Her brother (44y, M) developed dysarthria and gait ataxia in his early 40's with minimal progression and similar MRI findings, but has not had formal neuropsychological assessment. Their mother died at age 61 after onset at age 54 of a steadily progressive ataxic gait disorder with falls, dysarthria, dysphagia, behavioural disinhibition and sphincter dysfunction and showed bulbar, oculomotor and pyramidal abnormalities without palatal tremor. MRI changes were more severe than described above including cavitation in frontal white matter.

Results: DNA analysis of both siblings showed a previously unreported base pair duplication (c.821_826dup, p.Leu274_Leu275dup) in exon 5 of the GFAP gene (NCBI reference sequence NM_002055). DNA was not obtained from the mother.

Conclusions: This previously unreported GFAP gene mutation is phenotypically similar to other mutations in its association with AOAD of bulbar and gait onset presumed due to brainstem involvement, but differs in the presence of cognitive and behavioural symptoms, likely due to severe bifrontal white matter involvement. It also appears to show phenotypic variability, presenting earlier and with slower disease progression, at least at this stage, in the subsequent generation.

We-103

Mutation screening of GIGYF2 gene in familial and sporadic Parkinson's disease

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Objective: To investigate the role of GIGYF2 gene in familial and sporadic PD in Spanish population by sequencing the gene coding region.

Background: A linkage analysis performed in families with Parkinson's disease (PD) has identified a candidate locus in chromosome 2q36-37, thereafter named PARK11. One of the markers of the candidate region located in intron 21 of the GIGYF2 gene showed the

highest LOD score. Sequencing analysis of GIGYF2 gene identified several GIGYF2 segregating variants that were found only among PD individuals.

Methods: Seventy-four PD individuals and 72 healthy controls were recruited for the genetic study. Exons 2, 4, 8, 9-10, 11, 14, 25 and 26 of the GIGYF2 gene were sequenced in order to identify variants associated with PD.

Results: We failed to identify any of the previously described GIGYF2 pathogenic variants. We identified a missense change (p.Met48Ile) in exon 2 in a PD individual who was a carrier of two PARKIN gene compound mutations. We have also detected two novel variants located in exon 25: one of unknown significance (p.Q1222_Q1225del) in a PD individual and one novel variant in a healthy control (p.Q1210ins). p.Q1222_Q1225del mutation was not present in the 72 healthy controls and segregation analysis is undergoing.

Conclusions: Our findings suggest that coding mutations of GIGYF2 gene are not a frequent cause of PD in the Spanish population.

We-402

ALS phenotypes with mutations in SPG11

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Objective: The goal of this study is to investigate patients with ARHSP-TCC and amyotrophic lateral sclerosis (ALS) for mutations in *SPG11*.

Background: Mutation of the *spatacsin* gene (*SPG11*) is the single most common cause of autosomal recessive hereditary spastic paraplegia (ARHSP) with thin corpus callosum (TCC). *SPG11* and other HSP-related genes are candidate for other motor neuron disease with evidence of lower motor neuron (LMN) and upper motor neuron (UMN) degeneration.

Methods: Mutations in *SPG11* were screened by direct sequencing of genomic DNA obtained from patients' lymphocytes.

Results: We found eight already described *SPG11* mutations in 16 unrelated patients with ARHSP-TCC. Surprisingly, other six *SPG11* sequence alterations, of which one was novel, were identified in 25 unrelated affected individuals with autosomal recessive juvenile ALS (ARJALS). No mutations in *SPG11* were found in 33 unrelated subjects affected by JALS and with no family history of the disease.

Conclusions: Our study confirm that *SPG11* mutations are a frequent cause of ARHSP-TCC. In addition, these genetic defects could cause much wider spectrum of clinical features than previously recognized, including ARJALS.

We-403

Familial cases of paroxysmal kinesogenic dyskinesia

A.Q. Rana (Toronto, Canada)

Objective: To report a patient with Paroxysmal kinesogenic dyskinesia whose daughter developed the same condition.

Background: Paroxysmal kinesogenic dyskinesia is a very rare genetic condition which is infrequently seen even in movement disorder clinics. It is characterized by brief attacks of abnormal curling, jerking or twisting of a body part triggered by sudden movements. The attacks may be as frequent as 100 per day or as infrequent as twice a year. It is autosomal dominant and responds to carbamazepine. The mutation responsible is localized to chromosome 16 p12.

Methods: We report a case of a 43 year old female who presented to our clinic with history of brief episodes of abnormal twisting and curling of her hand induced by sudden movements lasting for about 2 minutes. These episodes started at age 14 years. She was started on carbamazepine and responded well. Interestingly her 13 year old daughter developed similar episodes and responded well to carbamazepine.

Results: MRI brain was normal.

Conclusions: This is an interesting case of paroxysmal kinesogenic dyskinesia as the daughter developed not only the same condition but the age of onset was also about the same. This emphasizes that in patients with suspected paroxysmal kinesogenic dyskinesia, history of children being affected with the similar condition should be asked carefully even if the children are young.

Th-87

Development of the Parkinson's disease mouse model resource

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Objective: The Parkinson's Disease Mouse Model Resource (PDMMR) was established within the mouse repository at The Jackson Laboratory to be a central resource for archiving and distributing genetic models useful to the study of PD, and to provide information on the selection and use of PD mouse models.

Background: Mouse models are valuable tools to understand the basic pathogenesis of Parkinson's disease (PD), to study the role of environmental factors in PD, and to be used as disease models to identify therapeutic targets and develop new therapies for PD.

Methods: We are actively seeking additional disease model and research tool strains to add to the PDMMR. This includes: rederiving strains to a high health status; moving key alleles to standard genetic backgrounds; and routine monitoring of transgenic copy number and phenotype. Submission of a strain to the repository, which can be initiated via a web form, facilitates distribution of a genetically consistent strain at a high health status and provides an archive of genetic material. If necessary, donating investigators can place licensing restrictions on the distribution and use of their models.

Results: Currently the resource contains alpha- and beta-synuclein knockout lines, and a collection of transgenic lines expressing human alpha-synuclein with various mutations driven by different promoters. Some of these display movement disorders, alpha-synuclein inclusions and neurodegeneration similar to that seen in PD patients. Other PD models distributed include Park2 (parkin), Park7 (DJ-1), Htra2 (Park 13) and Pitx3 mutants. Also available are strains that are specifically sensitive or resistant to toxins such as MPTP that can be used to study mechanisms of neuronal death in PD. The repository also distributes various "research tool" strains, such as transgenic lines that express: cre or the tetracycline regulated transactivator (tTA) protein in specific neuronal cell populations to enable regulated gene expression or deletion; or reporter genes such as GFP or lacZ in a neuronal-specific manner, including GFP lines that serve as reporters for ubiquitin/proteosome system activity in vivo.

Conclusions: For more information about the PDMMR including a list of strains, phenotype descriptions, allele and genotyping information and associated references, see www.jax.org/jaxmice/research/neurobiology/parkinsons.

Th-88

Association mapping of the chromosome 5 Parkinson's disease linkage region

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Objective: Identify genes associated with Parkinson's disease (PD) in the chromosome 5 linkage region.

Background: PD has a complex etiology comprising both genetic and environmental risk factors. Genetic studies of multiplex families (in which two or more related individuals are diagnosed with PD) have been used to implicate regions of the genome likely to contain genes underlying PD. One such region, on chromosome 5, has been

linked to PD in independent data sets (Scott et al., JAMA 2001; Hicks et al., Ann Neurol 2002). Subsequent efforts to evaluate plausible candidate genes in the region have failed to identify a gene responsible for the observed linkage peak.

Methods: We performed association mapping across the peak region (121 – 153 Mb) by genotyping 1,637 single nucleotide polymorphisms (SNPs) in 322 multiplex families. SNPs with the strongest evidence for association ($p<0.01$) with PD were selected for replication in an independent data set of 449 singleton families consisting of a single individual with PD and at least one sibling or spouse control. The family-based association in the presence of linkage (APL) and pedigree disequilibrium (PDT) tests were used to assess SNPs for allelic associations with PD.

Results: Thirty SNPs (2%) with the strongest evidence for association ($p<0.01$) with PD were selected for genotyping in the replication set. Of these, three were associated with PD in the replication set when analyzed using the APL test (rs917379, $p=0.04$; rs30264, $p=0.02$; rs30263, $p=0.008$). All three were located in a single gene (CSS3) and were in strong pairwise linkage disequilibrium (LD) with one another ($r^2>0.9$).

Conclusions: Association mapping of the chromosome 5 linkage region implicated a single gene. Three SNPs in the CSS3 gene were associated with PD in two independent samples, making this gene a top priority target in this region for further studies. None of the three markers has a known effect on gene expression or function. Further studies to identify a functional variant in this gene region are ongoing.

Th-89

Glucocerebrosidase (GBA) mutations and familial Parkinson's disease in Japan

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Objective: To evaluate the significance of heterozygous mutations in the glucocerebrosidase (*GBA*) gene among familial Parkinson's disease patients in Japanese population.

Background: Glucocerebrosidase is a lysosomal enzyme and the loss of function of this enzyme causes Gaucher disease (GD), which is the most popular sphingolypidosis presented with hepatosplenomegaly and sometimes with neural dysfunction. On the other hand, heterozygous mutations in *GBA* have been also recognized as an important risk factor for Parkinson's disease (PD) for these several years. However, the association studies between *GBA* mutations and sporadic PD were performed mainly in Jewish population, in which GD was especially frequent. And large studies for familial PD have not been reported in any ethnics. Thus, to further emphasize the role of GBA mutations in PD, we analysed *GBA* mutations in familial PD patients in Japanese population.

Methods: We performed direct DNA sequencing of all the coding sequences in the *GBA* gene among 285 Japanese PD patients with positive family history and 104 Japanese normal controls.

Results: Twenty nine PD patients had heterozygous *GBA* mutations, which were already known as causative mutations in GD (9.8% = 29/285). The two most frequent mutations were R120W and L444P. On the other hand, only one control had heterozygous *GBA* mutation (0.96% = 1/104). The frequency of *GBA* mutations was significantly higher in familial PD than in controls ($p<0.01$; odds ratio = 11.7, 95% CI = 1.6-87). We also found several new variants, which are not known in GD. Many of those PD patients with heterozygous *GBA* mutations had the clinical features of younger-onset and psychiatric symptoms.

Conclusions: The heterozygous mutations in *GBA* strongly affect about 10% of familial PD patients in Japan.

Th-90

Evaluation of the genetic contribution of Omi/HtrA2 to Parkinson's disease in an international collaborative study

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Objective: To accurately assess the risk estimate of Omi/HtrA2 gene in the general population, we performed a large multicenter study among 15258 cases and controls collected by the consortium of Genetic Epidemiology of Parkinson's disease (GEOPD).

Background: Recent genetic association studies provided conflicting results regarding the involvement of Omi/HtrA2 in the pathogenesis of Parkinson's disease (PD).

Methods: We performed a large multicenter collaborative genotyping of markers in the Omi/HtrA2 gene in PD cases and controls. Sites of the GEOPD consortium provided data including affected status, gender, ethnicity, age at study, age at examination (all subjects); age at onset and family history of PD (in cases). Genotyping was performed for the five most informative SNPs in the Omi/HtrA2 gene in approximately 2-3 kb intervals. Fixed as well as random effect models were assessed to estimate the risk estimate of Omi/HtrA2 variants.

Results: The 17 sites provided data for 6378 cases and 8880 controls. No overall effect of the SNPs in the Omi/HtrA2 gene could be observed in fixed effect as well as random effect models (Odds ratio 0.89 to 1.12). However, in the Caucasian cohort we observed a trend for SNP rs2241028 with an OR of 1.12 ($p=0.07$). This effect was strong in the Scandinavian population (Norway, Sweden) highlighting a potential ethnically specific effect of this SNP ($p = 0.04$; OR 1.41). In the same subpopulation, we observed a trend for a G420T substitution, a coding polymorphism in exon 1, with an OR of 1.45 ($p=0.07$).

Conclusions: This largest association study performed to define the role of a single gene in the pathogenesis of PD revealed ethnically specific effects for the Omi/HtrA2 gene. Our findings support evidence from animal models and histopathology in brains of PD patients suggesting a role of Omi/HtrA2 as a susceptibility factor in some populations of PD.

Th-91

Familial congenital mirror movements: Report of a large 4-generation family

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Objective: To describe a large family with congenital mirror movements.

Background: Mirror movements are involuntary movements that occur in the contralateral homologous muscle upon voluntary unilateral activation. Mirror movements are common in early childhood, however their persistence beyond the age of 10 is usually pathological, and can be associated with abnormalities of the corticospinal tract such as in X-linked Kallmann's syndrome, Klippel-Feil syndrome or congenital hemiplegia. There have been sporadic case series of persons with congenital mirror movements, but no large families have been described.

Methods: We report a large French-Canadian family with congenital mirror movements, with 11 affected individuals spanning 4 generations. Affected and unaffected individuals were examined and underwent quantitative assessment of contralateral motor activation during alternating pronation-supination arm movements.

Results: All affected members have predominant involvement of the hands, with occasional involvement of the forearms and legs. Severity is variable; symptoms generally do not substantially limit rou-

tine activities, although some find the movements socially embarrassing. Neurological examinations are otherwise normal. Results of the quantitative testing all confirmed clinical diagnosis. Amplitude and velocity of the involuntary mirror movements were 4-26% of values observed for the voluntary movements. The inheritance pattern is autosomal dominant with high penetrance.

Conclusions: Congenital mirror movements can be inherited in an autosomal dominant fashion. Future linkage studies will attempt to localize the causative genes.

Th-92

Glucocerebrosidase gene mutations and Parkinson's disease in Chinese population

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Objective: To evaluate the association between Parkinson's disease (PD) and mutations in the *glucocerebrosidase* gene (*GBA*) in Chinese population. Mutations in the *glucocerebrosidase* (*GBA*) gene have recently been identified as contributing to the development of Parkinson's disease (PD) in several populations.

Background: Mutations in the *glucocerebrosidase* (*GBA*) gene have recently been identified as contributing to the development of Parkinson's disease (PD) in several populations.

Methods: PCR restriction enzyme assay and DNA sequencing of four *GBA* common mutations (L444P, F213I, R353W and N370S) were carried out in 402 Chinese patients with PD and 413 age- and sex-matched controls.

Results: Among the 402 Chinese Parkinson's disease patients, we found eleven patients (2.74%) who carried a heterozygous mutant *GBA* allele. The eleven heterozygotes have the L444P mutation. The average age at disease onset of the eleven patients was 54.64 years, comparable to the disease onset in the total patient group (54.79). All eleven patients carrying a *GBA* mutation presented with a typical parkinsonian phenotype and had a good or excellent response to levodopa. No heterozygotes were found among the 413 age- and sex-matched controls. We compared the frequency of heterozygotes for *GBA* mutations among PD patients (11/402) and the control group (0/413) by means of the chi-square test. The difference was statistically significant (χ^2=11.456,P=0.0007).

Conclusions: Our results demonstrate that the *GBA* gene mutations appear to be a risk factor for Parkinson's disease in China.

Th-93

Domain location of heterozygous PINK1 mutations associated with differential stress induced cellular response

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Objective: To investigate the apotoptic propensity associated with copy number and domain location of PINK1 mutations using an invitro model.

Background: The pathogenicity of heterozygous PINK1 mutations has been debated. The effect of environmental stressors on the apotoptic propensity associated with copy number and domain location of PINK mutations has not been examined.

Methods: We utilized an invitro system that can co-express equally two different genes. Several PINK1 point mutants affecting different domains of the protein that have been reported to exist as a single heterozygous copy in Parkinson's disease patients were created using site-directed mutagenesis. To mimic the homozygous and heterozygous states in patients, plasmids which have been shown to co-express both genes equally were constructed by cloning two variants of the gene into a vector. Stable transfected SH-SY 5Y cell lines with the different PINK1 mutations were created. The cell lines harbouring different PINK1 mutations were exposed to cellular stressors such as hydrogen peroxide. Flow cytometry after staining the fragmented DNA characteristic of apoptotic cells with Propidium Iodide (PI) were used for analysis.

Results: There was a greater rate of apotopsis in cells harbouring two copies of PINK1 mutations compared to the heterozygous state. Mutations in the kinase domain and C-terminus mutants are associated with higher apotopsis compared to mutants in the N-terminus and wildtype (40% vs 20%, $p<0.05$). Cells harboring single heterozygous mutations in the kinase domain have a greater apotoptic propensity when subjected to oxidative stress compared to N-terminus mutants.

Conclusions: Using an invitro system that simulates heterozygous expression, we have demonstrated that single heterozygous point mutations reported in Parkinson's disease patients increases the risk of neuronal cell death. Heterozygous mutations in the kinase domains are less resistant to cellular stresses.

Th-94

Analysis of the UCHL1 genetic variant in Parkinson's disease among Chinese

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Objective: We conducted a multicenter analysis to investigate the age-of-onset effect of the *UCHL1* variant in PD among ethnic Chinese.

Background: The inverse association of the functional ubiquitin carboxy-terminal hydrolase L1 (*UCHL1*) S18Y variant with Parkinson's disease (PD) among Caucasian populations has been debated.

Methods: All the study subjects were ethnic Chinese recruited from tertiary institutions in 5 centers. Movement disorders neurologists examined the patients and the diagnosis of PD was made according to widely accepted UK Brain Bank criteria. Control subjects were healthy volunteers (with no evidence of neurodegenerative diseases) matched for age at onset of PD, gender and ethnicity and examined by the authors. Informed consent was taken from all study subjects.

Results: Individual data sets from 5 centers comprising a total of 4088 study subjects were analyzed. In the univariate analysis, only data from 1 center showed a trend towards a protective effect among young subjects. However, in the combined analysis, no significant association between the UCHL1 variant and PD was detected (A allele frequency 0.531 vs 0.528, p=0.87, OR 1.01 95%CI (0.92-1.1). Among subjects less than 60 years old, the OR is 0.99 95%CI 0.84-1.16, p=0.88). A multivariate logistic regression analysis showed that family history, *UCHL1* variant and the interaction of *UCHL1* variant and age at onset (p=0.816) were not significantly associated with PD.

Conclusions: The S18Y variant was not associated with PD. There was also no interaction between the age at onset and the S18Y variant.

Th-95

PLA2G6 mutations and Parkinson's disease

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Objective: We conducted a comprehensive analysis of the *PLA2G6* gene in a cohort of Parkinson's disease patients.

Background: *PLA2G6* mutations have been described in adult-onset levodopa-responsive complicated parkinsonism without brain iron accumulation on MRI. It is unclear whether *PLA2G6* is an important cause of other adult onset levodopa responsive parkinsonism conditions such as Parkinson's disease (PD).

Methods: Subjects diagnosed with PD based on the United Kingdom PD Brain Bank Criteria and healthy controls were initially recruited. The institution ethics committee gave approval and all the subjects provided written informed consent. We sequenced the entire coding exons and exon-intron boundary of the *PLA2G6* gene in a

cohort of PD patients with young age at onset/dystonia at presentation or those with a positive family history. Further screening of any suspected mutations was carried out in 100 healthy controls.

Results: We detected 5 single base substitutions. One resulted in an amino acid change. This substitution in exon 17 could possibly influence interaction of PLA2G6 with other proteins. The functional variant was not present in 100 healthy controls. The patient with this variant presented with typical features of PD with dystonic spasms and levodopa responsive parkinsonism. Brain imaging did not reveal evidence of any heavy metal deposition.

Conclusions: *PLA2G6* mutations are unlikely to be an important cause in typical PD patients with dystonia in our population. However, further characterization of potential rare putative mutations in PD patients will be needed.

Th-96

Analysis of SCA2 and SCA3/MJD repeats in Parkinson's disease in mainland China genetic, clinical, and PET findings

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Objective: To investigate the prevalence and clinical feature(s) of SCA2 and SCA3/MJD in patients with parkinsonism in a Mainland Chinese population and to find the difference in the SCA2 and SCA3/MJD mutations between ataxic and parkinsonian phenotypes.

Background: Recent reports suggest that CAG triplet expansions of SCA2 and SCA3/MJD are the cause of typical levodopa-responsive Parkinson's disease (PD), several of which were found in patients of Chinese ethnicity. It is unclear whether ethnicity alone can explain such an association.

Methods: CAG triplet repeat expansions of *ATXN2* and *MJD1* genes were analyzed in a cohort of 452 Mainland Chinese patients affected by typical parkinsonism, including 386 sporadic and 66 familial forms. Cloning and direct sequencing of the expanded allele was performed in patients positive for the *ATXN2* and *MJD1* expansion. Striatal dopamine transporter (DAT) was evaluated in one SCA2 and one SCA3/MJD-positive family members using carbon (C 11) [^{11}C]–radiolabeled-CFT positron emission tomography (PET).

Results: We found two patients in one familial PD (FPD) family and two sporadic disease patients with expanded CAG repeats in the *ATXN2* locus. The expansions ranged from 36 to 37 repeats and were interrupted by CAA as (CAG)n(CAA)(CAG)8 in all the *ATXN2* expansion-positive patients. Meanwhile, we found four patients in two FPD families and another three sporadic PD patients with expanded CAG repeats in the *MJD1* locus. The expansions ranged from 58 to 73 repeats and were not interrupted by CAA or other variants. All patients had levodopa-responsive parkinsonism without obvious cerebellar signs. [^{11}C]-CFT PET in affected members in SCA2 and SCA3/MJD families showed decrements of ^{11}C-CFT uptake in all patients listed above.

Conclusions: A mutation in SCA2 or SCA3/MJD is one of the genetic causes of PD, specifically FPD, in Mainland China. Parkinson's disease patients, especially those with a family history of PD are strong candidates for routine screenings of SCA2 and SCA3/MJD mutations. [^{11}C]–radiolabeled-CFT PET can provide a useful way to evaluate the degree of nigrostriatal dopaminergic damage in SCA2 and SCA3/MJD-related parkinsonism.

Th-97

GABA(A) receptor as susceptibility genes in essential tremor

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Objective: To investigate the possible association between gamma-aminobutyric acid (GABA) type A receptors (GABA(A)R) and GABA transporter genes with the risk for developing ET in humans.

Background: GABA(A)R are a family of ligand-targed ion channels responsible for mediating the effects of GABA, the major inhibitory neurotransmitter in the brain. It is known that GABA(A)R plays an important role in some neurological disorders. Different clinical aspects of essential tremor (ET) such as the positive effect of alcohol ingestion and cerebellar signs indicate the GABA(A)R, as putative candidate genes. In addition GABA(A)R α1 subunit knockout mice (Gabra1-/-) were reported to exhibit postural, kinetic, alcohol-responsive tremor that is similar to ET in humans.

Methods: Genotyping of 14 GABA(A)R and 4 GABA transporter genes with 219 haplotype tagging SNPs (htSNPs) in 184 ET patients and 426 controls of German origin was performed. The htSNPs most strongly associated with ET were analysed in a further 319 cases and 392 controls in independent sample series of German and Danish origin. All cases are unrelated and underwent examination by medical specialist of neurology. The unrelated controls were screened negative for ET and were specifically matched to the cases by gender and geographic origin.

Results: Overall thirteen significant htSNPs were found in the evaluation phase. The four most strongly associated htSNPs with the highest power and one haplotype consisting of two htSNPs were replicated in the second independent sample. The four single SNPs and the one haplotype did not survive the Bonferroni corrected P-value of 0.00833.

Conclusions: In our samples, no evidence of association between the investigated GABA(A)R and GABA transporter genes with ET susceptibility was detected.

Th-98

Predictive testing in Huntington's disease: The experience of a neurology clinic

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Objective: To find out whether screening in a Neurology consultation individuals at risk for Huntington's disease (HD) would increase adherence to the Predictive Diagnosis Protocol (PDP). Additionally, to assess factors influencing adherence to PDP.

Background: HD is a neurodegenerative autosomal dominant disorder. Because we felt that information on HD available to individuals at risk is often scattered and insufficient for them to adhere to the PDP, every subject is offered a non-commiting Neurology consultation in which they are given basic information about the nature of HD, their risk and the PDP. Subjects wishing to undergo PDP are referred to a Genetics Clinic.

Methods: Data collected from each individual evaluated at a Neurology Clinic, complemented by a structured interview.

Results: Sixty-six individuals from 21 families were identified as being at risk for HD. Seventy per cent (46 individuals) were evaluated and given information about the disease at a Neurology consultation. The mean age was 31,6 $\pm$ 10,1 years (range, 18-45). Thirty-one were females and 15 were males. Half of them had at least high-school education. Ninety-seven per cent of the individuals attended the first Genetics visit. Eleven females and 7 males completed the protocol. There was a negative relationship between completing the protocol and the level of education ($\chi^2 = 7{,}281$, $p < 0{,}001$). The reasons given for undergoing PDP were: planning a family, preparing for the future and helping other family members. The reasons for not taking the test were: inexistent treatment, coping well with the risk and fear of a positive test result. All subjects interviewed stated that the Neurology consultation helped their decision making.

Conclusions: Although the percentage of protocol completion is similar to that of other centers, a higher percentage of at risk individuals attended a first Genetics visit. We believe that Neurologists may play a role in improving adherence to PDP. The high number of possible carriers of the HD mutation that didn't complete the PDP is largely related to the lack of effective treatment of HD.

Th-99

Genome-wide association study for sporadic Parkinson's disease

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Objective: To identify susceptibility genes for sporadic Parkinson's disease (PD).

Background: PD, one of the most common neurodegenerativedisease, is caused by multiple genetic and enviromental factors. By candidate gene approach, we have established α-*synuclein* as the first definite susceptibility gene for sporadic PD ($P=1.7x10^{-11}$). Further, we have found that *calbindin 1 (CALB1)* is associated with PD independently of *SNCA* ($P=7.1x10^{-5}$).

Methods: We here performed a Genome-Wide Association Study (GWAS) of PD, using Illumina HumanHap550 Array. Subjects were 1,012 PD patients and 2,573 RIKEN controls of Japanese ancestry. After SNP QC filter (a SNP call rate>0.95, a MAF>0.05, and HWE with a P>0.001), high quality genotypes of 438,886 common SNPs were obtained. We excluded the samples with the cryptic duplicate and relatedness (MZ twin and 1-2 degree) through computing Identity-By-State probabilities, and the individuals who seemed to have non-Japanese ancestry were also excluded using multidimensional scaling.

Results: After these exclusions, 988 cases and 2,521 controls remained for the analysis. Genomic inflation factor λ was 1.05, indicating that the effect of population stratification is very small. We assessed each SNP for association with PD using a Cochran-Armitage trend test. A total of 127 SNPs were significant at the $P<10^{-4}$. The most significant SNP ($P=6.2x10^{-13}$) and its neighbors were located in the 7 kb downstream–intron 4 of α-synuclein. The *MAPT* locus was not identified significant in our study, because, unlike Caucasian, risk SNPs in the *MAPT* locus were monomorphic in the Japanese population, suggesting genetic heterogeneity of PD among races. Replication analysis of GWAS top-hit 384 SNPs with another 894 cases and 3893 controls (total 8296 samples) identified α-synuclein ($P=3.5x10^{-16}$) and other several significantly associated loci.

Conclusions: Our finding will play an important role for clarification of the etiology of PD.

Th-100

LRRK2 P755L variant in Parkinson's disease

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Objective: To further evaluate the role of *LRRK2* P755L variant in sporadic PD.

Background: PD is a neurodegenerative disorder of unknown etiology with probable involvement of genetic-environmental factors. The majority of PD cases (approximately 90-95%) are sporadic, while familial cases account for approximately 5-10% of PD. In a recent report, a heterozygous *LRRK2* P755L mutation within *LRRK2* exon 19 was found in 2% of Chinese sporadic PD patients and in 0% of normal controls, suggesting that the mutation is disease-associated.

Methods: We performed direct sequencing of *LRRK2* exon 19 in 501 Japanese sporadic PD patients (male 249, female 252, aged 28-92 years, mean 65.0 years) and 583 controls of Japanese general population as extended association study.

Results: In this group, we found 6 patients (6/501=1.2%) and 8 controls of general population (8/583=1.6%) with a heterozygous P755L variant ($P=0.80$, $\chi^2=0.064$). No other variants were found in exon 19.

Conclusions: Together with previous reports, our extended case-controlled study of large sample size suggests that *LRRK2* P755L is a non-disease-associated polymorphism in PD patients. So far, *LRRK2* P755L as well as G2385R variants, have been found in only Chinese, Taiwanese, and Japanese (Asians) with similar frequencies in some Asians but have not been found in Caucasians. Thus, these variants could occur independently in very ancient Asians with ethnic specificity based on a single founder effect.

Th-101

French experience for liver transplantation in Wilson's disease with severe neurological impairment

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Objective: The aim of this study was to evaluate the effect of liver transplatation (LT) in Wilson's disease with severe neurological symptoms.

Background: Wilson's disease (WD) is an autosomal recessive inherited disorder with copper overload mainly in the brain and in the liver. LT improves survival in hepatic form of the disease. This therapeutic approach is used in case of acute liver failure or end stage liver cirrhosis. LT in neurological form is more controversial.

Methods: This is a retrospective study. From November 2002 until November 2007, six patients underwent LT for severe neurological complications without acute hepatic failure or end stage cirrhosis and with no neurological improvement despite medical therapy (copper chelators and zinc salts).

Results: Three patients presented a dramatic neurological improvement after LT, with an important benefit on their quality of life. For these 3 patients, the mean age was 21 years, the mean time of follow-up was 42 months. Liver function before transplantation was Child A. Neurological symptoms were heterogeneous with dystonia, ataxia and chorea. Three patients, with a mean age of 26 years, died of infectious complications after LT. Neurological symptoms were more homogenous in this group with parkinsonian syndrome. No correlations between genetics status and prognostic were found. Our series underlines the emergency to determine the right time of the transplantation. Not too early because medical therapy efficacy can be delayed. Not too late because the risk of infections increase after LT in bedridden patients.

Conclusions: WD may be a good indication for LT for patients with progressive deterioration of neurological symtoms despite medical therapy but predictive factors are necessary to determine the right time and if neurological expressions influence the degree of improvement.

Th-102

The MAPT gene haplotype H1 and susceptibility to Parkinson's disease: The Norwegian ParkWest study

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Objective: To investigate possible associations between the MAPT gene haplotypes H1 and H2, and PD, age at onset in PD, and mild cognitive decline at the time point of diagnosis in the ParkWest cohort, representing an unselected cohort of patients with incident PD.

Background: Microtubule-associated protein tau (MAPT) has been associated with several neurodegenerative disorders including forms of parkinsonism and Parkinson's disease (PD). Interestingly the MAPT gene seems to be involved in protein aggregation and Lewy-body formation – the pathological hallmark of PD. The genetic region of MAPT contains two major-haplotypes blocks, H1 and H2, which differ in transcriptional activity. Although a recent genome-wide association study could demonstrate a possible association of the H1 hapltoype there exist conflicting reports. No data of MAPT associations exist in an unselected cohort of patients with incident PD.

Methods: Two-hundred and three patients with incident PD and 212 healthy controls from Western and Southern Norway were screened for the H1/H2 haplotype of the MAPT gene. All participants were Caucasians and donated pheripheral blood for genetic analysis. A genotyping assay was designed for the LightCycler 480 Instrument with melting curves as the detection format. Genomic DNA was extracted and typed for SNP rs9468, which differentiates between MAPT haplotype H1 and H2. The different haplotypes (H1/H1, H1/H2 and H2/H2) were verified by direct sequencing.

Results: Associations between the MAPT haplotype H1 and H2, PD, age at onset of PD and mild cognitive decline at the time of diagnosis will be presented. The work is still ongoing.

Th-103

Failure to find mutations in GIGYF2 gene in Chinese patients with Parkinson's disease

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Objective: To determine whether mutations of *GIGYF2* gene are responsible for Chinese patients with Parkinson's disease.

Background: *GIGYF2* gene has been reported as a PARK11 gene with a causal role in familial PD. There are conflicting results in Italian, French, Portuguese and American population. There is no report whether mutations of *GIGYF2* gene are responsible for Chinese patients with Parkinson's disease.

Methods: To detect small sequence alterations in *GIGYF2* gene, we performed direct sequencing analysis of the entire coding region in 8 familial PD and 100 sporadic cases.

Results: A novel variant, A367V, was found in one patient who suffered from parkinsonism typical features at 57 years old. We have also found 15 polymorphisms, and 6 of them have not been reported previously. They are Ivs3-94A→T, Ivs3-90G→T, c.T297C, Ivs5+24T→A, Ivs7+64G→A, Ivs17+95T→A and Ivs19-27C→A.

Conclusions: *GIGYF2* gene is not strongly related to Chinese patients with Parkinson's disease.

Th-104

Expanding the clinical phenotype of Perry disease

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Objective: To report two siblings with autosomal dominant parkinsonism, hypoventilation, depression/apathy and weight loss (Perry disease).

Background: Perry disease is a rapidly progressive, fatal neurodegenerative disease caused by mutations in the *dynactin* gene (*DCTN1*). We present two new patients from the French Perry family, expanding the clinical phenotype of this condition.

Methods: The two siblings were followed longitudinally and underwent neurological, neuropsychiatric, radiological and genetic investigations.

Results: The age of onset was 44.5 years (43-46) and the disease duration three years (brother, deceased) and six years (sister, alive). The brother presented with abrupt-onset tongue tremor (rest and protrusion), behavioral changes (apathy, loss of drive, and outbursts of anger), depression/anxiety, mild akinetic-rigid parkinsonism with partial response to levodopa and weight loss. Neuropsychometric testing and brain MRI did not reveal any significant abnormalities. He died suddenly, presumably of hypoventilation. His sister presented with hyperactive/obsessive-type behavior, engaging in relentless sport, gardening and repetitive cleaning activities. She reported weight loss, a shift in personal interests and resting tremor of the left lower limb. Her mild parkinsonism responded partially to levodopa, which she began to overuse. Standard psychometric tests did not reveal significant abnormalities and brain MRI was normal. Both patients were shown to harbor the p.G71E mutation in *DCTN1*.

Conclusions: Our two patients with genetically-proven Perry disease exhibited prominent albeit very different behavioral changes (apathy/loss of drive vs. hyperactive obsessive-type behavior), associated with parkinsonism, weight loss and fatal hypoventilation (brother). Both patients harbored the same causal mutation, illustrating intra-familial variability of Perry disease.

Th-105

Clinical and genetic study of an autosomal dominant PD family from eastern Switzerland

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Objective: To provide updated clinical and genetic data on a family with Parkinson's disease (PD).

Background: The Otto-Branger kindred is the largest Swiss family with PD reported so far (described in 1956 and 1983). We were able to directly examine two new patients. Herein, we present updated clinical and genealogical data on the family along with genetic screening for known causes of dominant PD.

Methods: Available clinical and genealogical information was reviewed with one of the initial investigators (FGO). Two new patients were examined by a movement disorders neurologist (CW); information on other family members was obtained through interviews. Patients were screened for mutations in LRRK2, SNCA and SCA2.

Results: The current pedigree has 16 affected individuals spanning six generations, with a mean onset age of 51 years. The index patient (current age: 57 years; disease onset: 51 years) and his paternal uncle (current age: 77 years; disease onset: 61 years) were examined directly. Both patients presented with levodopa-responsive, slowly progressive asymmetric parkinsonism with rest tremor, bradykinesia and rigidity. Six years after disease onset the index patient had mild parkinsonism (UPDRS III: 8) under a monotherapy of pramipexole. Seventeen years after disease onset, his uncle had marked parkinsonism (UPDRS III: 20) with axial involvement, dyskinesia and motor fluctuations; he was treated with levodopa/carbidopa/entacapone and ropinirole. An aunt of the index patient reportedly had RLS treated with levodopa. Genetic screening in two patients did not identify a mutation in LRRK2, SNCA or SCA2.

Conclusions: Apart from an early age at onset, patients from this family presented with a phenotype similar to that of sporadic PD. We excluded known causes of dominantly-inherited PD; therefore a new genetic defect is likely to be implicated.

Th-106

Molecular-genetic research of Torsion dystonia, Huntington's disease and Parkinson's disease in Belarus

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Objective: We are engaged in investigation molecular-genetic basis of Torsion dystonia, Huntington's disease and Parkinson's disease in Belarusian population.

Background: Basic gene of the idiopathic torsion dystonia is DYT1. The most frequent cause of dystonia is deletion of the 3 nucleotides GAG in 946 location of the 5th exon of the DYT1 gene. The mutation causing the Huntington's disease has been identified as an unstable expansion of a trinucleotide (CAG) n at the IT 15 gene on chromosome 4.

Methods: We provide PCR amplification and automatic capillary electrophoresis for the identification of mutation and diagnostics of the disorders.

Results: Eighty- seven patients and their family members were screened and deletion was found in three patients from one family. Proband have the classical phenotype of DYT1-dystonia and other two relatives phenotypically healthy. We have analyzed the distribution of CAG repeats in 12 Belorussian individuals from unrelated families with clinical diagnosis Huntington's chorea. All of them had

one expanded CAG allele and one normal allele. In these HD patients, expanded alleles varied from 39 to 51 CAG units and normal alleles varied from 10 to 24 triplets.

Conclusions: It is the first case of ascertainment of dopa-unresponsible torsion dystonia diagnosis by DNA-analysis in the Republic of Belarus. Further application of molecular-genetic analysis will contribute to more accurate definition of symptomatic image of the disorder, and potential for early diagnosis will permit the timely preventive measures and treatment. Our results showed that molecular confirmation of the clinical diagnosis in HD should be sought in all suspected patients, making it possible for adequate genetic counseling. Our study is the first report of molecular diagnosis of Huntington's disease among Belorussian population. Below we will start investigation of molecular-genetic basis of **Parkinson's disease** among Belorussian peoples and will continue research of Torsion dystonia and Huntington's disease.

Th-409

Effect of Val158Met COMT polymorphism in age of onset of Parkinson's disease

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Objective: Assess the effect of functional polymorphism Val158-Met of COMT gene in age of onset of sporadic Parkinson's disease.

Background: The pathophysiology of sporadic Parkinson's disease remains unknown, but it seems to results from an interaction between environmental factors and genetics. Therefore, the study of genetic polymorphisms with biological plausibility is essential in understanding its determinants. COMT is an enzyme responsible for degrades dopamine and shows a functional polymorphism (Val158Met), that determines high and low activities.

Methods: Patients from Movement Disorders clinic of "Hospital de Clínicas de Porto Alegre" with sporadic Parkinson's disease and age of onset beyond 45 years old were recruited. Blood samples were collected for DNA extraction. COMT gene was amplified by polymerase chain reaction and the product digested by NlaIII endonuclease. Fragments were separated through electrophoresis in acrilamide.

Results: In 81 patients the mean age of onset of symptoms was earlier in the group with Val/Val genotype (mean 57.18+/-3.2), that determines the faster enzyme activity, compared with Val/Met and Met/Met group (mean 62.25+/-2.73), that determines enzyme lower activity ($p=0.026$). In analyses with the three genotypes, there is a tendency to an allelic additive effect on age of onset. Sex does not show any confounding effect.

Conclusions: Patients with polymorphisms that determine enzyme isoform of higher activity (Val/Val) have an earlier age of onset. By this way, COMT polymorphism could modify the natural history of Parkinson's disease.

GENE THERAPIES AND CELL-BASED THERAPIES

Mo-105

Transplantation of stem cells for Parkinson's disease: Repair, replace, or regenerate?

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Objective: To determine the viability and potential of neural induced human embryonic stem cells (nhESCs), mononuclear fraction of human umbilical cord blood (MNF) and neural induced CD133 (nCD133) stem cells to repair, replace, or regenerate the loss of DA in the striatum of PD-like rats.

Background: The use of human stem cell transplantation therapy for various CNS diseases over the last decade has provided encouraging results and significant progress has been made for finding cures. These cells may regenerate damaged tissues by stimulating endogenous factors to aid in the repair that would induce improved behavior, even without the full integration with host tissue. We are there aiming to inhibit the progression of PD and not only to treat the symptoms.

Methods: Rats ($n=28$) were lesioned twice in the right medial forebrain bundle with 6-hydroxydopamine (6-OHDA) or sham lesioned ($n=8$). Baseline rotational, swing and forelimb placement behavioral testing were performed 1-2 days before lesion surgery and 3 weeks after for inclusion criteria. Unilateral cell transplantations were performed into the striatum with nhESCs, MNF, or nCD133s. Animals were sacrificed and brains were processed for immunohistochemical dependent measures. In each group of rats, the brains, spleens, bone marrow and peripheral blood were taken for immunohistochemistry. Tissue sections were stained for tyrosine hydroxylase (TH), neuronal nuclei (NeuN), human nuclei (HuN), or double-labeled for NeuN and HuN for cell counts.

Results: Significant behavioral improvements were observed in the nhESC group for both swing and forelimb placement, but not rotational, tests. In both MNF and nCD133 groups, significant improvements were observed across all behavioral tests. Histologically, both groups of transplanted hUCB cells appeared to be more numerous and widely distributed than the nhESCs.

Conclusions: In this study comparing hESC's to hUCB cells, we have demonstrated a novel treatment modality for Parkinson's disease. The cell transplantation in this rat model showed marked behavioral improvements and graft survival in the striatum.

Mo-106

Imaging of AAV2-hAADC infusion in a phase I study of AAV2-hAADC gene therapy for Parkinson's disease

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Objective: To evaluate by postoperative MRI and PET the gene delivery method used for administration of aromatic L-amino acid decarboxylase (AADC) in an open-label study of patients with moderately severe Parkinson's disease (PD).

Background: Convection-enhanced delivery (CED) uses fluid pressure at the tip of the delivery cannula and bulk flow to propagate substances within the extracellular fluid spaces. Parameters required for optimal delivery of AAV vector, such as infusion volume (Vi), rate of infusion, optimal cannula type and placement, were previously defined in experiments in nonhuman primates. Here, we show that the volume of distribution (Vd) could be visualized after vector infusion on T2-weighted MRI scans and that the region of increased T2 signal correlated well with changes in PET.

Methods: Ten patients received bilateral CED administation of AAV-AADC vector into two sites in each post-commissural putamen. Each putamen was infused using a reflux-resistant cannula with 50ul/site at 1ul/minute in 2 sites. Each hemisphere was treated separately. MRI scans were obtained after AAV administration. PET with the radiotracer, [18F]-FMT, allowed in vivo visualization of AADC transgene expression at 1 and 6 months after the treatment.

Results: Post-operative MRI confirmed that the stereotactic methods used accurately targeted the putamen and revealed T2-weighted changes corresponding to the AAV2-hAADC infusion. Over 50% of post-commissural putamen appeared to be covered by the infusate with Vi/Vd ratio consistent with preclinical work. These changes were strongest in patients whose post-operative scan was performed less than 2 hours after vector infusion. Visible infusions showed no reflux up the cannula tract. Co-registration of post-operative MRI and PET scans showed increased PET signal near the sites of infusion. PET imaging demonstrated a good correlation with MRI-based evidence of infusion.

Conclusions: These findings suggest that the CED methods used for AAV2 administration resulted in predictable and widespread coverage of the AADC gene. Intra-operative visualization of CED of AAV2-AADC vector with an MRI tracer may allow for more accurate and adequate infusion of vector.

Tu-100

Lentivirally-mediated overexpression of GRK6 alleviates L-dopa-induced dyskinesia in experimental Parkinson's disease

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Objective: We aim at developing an Anti-Dyskinetic Therapy.

Background: Parkinson's disease is caused by the progressive degeneration of dopaminergic neurons in the substantia nigra and the consequent deficit of dopamine (DA) in the striatum. Dopamine replacement therapy with the DA precursor L-DOPA or DA receptor agonists is the mainstay of current treatment. In the long-term, it leads to sensitization of DA receptors and L-DOPA-induced dyskinesia (LID). G protein-coupled receptor kinases (GRKs) control the desensitization of DA receptors.

Methods: Here we demonstrate that abnormal involuntary movements and dyskinesia are attenuated by lentivirus-mediated overexpression of the GRK6 in the striatum in both rodent and primate models.

Results: Remarkably, GRK6 suppresses LID in dyskinetic monkeys without compromising the antiparkinsonian effects of L-DOPA and prolongs the beneficial effects of lower doses.

Conclusions: Amelioration of LID combined with an increase in the duration of the antiparkinsonian action of L-DOPA offers the hope of achieving the elusive goal of controlling both LID and motor fluctuations in Parkinson's disease.

Tu-101

Functional effects of AAV2-GDNF on the dopaminergic nigrostriatal pathway in parkinsonian rhesus monkeys

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Objective: To investigate the safety and regenerative potential of an adeno-associated virus (AAV2) encoding human glial cell line-derived neurotrophic factor (GDNF) in an MPTP primate model of Parkinson's disease (PD).

Background: A number of studies have demonstrated the effectiveness of GDNF for the support of neuronal function in animal models of PD. Both rodent and non-human primate studies with striatal, nigral, and ventricular GDNF administration have shown beneficial effects, although these methods are limited in terms of protein distribution and the ability to deliver the protein chronically, both of which have safety implications for clinical use. Initial clinical trials have demonstrated beneficial effects in some patients but also raised safety concerns that may be attributable to protein delivery and distribution. These concerns prompted the exploration of alternative delivery methods using a non-pathogenic Adeno-associated virus (AAV) vector.

Methods: Dopaminergic function was evaluated by positron emission tomography (PET) with 6-[18F]fluoro-L-m-tyrosine (FMT) and behavioral testing before and after AAV2-GDNF or PBS was infused bilaterally into the putamen of parkinsonian monkeys using convection-enhanced delivery (CED).

Results: FMT uptake was significantly increased bilaterally in the putamen of AAV2-GDNF but not PBS-treated animals six months after infusion, indicating increased dopaminergic activity in the nigrostriatal pathways. AAV2-GDNF-treated animals also showed behavioral improvement without adverse effects. Behavioral improvement was correlated with increases in FMT uptake.

Conclusions: These findings are consistent with our previous report in aged non-human primates that showed evidence of enhanced utilization of striatal dopamine and dopaminergic nigrostriatal innervation. The use of CED has previously been shown to result in robust gene expression throughout the putamen in both monkeys and humans. Behavioral improvement and evidence of functional recovery in the nigrostriatal pathway, together with other findings, support the safety of this approach for the delivery of GDNF over a six month period.

Tu-102

Refining pleiotrophin gene transfer for Parkinson's disease: Quantification of developmental striatal levels

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Objective: To determine peak developmental levels of pleiotrophin (PTN) for optimized gene transfer therapy in parkinsonian animal models.

Background: Neurotrophic factors are integrally involved in the development of the nigrostriatal system and therefore possess therapeutic potential for Parkinson's disease (PD). In previous studies we have demonstrated that striatal overexpression of PTN can protect the rat nigrostriatal system from 6-hydroxydopamine (6-OHDA). PTN appears to function in the nigrostriatal system in a manner similar to glial cell line-derived neurotrophic factor (GDNF) however overexpression of GDNF in the striatum can cause detrimental morphological and biochemical alterations. Supraphysiological levels of GDNF may contribute to detrimental side effects, therefore knowledge of physiological PTN levels will be beneficial for future PTN gene therapy.

Methods: Western blot analysis was used to examine PTN expression in the rat striatum at multiple pre- and post-natal time points (E15, E18, E20, P1, P2, P14, P17, and P35). Striatal tissue was collected from Sprague-Dawley rats from multiple litters and separated by gender when possible. PTN expression at peak developmental age was quantitated.

Results: No gender differences in PTN levels were observed at any age. Peak protein expression occurred during P1-P2 with mean peak PTN expression estimated by digital densitometry to be 1171.46 ng/mg protein (+/- 312.14).

Conclusions: Knowledge of peak PTN expression is essential for the development of optimal transduction parameters for use of PTN gene transfer as an effective therapeutic strategy for PD. Our retrospective comparisons of reported peak PTN levels to striatal PTN levels produced utilizing recombinant adeno-associated virus 2 serotype 1 (rAAV2/1) mediated gene transfer revealed that neuroprotection was observed when striatal PTN levels were approximately double that of peak developmental levels. It is possible that a critical threshold of PTN expression is required to provide neuroprotection from 6-OHDA.

We-104

Effects of allogeneic bone marrow stromal cells and reduced glutathione in the unilateral 6-OHDA rat model of Parkinson's disease

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Objective: To investigate the effect of both allogeneic Bone Marrow Stromal Cells (BMSCs)and reduced glutathione (GSH) in the rat 6-hydroxydopamine (6-OHDA) lesion model of PD.

Background: BMSCs are capable of differentiating into both neural and glial cells. They also are able to secrete brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF). The consistent findings of decreased levels of the major antioxidant reduced glutathione (GSH) in substantia nigra in Parkinson's disease (PD) patients have considerably strengthened the oxidative stress hypothesis of PD pathogenesis.

Methods: Thirty eight rats were unilaterally and fully lesioned with 6-OHDA and randomly divided into five treatment groups: BMSCs + GSH group(n=8); BMSCs group(n=8); GSH group(n=6); sham-treated group(n=8); non-treated group (n=8). The functional outcome measurement of apomorphine-induced rotation was performed as a functional meaure of the extent of nigrostriatal pathway lesion within 1 week before treatment (6 weeks after 6-OHDA lesion) as well as 2, 4, 6 and 8 weeks after treatment. Anatomical assessments of the striatum included immunohistochemical detection of BrdU-labeled BMSCs expressing the astrocytic marker glial fibriliary acidic protein (GFAP).

Results: A decreased apomorphine-induced rotation was noted in rats of BMSCs + GSH group after treatment at every time point after treatment. The decrease was more significant in BMSCs + GSH than in BMSCs only group. Some of the BrdU-labeled BMSCs were reactive for GFAP.

Conclusions: Our findings suggested that treatment combining both allogenic BMSCs and GSH may reduce significantly the apomorphine–induced rotation for a longer time in a rat 6-OHDA model of PD.

We-105

The primate study of parkin gene therapy

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Objective: To establish innovative gene therapy for Parkinson's disease (PD) using viral vector carrying parkin cDNA.

Background: Parkin is known to mitigate α-synuclein-induced neuronal cell death in vitro, suggests that the parkin gene therapy is a candidate for therapeutic strategies for PD. A recombinant adeno-associated viral (rAAV) vector system has been frequently used for gene transfer to rat substantia nigra (SN), and we have previously demonstrated that this technique induced the α-synucleinopathy which closely resembles pathogenetic changes in PD.

Methods: In the present study, the effect of parkin was examined by co-infection of rAAV-parkin with rAAV-α-synuclein into dopaminergic neurons in SN of the two primates using Navigation system. We performed the behavior analysis by the videotape and the pathological examination.

Results: At 10 weeks post-rAAV infection, α-synuclein overexpression induced dopaminergic neuron loss while co-expression of parkin mitigated the α-synuclein toxicity. Moreover, α-synuclein-induced dopaminergic neuron loss consequently resulted in motor dysfunction, which was also mitigated by parkin.

Conclusions: Taken together, our results indicate that parkin gene therapy is effective against α-synuclein, suggesting its potential suitability for patients with PD.

Th-107

Expression of MHC class I antigens on the TH cells, which were derived from mouse ES cells, transplanted into syngeneic or allogeneic mouse PD models without immunosuppressive agents

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Objective: We examined graft survival and the functional recovery after transplantation of embryonic stem (ES) cell-derived tyrosine hydroxylases (TH) cells into the syngeneic or allogeneic mouse Parkinson's disease (PD) models without immunosuppressive agents. In addition, we examined whether or not major histocompatibility complex (MHC) class I antigens are expressed on the transplanted ES cell-derived TH cells *in vivo*.

Background: Recently it was reported that various PD models was recovered after the transplantation of ES cell-derived TH cells into their striatum.

Methods: TH-positive cells were derived from mouse ES cells, D3 line (H-2^b) labeled by *eGFP* gene, by five-step method. The syngeneic C57BL/6 (H-2^b) and allogeneic C3H/He (H-2^k) mice were used between 8 and 10 weeks old. 2 μg/ml of 6-hydroxydopamine was injected into the right substantia nigra of these mice. Two weeks later, methamphetamine-induced rotational behavior test was evaluated for 10 min. Mice with more than 50 ipsilateral turns were used in the subsequent experiments as PD mouse models.

Results: ES cell-derived neurons and astroglial cells, which did not possess MHC class I antigens, increased in number and eventually amounted to >65% and <15% of the total cells, respectively. Their cells were transplanted into the right striatum of these syngeneic and allogeneic PD models without immunosuppressive agents. Every week after transplantation, their motor abilities were evaluated by methamphetamine-induced rotational test. Four to five weeks after transplantation of these TH cells, their syngeneic and allogeneic PD models were normally recovered. Fourteen weeks after transplantation, glial fibrillary acidic protein and TH-positive donor cells were detected in both PD models. MHC class I antigens were expressed on three days after their transplantation, and then were faded away in 4 weeks. Eight to fourteen weeks after their transplantation, these donor cells were not detected MHC antigens in their syngeneic models, but were reproduced MHC antigens in their allogeneic models. Finally, two teratomas yielded in the syngeneic PD models, and one arose in the allogeneic models. These tumors expressed MHC antigens.

Conclusions: Immunological response in the brain is under investigation.

Th-108

Human bone marrow-derived mesenchymal stem cells protect monoaminergic neurones in vitro from oxidative stress via the secretion of glial cell line derived neurotrophic factor (GDNF)

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Objective: To employ cell culture techniques to assess *in vitro* the ability of bone marrow stems cells, via GDNF release, to afford neuroprotection to catecholaminergic and serotonergic neurones.

Background: Previously, the potential of stem cells to replace lost cells via trans-differentiation into neurons and glia has garnered particular interest. We believe, however, that other mechanisms, particularly the ability of MSCs to release neurotrophic factors, including glial cell line derived neurotrophic factor (GDNF), may be relevant in PD. Importantly, such protective mechanisms are likely to be applicable to all monoaminergic fibre types (dopaminergic, noradrenergic and serotonergic) as well as general neuronal survival and hence not simply afford protection to the dopamine system alone.

Methods: Following whole brain stem dissection we established rat E18 cell cultures in serum-free culture media. Employing immunohistochemistry we labelled these cultures using antibodies to either tyrosine hydroxylase (dopaminergic and noradrenergic neurones) or tryptophan hydroxylase (serotonergic neurones) at 5 days (with >95% of cells positive for ß-tubulin). Using a cell count approach post immunolabeling we investigated the potential neuroprotective effect that human MSCs confer upon catecholaminergic and serotonergic neurones following exposure to oxidative and inflammatory stress in the form of nitric oxide. We also assessed if such a protective effect was lost if the GDNF produced by MSCs was blocked.

Results: Our results show dramatic catecholaminergic and serotonergic cell loss (>95%) following nitric oxide exposure which is significantly mitigated (55%; $P<0.05$) by the presence of soluble factors produced by MSCs, requiring no cell-cell contact. Furthermore, this protective effect is abolished ($P<0.05$) if the GDNF released by MSCs is blocked.

Conclusions: We have shown that the media produced by bone marrow stem cells confers protection on cultured dopaminergic, noradrenergic and serotonergic neurones when exposed to oxidative and inflammatory stress and that, in part, this is due to bone marrow stem cell GDNF release.

Th-109

Activation of glial cell line-derived neurotrophic factor by an engineered ZFP transcription factor provides functional neuroprotection in a rat model of Parkinson's disease

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Objective: To explore a novel neurotrophic factor-based therapy for Parkinson's disease (PD) employing engineered zinc-finger protein transcription factors (ZFP TFs) designed to activate the endogenous glial cell line-derived neurotrophic factor (GDNF) gene.

Background: GDNF is a potent trophic factor for the dopaminergic neurons of the substantia nigra, whose loss is responsible for PD. Increasing GDNF levels is therefore an attractive strategy for the treatment of PD but methods that permit the appropriate magnitude and duration of GDNF expression remain elusive. Engineered transcription factors offer a potential solution to this problem. ZFP TFs can be designed to induce expression of virtually any gene, plus by acting on the natural promoter of the GDNF gene, which is present at just two copies per cell, ZFPs provoke a more physiological increase in GDNF levels. However, the efficacy of ZFP TFs in the brain has yet to be demonstrated.

Methods: A panel of GDNF-targeted ZFP TF activators was designed, assembled, and tested for GDNF up-regulation at the mRNA and protein (ELISA) levels. Adeno-Associated Virus (AAV) expressing the GDNF-activating ZFP (AAV-GDNF.ZFP) was infused using convection enhanced delivery into the striatum of rats lesioned with 6-hydroxydopamine (6-OHDA) and efficacy determined by behavioral testing.

Results: An engineered ZFP TF that significantly activates GDNF expression (>20 fold) in vitro was identified. Intrastriatal delivery of AAV-GDNF.ZFP into 6-OHDA-lesioned rats drove a modest but statistically significant increase in GDNF levels and led to significant functional improvements in forelimb akinesia, sensorimotor neglect and amphetamine-induced rotations.

Conclusions: ZFP-driven activation of GDNF confers functional neuroprotection in the rat 6-OHDA model. Moreover, efficacy was observed with the physiological increase of GDNF expression obtained with the ZFP TF. These data establish the utility of ZFP TF gene regulation in the brain and support the further development of the GDNF ZFP TF activator as a potential treatment for PD patients.

HISTORY

Mo-107

Parkinson's disease was known much before James Parkinson – A review of history of Parkinson's disease

A.Q. Rana (Toronto, Canada)

Objective: To review the history of Parkinson's disease in the ancient times before James Parkinson described it.

Background: The features of many neurological conditions known today were noted by ancient practitioners and make the foundation of today's modern concepts. This shows the close observation of patients by these ancient practitioners. Although full composite of the clinical features of Parkinson's disease was given by James Parkinson in 1817 in his esssay on Shaking Palsy but the features of Parkinson's disease have been described in ancient literature much before James Parkinson's time. The ancient practitioners also used tropical beans Mucuna pruriens for treatment whcih was found to be the source of dopmaine precurssor.

Methods: We reviewed web based information, chapters of many text books, and other publications on the subject of history of Parkinson's disease.

Results: Although major features of Parkinson's disease were described by James Parkinson in 1817 in his essay Shaking Palsy but partial reports of symptoms of Parkinson's disease are found since 5000 B.C. The medical doctrine of the ancient Indian civilisation "Ayurveda" described the symptoms of Parkinson's disease under the composite called Kampavata and reports use of a tropical legume Mucuna Pruriens, called Atmagupta to treat these symptoms. The seeds of Mucuna Pruriens are a natural source of L-dopa which is precursor of dopamine. Other practitioners such as Erasistratus of Ceos (310BC- 250BC), Aulus Cornelius Celsus (c25BC-c50AD), Pedanius Dioscorides (c40-c90), Yahya Ibn Sarafyun in the second half of the 9th century, Ibn Sina (c980-1037), John Gerard (1545-1612), Nicholas Culpeper (1616-1654), John Aubrey (1626-1697), George Cheyne (1671-1743), Francois Boissier de Sauvages de la Croix (1706-1767), Johannes Baptiste Sagar in1776, John Hunter (1728-1793), and Marshall Hall in 1841described the features of Parkinson's disease.

Conclusions: The features of Parkinson's disease have been known in human history for at lease 5000 B.C. much before James Parkinson described it.

Mo-410

Case of progressive supranuclear palsy with unusual clinical course

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Objective: To present an unusual clinical syndrome which possibly is a case of progressive supranuclear palsy (PSP).

Background: Clinical diagnostic criteria for PSP require as an obligatory signs development of postural instability and falls early in the course of the disease along with either vertical gaze paresis or slowing of vertical saccades. However, every now and then the clinical cases very similar to PSP but not matching clinical diagnostic criteria can be seen.

Methods: 63-years-old previously healthy woman 4 years ago developed dysarthria as a single symptom. Articulation problems were qualified as a scanned speech, though no other signs or symptoms of cerebellar dysfunction were found. She had no cognitive disturbances, no postural instability. Her eye movements were normal. Brain MRI was normal. Dysarthria had been progressing during 1st year of the disease, than have become stable. After 4 years since the first symptom she has dysarthria without any swallowing problems. There are restriction of upward gaze and slowness of vertical saccades, retraction of upper lids, deep forehead wrinkles that gave her face a "surprised" expression. She has slight symmetric limb bradikinesia, rigidity in axial muscles, brisk reflexes and extensor plantar responses. Still there are no falls, no cognitive decline or emotional lability. She has been moderately depressive and is receiving sertraline. Her gait is normal.

Results: As brain MRI, blood and urine investigation didn't reveal any cause of her disorder and there is no family history of neurological diseases, a most probable diagnosis we consider is progressive supranuclear palsy.

Conclusions: We haven't found in literature description of PSP patients with predominate articulation problems without any postural instability on advanced stages. The confirmation of diagnosis in our case needs of course the pathological assessment. Can it be a phenotype of PSP with mild tau-pathology (as it is in pure akinesia with gait freezing) that only represents an exception to the rule?

Tu-104

Who introduced surgery for movement disorders?

A.Q. Rana (Toronto, Canada)

Objective: To review the history of Surgical treatments of Movement Disorders.

Background: Surgical treatments of movement disorders in particular Parkinson's disease are increasingly being used. Carefully selected patients with PD benefit significantly from surgical treatments. In short surgical treatments have become an important adjunc-

tive treatment of PD. The surgical treatments are also being used for other movement disorders.

Methods: We reviewed the web based information and text book chapters to study this topic.

Results: Victor Horseley used cortical motor strip resection for treatment of athetosis and tremor. During 1930s and 1940s cerebral pedunculotomies and partial cordectomies were introduced to treat choreoathetosis and hemiballismus. Myer in 1940s did anterior caudate nucleus resections for postencephlitic tremors. During 1950s and 1960s ablations of ventrolateral thalamus at the nucleus ventralis intermedius (VIM) and ventralis oralis anterior and ventralis oralis posterior nuclei (VOA-VOP) were done to relieve tremor and rigidity of Parkinson's disease. Because of introduction of levodopa in 1967 surgical treatments of Parkinson's disease became less popular but in 1980s surgical therapies remerged after levodopa induced motor fluctuations and dyskinesias were increasingly recognized. Surgical treatments such as deep brain stimulation and thalamotomy are used for patients who have very advanced and refractory essential tremor. Surgical treatments have also shown successful results in other movement disorders.

Conclusions: The review of history of surgical treatments of Movement disorders leads to an optimism that these interventional treatments will keep on developing further to play an important role in improving the quality of life of patients.

Tu-105

Dystonia-psychogenic or organic, historical review

A.Q. Rana (Toronto, Canada)

Objective: To review the history of dystonia.

Background: Dystonia is the second most common symptom of movement disorders after tremor.

Methods: We reviewed the web based information and other resources to study this topic.

Results: Focal dystonias were initially termed as "cramps" or "occupational spasms". In 1836, German neurologist J.H. Kopp described the writer's cramp. In 1887, Wood described facial and oromandibular dystonia. In 1901, Destarac reported idiopathic torsion dystonia (ITD), which he initially thought was a psychogenic condition. Later he coined the term idiopathic torsion dystonia. He also noted that sensory tricks improved dystonia whereas the motor activity worsened it. Schwalbe in 1908 wrote an essay on dystonic spasms "Tonic Cramps with Hysterical Symptoms" He described hereditary pattern and progression of generalized torsion dystonia. The terminology used by Schwalbe in his essay created an uncertainty of dystonia as a neurological or psychogenic condition. In 1911, Ziehen described torsion neurosis and determined that it was not hysterical. He also observed that "convulsive movements increased during voluntary movement and emotional excitement". In 1911 Oppenheim thought that dystonia was associated with an abnormal tone of muscles. Oppenheim described dystonia musculorum deformans and also concluded that "dystonia" was an organic illness, and not psychogenic, as initially thought by Schwalbe. In 1911 Flatau and Sterling noted the repetitive pattern and jerkiness of the progressive torsion spasm. They objected the term deformans and also disapproved the term musculorum. In 1916, Hunt observed slow and twisting movements which he related to dystonia. In 1919 Mendel coined the term "Torison dystonia." He called it "a morbid disease entity." In 1923, Wimmer described dystonia as a syndrome after observing dystonia in Wilson's disease, perinatal and postencephalitic brain damage. In 1944 Herz presented a compilation of generalized dystonia which he called dystonia musculorum deformans. He described dystonic movements as slow, continual, and non- patterned deviations of the axial and appendicular muscles. Herz particularly focused on the spread of dystonic movements from one body part to another and also discussed the generalized involvement of dystonia in the human body.

Conclusions: It is interesting to note how the concept of dystonia changed from a psychogenic to organic condition.

Tu-410

History of levodopa use in Parkinson's disease

A.Q. Rana (Toronto, Canada)

Objective: To discuss how Levodopa was introduced for symptomatic treatment of Parkinson's disease.

Background: Levodopa is still gold standard treatment of Parkinson's disease. Although levodopa was introduced in 1967 for use in Parkinson's disease but review of literature shows that levodopa precursors have been used for treatment of Parkinson's disease since 5000 BC.

Methods: We reviewed the web based information and text book chapters to study the history of levodopa.

Results: Levodopa is found in leguminous plants, with a highest concentration in bean plant Mucuna Pruriens which was used in ayurvidic medicine since 5000 B.C. to treat parkinsonism. In 1957 Arvid Carlsson a Swedish scientist found that dopamine was a neurotransmitter in the brain and that dopamine levels in the basal ganglia were particularly high. He then showed that decrease in dopamine levels resulted in bradykinesia seen in PD. In 1959 at the international pharmacology meeting, he speculated that dopamine deficiency was responsible for causing PD and won Nobel Prize in 2000. In 1960 Oleg Hornykiewicz, in Vienna found dopamine deficiency in striatum of Parkinson's disease patient in post mortem analysis and observed the decreased dopamine excretion in the urine in PD. In 1966 he concluded that dopamine deficiency was the cause of most of the motor symptoms of Parkinson's disease Two separate centres from Vienna and Montreal, Canada independently reported beneficial effects of open label levadopa in PD in 1961. George Cotzias in 1966 started using very small doses of L-DOPA in PD patients. symptoms. Levodopa was developed by DuPont during 1970's.

Conclusions: This is an intereting review of history of levodpa. Although levodopa was introduced in 1967 for use in Parkinson's disease but historical review shows that levodopa precursors have been used to treat Parkinson's disease like symptoms since ancient times.

We-106

Contribution of James Parkinson to movement disorders

A.Q. Rana (Toronto, Canada)

Objective: To review contribution of James Parkinson to movement disorders.

Background: James Parkinson initially described the composite of features of Shaking palsy today called Parkinson's disease.

Methods: We reviewed the web based information and text book chapters to study the work of James Parkinson.

Results: James Parkinson (1755-1824) was a general practitioner in London, England who lived in Hoxton Square. In 1817, at age 62 he published "An Essay on Shaking Palsy" in which he described six individuals who he might have observed while walking in streets of London. He described them as having "*Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported, with a propensity to bend the trunk forwards, and to pass from a walking to a running pace, the senses and intellect being uninjured.*" He mentioned that the disease was of prolonged duration and trauma to the cervical spine and toxins, as a result of environmental pollution in London due to the industrial revolution, may have a causative role in the development of this conditions. James Parkinson attended lectures of John Hunter and took shorthand notes which were transcribed by James Parkinson's son John Parkinson after his father's death in a book "Hunterian Reminiscences" published in 1833. These observations of John Hunter may have given James Parkinson an idea of features of what he

called Shaking Palsy. John Hunter (1728-1793), a prominent Scottish surgeon from Leister square Lyceum and London Hospital in 1776 gave a description of Lord L, and said, *"Lord L's hands are perpetually in motion, he never feels the sensation of them being tired. When he is asleep his hands are perfectly at rest but when he wakes in a little time they begin to move"*. These features are characteristic of resting tremor of Parkinson's disease.

Conclusions: James Parkinson's description of Shaking Palsy makes foundation of current concepts of Parkinson's disease.

We-107

What ancient practitioners said about tremor?

A.Q. Rana (Toronto, Canada)

Objective: To review the history of tremor.

Background: Tremor is the most common symptom of movement disorders.

Methods: We reviewed the web based information and other resources from libraries to review this topic.

Results: A Sanskrit book in the University of Benares, India, 2500 B.C. "Charakasamhita" compiled by Agnivesha in chapter 20 entitled Vepathu contains comprehensive description of tremors. Old Testament: *"When the guardians of the house tremble, and the strong men are bent"* Aulus Cornelius Celsus (c25BC-c50AD), a Roman scholar, compiled an encyclopedia entitled De artibus that included De medicina octo libri (The Eight Books of Medicine) in which he distinguished the fine tremor from a coarse tremor. Greek physician Claudius Galen (130-201 AD) wrote a book on tremor and described the tremor of the hand at rest. He distinguished between the different types of tremor and called tremor "*an involuntary alternating up and down motion"* Ibn Sina (980-1037), author of Kitab-al-shifa(the book of healing) described tremor as "*motor unrest"* Leonardo da Vinci (1452-1519) an Italian scientist described tremor of hand and head as "*how nerves sometimes operate by themselves without any command from soul"* William Shakespeare (1564-1616) referred to tremor in Henry VI, as "*Why dost thou quiver, man*?" "*The palsy, and not fear, provokes me."* John Hunter (1728-1793), a prominent Scottish surgeon in 1776 described tremor at rest as *"Lord L's hands are perpetually in motion, he never feels the sensation of them being tired. When he is asleep his hands are perfectly at rest but when he wakes in a little time they begin to move"*. James Parkinson (1755---1824) 1817, in essay on "Shaking Palsy" described resting tremor as "*Involuntary tremulous motion"* In 1836 Most described several cases of tremor in a single family. In 1887 Danna reported three families with 45 patients with tremor within a single pedigree. In 1889 Charcot described head tremor in two elderly patients. In 1909 Raymond related the essential tremor to neuropathic shock. In 1948 Katzenstein and in the 1920s a Russian neurologist Minor linked essential tremor with longivity. In 1949 Critchley also thought that essential tremor was linked to high intelligence and accomplishment.

Conclusions: There has been interesting associations reported with tremor in history.

We-108

When, where and who described different movement disorders?

A.Q. Rana (Toronto, Canada)

Objective: To review the history of different movement disorders.

Background: Although most of the movement disorders were described by the individuals after which they are named, but some features of the movement disorders have been known in human history for centuries due to their uniqueness of attracting visual attention.

Methods: We used web based information and text book chapters to study the history of different movement disorders.

Results: ***Restless leg syndrome*** features were initially described by Thomas Willis (1622–1675) and by Theodor Wittmack. Other description were done by George Miller Beard (1839-1883). In 1945 a publication 'Restless Legs', by a Swedish neurologist Karl-Axel Ekbom (1907-1977) described eight cases of this disease.***Sydenham's Chorea*** was described by Thomas Sydenham in 1686. James Parkinson in London, England in 1817 described features of Shaking Palsy today called ***Parkinson's disease***. A German neurologist JH Kopp in 1836 described ***Writer's Cramp.*** George Huntington in United States in 1872 described chorea, one of the major features of ***Huntington's disease***. George Gilles de la Tourette in 1885 described features of tic disorder called ***Gilles de la Tourette's*** syndrome. Wood in 1887 described ***facial and oromandibular dystonia.*** Oppenheim in 1911 described ***dystonia musculorum deformans***. Kinnier Wilson in England described the features of ***Wilson's Diseas*** in 1912. Features of ***Hellervorden-Spatz disease*** were described by Hellervorden and Spatz in 1922. Steele Richardson and Olszewski in 1964 described the clinical features of a condition called Steele Richardson Olszewski syndrome which is also known as ***progressive supranuclear palsy***. ***Corticobasal degeneration*** was first described by Rebeiz in 1968.

Conclusions: This is an interesting review of history of Movement disorders.

We-404

Charcot's contribution to the study of Tourette's syndrome

H.A.G. Teive, C.H. Fein, R.P. Munhoz, E.R. Barbosa (Curitiba, Parana, Brazil)

Objective: The aim of this paper is to analyze some historical aspects of TS, particularly Charcot's contribution to defining the syndrome.

Background: Tourette's Syndrome (TS) is a chronic neuropsychiatric disorder characterized by multiple motor tics associated with the presence of one or more vocal tics, which alternately increase and decrease in severity.

Methods: The 19th century French neurologist Gilles de la Tourette, one of the disciples of professor Jean-Martin Charcot (considered the father of French neurology and one of the world's pioneers of neurology), is considered to have made a major contribution to the understanding of TS by characterizing the disease and distinguishing it from other neurological disorders.

Results: In his traditional "Leçons du mardi à la Salpêtrière" in 1887 and 1888, Charcot described nine general neurology cases, which were translated and published in 1987 by Goetz. Among the various cases described by Charcot, one stands out, namely, that of a 12- to 13-year-old child suffering from a disease defined as convulsive tics associated with coprolalia, which was subsequently renamed as Gilles de la Tourette syndrome. Charcot also defined tics clearly, separating them from choreas (which he divided into true choreas, such as Sydenham's chorea, and the others, most of which were considered to be of an hysterical nature. Charcot characterized TS as being associated with the presence of obsessive-compulsive disorder (which he defined as "des idées fixes") and gave the example of a patient whom he had examined: "not being able to open the door without first turning the door knob three or four times, or saying out loud .. one, two, three, four...."). Another characteristic of TS defined by Charcot was the presence of imitative behavior in patients (called echokinesis and today referred to as echopraxia) as well as echolalia and coprolalia. Charcot also suggested that TS had a hereditary factor and defined the course of the disease as one of waxing and waning symptoms. He also differentiated the disease from other diseases known as Jumping, Latah and Myriachit, which had been incorrectly classified by Gilles de la Tourette as clinically identical to TS.

Conclusions: In conclusion, we can say that TS is one of the countless neurological diseases to whose nosological definition Charcot's genius contributed significantly.

Th-110

Belladonna plant and Parkinson's – A review of history of non-dopaminergic treatments of Parkinson's disease
A.Q. Rana (Toronto, Canada)

Objective: To review the historical developments of the non dopaminergic treatments of Parkinson's disease.

Background: Anticholinergics, amantadine, and MAOB inhinbitors are currently available non dopaminergic treatements of PD. Indeed the precursors of some of these agents have been used for the treatment of PD since decades or centuries before these agents were obtained in the purified form.

Methods: We reviewed the web based information and text book chapters to study the historical developments of non-dopaminergic treatments of PD.

Results: In 1860s Ordenstein and Charcot in Paris used extracts of Belladonna and Datura Stramoniun containing anticholinergic compounds hyoscine and scopolamine to treat PD. The Belladonna alkaloid containing atropine was noticed to improve tremor and other symptoms of PD. Gowers in 1888 noticed beneficial effect of Indian hemp, containing cannabis sativa, hyoscyamine and scopolamine in reducing the tremor and rigidity. Therefore Belladonna alkaloid used to be the main treatment of PD before synthetic anticholinergics were introduced in the 1960s. Amantadine was initially introduced in 1960 as an antiviral agent against influenza virus but was noted to improve symptoms of PD. Its use in PD at large scale started in 1969.

Conclusions: The history of development of non-dopaminergic treatments of PD is interesting. The precusors of current agents used to treat Parkinson's disease have been used in history for long time.

Th-111

A film of patients with movement disorders made in Queen Square in the mid-1920's by Samuel Alexander Kinnear Wilson
E.H. Reynolds, D. Healy, A.J. Lee (London, United Kingdom)

Objective: To show the early use of cinematographic methods at the National Hospital for Neurology and Neurosurgery, Queen Square, London UK by SAK Wilson the 'Marco Polo' of the Extrapyramidal System.

Background: Through EHR's collaboration with SAKW's son, James, on Babylonian epilepsy and stroke and his contact with James' nephew, Jim, grandson of SAKW, a remarkable film of patients with movement disorders, made by SAKW in the mid-1920's, has come to light. The 20 minute silent film with captions by SAKW includes patients with senile tremor, Parkinson's disease and post-encephalitic parkinsonism, hemiballismus, Huntington's chorea, Sydenham's chorea, hysterical palsy and tremor, multiple sclerosis and Wilson's disease. Most of the patients are filmed in the Square outside the National Hospital.

Methods: A film will accompany the poster.

Results: The British Film Institute dates the film to either 1924 or 1925. SAKW may have been stimulated and facilitated to make this film through his personal contact with Charlie Chaplin with whom he stayed at his Californian estate, probably in the summer of 1924. The first films of neurological patients were made in Europe and the USA at the beginning of the 20th century, but this may be one of the oldest examples from the UK and is also notable for the inclusion of Wilson's disease and a brief shot of SAKW himself.

Conclusions: The film represents the earliest known cinematographic record of patients seen at the National Hospital for Neurology and Neurosurgery, Queen Square London.

HUNTINGTON'S DISEASE

Mo-109

Predictors of functional capacity, quality of life and caregivers' burden in Huntington's disease
K. Banaszkiewicz, M. Rudzinska, A. Szczudlik (Cracow, Poland)

Objective: The aim of this study was to evaluate which symptom is the most influential on functional capacity, quality of life (QoL) and caregivers' burden.

Background: Huntington's disease (HD) is a genetically determined neurodegenerative disorder with variable clinical presentation including cognitive impairment, involuntary movements and neuropsychiatric symptoms.

Methods: 43 HD patients with borderline to moderately advanced disease were included. Motor disturbances, cognitive impairment and depression were assessed using respectively: Motor Examination of the Unified Huntington Disease Rating Scale (UHDRS), UHDRS Cognitive Score, Hamilton and Beck scales. The prevalence and magnitude of each behavioral symptom was evaluated using UHDRS Behavioral Assessment. To assess disability, QoL and caregivers' burden the following scales were used respectively: UHDRS Functional Assessment Score and Independence Scale, SF-36, Caregiver Questionnaire. The severity of the disease was assessed using Global Clinical Impression scale (GCI).

Results: Univariate regression analysis showed that motor disturbances, cognitive impairment, depression, apathy and anxiety were significant predictors of functional capacity with the highest coefficient of determination (R-square) for motor disturbances (67%), cognitive impairment (56%), apathy (24%) and depression (23%). The regression analysis showed also that the most influential predictors of QoL were depression (55%), apathy (32%), cognitive impairment (19%) and motor disturbances (17%), while the results of the Independence Scale and GCI were the most influential on caregivers' burden with R-square 42% and 39% respectively.

Conclusions: The predictors of functional capacity, QoL and caregivers' burden in HD are different what should be taken into consideration while planning treatment strategy.

Mo-110

Longitudinal study of cognitive and affective functioning in Huntington's disease
B.A. Bernard, G.T. Stebbins, K.M. Shannon (Chicago, Illinois)

Objective: To assess cognitive and affective functioning annually in a series of Huntington's disease (HD) outpatients over a three year period.

Background: Although the movement disorder is the hallmark of HD, cognitive impairment can be the most disabling aspect of the disease process. However, there are few longitudinal studies of cognitive and affective functioning in HD. A broader understanding of the pattern of cognitive and affective changes in HD will aid in the evaluation of therapeutic efficiency of new treatments.

Methods: As part of regular outpatient care, HD patients in our movement disorder clinic are annually recommended to have cognitive and affective screening tests. These tests include the Mini-Mental State Exam, Word List Memory, WAIS-III Digit Span, Symbol Digit Modalities Test (SDMT), Controlled Oral Word Association (COWA), and Stroop Interference Test. Depressive symptomatology is assessed with the Hamilton Depression Rating Scale. To assess annual progression, an individual slope was estimated for each cognitive measure by using a mixed model general linear model.

Results: 50 patients with HD were seen for at least three visits over a three year period. Mean MMSE score at baseline was 25.4. There were significant declines in MMSE ($p = .001$), WAIS-III Digit Span scaled score ($p = .002$), SDMT ($p = .001$), COWA ($p = .002$), and Stroop ($p < .0005$). Word List Memory did not signifi-

cantly change. Hamilton depression scores increased over time ($p < .005$).

Conclusions: Over a three year follow-up period, HD patients evidenced overall cognitive decline as well as progressive impairment in attention and executive functioning, while recent memory remained relatively stable. Depressive symptoms increased over time. New treatments being considered for HD will need to address motor, cognitive, as well as affective functioning in these patients.

Mo-111

Dopamine D2 receptors vulnerability in Huntington's disease: A role of the Rho/ROCK signaling pathway

S. Betuing, C. Deyts, E. Martin, N. Bouveyron, B. Galan-Rodriguez, D. Charvin, E. Roze, J. Caboche (Paris, France)

Objective: Despite ubiquitous expression of huntingtin throughout the brain and other tissues, GABAergic neurons expressing dopamine (DA) receptors in the striatum predominantly degenerate in Huntington's disease (HD). We previously showed that DA participates to this striatal vulnerability via D2 receptor stimulation. Our objective was to analyze the cellular effect of D2 receptor stimulation on HD vulnerability.

Background: HD is caused by abnormal expansion of a CAG tract in exon 1 of the IT15 gene (expHtt). Factors in addition to the mutation in the IT15 gene enhance the vulnerability of the striatal neurons. In early grade HD patients, dystrophic neurites with anormal recurving have been reported. We previously showed that D2 receptor stimulation potentiates expHtt-induced aggregate formation and striatal death in vitro and in vivo. In the present study we asked whether D2 receptor stimulation could disturb dentritic arbors in striatal neurons and investigated the role of the Rho/ROCK signalling pathway a well described pathway in cytoskeleton regulation, in D2-mediated vulnerability in HD.

Methods: Primary striatal neurons transfected with 25CAG exon1 Htt (Htt) or 103CAG exon1 Htt (expHtt) were stimulated with Quinpirole (a specific D2 agonist) after inhibition of ROCK pathway (specific pharmacological inhibitors or siRNA). Growth cone collpase, neuritic retraction, aggregates formation and neuronal cell death were analyzed by comparing D2-treated and non treated neurons.

Results: We show a direct coupling of D2 receptor to the Rho/ROCK/coffilin pathway. Cofilin is a downstream target of ROCK involved in actin polymerisation. D2 agonist potentiates expHtt-mediated neuritic retraction and growth cone collapse. This potentiating effect of D2 agonist treatment on exp-Htt-mediated toxicity (growth cone collapse, neuritic retraction, aggregate formation and neuronal death) was blocked by specific inhibitors of ROCKs or siRNAs that knock-down ROCK2 proteins. Similar results were obtained using the same cellular model with a specific knock-down of D2-receptor.

Conclusions: We conclude that D2 receptor toxicity in HD involves the Rho/ROCK pathway; a possible interesting new target to focus on for therapeutical strategy.

Mo-112

A phase 2 trial of minocycline in Huntington's disease

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Objective: 1) To assess the futility of proceeding with an advanced phase clinical trial of minocycline in Huntington's Disease (HD); 2) To determine the safety and tolerability of minocycline in HD over 18 months.

Background: Minocycline inhibits release of cytochrome C from mitochondria, subsequent caspase 1 and 3 activation and microglial reaction. Minocycline has neuroprotective effects in animal models of HD and other neurodegenerative disorders. It was safe at dosages of 100 and 200 mg/day in 60 people with HD over 8 weeks.

Methods: A randomized, double-blind study of minocycline was conducted at 12 centers. One hundred fourteen research participants with HD were randomized, 87 to minocycline (200 mg/day) and 27 to placebo. HD progression was measured by the change in Total Functional Capacity (TFC) score from baseline to Month 18. Using a futility design, we tested the null hypothesis that minocycline would reduces the mean decline in TFC score over 18 months by $\geq 25\%$, i.e., that the mean decline is no greater than 1.31 TFC units (based on a fixed value obtained from a historical database), using a one-tailed significance level of 10%. The placebo group was included mainly to facilitate blinding. Rejection of the null hypothesis would discourage further study of minocycline in HD. For the primary analysis, missing data was handled by a pre-specified approach using the last observation carried forward.

Results: There were no important differences at baseline among the minocycline, placebo, and historical control groups. The mean decline in TFC for the minocycline group was 1.51 (SD 1.85) and futility was not declared ($p = 0.12$) for the primary analysis. When multiple imputation was used to handle missing data, the mean TFC decline in the minocycline-treated group was 1.70 (SD 1.96, $p = 0.08$), suggesting futility. Secondary outcome measures from the UHDRS (Independence Scale and total motor score) also suggested futility. There were no treatment-related increases in adverse event rates or changes in laboratory values or vital signs.

Conclusions: Although minocycline at 200 mg/day was well tolerated and safe in participants with HD over 18 months of treatment, the overall trial results suggest that further study of minocycline 200 mg/day in HD is not warranted. Such phase 2 study designs aid in screening potential therapies for HD.

Mo-113

Extrastriatal dopamine D_2 receptor distribution in Huntington's disease using PET

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Objective: To examine the density of extrastriatal dopamine D_2 receptors in patients with mild to moderate stage Huntington's disease.

Background: Huntington's disease (HD) is an autosomal-dominant, progressive neurodegenerative disorder with a phenotype, including movement disorders and cognitive deficits, presented with a considerable variability. Dopaminergic neurotransmission has been implicated to play a crucial role in the pathogenesis of HD. The classical hallmark is degeneration of medium spiny neurones in the striatum, and thus a marked loss of postsynaptic dopamine D_2 receptors. Albeit at low density, dopamine D_2 receptors are also present in the cerebral cortex and subcortical regions. The distribution of dopamine D_2 receptors in extrastrial regions is poorly described and may have implications for the pathophysiology as well as for the treatment of HD.

Methods: Regional D_2 receptor binding potentials were calculated and used as an index of D_2 receptor density in nine early to moderate staged HD patients and an age-matched set of control subjects using high resolution (HRRT) positron emission tomography (PET) system and the high affinity radioligand [^{11}C]FLB457. None of the subjects were treated with neuroleptic medication nor had previously been exposed to such medication. Clinical assessments were performed according to the Unified Huntington's disease Rating Scale and CAG repeat length was measured. To control for structural abnormalities all subjects underwent MRI examination.

Results: Preliminary analysis show that the cortical D_2 receptor binding potentials are generally well preserved in subjects with mild to moderate Huntington's disease.

Conclusions: This is the first study describing the extrastriatal D_2 receptor distribution *in vivo* in Huntington's disease patients. The findings of the present study support the view that HD pathology does not affect extrastriatal D_2 receptor baring neurons to the same extent as striatal neurones. The observations also demonstrate that

the molecular substrate for potential efficacy of experimental dopaminergic compounds such as ACR16 is preserved in HD patients.

Mo-114

Huntington's disease and age at onset in a cohort from Argentina

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Objective: To correlate the size of the normal and expanded CAG repeats and the age at onset (AO) of Huntington's disease (HD) in a cohort of Argentinean patients.

Background: HD is a neurodegenerative disorder caused by the abnormal expansion of CAG repeats in the HD gene on chromosome 4p16.3. Several studies support a negative correlation between the number of CAG repeats on the expanded allele and AO of the disease. However, other genetic and environmental factors could account for the AO. Some authors suggest that an increase in the size of the normal CAG repeat may modify the expression of HD among patients with large expanded CAG repeats.

Methods: We evaluated 27 non-institutionalized HD patients from 26 families. All patients were genotyped for CAG repeat length.

Results: Our study group comprised 13 females and 14 males with a mean age of 49.67±13.55years (range 23-70). The mean age at onset of HD was 43.16±11.74years (range 22-66), with 40.67±9.79 years (range 23-58) for females and 45.46±13.26 years (range 22-66) for males. Motor and psychiatric symptoms at onset were identified at the same percentage (48%). Western European ancestry was identified in 79.3% of patients. Expanded HD alleles varied from 36 to 55 repeats (mean 44±3.78); normal alleles ranged from 15 to 24 repeats (mean 18.75±2.22). Ten cases showed a paternal transmission. The mean size of the expanded CAG repeat was non-significant for paternal or maternal transmission (mean 44.52±5.46 vs 43.20±2.66). There was a negative correlation between the number of CAG repeats on expanded allele and the AO of the disease (r=-0.7017 for Pearson correlation coefficient), r^2 = 49.24%. However, we failed to demostrate a relation between the normal allele length and AO.

Conclusions: In our series, expanded CAG repeat was inversely associated with AO, as has been previously reported in the literature. However, we failed to identify a correlation between the normal allele length and the AO of HD; a more extensive number of patients is most likely required. Nevertheless, considering that several genetic and/or environmental factors may fix the AO of HD, knowledge of their influence may contribute to the identification of different subpopulations and target future treatments.

Mo-115

Effect of rTMS on motor functions in Huntington's disease

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Objective: To evaluate the effects of subthreshold repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex (M1) on motor performance in patients with Huntington's disease (HD).

Background: rTMS is an effective non-invasive tool to modulate cortical excitability. Higher frequency rTMS results in increases in cortical excitability while low frequency rTMS decreases excitability. In patients with HD, results of TMS studies of M1 excitability are variable and controversial. Reduced M1 excitability is suggested in some studies while others found increased facilitation. Here we used rTMS at different frequencies to modulate M1 excitability.

Methods: Eight patients with genetically confirmed HD (49,4 ± 11,2 years of age, 5 male, Unified Huntington Disease Rating Score (UHDRS) motor score: 20 ± 12.13) were enrolled in the present study. They fulfilled the inclusion criterion of an abnormal nine hole peg test (NHPT). In a blinded double cross-over design the effects of rTMS applied to M1 of the dominant hemisphere at 1 or 10 Hz frequency on motor performance was tested. Effects on mood and cognitive function were explored. Outcome measures were the UHDRS motor score, choice reaction times, time to perform the NHPT, Digit Span Test (DST) and depression according to the Beck Depression Inventory. Patients were evaluated immediately after rTMS, and again one and two hours and one and two weeks after rTMS. This was compared to sham stimulation applied to M1 of the dominant hemisphere.

Results: rTMS at 10 Hz shortened the choice reaction times immediately after the intervention (pre 741.14 ± 256.54 ms; post: 600.40 ± 179.97 ms, $p < .05$) while rTMS at 1 Hz or sham had no effect. rTMS at 1 Hz resulted in a sustained improvement of the patient's mood (pre: 17.00 ± 14.20, post 1 week: 12.75 ± 8.61, post 2 weeks: 10.25 ± 7.63, $p < .05$). There was no statistically significant effect of rTMS on UHDRS motor score, time to complete NHPT or DST.

Conclusions: High frequency repetitive, subthreshold motor cortex stimulation may improve performance in patients with HD and could be useful therapeutically. Improved performance with high frequency rTMS would support reported results of reduced M1 excitability in HD. However, further investigations are needed to define the optimal stimulation parameters and target sites.

Mo-411

Treatment of chorea in Huntington's disease with ropinirole and pramipexole

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Objective: To describe a case of Huntington's disease chorea responding to ropinirole and pramipexole.

Background: Huntington's disease (HD) is a progressive neurodegenerative disorder that causes chorea, parkinsonism, and cognitive and psychiatric symptoms. Chorea, an abnormal involuntary movement, is conventionally treated with neuroleptic medication or tetrabenazine. However, the ergot-derived (lisuride and bromocriptine) and morphine-derived (apomorphine) dopamine agonists reduced chorea in several open-label and randomized controlled studies[1]. There has been no previous report to our knowledge of treatment of chorea with an oral non-ergot dopamine agonist.

Methods: The Unified Huntington's Disease Rating Scale Motor Assessment (mUHDRS) was performed before and after a dose of ropinirole.

Results: A 42 year old male with a family history of HD had onset 2 years ago of falls, depression, dyscoordination, and diminished memory. He tested positive for HD with 45 CAG repeats. Chorea was mild and intermittent at first, and slowly became continuous. He developed tics characterized by hitting himself in the abdomen or pelvis with his left hand. Because of restless leg syndrome, he was started on pramipexole. At a dose of 0.25mg four times daily, he noted reduced frequency of tics and improved severity of chorea. When he missed a dose, chorea worsened. Chorea and tics were similarly well controlled when ropinirole 0.5mg four times daily was substituted for pramipexole. On examination 24 hours off ropinirole, he scored a 36 on the mUHDRS (the chorea subscore was 8). Chorea was continuous in the arms and intermittent in the face, trunk, and legs. One hour after taking ropinirole 0.75mg, his mUHDRS score was 23 (the chorea subscore was 5). Chorea was mild and intermittent in the arms, face, trunk, and legs.

Conclusions: This case demonstrated that low doses of oral non-ergot dopamine agonists treated chorea in a patient with HD. Ropinirole reduced tics in an open-label study[2]. However, experience with ropinirole and pramipexole in HD is limited. Clinical studies will be needed to determine whether these dopamine agonists can play a useful role in the treatment of chorea. 1. Bonelli RM, Wenning GK. Pharmacological management of Huntington's disease: An evidence-based review. *Curr Pharm Des* 2006; 12:2701-20. 2. Anca MH, Giladi N, Korczyn AD. Ropinirole in Gilles de la Tourette syndrome. *Neurology* 2004; 62:1626-7.

Tu-107

Acoustic analysis of voice in Huntington's disease patients

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Objective: The aim of this study was to assess the degree of voice and speech abnormalities in a group of patients with a molecular genetics diagnosis of Huntington's disease, and to analyse possible correlations with degree of disease severity.

Background: Alterations of voice and speech are frequently observed in Huntington's disease.

Methods: An observational study was carried out on diagnosed cases and controls. The voices of 20 patients were analysed and compared with an age and sex matched control group. Variables analysed included subjective voice exploration, analysis of aerodynamic efficiency acoustic analysis measures, and, laryngeal examination descriptions. Results obtained were correlated with degree of disease severity.

Results: Changes in the Voice Handicap Index and clinical characteristics of the voice were observed. Maximum Phonation Time was reduced. Acoustic analysis revealed higher values of Standard Deviation of Fundamental Frecuency and semi-tone phonatory range, and changes in Frequency and Amplitude Perturbation parameters, the NHR parameter, and Subharmonic, Aperiodical and Voice Break segments. The most significant finding revealed by laryngeal examination was the presence of uncontrolled adduction-abduction movements. All results showed a positive correlation with degree of disease severity assessed by the Unified Huntington's Disease Rating Scale.

Conclusions: Huntinton's disease causes alterations in subjective voice features, aerodynamic and acoustic analysis measures that are correlated with disease severity.

Tu-108

Neuroprotective effects of kynurenic acid analog in a transgenic mouse model of Huntington's disease

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Objective: In our experiments we tested a novel blood-brain penetrating KYNA analog, SZR-72 and KYNA precursor L-kynurenine (L-KYN) in the N171-82Q transgenic mouse model of HD.

Background: Huntington's disease (HD) is a progressive neurodegenerative disorder which pathomechanism is not fully understood as yet. The excitotoxicity may be involved in the development of the disease, so antiglutamatergic agents could exert neuroprotective effects. The tryptophan metabolite kynurenic acid (KYNA) is the only known endogenous N-methyl-D-aspartate (NMDA) receptor antagonist, however, its blood-brain penetrance is very poor rejecting the possibility of exogenous systemic administration in central nervous system disorders.

Results: The SZR-72 administration significantly prolonged the survival of transgenic mice and significantly ameliorated their diminished spontaneous locomotor activity without showing any remarkable side effect in behavioral tests. The results were confirmed with histological examinations, i.e. the analog could prevent the decrease in striatal neuron number and it could reduce the number of immunoreactive neurons containing huntingtin aggregates in the striatum and in the piriform cortex. The L-KYN applied at equimolar dose could not exert any significant protective effect according to the observed parameters.

Conclusions: These data indicate that glutamate mediated excitotoxicity may play an important role in the pathomechanism of HD, as an analog of the endogenous NMDA receptor antagonist exert neuroprotective effect. While the SZR-72 surely did not induce considerable side effects in this mouse model, it could be capable of entering clinical trials after further thorough investigations.

Tu-109

Olanzapine in different phenotypes of Huntington's disease: First experience in Russia

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Objective: To present the first experience of Huntington's disease treatment with Olanzapine in Russia.

Background: Huntington's Disease (HD) is a severe neurodegenerative autosomal dominant disorder characterized by motor, cognitive and psychiatric symptoms, marked phenotypic polymorphism and fatal clinical course. At present there is no effective cure for HD. Neuroleptics and tetrabenazine (the latter not available in Russia) are most commonly used for the treatment of choreic involuntary movements. We present our first experience of using the atypical antipsychotic drug Olanzapine in Russian HD patients.

Methods: We used Olanzapine in six patients with HD, including one atypical and five typical cases. Atypical case was a 25-year old patient, K.A., with severe chorea and agenesis of the corpus callosum. The disease started at 20 years. His father suffered from HD and died at 48 years of age. Neurologically, the patient displayed typical severe choreic hyperkinesias of perioral muscles, tongue, neck, trunk and extremities. The UHDRS score (motor section) was 26. Neuropsychological testing showed moderate cognitive decline and short memory loss. Examination of cognitive evoked potentials revealed absence of P300 components. On MRI, total agenesis of the corpus callosum was found. The number of CAG repeats in huntingtin gene was 54. The initial Olanzapine dose was 10 mg once a day, with graduate increase up to 20 mg per day. Treatment with Olanzapine was also initiated in five more Russian HD patients with a typical phenotype.

Results: We observed significant improvement in patient K.A. for most subscores of the UHDRS (motor section) two weeks after the beginning of treatment. Clinical benefit was maximal in two months. The observed effect of Olanzapine was comparable in typical and atypical phenotypes of HD. No adverse effects were recorded during the treatment. The comparison of Olanzapine and some other "anti-choreic" medications are currently under way and will be presented.

Conclusions: Olanzapine is very useful for the treatment of severe chorea in both typical and atypical HD. In Russia it may be the first choice medication for these patients. The study was supported by the Russian Foundation for Humanities (grant #07-06-00292).

Tu-110

An ADORA2A polymorphism modifies age at onset in Huntington's disease

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Objective: To evaluate whether one exonic adenosinergic A2A receptor (ADORA2A) gene polymorphism (1976C>T, formerly 1083C>T; rs5751876) is associated with a variation of age at onset (AAO) in a large cohort of French Huntington's disease (HD) patients.

Background: HD is a neurodegenerative disease caused by an expansion of CAG trinucleotide in the IT15/HD1 gene. This mutation statistically predicts for the AAO, but on an individual basis, repeat length accounts for about 60% of its variance. These observations have led to a search for genetic factors that influence the AAO. ADORA2A is a G-protein-coupled receptor essentially localized on the striatal subpopulation of medium-spiny neurons expressing enkephalin and D2 receptors, known to be the most vulnerable in HD.

Methods: 791 unrelated patients with clinical diagnosis of HD were recruited from 8 centres belonging to the Huntington French

Speaking Network. 106 French healthy individuals were included as control subjects. PCR was used to determine the CAG repeats sizes and the silent 1083C/T polymorphism (rs5751876) (taken from the Single Nucleotide Polymorphism Database). Deviation from Hardy-Weinberg equilibrium for alleles of rs5751876 variant and differences in allele and genotype distributions between groups were assessed by X^2 test. The variability in AAO attributable to the CAG repeats number was calculated by linear regression.

Results: ADORA2A genotypes were not significantly different between HD cases and controls. The expanded CAG repeats explained 67.63% and addition of the genotype variations in ADORA2A to the effect of CAG repeat length indicate a deleterious effect of the T/T genotype. Furthermore, a significant 3.8-year difference in the mean AAO between the C/C and T/T genotype classes was found.

Conclusions: This study reinforces the role of A2A receptors in HD physiopathology and supports further studies on the functional consequences of the rs5751876 ADORA2A polymorphism.

Tu-111

Effect of sertraline against 3-nitropropionic scid induced behavioral, oxidative stress and mitochondrial dysfunctions in rat brain

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Objective: The present study evaluated the possible role of sertraline on the 3-nitropropionic acid induced behavioral, biochemical, and mitochondrial alterations in discrete areas of rat brain.

Background: Oxidative stress and related reactive oxygen species is one of the common cooperative sharing pathways involved in neurodegenerative disorders including Huntington's disease.

Methods: 3-nitropropionic acid (10 mg/kg) administration for 14 days significantly induced Huntington's disease like symptoms in rats as indicated by change in locomotor activity, body weight, rotarod activity performance, oxidative damage (elevated levels of lipid peroxidation, nitrite concentration, depletion of antioxidant enzyme levels) and mitochondrial dysfunction (Complex –I, II, II and IV) in striatum, cortex and hippocampal region of brain.

Results: Treatment with sertraline (5 and 10 mg/kg) significantly reversed behavioral, biochemical and mitochondrial enzyme dysfunctions in 3-nitropropionic acid treated group. Further, combination of yohimbine (2 mg/kg) (non selective serotonin with the higher dose of sertraline (10 mg/kg) did not influence the protective action of sertraline.

Conclusions: The present study suggests the possible antioxidant role of sertraline against 3-nitropropionic acid induced alterations in animals.

Tu-112

Restoration of mitogen and stress-activated kinase: A new therapeutic approach in HD?

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Objective: To provide evidence that restoration of MSK-1 is neuroprotective in HD models *in vivo*.

Background: Huntigton's disease is a neurodegenerative disorder due to an abnormal polyQ expansion in N-terminal region of huntingtin protein (Exp-Htt). It causes protein aggregation wich leads to transcription dysregulation, and neuronal dysfunction and finally death. Gene expression profiling studies have shown decreased levels of mRNAs encoding immediate-early genes in the striatum of R6/2 mice (Luthi-Carter et al), a transgenic mouse model of HD. Alteration of chromatin remodeling is thought to be an important event in gene dysregulation induced by Exp-Htt. Exp-Htt has been shown to interact with CBP *in vitro*, and as such to inhibit its HAT activity (Steffan et al., 2001). Furthermore histone deacetylase inhibition ameliorates the histopathological and phenotype in R6/2 mice (Ferrante et al., 2003).

Results: Using the R6/2 mouse model of HD, we identified a new molecular alteration that could accout for gene dysregulation in these mice. Despite a nuclear activation of the MAP kinase/ ERK along with Elk-1 and CREB, two transcription factors involved in c-Fos transcription, we failed to detect any Histone H3 phosphorylation, wich is expected after nuclear ERK activation. Accordingly, We found in the striatum of these mice, a deficiency of of Mitogen and Stress-activated Kinase (MSK-1), a kinase downstream ERK, critically involved in H3 phosphorylation and c-Fos induction. We extended this observation to Exp-Htt-expressing striatal neurons and *post-mortem* brains of HD patients. *In vitro*, knocking_ou MSK-1 expression potentiated Exp-Htt-induced striatal death. Its overexpression induced H3 phosphorylation and c-Fos expression and totally protected against neurodegeneration induced by Exp-Htt. *In vivo*, using lentiviral vector allowing overexpression of mutant huntintin (LV_82Q) injected stereotaxically within the striatum, we showed at 4 weeks after lentiviral injection a down-regulation of MSK-1 in LV_82Q -infected areas, specifically. At 10 weeks after lentiviral vectors allowing overexpression of MSK-1 (LV_MSK-1) along with mutant huntingtin (LV_82Q) injection, we found that MSK-1 protected cell death in neurons expressing mutant huntingtin. Restoration of MSK-1 expression may be a new therapeutic target in HD.

Tu-411

Multidisciplinary approach to Huntington's disease in North Staffordshire

A. Valanciute, G. El-Nimr (Stoke on Trent, Staffordshire, United Kingdom)

Objective: To describe in quantitative terms, the multidisciplinary care provided for HD patients in North Staffordshire. This work is to form a basis to formulate specific outcome measures and inform future studies.

Background: Giving the progressive nature and wide range of clinical and psychological effects of Huntington's disease (HD) on patients and families, a multidisciplinary approach to care is essential.

Methods: A retrospective review of demographic, clinical and service data of HD patients who are under the care of our Neuropsychiatry service by the end of October 2008 was collected and analyzed from case notes & HD electronic database.

Results: Seventy seven HD clients (F: 43, M: 34) with an average age of 54 years were identified. About 41% have a long term partner. Sixty two percent are unemployed and a similar percentage still live at home. The average time from initial diagnosis to full nursing care was 7.3 years. Most referrals come from GPs and clinical genetics (at 40% and 29% respectively). Motor symptoms formed the initial presentation in 57%. Slightly over half of the patients whose genetic data is available (73%) had a paternal gene transmission. Twelve percent of individuals are asymptomatic gene carriers. Virtually all HD clients receive outpatient reviews and 74% receives CPN follow up. About half had a period of inpatient assessment; 13% of which was under the MHA. Respite admissions and day care are offered to 22% and 29% respectively. Approximately 75% receive input from Neuropsychology and SALT. Physiotherapy and OT offer input to 56% and 61% respectively. Input from other disciplines/agencies was also quantified.

Conclusions: The management of HD extends beyond traditional patient care. Giving the complexity of the disease and its familial nature, a robust multidisciplinary approach is crucial.

We-109

Social intelligence in Huntington's disease

S.L. Mason, M. Armstrong, A.A.O. Goodman, R.A. Barker (Cambridge, Cambrdigeshire, United Kingdom)

Objective: To evaluate the extent to which patients diagnosed with Huntington's disease (HD) are able to put themselves into the

mind of others and accurately attribute a relevant mental state to that person.

Background: Along with the classic triad of motor, cognitive and psychiatric symptoms, HD is associated with altered social conduct and a breakdown in interpersonal relationships, although the factors underlying these changes remain poorly defined. Theory of mind describes the ability of an individual to understand that others have mental states that can differ from their own and from reality; this information can be used to predict the behaviors of others. Problems with theory of mind may provide a rationale to better understand some of the social problems experienced by HD patients.

Methods: All patients were recruited from the HD research clinic at the Cambridge Centre for Brain Repair. We administered a previously validated advanced theory of mind task ("Reading the Mind in the Eye's" task) to 83 HD patients. Motor impairment and daily functioning were evaluated using the UHDRS (Unified Huntington's disease Rating Scale); global cognitive functioning was measured using the MMSE (Mini Mental State Exam) and the NART (National Adult Reading Test) was used to assess verbal IQ.

Results: The total number of mental states correctly attributed significantly correlated with motor impairment, daily functioning, global cognitive performance, and to a lesser degree, verbal IQ. Interestingly, the performance of pre-symptomatic HD gene carriers appeared to relate to estimated proximity to disease onset.

Conclusions: As the disease advances HD patients get progressively worse at "reading the mind in the eyes". In the later stages of the disease their ability to perform this task appears to be more impaired than that of adults with high functioning autism (HFA) or Aspergers Syndrome (AS) whose primary deficit is thought to be with theory of mind. This work is only a preliminary study, and as such has methodological flaws however the apparent decline in social intelligence with advancing disease warrants further exploration. A better understanding of theory of mind deficits in HD patients may provide an insight into the processes underlying the reduced capacity to work which is often cited as one of the first functional changes associated with phenoconversion.

We-110

Exploratory 7T MRS in Huntington's disease

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Objective: To examine differences in brain metabolites and correlations with clinical parameters in Huntington's disease (HD) which can serve as markers for disease progression.

Background: To date, imaging techniques have shown structural and functional abnormalities in various brain structures in HD gene carriers. Further understanding of the pathophysiology of brain changes, as related to clinical manifestations, in HD is crucial in light of developing neuroprotective interventions. Low field MRS has shown generalised changes in large brain areas. Ultra high field (7T) MRS has the potential to perform measurements in small defined areas.

Methods: To date 8 gene carriers (TFC≥7, CAG≥40) and 11 controls were included. UHDRS and the MMSE were performed. A Philips 7 Tesla scanner was used. In the caudate nucleus (CN), frontal lobe, putamen, hypothalamus and thalamus STEAM single voxel MRS was acquired: TR/TE/TM = 2000/19/25 ms, BW 4kHz, 2048 data points and 128 averages. MRS data was analysed with the LCModel.

Results: Group characteristics are shown in Table 1. A lower NAA concentration in the caudate nucleus in gene carriers as compared to controls (4.96 ± 1.05 vs 6.35 ± 1.19 mM, p = 0.017) (t-test) was found. Also, the NAA/Cre ratio in the CN was reduced in gene carriers (0.75 ± 0.15 vs 0.93 ± 0.18, p = 0.042). The choline concentration in the thalamus was found to be higher in gene carriers (1.82 ± 0.21 vs 1.57 ± 0.25 mM, p = 0.035) and in the hypothalamus, gene carriers showed significantly higher mI/Cre ratio (1.96 ± 0.43 vs 1.47 ± 0.29, p = 0.012) and a tendency for higher Glu/Cre ratio (1.37 ± 0.47 vs 1.01 ± 0.21, p = 0.055).

Table (We-110). Group characteristics

	Controls			Gene Carriers		
	Mean	Standard deviation	Range (min-max)	Mean	Standard deviation	Range (min-max)
CAG repeat length	NA	NA	NA	42.5	3.1	40–49
TFC	12.9	0.3	12–13	12.1	1.6	9.13
Independance scale	100	0	NA	96.3	6.9	85–100
UHDRS TMS	2.4	2.9	0-7	7.1	10.5	1–32
MMSE	29.5	0.8	28–30	28.8	1.9	25–30

NA = not applicable, TFC = total functional capacity (range 0-13), Independence scale (range 0-100%), UHDRS TMS = Total Motor Score from the Unified Huntington's Disease Rating Scale (range 0-124), MMSE= Mini Mental State Examination (range 0-30).

Conclusions: HD gene carriers show significantly lower NAA concentration and NAA/Cre ratio in the caudate nucleus as compared to controls. Furthermore, this study demonstrates that choline levels in the thalamus and mI/Cre ratio in the hypothalamus are elevated in HD. As the gene carriers in this study were predominantly pre-manifest, these findings point to early brain metabolite changes, making 7T MRS a promising tool for tracking neuropathological progression even before clinical symptoms appear. This study is ongoing and aims for a total of 45 participants. MRI findings and clinical correlations will be presented.

We-111

Dysfunctional error monitoring in the anterior cingulate cortex in prediagnostic and manifest HD during an anti-saccade task

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Objective: To examine the differences in fMRI activation patterns between prediagnostic and manifest Huntington's disease (HD) subjects and non-gene carriers when performing an anti-saccade (AS) task.

Background: We previously reported that performance on an anti-saccade (AS) task is a sensitive and specific biomarker in early, prediagnostic HD. To extend this work, we adapted our previous protocol into an event-related fMRI paradigm.

Methods: Individuals with a family history of HD were recruited. Twelve individuals without a CAG expansion (CAG-) and nineteen with an expansion (CAG+) completed the study protocol. A neurological evaluation was performed for all subjects. Among the nineteen CAG+, ten were classified as prediagnostic (UHDRS=0-2) and nine as clinically diagnosable (UHDRS=3-4). The event-driven fMRI protocol consisted of a visual instruction to perform either a prosaccade (PS) or an AS followed by the stimulus presentation. The subjects were instructed to look directly at the stimulus for a PS trial, and to look directly opposite the stimulus for an AS trial. Each 5:20 minute imaging run consisted of 16 PS and 16 AS trials, with subjects completing 3 or 4 runs. Eye movement data collected during the scan allowed AS trials to be classified as either correct or incorrect. A random effects factorial model was employed in SPM 5 to test for pair-wise activation differences between the three groups for incorrect AS trials as compared to correct AS trials.

Results: We found that both prediagnostic and manifest HD subjects have less dorsal anterior and middle cingulate cortex activation than non-gene carriers when comparing the activation during error trials greater than correct trials.

Conclusions: These results suggest that the CAG+ groups have dysfunctional error monitoring when performing an AS task and that this deficit is detectable early in disease progression. Further work is ongoing to identify clinical measures that correlate with activation. In addition, morphological changes in the cingulate will be examined

to better delineate the relationship between functional and structural changes that occur during the prediagnostic and early manifest period of disease progression.

We-112

Neuroendocrine disturbances in Huntington's disease

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Objective: The aims of this study were to look for neuroendocrine disturbances in patients with Huntington's disease (HD) and to determine the relationship with weight loss seen in HD.

Background: Huntington's disease (HD) is a severe inherited neurodegenerative disorder characterized, in addition to neurological impairment, by weight loss suggesting endocrine disturbances.

Methods: We compared plasma levels of hormones from the five pituitary axes in 219 patients with genetically documented HD and in 71 sex- and age-matched controls. Relationships between hormone levels and disease severity, including weight-loss severity, were evaluated.

Results: Growth hormone (GH) and standard deviation score of insulin-like growth factor 1 (SDS IGF-1) were significantly higher in patients than in controls (0.25 (0.01-5.89) vs. 0.15 (0.005-4.89) ng/ml, $p=0.013$ and 0.16 ± 1.02 vs. 0.06 ± 0.91, $p=0.039$; respectively). Cortisol was higher ($p=0.002$) in patients (399.14 ± 160.5 nmol/L vs. 279.8 ± 130.1 nmol/L), whereas no differences were found for other hormone axes. In patients, elevations in GH and IGF-1 and decreases in thyroid-stimulating hormone, free triiodothyronine and testosterone (in men) were associated with severity of impairments (Independence scale, Functional score, Total Functional Capacity, Total Motor score, Behavioral score). Only GH was independently associated with body mass index ($\beta= -0.26$, $p=0.001$).

Conclusions: Our data suggest that the thyrotropic and in men gonadotropic axes are altered in HD according to the severity of the disease. The somatotropic axis is overactive even in patients with early disease, and could be related to the weight loss seen in HD patients.

We-113

Abnormal explicit but intact implicit sequence learning in pre-symptomatic and early Huntington's disease

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Objective: To study explicit and implicit sequence learning in pre-symptomatic and early Huntington's disease patients.

Background: Acquisition of knowledge, its storage and application are elementary for adaptive behaviour and survival. Learning may occur with or without awareness, as explicit (intentional) or implicit (incidental) learning. The caudate nucleus and the putamen, which are affected early in Huntington's disease (HD), are thought to be essential for motor sequence learning. However, the results of existing studies are inconsistent concerning presence/absence of deficits in implicit and explicit motor sequence learning in HD.

Methods: We assessed both implicit and explicit motor sequence learning in patients with HD using sequences of equivalent structure. In addition, we tested pre-manifest HD gene mutation carriers to test whether learning parameters may be a useful biomarker reflecting the disease process in HD. We assessed implicit and explicit motor sequence learning in fifteen individuals with a positive HD genetic test (7 pre-manifest subjects; 8 early stage disease patients) and 11 controls.

Results: The HD group showed evidence of implicit motor sequence learning, which was intact relative to matched controls, whereas explicit motor sequence learning was impaired in symptomatic but also in pre-symptomatic HD gene carriers.

Conclusions: Our data suggest a progressive decline of motor sequence learning with progressive disease. Sequence learning parameters may be a useful cognitive biomarker of HD progression.

We-114

DNA instability in replicating Huntington's disease lymphoblasts

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Objective: Our purpose in this study was to investigate whether, besides the mechanisms influencing the CAG repeat mutability in Huntington's disease (HD) terminally differentiated and nondividing neurons, cell division may contribute to DNA instability.

Background: The expanded CAG repeat in the Huntington's disease gene may display tissue-specific variability (e.g. triplet mosaicism) in repeat length, the longest mutations involving mitotic (germ and glial cells) and postmitotic (neurons) cells. What contributes to the triplet mutability underlying the development of HD nevertheless remains unknown. We investigated whether, besides the increased DNA instability documented in postmitotic neurons, possible environmental and genetic mechanisms, related to cell replication, may concur to determine CAG repeat mutability.

Methods: To test this hypothesis we used, as a model, cultured HD patients' lymphoblasts with various CAG repeat lengths. A total 58 HD lymphoblastoid cell lines from subjects with a wide range of CAG expanded repeats, including low (39-41 CAG) and highly penetrant (60 CAG and more) mutations conventionally considered causing juvenile HD, were serially passaged for at least 6 months to analyse longitudinal repeat variation during the passage time.

Results: Although most lymphoblastoid cell lines (88%) showed little or no repeat instability even after six or more months culture, in lymphoblasts with large expansion repeats beyond 60 CAG repeats the mutation size and triplet mosaicism always increased during replication, implying that the repeat mutability for highly expanded mutations may quantitatively depend on the triplet expansion size. None of the investigated genetic factors, potentially acting *in cis* to the mutation, significantly influence the repeat changes. Finally, in our experiments certain drugs controlled triplet expansion in two prone-to-expand HD cell lines carrying large CAG mutations.

Conclusions: Our data support quantitative evidence that the inherited CAG length of expanded alleles has a major influence on somatic repeat variation. The longest triplet expansions show wide somatic variations and may offer a mechanistic model to study triplet drug-controlled instability and genetic factors influencing it.

Th-112

Riluzole protects Huntington's disease patients from brain glucose hypometabolism and grey matter volume loss and increases production of neurotrophins

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Objective: To search whether the antiglutamatergic drug Riluzole has neuroprotective effects in Huntington's disease (HD) in vivo.

Background: HD mutation increases gain-of-toxic functions contributing to glutamate-mediated excitotoxicity. Riluzole interferes with glutamatergic neurotransmission, thereby reducing excitotoxicity, enhancing neurite formation in damaged motoneurons and increasing serum concentrations of BDNF, a brain cortex neurotrophin protecting striatal neurons from degeneration.

Methods: We analyzed metabolic and volumetric differences in distinct brain areas of 23 subjects (12 affected vs 11 placebo) by magnetic-resonance-imaging (MRI) and [fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) positron-emission-tomography (PET) scanning, according to fully automated protocols.

Results: Untreated patients showed significantly greater proportional volume loss of fGM and metabolic decrease of FDG uptake than patients treated with riluzole, in all cortical areas ($p<0.05$). The decreased rate of metabolic FDG changes correlated with worsening clinical scores in untreated patients, compared to those who were treated with riluzole. The progressive decrease of metabolic FDG uptake observed in frontal, parietal and occipital cortex correlated

linearly with the severity of motor scores calculated by Unified Huntington Disease Rating Scale (UHDRS-I), in patients with no riluzole treatment. Similarly, the rate of metabolic changes in frontal and temporal areas of brain cortex correlated linearly with worsening behavioural scores calculated by UHDRS-III, in the same cohort of untreated patients.

Conclusions: The decreased metabolic FDG uptake linearly correlating with worsening clinical scores in the untreated group of patients suggests that the FDG-PET scanning may represent a valuable procedure to assess brain markers of HD. Finally, we analyzed the influence of riluzole on peripheral growth-factor blood levels and found BDNF and Tranforming Growth Factor beta-1 serum levels significantly increased in patients' treated with riluzole.

Th-113

Cerebral spinal fluid (CSF) is the main marker of Huntington's disease progression severity and age at onset prediction

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Objective: Searching brain and peripheral biomarkers is a requisite to cure Huntington's disease (HD). To search for markers indicating the rate of brain neurodegenerative changes in the various disease stages we quantified volume changes of the different brain compartments in HD subjects and age matched controls.

Background: Mutated huntingtin exerts its main pathological effects on brain neurons. Neuronal dysfunction and degeneration cause progressively invalidating extrapyramidal symptoms, cognitive decline and behavioural changes. Neuropathological studies showed progressive striatal dysfunction and degeneration since the beginning of the disease.

Methods: We analysed the cross-sectional and longitudinal rate of brain atrophy, quantitatively measured by fully-automated multiparametric magnetic resonance imaging, as fractional grey matter (GM, determining brain cortex volume), white matter (WM, measuring the volume of axonal fibres) and corresponding cerebral spinal fluid (CSF, a measure of global brain atrophy), in 94 gene-positive subjects with pre-symptomatic to advanced HD, and age-matched healthy controls.

Results: Each of the three brain compartments we studied (WM, GM and CSF) had a diverse role and their time courses differed in the development of HD. GM volume decreased early in life. Its decrease was associated with decreased serum Brain-Derived-Neurotrophic-Factor and started even many years before onset symptoms, then decreased slowly in a non-linear manner during the various symptomatic HD stages. WM volume loss also began in the pre-symptomatic stage of HD a few years before manifest symptoms appear, rapidly decreasing near to the zone-of-onset. Finally, the CSF volume increase began many years before age at onset. Its volume measured in pre-symptomatic subjects contributed to improve the CAG-based model of age at onset prediction.

Conclusions: The progressive CSF increase depended on CAG mutation size and continued linearly until the last stages of HD since the presymptomatic life stage, representing the best marker of progression rate and severity in HD ($R^2=0.25$, $P<0.0001$) and improving the CAG-based prediction of age at onset.

Th-114

Early defect of transforming growth factor b-1 formation in Huntington's disease

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Objective: To search for new growth factor-related mechanisms of Huntington's disease (HD).

Background: HD is a neurodegenerative disease due to an abnormal accumulation of a mutated protein, huntingtin with toxic effects in cortical and subcortical brain areas. Neuropathological studies have demonstrated an increased reactivity of astrocytes and oligodendroglial cells in striatum and cortex. Activation of astrocytes and microglia, which reflects a process of neuroinflammation, is already observed during the presymptomatic stage of HD, and is related to the severity of HD progression. Activated astrocytes and microglia critically regulate processes of neuronal death and survival by secreting glutamate, neurotrophic factors, and pro- and anti-inflammatory cytokines.

Methods: We carried out experiments in two transgenic animal models of HD (R6/2 and YAC128 mice), HD mouse and human brain samples and controls, cell line cultures (R6/2 mouse astroglial and neuronal cell lines and striatal knock-in cell lines), and blood serum from presymptomatic and affected subjects.

Results: Immunohistochemical analysis of brain cortex from human HD and biochemical analysis of human serum showed a reduction of TGF-b1 levels in presymptomatic subjects, which correlate with decreased brain glucose metabolism and loss of white matter volume as assessed by nuclear magnetic resonance image analysis. TGF-b1 levels increased with the progression of disease up to the late phase of disease being linearly associated with worsening of motor clinical scores and progression rate. As the production of TGF-b1 by glial cells is under the control of mGlu3 metabotropic glutamate receptors and activation of glial mGlu3 receptors is neuroprotective *via* a paracrine mechanism mediated by TGF-b1, we examined the ability of mGlu2/3 receptor agonists to regulate brain TGF-b1 levels in the R6/2 and YAC128 mouse models of HD. Biochemical analysis of TGF-b1 levels showed an increase of TGF-b1 levels in the striatum of wild-type mice, whereas no increase was observed in pre-symptomatic and symptomatic R6/2 mice.

Conclusions: These data suggest that TGF-b1 production could be defective in the HD brain and this could contribute to the pathophysiology of neuronal death in HD.

Th-115

Patients with clinical features suggestive of Huntington's disease carrying CAG repeats of intermediate length below the pathological range of 36, in the HTT gene

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Objective: To search whether Huntington's disease (HD) can manifest in subjects carrying a repeat length below the pathological CAG edge of 36 repeats.

Background: Huntington's disease is a dominantly transmitted disease caused by a CAG repeat expansion beyond 35 triplets; the intermediate triplet number $27<CAG<35$ is considered pre-mutated and has never been described in association with signs and symptoms of HD.

Methods: The study describes the clinical and genetic features of four patients who were followed over several years. Patients belonged to an inbred family in whom progressive chorea, manifesting predominantly with dystonia and cerebellar features, developed during middle age. Although severe psychiatric symptoms ultimately developed in two of the four patients, cognitive function remained reasonably well preserved in all of them even after several disease years.

Results: Moderate cognitive deficits were limited to the visuomotor organization and abstract thinking subtests in three of the four patients. Qualitative brain imaging showed atrophy of brain predominantly involving cortex and cerebellum. Genetic testing revealed a variable mutation penetrance among family members, some affected members showing an upper allele size ranging from 34 to 49, whereas others remained unaffected despite the presence of the full mutation beyond 40 CAG repeats.

Conclusions: We focus on a cluster of patients from a Karaite Jew community with HD, in some cases associated with repeat lengths below the edge of 36 CAG repeats. Although the main diagnosis of HD remains to be confirmed by further neuropathological studies, these cases may suggest that HD could manifest with as few as 34 CAG repeats, in some geographic areas, the disease phenotype most probably being influenced by additional, as yet unidentified, genes.

Th-116

The degree of atrophy of striatum and pallidum in preclinical Huntington's disease strongly predicts estimated years to clinical onset

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Objective: We aimed to more precisely determine the topography of subcortical changes in preclinical Huntington's disease (HD), using a sophisticated automated method for brain segmentation that allows for an objective delineation of atrophy in individual basal ganglia nuclei.

Background: Previous studies using mainly manual brain segmentation techniques on structural magnetic resonance (MR) scans have shown that individuals with HD have substantial striatal atrophy, which antedates the onset of motor symptoms.

Methods: We studied 35 individuals (mean age ± SD = 41.3 ± 10.6 yrs) who were positive for the HD gene expansion (mean CAG repeats ± SD = 42.3 ± 2.5), yet still asymptomatic motorically ("preclinical HD"), and 25 age-matched controls (mean age ± SD = 39.0 ± 12.1 yrs). Estimated years to onset in individuals with preclinical HD was determined using the equation from Aylward et al. (2004); mean = 4.8 yrs, range -10 to 21 yrs. Whole-brain segmentation, using automated probabilistic labeling of neuroanatomical structures, was performed and segmented volumes (corrected for total intracranial volume) of the caudate, putamen, pallidum and presumed accumbens area were compared between individuals with preclinical HD and controls. In individuals with preclinical HD, partial correlations (controlling for age) were computed for estimated years to onset and volumes.

Results: We observed a 16% volume loss in the putamen, 12% in the caudate, 12% in the accumbens area and 10% in the pallidum in individuals with preclinical HD when compared to controls (all P-values<.005). Strong correlations were observed between estimated years to onset and volumes of the putamen (R=.527, P=.001), caudate (R=.515, P=.002) and pallidum (R=.440, P=.009), but not the accumbens area (R=.270, P=.090).

Conclusions: Although previous studies have suggested that atrophy of the caudate and putamen is substantial in preclinical HD, the current methodology allowed us to also demonstrate volume loss in the pallidum and accumbens area. Assessment of atrophy on MR imaging using automated probabilistic labeling may prove more reliable for both predicting HD onset and tracking its progression in future therapeutic trials in individuals with preclinical HD.

LEWY BODY DEMENTIA AND OTHER DEMENTIAS IN MOVEMENT DISORDERS

Mo-116

Screening for REM sleep behavior disorder in patients with cognitive impairment and/or parkinsonism: Updated validation data on the Mayo Sleep Questionnaire

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Objective: To validate a questionnaire for the diagnosis of REM sleep behavior disorder (RBD) in patients with cognitive impairment and/or parkinsonism.

Background: Several sleep disorders, including RBD, are associated with or reflect an underlying neurodegenerative disease, and their presence may offer diagnostic insights as well as affect morbidity and mortality. RBD requires polysomnography (PSG) to establish the diagnosis. A simple screening measure for RBD would be desirable for clinical and research purposes.

Methods: We developed the Mayo Sleep Questionnaire (MSQ)–a concise 16 item measure–to screen for the presence of RBD and other sleep disorders. We assessed the validity of the MSQ by comparing the responses of a large group of patients' bedparters with the findings on PSG. All subjects recruited in the Mayo Alzheimer's Disease Research Center at Mayo Clinic Rochester and Mayo Clinic Jacksonville from 1/00 to 7/08 with cognitive impairment and/or parkinsonism who underwent a PSG were the focus of this analysis.

Results: The study sample was comprised of 142 subjects [122 male, median age 71 years (range 39-90), with clinical diagnoses as follows: MCI (38), AD (22), DLB (57), PD (10), FTLD spectrum (14), and PSP (1)]. The core question on recurrent dream enactment behavior yielded a sensitivity (SN) of 97% and specificity (SP) of 69% for the diagnosis of RBD. Among those who answered affirmatively to the core question, the profile of responses on 4 additional questions provided an optimal SP of 97%. All remaining false positive cases (n=3) had affirmative responses to at least 1 of 2 questions on obstructive sleep apnea (OSA), and all had OSA confirmed on PSG.

Conclusions: These data suggest that among patients with cognitive impairment and/or parkinsonism, the MSQ has high SN and SP for the diagnosis of RBD, and is particularly specific for RBD in the absence of classic historical features of OSA.

Mo-117

Association of neuropsychiatric symptoms and dopamine transporter levels in dementia with Lewy bodies: A ^{123}I-FP-CIT SPECT study

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Objective: To explore the relationship between neuropsychiatric symptoms and striatal DAT levels in dementia with Lewy bodies (DLB).

Background: Neuropsychiatric symptoms are frequent in DLB. Dopamine transporter (DAT) imaging with ^{123}I-FP-CIT, which reliably measures midbrain dopaminergic dysfunction, has provided important evidence on the neurobiological substrate of some of these symptoms including apathy and depression. However, little is known on DAT levels and other distressing symptoms such as delusions and hallucinations.

Methods: ^{123}I-FP-CIT imaging was performed in 18 well-characterized patients with DLB, and striatal DAT levels were correlated with the frequency/severity ratings of several neuropsychiatric symptoms. Severity of neuropsychiatric symptoms was assessed by NPI subscores.

Results: Significant correlations were observed between decreased striatal DAT levels and hallucination severity (Spearman's rho -0.698, p<0.001). Although there were no correlations between striatal DAT levels and other neuropsychiatric symptoms, when considering the putamen and the caudate nucleus separately, caudate DAT levels were inversely correlated with severity of delusion (-0.466, p=0.049), depression (-0.532, p=0.023), and apathy (-0.542, p=0.020). In the subgroup of delusional patients (11/18), a significant inverse correlation was found between delusion severity and DAT level in the right (-0.609, p=0.020) but not in the left (-0.506, p=0.70) caudate nucleus.

Conclusions: These results provide intriguing evidence on the involvement of the mesocortical dopaminergic pathways in neuropsychiatric symptoms in DLB and underscore the role of right caudate-prefrontal circuit in the genesis of delusion.

Mo-118

Mesencephalic ^{123}I-FP-CIT uptake differentiates Lewy body dementia from other parkinsonisms

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Objective: to test the usefulness of simultaneous quantification of DAT and SERT for the differential diagnosis of parkinsonisms.

Background: [^{123}I]FP-CIT Single Photon Emission Computed Tomography (SPECT) has proven useful in assessing the levels of dopamine transporter (DAT) in basal ganglia and it is widely exploited in the differential diagnosis of PD and DLB. However, decrease in DAT levels does not differentiate PD and DLB from each other and from other parkinsonisms. [^{123}I]FP-CIT has high affinity for DAT but also displays a sizeable affinity for serotonin transporter and the uptake related to latter can be differentiated in areas devoid of DAT, such as the mesencephalon and thalamus.

Methods: Fifthy-one patients attending the Department of Neurology-University of Bari clinically diagnosed with PD (15), LBD (15), PSP (6), ET (15) underwent standard [^{123}I]FP-CIT SPECT imaging and MRI imaging of the brain. SPECT data were coregistered to a MR data set using the software "Image Registration". Coregistration included manual reorientation of the originally reconstructed SPECT using a mutual information algorithm. After realignment one ROI was placed on the midbrain and four ROI on basal ganglia were used to measure radiotracer uptake (the occipital lobe as background value).

Results: DAT levels were significantly reduced in PD, DLB and PSP when compared with ET patients; however, no significant difference was detected among PD, DLB and PSP patients. In contrast, mesencephalic [^{123}I]FP-CIT undetectable in DLB patients (0.07 ± 0.03) but was clearly above the background in PD (0.79 ± 0.18) and ET (0.86 ± 0.08) and reduced, but not absent, in PSP (0.16 ± 0.03) patients. Mesencephalic uptake was not correlated with disease duration, age, sex and UPDRS scores.

Conclusions: Our data show that MRI-guided, ROI-based quantification of [^{123}I]FP-CIT uptake in the midbrain and basal ganglia identifies LBD and PSP patients from PD patients and may be a valuable addition in the differential diagnosis of parkinsonian syndromes.

Mo-119

Prevalence of parkinsonism and other movement disorders in outpatients with Alzheimer's disease using cholinesterase inhibitors and/or memantine

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Objective: To evaluate the (1) prevalence of parkinsonism and other movement disorders(MD) in outpatients with Alzheimer's disease(AD), in use of Cholinesterase inhibitors and memantine, (2) possible risk-factors for its development, (3) influence of the drugs on the development of MD.

Background: MD have been reported in as many as 60% patients with AD. Parkinsonian like signs are common in older persons with or without dementia. Parkinsonianlike signs in patients with AD may be associated to a poor prognosis. Cholinesterase inhibitors such as rivastigmine, galantamine and donepezil and memantine are used for the treatment of AD and were shown to be effective in improving cognition in patients with AD. Because of their cholinergic nature, however, ChEI theoretically could exacerbate parkinsonian features.

Methods: Fifty-nine consecutive patients (36 women and 23 men) with AD were enrolled into this study. They have received a diagnosis of dementia according to the DSM-IV. The patients had mild-to-moderately severe dementia, with a MMSE score of 6 to 23. Those patients with parkinsonian symptoms were diagnosed according to the clinical diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank. The study participants were assessed by the Hoehn & Yahr score and the UPDRS to precisely quantify their motor status at baseline and after the treatment. The family gave written informed consent.

Results: A total of 59 patients participated of our study. The mean age of the patients was 76.7 years, and 61 percent were women. The mean years of education were 5,65. The most used drug was rivastigmine. The mean time of treatment was 15.4 months for the patients without MD and 24.1 months for those with MD. A total of 40.7 percent presented MD(mainly PK). Most presentedthe MD prior to the onset of the medication (62.5 percent). Familial history for AD was present in 39 percent of the patients. The baseline UPDRS was 1.94 for the non-affected patients and 23.62 for those with MD, and the final UPDRS was 3.05 for the non-affected patients and 30.87 for those with MD.

Conclusions: Persons with AD have a high prevalence of MD, mainly parkinsonism. In our study the most common MD was parkinsonism. There was an uncertain relationship between the time of treatment and the onset of the symptoms.

Tu-113

Rapidly progressive diffuse Lewy body disease

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Objective: To evaluate the clinical features of patients with rapidly progressive DLB.

Background: Diffuse Lewy bodies (DLBD) disease is usually a slowly progressive disorder with a mean survival of 5 to 8 years. Some DLBD patients may show rapid symptom progression and death within 1-2 years. In this cases Creutzfeldt-Jacob disease (CJD) can be suspected.

Methods: Review clinical records of pathologically proven cases of DLBD and known disease progression of less than 15 months.

Results: Six cases (4 men and 2 women) were identified; mean age at onset of symptoms was 72.5 years (range: 71-75) and mean disease duration was 9 months (range: 3-15). Onset consisted of delirium in three patients and rapidly progressive dementia (RPD) in the other cases. In one patient delirium presented as an acute syndrome that lead the relatives to consult to the emergency room; in the other two, cognitive and behavioral symptoms were observed within several months before the appearance of delirium. The three patients with RPD presented prominent deficits on attention, executive and visuospatial functions and short-term memory that developed within 3-6 months. Two of them had fluctuating symptoms. All the six patients presented visual hallucinations and delusions; parkinsonism occurred in four, myoclonus in three and REM sleep behavior disorder in two; neuroleptic sensitivity in two, and severe dysautonomia in one. Brain MRI showed whole brain atrophy in all patients. EEG showed diffuse or asymmetrical temporal-occipital slowness but periodic sharp waves were not observed in any. In all patients in whom it was tested the 14-3-3 protein in CSF was negative and myocardial MIBG-SPECT showed marked reduction in tracer uptake. The final clinical diagnosis was CJD in two cases, DLBD in three and DLBD plus CJD in one case.

Conclusions: DLBD disease should be included in the differential diagnosis of subacute delirium particularly when no cause for such delirium is found after diagnostic workup. In patients with RPD the presence of core features (fluctuating cognition, hallucinations and parkinsonism) should raise the suspicion of DLBD. The results of laboratory (14-3-3 protein, EEG) and neuroimaging tests (Brain MRI, MIBG-SPECT) may reinforce or refute the diagnosis of DLB disease.

Tu-114

Creutzfeldt-Jakob disease presenting as acute corticobasal degeneration syndrome: A videoclinical and neuropathological study

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Objective: To report the case of a 54 old man presenting initially as an isolated unilateral right limb apraxia and a left parietal defect

(SPECT) suggestive of corticobasal degeneration syndrome (CBS) finally due to sporadic creutzfeldt jakob disease (CJD).

Background: The classic parietal syndrome that often accompanies the pathological state of CBS is not specific to this disorder. When symptoms develop rapidly over weeks to months, Creutzfeldt–Jakob disease (CJD) is a diagnostic possibility important to consider. The clinical picture of CBS is an unusual presentation of CJD. However, some studies like Vandenberghe & al (Mov Disord. 2007, 22(11):1668-9) or Magherini & al (Mov Disord. 2007, 22(6):898-9) have reported this unusual clinical phenotype of CJD.

Methods: A 54-year-old man developed a unilateral right-hand apraxia. On initial examination, he had a mild ataxia and associated proprioceptive sensory deficit of the upper limb (first video section). The SPECT showed a marked hypoperfusion of the left parietal lobe. So the diagnosis at this point was CBS. However, over a three month course, his symptoms evolved (second Video section) with evidence of continuous myoclonic jerks, right-sided proprioceptive ataxia and drowsiness. His condition still worsened and was rapidly fatal. A neuropathological study was then performed.

Results: The initial clinical presentation of unilateral apraxia and sensory deficiency was suggestive of CBD. However, the clinical course became inconsistent with this diagnosis. The rapid evolution to death over 3 months, the EEG findings and positive 14-3-3 protein in CSF led to the diagnosis of CJD. Finally, the neuropathologic study confirmed the presence of Prion's protein. Atypical CJD have been described in some variant of this disease with this clinical phenotype of unilateral limb apraxia like in CBS.

Conclusions: When a patient develops a rapidly evolutive CBS, the hypothesis of CJD should be first considered, and all the classical paraclinical exams have to be performed (CSF 14-3-3, MRI diffusion, EEG, genetic analysis of codon 129). However, only neuropathological study can definitely confirm this hypothesis as in our case report.

Tu-115

Computerized tracing in Huntington patients: A standard measure for hyperkinetic activity

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Objective: Development of a simple and useful objective test for quantification of hyperkinetic activity.

Background: The most prominent symptom of Huntington's Disease (HD), which is historically also named Chorea Huntington, is hyperkinesia, which initially increases during the course of the disease. This symptom impairs both fine and–in progression increasingly–large and postural motorial co-ordination. For the staging of HD patients the Unified Huntington's Disease Rating Scale (UHDRS) is well established. Beyond already early in history there are very different approaches to quantify the motor impairment objectively with instrumental methods. These up to now only were poorly accepted for routine examination however due to lacking standardization and complex requirements on equipment.

Methods: We developed a new fully computerized technology for the analysis of special drawing tasks (Graphimetry), in order to quantify the motor impairment in HD. For this purpose we use standardized forms that are scanned with the patients' drawings. We analyzed the relation between measurement outcomes and clinical rating as well as the differences between HD-patients (n=54) and healthy controls (n=32).

Results: Our results of comparison of HD patients in different clinical stages with healthy control persons are particularly promising concerning selectivity between healthy control persons and patients with very slight hyperkinesia. Graphimetric parameters showed high correlation with clinical ratings (UHDRS).

Conclusions: Graphimetry can contribute to staging and standardized therapy control. Since it can be used also at patient's home repeatedly it can provide more detailed information about course of degeneration. During longitudinal examination of gene carriers without any symptoms it could help to identify the onset of disease more exactly.

Tu-116

Intrahippocampal NAC_{61-95} injections in the rat: Attenuation of behavioural effects following vitamin-E treatment

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Objective: The objective of the current study was to evaluate the behavioural effect of pre-aggregated NAC_{61-95} injection into the CA3 area of the dorsal hippocampus of the rat, and to determine whether this effect could be attenuated following treatment with the antioxidant, vitamin-E.

Background: Parkinson's disease (PD)-related dementia affects approximately 40% of patients and the severity of the dementia correlates significantly with the desity of Lewy body (LB) deposition in the brain. Aggregated alpha-synuclein protein is the major component of LB's and the non-amyloid component (NAC) region of alpha-synuclein, residues 61-95, is essential for the aggregation and toxicity of this protein. Previous research has suggested that processes related to oxidative stress may play a role in the neuropathology of PD, therefore the effect of treatment with vitamin-E, an antioxidant, was also evaluated.

Methods: Twenty four male Sprague-Dawley rats were trained under an alternating-lever cyclic-ratio operant schedule of food reinforcement. When responding showed no trends, subjects were divided into four groups. Two groups were injected bilaterally into the CA3 area of the hippocampus with aggregated NAC_{61-95} (5 ul suspension), and two groups with sterile water (5 ul). Subgroups were treated with either vitamin-E (150 mg/kg in Soya oil) or vehicle (Soya oil) administered orally twice daily.

Results: The results showed that NAC_{61-95} induced learning and memory deficits and that vitamin-E treatment alleviated these effects. In addition, NAC_{61-95} induced astrocytic activation and vitamin-E treatment significantly reduced the numbers of activated astrocytes.

Conclusions: The results of this study suggest that aggregated NAC_{61-95} and associated oxidative stress may play a role in the pathogenisis of cognitive deficits seen in PD-related dementia.

We-115

Quantitative map of hypoperfusion in 62 stereotactic cerebral cortical segments by IMP-SPECT reveals a specific pattern of Lewy body dementia

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Objective: This study aimed to display quantitatively cerebral hypoperfusion map consisting of 62 anatomical segments of Lewy body dementia (LBD) patients, and to reveal its difference from Alzheimer's disease (AD).

Background: SPECT has demonstrated localized hypoperfusion of cerebral cortex characteristic to LBD or AD. Although these localizations have been demonstrated regarding anatomical structures such as gyri of brain, visual assessment of hypoperfused structures is often obscured by usual pixel-by-pixel images of SPECT.

Methods: In age-matched LBD (n=5) and AD patients (n=5), IMP-SPECT data were collected. 3D-SSP analysis[1] was employed to evaluate the cortical distribution of hypoperfusion. Normalized brain activity of each patient was compared with normal controls by pixel-by-pixel Z-score = (control mean value – patient value)/control SD. Stereotactic extraction estimation (SEE) method[2] was used to classify anatomically the cerebral cortex into 31 segments for each hemisphere on gyrus-basis, and to estimate the extent of hypoperfusion of each segment (E(Z≥2)) by calculating the rate of pixels with Z-score≥2 in each segment.

Results: In LBD, differences in E(Z≥2) were often found between the right and left sides of cerebral hemisphere. Mean E(Z≥2) ratio of the larger/the smaller side was 9.9 in the superior occipital gyrus.

Hypoperfused segments exceeding E(Z≥2) 60% were the superior, middle and inferior occipital gyri and lingual gyrus in LBD, and the superior and inferior temporal gyri and cingulated gyrus in AD (Table 1). Statistical comparison between LBD and AD revealed hypoperfusion with significantly more E(Z≥2) in the superior occipital gyrus (81±22 vs 32±40%, mean±SD), middle occipital gyrus (69±15 vs 37±24), inferior occipital gyrus (89±8 vs 10±13), cuneus (53±18 vs 0.6±1.1) and lingual gyrus (70±11 vs 0±0) of LBD. The superior temporal gyrus and cingulate gyrus tended to show hypoperfusion with more E(Z≥2) in AD.

Table (We-115). Extent of hypoperfusion (E(Z≥2)) in selected 12 anatomical segments of the brain

	Lewy body dementia	Alzheimer's disease
Superior Temporal Gyrus		♠♠
Middle Temporal Gyrus	♠	♠
Inferior Temporal Gyrus	♠	♠♠
Transverse Temporal Gyrus	♠	♠
Superior Occipital Gyrus	♠♠♠*	
Middle Occipital Gyrus	♠♠*	
Inferior Occipital Gyrus	♠♠♠*	
Cuneus	♠*	
Lingual Gyrus	♠♠*	
Cingulate Gyrus		♠♠
Anterior Cingulate		♠
Uncus		♠

♠40–59%, ♠♠60–79%, ♠♠♠80–100%, mean values of E(Z≥2), n=5., *p<0.05 compared with Alzheimer's disease by Student t-test.

Conclusions: Cerebral E(Z≥2) map consisting of 62 anatomical cortical segments has demonstrated a different pattern of hypoperfusion between LBD and AD patients. This automatic method of SPECT analysis will provide practical information for differential diagnosis of dementia. References: (1) Minoshima S, et al. J Nucl Med 36:1238, 1995. (2) Mizumura S, et al. Ann Nucl Med 17:289, 2003.

We-116

Whole brain diffusion tensor imaging in Parkinson's disease, Parkinson's disease with dementia and dementia with Lewy bodies

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Objective: To evaluate the changes of white matters(WM) in the brain of patients with Parkinson's disease (PD), Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB), using fractional anisotropy (FA) valvues.

Background: The relationship between PDD and DLB is not fully understood. They are considered as a same disease spectrum or not.

Methods: 65 subjects (PD n=25, PDD n=15, DLB n=10 and 15 age-matached controls) were included in this study. The patients with PD fulfilled with the UK Parkinson's Disease Society Brain Bank criteria. Diagnosis of PDD was based on the diagnosis on the MDS Task Force and probable DLB was diagnosed accordig to the criteria suggested by the third report of the DLB Consortium. FA images were generated from high-resolution diffusion tensor imaging protocol at 3.0 T with using an eight-chnnel sensitivity-encoding (SENSE) head coil and they were analyzed with statistical parametric mapping.

Results: In patients with PD, there were more FA reduction in bilateral parietal and occipital WM compared with controls ($p<0.005$). The PDD group showed significant FA reduction in the WM of the right frontal, left temporal, bilateral parietal and corpus callosum compared with controls ($p<0.005$). The PDD groups had more FA reduction only in the WM of right temporal lobe than the PD group ($p<0.005$). The DLB group showed more FA reduction in the WM of bilateral frontal, temporal, left parietal and right middle cerebellar peduncle (FDR $p<0.05$). Compared with the PDD patients, the patients with DLB exhibited significantly reduced FA in the WM of the bilateral frontal, tempoal, left temporal and right cerebellum ($p<0.005$).

Conclusions: Our study demonstrated that the patients of DLB had more FA reduction than those of PDD. Our results suggest that PDD and DLB may be not one spectrum of disease but different subtypes of dementia.

We-117

The CERAD-(plus) neuropsychological battery does not clearly differentiate Parkinson's disease dementia from Alzheimer's disease and mixed dementia

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Objective: Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are characterized by impairment in attention, memory, executive and visuospatial functions, and behavioural and psychiatric symptoms. The question arises whether cognitive impairment in PDD and DLB is different from that in Alzheimer (DAT) or mixed dementia (MD; DAT and vascular dementia).

Background: Suggestions have been made to operationalize the neuropsychological diagnosis of PDD (Dubois 2007). We tried to find out whether the CERAD-(plus) battery differentiates PDD/DLB from DAT and MD.

Methods: 133 patients with DAT (McKhann 1984), 165 with MD, and 64 patients with PDD/DLB (Emre 2007, McKeith 2005) were tested by means of the CERAD-(plus). The trail making test was not included because of the slowing of motor functions in PDD/DLB. Results of the CERAD-plus subtests are expressed as Z-scores related to historical normal controls of comparable age, years of education, and gender (Monsch 1998). Z-scores lower than –1.28 indicate significant impairment.

Results: PDD/DLB patients demonstrated significant deficits in semantic word fluency (animals; Z-score -1.5), naming of objects (Boston naming test; -1.4), learning (-2.3) and retention (-1.6) of 10 words, discrimination of the learned words from other words (-1.6), copy (-1.8) and retention (-1.9) of geometrical figures. There were no significant differences in the Z-scores between PDD/DLB patients, patients with MD, and DAT patients except for retention of 10 words. In this subtest PDD/DLB patients scored better than DAT and MD patients (p=.05). ROC-curves, however, showed no discrimination of the subtests between the dementias (AUC values not significant).

Conclusions: CERAD-plus did not differentiate between DAT, MD, and PDD/DLB. Unexpectedly, CERAD-subtests of visuospatial and frontal-executive functions did not reveal differences between the groups. Overlap of Lewy and Alzheimer pathologies might explain the lack of discrimination between DAT and PDD/DLB. The differential diagnosis between these three groups is primarily based on clinical criteria including differences in attention and behavioural and psychiatric symptoms.

We-118

Olfactory dysfunction in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17)

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Objective: To evaluate olfactory dysfunction in the large Polish family with FTDP-17 due to the P301L mutation in the tau gene (*MAPT*).

Background: FTDP-17 is characterized clinically by cognitive impairment, behavioral changes and motor symptoms (parkinsonism). The mean age of onset (49 years) is younger than that of the overall FTLD population. Olfactory dysfunction is recognized as a common non-motor symptom in neurodegenerative disorders (e.g. in Parkisons disease) and may precede the occurence of motor, psychiatric or cognitive impairment (it might be a possible early marker).

Methods: 35 members of large Polish FTDP-17 family were screened for *MAPT* mutation and 2 symptomatic and 5 asymptomatic P301L mutation carriers(AS) were identified. The University Pennsylvania Smell Identification Test (UPSIT) was performed in 11 family members (4 AS and 7 non-carriers (NC)). 2 symptomatic mutation carriers were not able to perform UPSIT due to advanced stage of disease. Beside UPSIT, full neurological examination, as well as medical and family history was obtained. The examiners were blinded to carrier status before conducting the evaluations and analyses of data.

Results: We compared UPSIT score of 4 AS (1 male(m), 3 female(f)), mean age at UPSIT(AAT): 29 years and 7 NC (5 m, 2 f), AAT: 37 years. UPSIT of AS was between 27-33 points. 2 AS subjects presented with mild-(1 m, 1 f) and 2 with moderate microsmia (2 f). UPSIT of NC was between 24-35 points. 2 NC subjects presented with normosmia (2 m), 1 subject with mild- (1 f), 2 subjects with moderate- (1m, 1 f), and 2 subjects with severe microsmia (2 m).

Conclusions: Some olfactory deficits were observed, but there was no significant difference in the UPSIT score between asymptomatic mutation carriers and non-carriers**.** The lack of an association between olfactory deficits and carrier status in our family may results from relatively young age of mutation carriers with presumably long-time period to possible occurence of disease symptoms. Follow-up would be helpful for early recognition of a deterioration.

Th-117

Visual hallucinations are related to gray matter volume in the dorsal visual pathway in Dementia with Lewy bodies and in the orbitofrontal cortex in Parkinson's disease with dementia

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Objective: To investigate the gray matter correlations of visual hallucinations in clinically diagnosed patients with DLB and PDD.

Background: Visual Hallucinations (VH) are one of the core features of Dementia with Lewy Bodies (DLB), but are also present in Parkinson's disease with Dementia (PDD). There is controversy regarding whether DLB and PDD may or not be different manifestations of the same disorder. In both VH are quite prevalent.

Methods: Conductual and a voxel-based morphometry study to 12 patients with clinical diagnosis of DLB (6 with VH and 6 without them) and 15 with PDD criteria (8 with VH and 7 without them). The brain structures related to visual hallucinations in DLB and PDD were assessed using statistical software SPM5. The severity of visual hallucinations was quantified by using the Neuropsychiatric Inventory Scale (NPI – Cummings, 1994) and qualitatively by the Visual Changes Questionnaire (Barnes J., Davis AS., 2001). Formed visual hallucinations were defined as "repetitive involuntary images of people, animals or objects that were experienced as real during the waking state but for which there was no objective reality" (Collerton 2005). Demographics are shown in table 1.

Results: There were no significant differences in between groups concerning severity and frequency of VH. In the brain volume group-comparisons, we didn't find gray matter volume differences between the DLB with VH and PDD with VH. Furthermore, the PDD patients with VH had greater gray matter atrophy in the left orbitofrontal area (BA 10) than the PDD without them (table 2, figure 1). We did not find differences in gray matter volume between DLB with VH and DLB without them. However, in the DLB group visual hallucinations were inversely related to right inferior frontal gyrus (r = 0.89) and left precuneus (r = 0.95) volume but not in the PDD group.

Table 1 (Th-117). Demographic and clinical characteristics of the sample

	PDD (n=15)	DLB (n=12)	p-value
Sex (M:F)	10:5	8:4	NS*
Age	72,7 (6,4)	71,1 (10,8)	NS**
Education	6,3 (6,2)	11 (6)	NS**
GDS	4,2 (1)	4,1 (1)	NS**
Corrected MMSE	22,3 (3,7)	19 (6,2)	NS**
UPDRS-III	35,8 (12,2)	27,2 (11)	0.032
Hoehn and Yahr	2,7 (0,7)	2,8 (0,6)	NS**
Disease duration (months)	24 (18)	34 (16,2)	NS**
Levodopa dose (mg)***	634,2 (271,5)	412,5 (466,6)	NS**
Visual Hallucination (NPI)	2,5 (2,3)	2,6 (3,1)	NS**

Values expressed as mean (SD). NS = not significant. *Pearson's Chi-square. **U-Mann Whitney. ***Including dopamine agonists.

Table 2 (Th-117). Location and Talairach coordinates of significant clusters of gray matter volume loss in PDD with VH compared with PDD without them (ANOVA)

Location (BA)	Cluster p corrected	Cluster size (mm)	Talairach coordinates (x, y, z)	t-value
Left orbitofrontal (10)	0.012	665	−45, 47, 17	5,43

Conclusions: There were no differences in the presence of VH in DLB and PDD. In the PDD group, the patients that present VH had greater gray matter atrophy in the left orbitofrontal area. However, in the DLB group, the dorsal visual pathway structures were related to visual hallucinations.

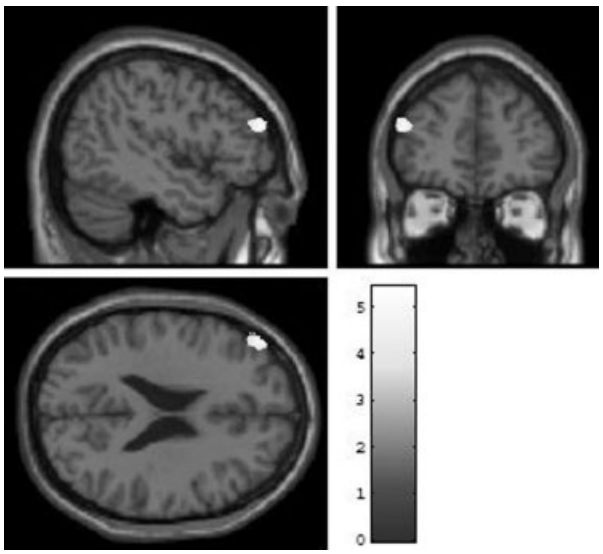

FIG. 1 (Th-117).

Th-118

Effects of daytime or nocturnal hypoxemia on cognitive impairment in patients with multiple system atrophy

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Objective: To investigate whether cognitive impairment in patients with multiple system atrophy (MSA) results from daytime hypoxemia or nocturnal desaturation associated with sleep-disordered breathing.

Background: Recent studies have demonstrated that MSA patients develop cognitive impairment. However, little is known about the factors influencing the symptom. Recent studies also demonstrated that MSA patients develop daytime hypoxemia and nocturnal desaturation associated with upper airway obstruction or central respiratory dysfunction. Because hypoxemia has been shown to be one of the contributors to frontal lobe impairment in patients with amyotrophic lateral sclerosis, we investigated whether cognitive impairment in MSA is influenced by daytime or nocturnal hypoxemia.

Methods: Consecutive patients with probable MSA were recruited and prospectively performed Unified Multiple System Atrophy Rating Scale (UMSARS), cognitive function tests such as mini-mental state examination (MMSE) and frontal assessment battery (FAB), daytime blood gas analysis, and polysomnography. We investigated the relationships between cognitive impairment and parameters representing daytime and nocturnal hypoxemia such as daytime PaO2, nocturnal SpO2, apnea index (AI), and apnea-hypopnea index (AHI).

Results: Seventeen patients with probable MSA (13 MSA-C, 4 MSA-P) were recruited. The mean age at onset was 60.5±7.6 years, and mean disease duration was 47.5±5.5 months. Cognitive impairment based on MMSE was seen in 5 patients (31.3%), and frontal lobe impairment based on FAB was seen in 6 patients (40.0%). Daytime PaO2 was 80.1±9.3 torr, and nocturnal SpO2 was 88.1±4.5%. Although a correlation between MMSE and UMSARS was observed (r2=0.345, P=0.021), there were no significant correlations between MMSE and disease duration or age at onset. Furthermore, there were no correlations between MMSE and daytime PaO2, nocturnal SpO2, AI, or AHI. A decrease in FAB score was not influenced by the disease duration, age at onset, daytime PaO2, nocturnal SpO2, AI, or AHI.

Conclusions: We demonstrated that cognitive impairment in MSA is not correlated with the severities of daytime and nocturnal hypoxemia, suggesting that cognitive impairment in MSA represents an important and independent part of the phenotype of MSA.

Th-119

Interhemispheric inhibition in Alzheimer's disease

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Objective: To investigate interhemispheric inhibition (IHI) in Alzheimer's disease (AD) using transcranial magnetic stimulation (TMS).

Background: Several reports showed that the corpus callosum was abnormally small in some patients with AD. Since the bilateral primary motor cortices have mutual connection through the corpus callosum, we hypothesized that IHI is abnormal in AD.

Methods: Seven AD patients (4 male and 3 female patients) and 7 healthy subjects were enrolled. All the patients were classified as probable AD based on NINCDS-ADRDA Work Group criteria. The patients were 71 to 82 years old, their mean duration of the disease was 3 years and the mean Mini-Mental State Examination (MMSE) score was 23. The IHI was studied with a paired-pulse TMS technique. The conditioning TMS was given over the right motor cortex and the test TMS over the left motor cortex at interstimulus intervals (ISIs) of 4 to 12 ms. Motor evoked potentials (MEPs) were recorded from bilateral first dorsal interosseous (FDI) muscles. The intensities of both conditioning and test stimuli were set to elicit 0.5 to 1 mV MEPs in relaxed FDI muscles.

Results: The size ratios (conditioned MEP/ control MEP) at ISIs of 6 to 10 ms were significantly greater ($p<0.05$) in AD patients than normal subjects. Neither MMSE score nor duration of the disease had any significant correlation with the degree of IHI abnormality.

Conclusions: Our results suggest that transcallosal connection between bilateral primary motor cortices is impaired in AD. This physiological finding may reflect morphological atrophy of callosal fibers and also explain some disinhibition of the motor cortex, such as myoclonus. The abnormal IHI reduction in AD patients may partly explain some motor dysfunction in AD.

Th-120

Autopsy proven diffuse Lewy body disease (DLBD) and Alzheimer's disease (AD) presenting as progressive aphasia and levodopa-responsive parkinsonism

S.E. Zauber, E.J. Cochran (Chicago, Illinois)

Objective: Report an unexpected clinicopathological correlation.

Background: The combination of aphasia and parkinsonism occurs in frontotemporal dementias, but has rarely been described with AD or combined AD/DLBD pathology. We have not found a prior report of the combination of expressive aphasia with clear levodopa responsive parkinsonism with pathological correlation.

Methods: Clinical, pathological, and imaging data are reviewed.

Results: A 57-year-old, right handed woman had a 3 year history of slowly progressive language dysfunction and falls. Behavioral changes included impulsivity, poor driving, and difficulty managing finances. A right arm rest tremor, bradykinesia, slow gait improved markedly with dopaminergic medicines, but wearing off and peak dose dyskinesia occurred. Her mother died at age 79 of dementia. On exam, she had a non-fluent aphasia, rest tremor with myoclonus and severe bradykinesia in the right arm, stooped posture, and decreased stride length. Postural instability, bradykinesia, and tremor resolved fully in the ON state, but she developed dyskinesia. SPECT scan showed decreased perfusion in left frontal, temporal and parietal lobes, despite normal MRI and CT angiography. Motor fluctuations improved with changes in timing of doses; however aphasia, mood, and behavior worsened. Autopsy showed changes of both AD and diffuse Lewy body disease (DLBD). There was moderate neuronal loss and frequent Lewy bodies in the substantia nigra. Numerous cortical Lewy bodies (α-synuclein immunohistochemistry) and moderate to numerous neuritic plaques were present in the neocortices, as well as Braak stage 5 neurofibrillary tangle deposition (modified Bielschowsky stain). Broca's area contained numerous neuritic plaques, but no neurofibrillary tangles.

Conclusions: We have presented a patient with expressive aphasia and drug-responsive parkinsonism who had AD and DLBD at autopsy. This uncommon clinical presentation of AD and DLBD should be kept in mind with patients with symptomology and findings suggestive of frontotemporal dementia.

MYOCLONUS

Mo-120

Intractable hiccup (IH): Underlying causes and management

C. Ha (Inchon, Korea)

Objective: To evaluate (1) underlying causes and (2) management of patients with intractable hiccup (IH).

Background: Hiccup is a sudden contraction of the inspiratory muscles terminated by abrupt closure of the glottis with the characteristic sound. It may be 'persistent' (over 48 hours) or 'intractable' (over a month). Intractable hiccup is a very troublesome entity,

which disturbs speech, respiration, eating and sleep, and subsequently impacts on quality of life.

Methods: We define that IH is a continuous hiccup over 4weeks. We have enrolled 12 patients with IH over last 5years. We reviewed medical records and imaging studies.

Results: Of 12 patients man was 10, mean age of onset was 61.91 year (range 50-71). Mean duration of IH was 7.12 weeks (range 4-12). The most common cause of IH was ischemic cerebral infarction(7), of which lateral medulla infarction were 3, pontine infarction 3 and bilateral middle cerebral artery infarction 1. Other causes were esophageal varix with liver cirrhosis(2), lung cancer with pleural invasion(1), reflux esophagitis(1) and idiopathic(1). All patients were tried to treat with the combination of Levosulpride, Baclofen and/or Omeprazole. Seven patients were effectively subsided with combination of Levosulpride and large dose of Baclofen. IH in others stopped with add of Omeprazole. IH usually reduced in frequency over 1-2 days and completely disappeared in 3-4 days after use of above drug combination.

Conclusions: We observed the most common cause of IH was pontomedullary lesion and combined drug therapy of Levosulpride, Baclofen and/or Omeprazole was very successful in management of IH with any underlying cause.

Mo-412

Myoclonic hypoxic encephalopathy: Presentation of 2 cases and review of the literature

R. Zaidan, A.A. Al Zeer (Riyadh, Saudi Arabia)

Objective: Study the clinical features of myoclonic hypoxic encepalopathy in 2 young patients. Show improvement of myoclonus on Piracetam.

Background: Myoclonic hypoxic encephalopathy is a rare disabling situation occurring after exposure of the brain top hypoxia. The severity of this disorder depend of the duration and severity of hypoxia. Myoclonus is a manifestation that may disable the patient for long time after improvement of higher mental functions and improvement may be fascinationg in some cases.

Methods: We studied the clinical features in 2 patients admitted in ICU care of KK University Hospital with the diagnosis of hypoxic encephalopathy. They have been followed up after their discharge in OPD neurology clinic. Video EEG has been done at during admission and later on.

Results: Both patients have been mechanically and had higher mental dysfunctions, initially severe, that have improved progressively and developped severe and disabling postural myoclonus short time after their admission. The myoclonus has persisted longer time before starting improving slowly and progressively. Relatively high dose of Piracetam has been given to the patients and video recording done 2 times, has shown dramatical improvement.

Conclusions: Myoclonic hypoxic encephalopathy may improve dramatically as in our patients who received Piracetam medication.

Tu-117

Altered motor cortical plasticity induction by quadripulse stimulation in benign adult familial myoclonic epilepsy

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Objective: Quadripulse stimulation (QPS) is a promising tool to induce bidirectional motor cortical plasticity in normal subjects (Hamada et al., J Physiol, 2008). There was a non-linear relationship between the sign and duration of QPS-induced plasticity and the inter-stimulus interval between the succeeding four monophasic pulses in the QPS burst; QPS at short-intervals induced long-lasting facilitation of motor evoked potential (MEP), whereas QPS at long-intervals produced lasting depression. The results showed that the mechanism of QPS-induced plasticity favors the long-term alteration of synaptic efficacy, such as long-term potentiation (LTP) or long-term depression (LTD). Here we investigate whether long-interval QPS induces LTD-like plasticity in patients with benign adult familial myoclonic epilepsy (BAFME).

Background: Several lines of evidence suggest that gamma-animobutyric acid (GABA) plays an important role for a regulation of synaptic plasticity: GABA blocker occluded LTD in hippocampal slices. Since dysfunction of GABAergic interneurons in the primary motor cortex has been suggested in BAFME, we hypothesized that LTD-like plasticity induced by long-interval QPS is also occluded in patients with BAFME.

Methods: Four patients with BAFME and 10 normal subjects were enrolled. Conditioning protocols consisted of 360 trains of TMS pulses with inter-train interval of 5 s (i.e., 0.2 Hz) for 30 min applied over the primary motor cortex. Each train consisted of four monophasic pulses separated by 50 ms interval (i.e., long-interval QPS). Cortical changes after QPS were evaluated with MEPs for 60 min.

Results: In normal subjects, MEPs were inhibited by long-interval QPS for 60 min, in line with our previous reports. By contrast, there were no changes in MEPs in BAFME.

Conclusions: Results indicate that the patients with BAFME are less susceptible to LTD-like effect by long-interval QPS. Although further studies are needed to clarify its mechanisms in detail, the activity of GABAergic interneurons might be essential for QPS-induced LTD-like plasticity.

Tu-118

Paroxysmal unilateral cortical arm myoclonus induced by holding a weight

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Objective: To report a novel form of reflex seizures induced by holding a weight in a certain position.

Background: Reflex seizures are epileptic events triggered by specific stimuli, either simple sensory stimuli or less commonly more complex or cognitive activities, often with an emotional component. Visual stimuli are the most common triggers, seizures induced by auditory, olfactory, or vestibular stimuli, thinking, reading, eating, music, praxis, somatosensory and proprioceptive stimuli, hot water, sexual arrousal or startle are less frequent.

Methods: We performed a diagnostic workup including MRI, Video-EEG telemetry, EEG-EMG recording during an attack, SEPs and extensive blood analysis in a patient who presented with paroxysmal involuntary movements of his right arm almost invariably elicited by holding a weight in his right hand in a certain position. The jerks which were not associated with any alteration of consciousness exceeded the actual holding of the weight lasting up to 20 minutes.

Results: Video-EEG telemetry recorded typical attacks triggered by holding a weight in the outstretched right arm. The semiology consisted of dystonic posturing of the right hand with myoclonic jerks affecting mainly index finger and thumb but spreading to other muscle groups in the hand and forearm. Ictal EEG demonstrated a focal build up of sharp activity over the left centroparietal region, interictal EEG was normal. EMG-EEG during an attack showed brief burst of muscle activity lasting 50-100 ms, "silent periods" lasting 50-300ms and a rhythmic slow activity in the left frontocentral area, suggestive of cortical myoclonus. Video-EEG-EMG with back averaging revealed a definite correlation of forearm EMG activity with EEG activity at C3. MRI brain scan, SEPs and blood analysis were reported as unremarkable. In consideration of the clinical presentation and the results of the investigations a diagnosis of reflex epilepsy was made and the frequency of attacks was significantly reduced with carbamazepine.

Conclusions: To our knowledge this is the first report of reflex seizures (cortical myoclonus) triggered by holding a weight in a certain position. Therefore weight-induced reflex seizures can be added

to the possible differential diagnosis in patients with paroxysmal hyperkinetic movement disorders.

Tu-119

Multifocal cortical myoclonus in a patient with middle pharyngeal cancer

Y. Motoi, N. Izawa, K. Chijiiwa, K. Sakai, A. Hayashi, Y. Okuma, M. Nagaoka, H. Miwa, Y. Mizuno, N. Hattori (Tokyo, Japan)

Objective: To describe cortical myoclonus in a patient with middle pharyngeal cancer

Background: there was no report in that patients with paraneoplastic neurological disorders showed cortical myoclonus.

Methods: We analyzed clinical features and electrophysiological examinations of a patient who developed cortical reflex myoclonus with middle pharyngeal cancer.

Results: A 69-year-old man was admitted because of rapidly progressive involuntary movement of the right leg and the left arm for two weeks in August 2004. He had been diagnosed with left middle pharyngeal cancer two weeks before the onset. There was involuntary arrhythmic myoclonus in the right leg, left arm, left diaphragma and the left soft palate. Myoclonus was most prominent on action, but also occurred at rest. Finger-to nose testing of the left arm and heel-to knee testing of the right leg were ataxic probably due to enhanced action myoclonus. His blood testing revealed normal. The surface electromyogram (EMG) showed irregular and brief discharges involving agonist and antagonist muscles synchronously. Giant somatosensory evoked potentials (SEPs) evoked by a stimulation of the median nerve and tibial nerve were recorded and the C reflex was also recognized. Jerk-locked back averaging (JLA) demonstrated EEG discharges in the left extensor carpi radialis and in the right tibialis anterior. The patient received 1 g methylprednisolone intravenously daily for 3 days. His neurological symptoms slightly relieved. Two weeks later he received total tumor removal. The cytology revealed squamous cell carcinoma. Two weeks later he developed secondary generalized myoclonic seizure starting in the right leg spreading to the left leg and both arms. After this complex partial seizure, his myoclonus worsened in his right leg and left arm. Four mg of clonazepam and 1 g methylprednisolone alleviated his symptom. His symptoms gradually relieved. In August 2008, the patient is, apart from a remaining myoclonus of the right leg, in good general condition and without signs of tumor recurrence.

Conclusions: The present case illustrates the possible link between cortical myoclonus and paraneoplastic neurological syndrome.

Tu-412

Hemifacial spasm resulting from a herpes zoster ophthalmicus infection: A new causative etiology with review of the English literature

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Objective: To report a new causative etiology of hemifacial spasm (HFS) that has not been previously reported.

Background: Hemifacial spasm (HFS) is a unilateral or bilateral involuntary contraction of the muscles innervated by the facial nerve. It is well established that the etiology of HFS results from a variety of causative conditions which irritate the facial nerve. In reviewing the English literature, these conditions are usually secondary to vascular compression, but could include both compressive and non-compressive lesions such as tumors, aberrant blood vessels, and multiple sclerosis plaques. Herpes zoster is known to affect the facial nerve in Ramsay Hunt Syndrome; however, viral illnesses, specifically herpes zoster, have never before been reported as a causative etiology for HFS.

Methods: We conducted a case study of a patient seen in the Movement Disorders center at our institution. A review of the English literature was conducted using PubMed and Ovid.

Results: A 54 year old Caucasion male was diagnosed by his primary care physician as having a herpes zoster rash in the distribution of the left ophthalmic division of the trigeminal nerve, with additional peri-auricular erythema without discernable blisters in the ear, and without facial palsy. He completed a course of valcyclovir 500 mg tid for 10 days. Approximately 2 weeks after the infection, he began experiencing involuntary left periorbital muscle contraction which over the next year progressed to also involve the left lower face resulting in severe left hemifacial spasm. He was evaluated at the Movement Disorders Clinic at our academic institution. An MRI and MRA of the brain was normal including the posterior fossa and facial nerve. The patient's HFS has responded well to botulinum toxin injections.

Conclusions: This is the first case report of HFS resulting from herpes zoster ophthalmicus. This expands the differential diagnoses for causative etiologies of HFS. The use of Corticosteriods along with antiviral therapy in acute herpes zoster infection has been under debate; however we speculate that the use of Corticosteriods potentially reduces inflammation decreasing the chance of facial nerve irritation and damage thereby potentially preventing not only Ramsay Hunt syndrome, but also potential HFS.

We-119

Anti-Glutamic acid decarboxylase antibodies: A Brazilian neurological series

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Objective: To present the clinical and laboratory data of nine neurological patients with anti-glutamic acid decarboxylase antibodies (GAD-Ab) syndrome.

Background: GAD-Ab has been described in patients with insulin-dependent (type 1) diabetes mellitus, stiff-person syndrome (SPS) and rarely in patients with cerebellar ataxia, epilepsy and progressive encephalomyelitis with rigidity.

Methods: During a three year period, 11 patients with different neurological syndromes were assessed at our service presenting positive GAD-Ab. All underwent complete clinical and paraclinical investigations including immunological and imaging studies.

Results: Six (54,5%) of the 11 cases were men, with mean age 42 years. SPS was diagnosed in 8 patients (2 with the classical form, 4 with stiff-lower-limbs, 2 with stiff-limb syndrome), and three with cerebellar ataxia. GAD Ab titers were elevated in all cases, ranging from 1.4 U/ml to 85.8 U/ml. EMG testing showed the classical findings of SPS in two cases. Hypothyroidism with Hashimoto's thyroiditis was found in 4 cases, three had epilepsy and one had diabetes mellitus type 2. Brain and spine imaging were normal and CSF analysis showed mild lymphocytic pleocytosis in two cases.

Conclusions: In this series of 11 Brazilian cases of GAD-Ab syndrome we found 8 cases with the SPS, showing different presentations and three cases of cerebellar ataxia. Cases were associated with autoimmune hypothyroidism, epilepsy and DM.

We-120

Neurologic outcome in adult onset idiopathic Opsoclonus-Myoclonus syndrome

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Objective: To study the phenomenology and response to treatment of adult onset idiopathic Opsoclonus-Myoclonus Syndrome (OMS).

Background: In adults, OMS is often attributable to underlying neoplasm but is just as commonly idiopathic. Previous reports suggest variable outcomes in idiopathic versus paraneoplastic OMS.

Methods: 3 cases of adult onset idiopathic OMS which presented at our institution over a 4 month period were included in the study. All patients were followed up for an average of 7 months. All patients were video taped prior to treatment.

Results: The patients were females with a mean age of 53 (range 27 to 78 years). All had an acute onset of visual disturbance, gait difficulty, and uncontrollable jerking, with exam consistent with

OMS. Two of the patients experienced antecedent viral illnesses: one sinusitis, the other gastroenteritis. All had ataxia requiring the aid of assistive devices. Imaging and paraneoplastic serology revealed no evidence for neoplasm. All patients received a combination of Intravenous Immunoglobulin (IVIg, 0.4 g/kg) and plasmapheresis (TPE). The first patient underwent TPE (7 treatments), followed by 5 doses of IVIg. At 9 month follow-up, she had mild residual opsoclonus, no myoclonus and a normal gait. The second patient received 5 doses of IVIg and was readmitted one month later with persistent symptoms for TPE (5 treatments). At 4 month follow-up, she was ambulating independently with mild opsoclonus. The third patient received 5 days of IVIg with improvement in vision and resolution of myoclonus. Five months later, she experienced worsening vision and gait and was readmitted for TPE (5 treatments) after which she had a normal gait and improved vision. No adverse side effects were noted with either IVIg or TPE. In these patients, opsoclonus, myoclonus and gait all improved with myoclonus and ataxia showing the greatest degree of improvement.

Conclusions: IVIg and TPE are well tolerated and should be considered as a treatment for adult onset idiopathic OMS. In idiopathic OMS, gait ataxia and myoclonus might be more likely to improve than opsoclonus. Further studies are indicated to elucidate whether this recovery is due to IVIg, TPE, or is the natural course of the disease.

We-121

Movement disorder turned out to be Epilepsy-Unverricht-Lundborg disease presenting to movement disorders clinic – A dilemma of epilepsy versus movement disorder

A.Q. Rana (Toronto, Ontario, Canada)

Objective: To discuss the dilemma of movement disorders versus epilepsy as shown by this interesting case of Unverricht-Lundborg Disease referred to Momvement Disorders Clinic for Kinesogenic Myoclonus.

Background: Sometimes patients with seizures are reffered to the movement disorder clinics considering they primarily have a movement disorder condition. This is particularly true in cases of myoclonic epilepsy. Carefull history taking may be all that is required to differentiate these two conditions. Unverricht-Lundborg Disease is an interesting example of such a dilemma. This is a rare cause of progressive myoclonic epilepsy caused by trinucleotide repeat expansion in the cystatin B gene located on chromosome 21. It is characterized by severe stimulus-sensitive myoclonus, generalized tonic-clonic seizures and abnormal EEG findings.

Methods: We present a case of 21 year old female referred to our movement disorders clinic to rule out a movement disorder. She had brief shock like jerking episodes triggered by emotional stress or other sudden movements. Her past history revealed that she had a generalised tonic- clonic seizure only once at the age of 11 years while in Pakistan and was started on Valproic acid without any recurrent episodes. At the age of 21, when she got pregnant, she stopped taking valproic acid and developed episodic jerks induced by sudden movement or emotional stress.

Results: MRI brain was normal. Genetic testing confirmed Unverricht-Lundborg disease.

Conclusions: Sometimes it may be chellanging to differentiate epilepsy from movment disorders. However epilepsy should be considered in differential diagnosis of certain movement disorders. Carefull history taking is very important in these cases.

Th-122

TENS for the treatment of propriospinal myoclonus

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Objective: To evaluate the effect of transcutaneous electrical nerve stimulation (TENS) on propriospinal myoclonus (PSM).

Background: The pathophysiology of PSM remains unclear, however, it has been suggested that an underlying mechanism may be a partial release of a limited spinal motor generator. While symptomatic treatment of PSM is often disappointing, TENS has been reported to be effective in certain movement disorders.

Methods: A 50- year-old man presented with a 6-year history of PSM beginning in the low-thoracic spinal level T9-T10 before spreading up to the intercostals (T6) and down to the iliopsoas (L3) muscles. All the medical he received were ineffective. By chance he noted that gentle self-rubbing of abdominal skin consistently suppressed the jerk. Then, TENS (80 Hz, 150-msec pulse width) was proposed as a symptomatic treatment. Electrodes were placed so that the electrical current was delivered over the area controlled by the low-thoracic spinal level.

Results: The intensity of the stimulation was gradually increased during an acute test: the abdominal contraction and its propagation decreased at 10 mA, disappeared at 12 mA and resumed immediately after TENS discontinuation. The intensity of 12 mA was considered as the efficacy threshold and TENS was then delivered chronically. Within the following three months the patient gradually decreased the intensity until 6 mA while at the same time maintaining efficacy.

Conclusions: We postulated that TENS mediated by large diameter afferent fibres, travelling in the dorsal root nerves might lead to recruitment of inhibitory interneurons active on the propriospinal premotoneurons. Interestingly, the antimyoclonic effect threshold decreased from 12 to 6 mA over several months with a maintained efficacy. This suggests that chronic TENS may: 1) modulate neuronal inhibition by changing levels of neurotransmitter within spinal chord and supraspinal pathway; 2) provoke plastic reorganization of cortical and chord circuits. This latest hypothesis is corroborated by the fact that prolonged TENS have been demonstrated to induce reciprocal changes in corticospinal motor neurons excitability. These changes are likely to occur at the cortical level and mainly depend on muscles afferents activation.

Th-123

Psychogenic "propriospinal myclonus" and transcutaneous electrical nerve stimulation

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Objective: To report a case of a myoclonus of thoracic spinal muscles with most likely psychogenic origin which showed a transient response to transcutaneous electrical nerve stimulation (TENS).

Background: Priopriospinal myclonus (PSM) involves muscles innervated by several segments of the spinal cord. Due to spreading activity via intrinsic propriospinal pathways slow intraspinal conduction velocity and selective recruitment of truncal and proximal limb muscles are features of this movement disorder. TENS has been reported to be effective in PSM. However, it has also been reported that clinical and polymyographic features can be mimicked voluntarily and can occur in psychogenic myoclonus. Thus it remains unclear whether TENS effects can also be found in psychogenic PSM reflecting placebo components of this treatment.

Methods: A 49 year old man with symmetric thoracalumbar muscle jerks was clinically and electrophysiologically examined including polymyography, jerk locked back averaged (JLBA)-EEG, somatosensory evoked potentials (SSEP) and long-loop reflexes (LLR). TENS effects on different thoracic, lumbar and sacral dermatomes were examined.

Results: Clinical features were suspicious of a psychogenic origin: sudden onset, changes in clinical occurrence and muscle recruitment, gait unsteadiness, different jerk patterns during standing and sitting, slowing of inter-jerk-interval when sitting for longer, jerk pauses during distraction. Myographic features were also not typical for true PSM: recruitment velocity between trunk muscles faster than 10 m/sec and jerk length of 500ms. LLR and SSEP showed no abnormalities, JLBA-EEG showed no pre-myoclonic spikes but revealed a

readiness potential beginning one second before movement onset proving a voluntary component of the jerks. TENS treatment of the L5/S1 dermatome was associated with a subjective electrical sensation and relief of pre-existing lumbar pain. Myoclonus was also decreased for a few days and gait unsteadiness was relieved. After one week this transient positive effect showed wearing off.

Conclusions: Clinical and electrophysiological findings suspect a psychogenic form of PSM. This psychogenic PSM was transiently decreased by TENS. TENS was subjectively related to electrical sensations and pain relieve. Thus, a placebo effect of TENS on PSM is considered.

NEUROIMAGING

Mo-121

Arterial spin labeling (ASL) perfusion with statistical parametric mapping in Parkinson's disease

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Objective: To investigate alterations in cerebral blood flow (CBF) as measured by Arterial Spin Labeling (ASL) MRI in patients with Parkinson's disease (PD) using statistical parametric mapping (SPM).

Background: Radiotracer studies have demonstrated changes in cerebral blood flow associated with Parkinson's disease. Non-invasive ASL MRI provides a new method to further investigate potential imaging biomarkers for PD.

Methods: We used a novel ASL sequence on a 3T GE HDx scanner to investigate CBF perfusion in a group of 31 PD participants (mean age: 68.2±10 years). Seventeen matched controls (mean age: 71.6±8 years) also completed MRI scans and neuropsychological testing. The PD participants were grouped into cognitively unimpaired (PDU; n = 16) and impaired (PDI; n = 15, comprising of 9 with mild cognitive impairment and 6 with dementia). CBF maps were preprocessed using SPM5. We employed a voxel-based analysis to identify differences in perfusion between groups; $p<0.05$ corrected for multiple comparisons by false discovery rate was considered significant.

Results: PDI showed significant hypoperfusion compared to controls in the posterior cingulate, precuneus, bilateral occipital cortex, superior parietal area, prefrontal cortex, temporal cortex, thalamus and caudate (fig 1). Neither PDI vs PDU nor PDU vs control comparisons reached statistical significance. Comparisons identified no hyperperfusion. A similar, more extensive pattern emerged when all PD patients were included (fig 2).

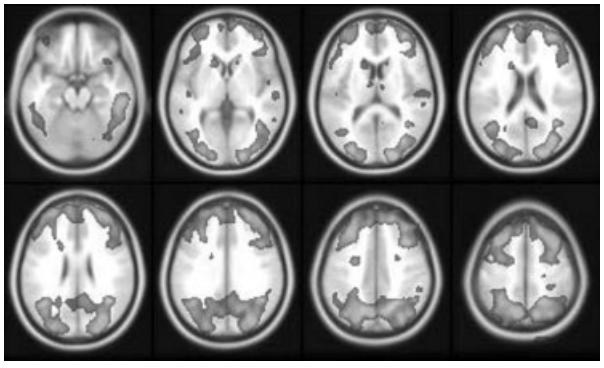

FIG. 1 (Mo-121).

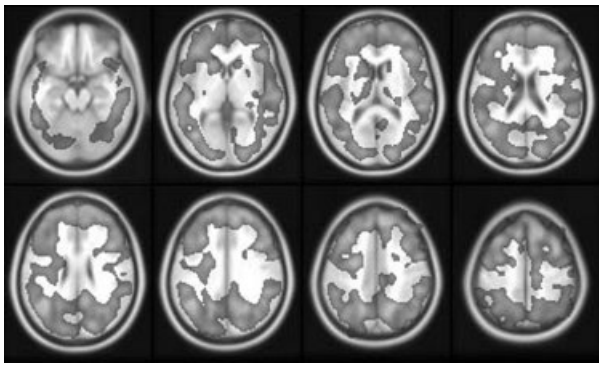

FIG. 2 (Mo-121).

Conclusions: This ASL study used a voxel-based approach to identify significantly decreased perfusion in PDI compared to controls. Although not significantly different, the PDU subgroup added to the cumulative PD hypoperfusion pattern. The combination of ASL and SPM is a potentially useful investigatory tool that in this study revealed reduced CBF in specific cortical and subcortical areas in PD persons with cognitive impairment.

Mo-122

Voxel-based morphometry and voxel-based relaxometry in the parkinsonian variant of multiple system atrophy

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Objective: To assess regional brain atrophy and iron content using Voxel-Based Morphometry (VBM) and Voxel-Based Relaxometry (VBR) respectively, in MSA-P patients and to assess whether brain atrophy affects regional T2 measurements, by combining VBM and VBR data using Biological Parametric Mapping (BPM).

Background: Multiple system atrophy (MSA) is a progressive, neurodegenerative disorder divided into a parkinsonian (MSA-P) and a cerebellar (MSA-C) variant, characterized on Magnetic Resonance Imaging by regional brain atrophy and changes in T2 relaxation time (T2).

Methods: Eleven patients with MSA-P (aged 61.9± 11.7years, disease duration 5.42 ± 2.5years) and eleven controls were studied. VBM and VBR analysis were conducted using Statistical Parametric Mapping (SPM 5) software. With BPM the effect of brain atrophy was evaluated in T2 measurements by applying ANCOVA and correlation analysis to the VBM and VBR data.

Results: In comparison to controls, patients showed decreased grey matter in the putamen, the caudate nuclei, the thalami, the anterior cerebellar lobes and the cerebral cortex, and white matter atrophy in the pons, midbrain and peduncles. VBR analysis showed prolonged T2 in various cortical regions. When controlling for grey and white matter volume, on ANCOVA, these regions of prolonged T2 relaxation time were reduced to insignificance. Negative correlation was demonstrated between T2 and grey and white matter volume.

Conclusions: Diffuse brain atrophy, mainly along the motor circuitry is observed in MSA-P patients. Normalization for atrophy should always be performed when evaluating T2 measurements.

Mo-123

Changes in brain metabolism and hyposmia in Parkinson's disease

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Objective: The purpose of this study is to determine whether changes in brain metabolism are related to the olfactory deficit in PD or not.

Background: Hyposmia is one of major non-motor symptoms in Parkinson's disease (PD), and it has been attributed to early pathological changes in the olfactory bulb. Moreover, recent studies on brain pathology suggested that the limbic system, especially amygdala, may also be responsible for hyposmia in PD. However, it remains to be elucidated whether any brain lesions are associated with olfactory dysfunction in PD.

Methods: We evaluated the brain glucose metabolism and smell identification ability in 64 cases with PD. Olfactory function was assessed using the odor stick identification test for Japanese (OSIT-J) and the regional cerebral metabolic rate of glucose consumption (rCMRGlc) was measured by using ^{18}F-FDG PET.

Results: Positive correlation was observed in bilateral temporal pole, bilateral parieto-occipital area and right thalamus. After defining regions of interest on the olfactory structures, only bilateral temporal pole hypometabolisms were significantly correlated with hyposmia. The distribution of brain hypometabolisms associated with hyposmia could be explained by the extension of pathologic process from the olfactory bulb to the amygdala.

Conclusions: Our results suggest that cognitive deficit in olfactory perception is an important aspect of hyposmia in PD, and lesions in the amygdala seem to play a major role in it. Further brain imaging studies will elucidate pathophysiological processes of PD, in which hyposmia is one of the early symptoms.

Mo-124

Dopamine transporter SPECT and motor cortex excitability in de novo Parkinson's disease

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Objective: Evaluation of the motor cortex (MC) excitability with transcranial magnetic stimulation (TMS) in de novo patients with Parkinson's disease (PD) and correlation with ^{123}I-FP-CIT SPECT measurements.

Background: Changes in MC excitability even at early stage of the disease have been reported in PD. Hypothesis attributed them to either the nigrostriatal denervation or compensatory mechanisms to limit the impact of dopaminergic dysfunction.

Methods: Eighteen de novo PD patients with unilateral symptoms and 18 healthy subjects age-matched were included. TMS was performed through a 9 cm circular coil over the MC contralateral to the more affected side of patients and to the dominant hemisphere of healthy subjects. TMS measurements included resting motor threshold (RMT), intracortical inhibition (IIC) and facilitation (IFC) obtained with a conditioning stimulus set at 0.8RMT followed respectively 3 ms and 15 ms after by a test stimulus set at 1.2RMT and silent period (SP) at the maximum intensity of the stimulator. Motor signs were assessed with motor UPDRS scale. For the ^{123}I-FP-CIT SPECT, quantitative analysis in the caudate, putamen nuclei of the most affected side and averaged of both hemispheres were assessed in 15 patients and 9 healthy subjects.

Results: TMS data were not significantly different between patients and healthy subjects. All patients had abnormal SPECT consistent with PD. UPDRS and bradykinesia were correlated with the radiotracer binding in the averaged putamen ($r=-0.6$, $p=0.02$ and $r=-0.56$, $p=0.03$ respectively). Correlation between TMS and SPECT data showed a positive correlation between IFC ($r=0.65$, $p<0.01$), SP ($r=0.61$, $p=0.015$) and radiotracer uptake in the averaged putamen and a negative correlation between IIC and the radioligand uptake in the putamen of the most affected side ($r=-0.67$, $p<0.01$). A positive correlation between SP and the radiotracer uptake in the averaged caudate ($r=0.64$, $p=0.01$) and the caudate of the most affected side ($r=0.60$, $p=0.02$) were found.

Conclusions: We did not find any changes in MC excitability in the more affected hemisphere of de novo PD patients. Changes might be observed above a threshold of nigrostriatal dysfunction which was not raised in these patients, as suggested by the correlation obtained between SPECT and TMS measurements.

Mo-125

Unilateral decrease of T1 in brainstem and midbrain in early Parkinson's disease (PD) revealed by quantitative MRI

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Objective: To investigate changes in longitudinal relaxation time (T1) in early asymmetric stages of PD using quantitative MRI.

Background: PD is characterized by unilateral onset of motor symptoms due to loss of neurons in the contralateral substantia nigra pars compacta (SNc). Histological findings suggest that the accumulation of misfolded α-synuclein and the formation of Lewy bodies play a key role in the underlying pathomechanism. Those morphological changes are commonly observed not only in the midbrain but also in pons and medulla even in preclinical stages of PD (1). In theory, both, accumulation of insoluble α-synuclein and loss of grey matter accelerate longitudinal (T1) relaxation which is measurable with quantitative MRI.

Methods: 20 patients (age 62.3+/-10.5y) diagnosed with PD H&Y stage I or II (UPDRS 18.4 +/- 6.1) and 20 age and gender matched healthy controls underwent quantitative T1-mapping as described in (2). 10 subjects were predominantly affected on the right and 10 on the left body side. Preprocessing consitsted of normalization and smoothing with a 2.5mm isotropic Gaussian using SPM5. Images were flipped (left to right) for appropriate pooling of the left side affected patients with those affected on the right side. The results for the paired t-test design [T1(affected side)<T1(contralateral side)] are displayed in Fig.1, those for the unpaired t-test design [T1(PD)<T1(healthy controls)] in Fig. 2 (radiologic convention, t-maps thresholded at $p<0.05$, uncorrected). Patients were pooled as if affected on the right side. Cluster level significance was assessed using permutation analysis.

Results: Fig.1 and Fig.2 reveal large clusters of T1-decrease comprising cranial pontine and midbrain areas including the pedunculopontine nucleus and the SNc contralateral to the most affected body side (Fig. 1: $p = 0.01$, corrected cluster level; Fig. 2: $p = 0.02$, uncorrected cluster level).

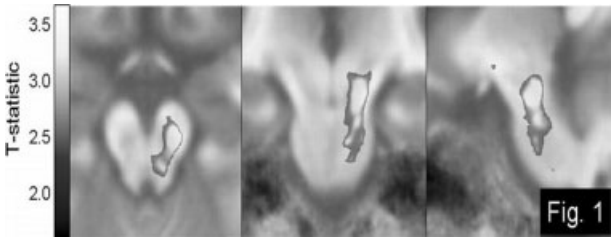

FIG. 1 (Mo-125).

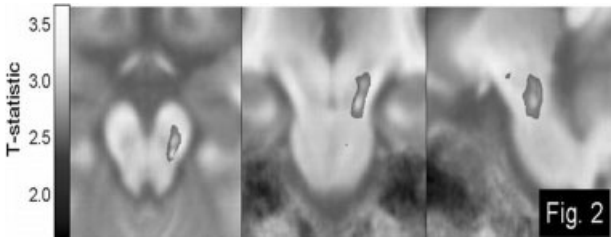

FIG. 2 (Mo-125).

Conclusions: The results are in good agreement with histopathological findings in brainstem and midbrain and, therefore, likely reflect real pathology. Thus, T1-mapping might be of considerable value for early diagnosis and also for monitoring PD in longitudinal studies. (1) Braak et al. Cell Tissue Res 2004; 318:121-134 (2) Preibisch et al. Magn Reson Med 2009; 61(1):125-35

Mo-126

Substantia nigra hyperechogenicity in healthy controls: Correlation with neuropsychological deficits

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Objective: To define the prevalence of cognitive deficits in healthy controls with substantia nigra hyperechogenicity (SN+) and to describe their further course.

Background: SN+ as assessed by transcranial ultrasound (TCS) is a regular finding in patients with Parkinson's disease (PD). About 10% of healthy controls exhibit the same echofeature suggested to be a risk factor for PD. SN+ has been found to be associated with subtle signs of motor slowing and with olfactory deficits, a possible premotor marker of PD. First evidence could be provided that mild neuropsychological impairment may be associated with SN+, too, suggested to correspond to subthreshold dopamine deficit.

Methods: 500 healthy volunteers aged 50 to 65 years underwent TCS, neuropsychological assessment, and a neurological examination performed by experienced examiners blinded for the results of the others. Subtests of the Consortium to establish a Registry for Alzheimer's disease (CERAD) -Verbal Fluency, Boston Naming Test, Word-list (WL), and Constructional Praxis- and the Unified Parkinson's Disease Rating Scale (UPDRS part III) were applied. In 375 participants the examinations could be repeated after 5 years.

Results: 61 subjects had uni- or bilateral SN+ areas above the 90th percentile (SN+ group). Group differences between SN+ and SN- subjects were significant considering WL learning at baseline ($p=0.01$). In the other subtests and in the whole follow-up, groups did not differ significantly. SN+ probands with UPDRS scores >0 showed significantly worse WL learning and recall at both time points ($p<0.01$ and <0.05).

Conclusions: We could confirm the formerly described cognitive deficits associated with SN+. Changes are mild and perceptible only in defined tests. In our study population, group differences between the SN+ and SN- group dissolved over time. Only those SN+ subjects with subtle signs of motor slowing still showed significantly reduced cognitive performance after 5 years. We hypothesize that within the SN+ healthy population those individuals exhibiting both deficits of cognitive and motor performance as putative preclinical markers may be at risk for progressing dopaminergic cell loss towards manifest PD.

Mo-127

Brain metabolic correlates of dopaminergic degeneration in de novo idiopathic Parkinson's disease patients

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Objective: To evaluate the relation between severity of dopaminergic degeneration and regional cerebral glucose metabolism (rCMRglc) in de novo idiopathic Parkinson's disease (PD) patients.

Background: Limited data exist about the direct relation between dopaminergic impairment and rCMRglc. This kind of correlation might reveal in which regions metabolic changes are more directly related to dopaminergic neuronal loss.

Methods: Twenty-six de novo PD patients were examined with 123I-FP-CIT SPECT and 18F-FDG PET. The severity of motor impairment and of dopaminergic degeneration were measured respectively with UPDRS III and with 123I-FP-CIT binding potential (BP). Among all striatal regions, putaminal BP was considered the most accurate measure to determine the severity of dopaminergic degeneration and to test the correlation with UPDRS III and with rCMRglc. Statistical Parametric Mapping (SPM) was used to explore regions in which UPDRS III and putaminal BP correlated with rCMRglc ($p<0.001$).

Results: There was a significant correlation between UPDRS III and putaminal BP: in particular, the putamen contralateral to the most affected body side correlated with UPDRS III better and more significantly than the ipsilateral putamen ($r=-0.437$, $p<0.03$ and $r=-0.399$, $p<0.05$, respectively). SPM analyses demonstrated a significant negative correlation between UPDRS III and rCMRglc in left premotor cortex (PMC, BA 6). Right putaminal BP positively correlated with rCMRglc in right anterior cingulate cortex (ACC, BA 32), bilateral PMC (BA 6), bilateral dorsolateral prefrontal cortex (DLPFC, BA 9) and right anterior prefrontal cortex (BA 10). Left putaminal BP positively correlated with rCMRglc in bilateral orbitofrontal cortex (BA 11), bilateral PMC (BA 6) and left DLPFC (BA 9).

Conclusions: Putaminal BP may be a reliable estimate of PD severity, as demonstrated by the correlation with UPDRS III, and could be a sensitive parameter to explore correlations with rCMRglc. The finding that PMC and prefrontal areas are the cortical areas most affected by dopaminergic degeneration agrees with the pathophysiological alterations of basal ganglia circuits in PD. Metabolic changes in these areas could be used as reliable biomarker of brain functions modifications due to dopaminergic degeneration.

Mo-128

Gray matter volume increase in Friedreich ataxia after treatment with erythropoietin

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Objective: Aim of the magnetic resonance imaging (MRI) study was to determine possible therapy dependent intracranial volume changes in Friedreich Ataxia (FRDA) patients after treatment with recombinant human erythropoietin using voxel-based morphometry (VBM).

Background: RhuEPO has received considerable attention because of its neuroprotective properties. In an in vitro study our study group found that rhuEPO increases Frataxin levels in lymphocytes of FRDA patients.

Methods: In an open-label pilot study FRDA patients received 5000IU rhuEPO three times weekly subcutaneously for a time period of 8 weeks. Thereafter, patients entered in a six months follow-up study receiving 2000 IU rhuEPO three times weekly. Twelve FRDA patients were scanned on the same 1.5 Tesla MRI scanner before and after rhuEPO treatment with a scan interval of 6 – 12 months. Statistical parametric mapping software was used for image processing and statistical analysis.

Results: When comparing follow-up scans after treatment with rhuEPO with baseline scans ($p<0.001$ uncorrected) an increase of gray matter volume was observed bilaterally in the posterior part of the thalamus (pulvinar) and in the parietal lobe (Brodmann area 7). After applying a small volume correction only findings in the thalamus bilaterally reached significance (right $p=0.026$, left $p=0.02$).

Conclusions: The involvement of thalamus might be consistent with the known degeneration of the projection fibres from the dorsal column of the spinal cord. The increase in cellular volume in the dorsal thalamus detected via VBM might be due to several mechanisms: (1) An increase of glucose supply through autoregulatory mechanisms of the blood flow as previously seen in PET studies. (2) On a cellular level, increases in cell size after rhuEPO exposure might be due to enhanced levels of brain derived neurotropic factor (BDNF), associated with increased intracellular Ca2+ levels and cAMP response element binding protein (CREB) phosphorylation. The impact of rHuEPO as measured in our study could therefore be

related to both an improvement of energy metabolism and/or restorative cellular processes.

Mo-129

Imaging characteristics in Parkinson's disease and atypical parkinsonian syndromes using 3T MR siderotractography

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Objective: To study the imaging characteristics and their clinical correlation in patients with idiopathic Parkinson's disease (IPD) and atypical parkinsonian syndromes using 3T MR siderotractography.

Background: Imaging with 3T MRI with imaging of iron content and tract involvement may be useful in differentiation between various parkinsonian types in early disease.

Methods: 12 normal controls and 12 patients [IPD -3, MSA -5, CBD-3, DLBD -1] were included. All were imaged on a 3Tesla Achieva XR system (Phillips medical systems,Netherlands) with movement disorder protocol followed by MR siderography sequence, which is an isotropic susceptibility Venous BOLD sequence. Movement disorder protocol also included a conventional DTI sequence to generate directional color coded tractograms which were fused with 3D Venous BOLD images. The data was used to reconstruct siderographic trajectories of striatonigral pathways in controls and patients. The following features were then evaluated: Venous Bold and minimal intensity projection reconstruction–1. Thickness of pars compacta, 2. Red nucleus and substantia nigra susceptibility, 3. Hot cross bun sign, 4. Putaminal hypointensity, 5. Slit like putaminal hyperintensity, 6. Dentate nuclear hypointensity, 7. Cortical subcortical hypointensity DTI -Thickeness of transverse pontocerebellar fibers.

Results: 12 patients [Idiopathic Parkinson's disease (3), probable MSA (5; MSA-P-3, MSA-C-2), CBD (3), DLBD (1)] and 12 age matched controls of age range-55-75 years with M:F ratio of 3:2 were included in this study. Diagnosis was based on clinical findings. Mean disease duration was 2.65 years. Mean H and Y score was 2.7.

Conclusions: MR siderotractography using 3T MRI with the 4 patterns of suceptibility signal characterstics of striatonigral pathways may help in differentiating between idiopathic Parkinsons disease and atypical parkinsonian syndromes.

Table (Mo-129).

Category	SNPC thickness	Hot cross Bun sign	MCP thickness (cm)	Cortical susceptibility	Dentate nuclear susceptibilty (intensity units)	Putaminal hypointensity	Slit like putaminal hyperintensity
Controls	>3	Absent	>2	Absent	1800	Absent	Absent
IPD Pattern A	1.4 symmetrical	Absent	1.5–2	Absent	830	Present	Absent
MSA-P Pattern B	1.8	Absent	1.0–1.5	Absent	1166	Present Asymmetrical	Present
MSA-C Pattern C	2.6	Positive	0.5–1	Absent	1200–1400	Present Asymmetrical	Present
CBD/DLBD Pattern D	3.1	Absent/ Asymmetrical thinning	1.0–1.5	Present Asymmetrical	1100–1200	Not marked	Not marked

Mo-130

Life-long increase of substantia nigra hyperechogenicity in healthy children and adults

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Objective: To determine the age-related development of the SN signal in healthy children and adults.

Background: Transcranial ultrasound of the substantia nigra (SN) has been demonstrated to show a distinct hyperechogenicity in the majority of patients with Parkinson's disease. Recent studies indicate higher SN signals in elderly healthy adult subjects.

Methods: A total of 121 children (mean age 6.7 years) and 64 healthy adults (mean age 46.5 years) were included. TCS was performed using the SONOS 5500 ultrasound system (Philips) with a 2.0-2.5 MHz sector transducer. The midbrain structures were examined through the temporal bone window. The area of the hyperechogenic SN (aSN) and the area of the midbrain (aMid) were manually encircled and measured using a computerized algorithm. For further analysis, the larger aSN and aMid were selected separately and labeled as aSNmax and aMidmax, respectively. We further calculated the mean, designated as aSNmean and aMidmean. The aSN was calculated based on the area of the ipsilateral midbrain (aSN/aMid=S/M ratio), since brainstem images may vary interindividually due to shifts of the probe. Statistical analysis was performed using the Mann-Whitney U-Test and fractional polynomials (FP).

Results: We found a distinct positive correlation between age and aSNmax (rho=0.39, adjusted p=8.6*10-8), and between age and aSNmean, respectively, (rho=0.17, adjusted p=1.0*10-6). Using FPs, we demonstrated that the relationship between these variables followed a linear pattern. Exploratory analyses suggested that increasing age was also associated with a higher S/M ratio max (rho=0.17, exploratory p=0.0292) and S/M ratio mean (rho=0.15, exploratory p=0.0417). The values for aSN parameters were smaller in infants and children compared to healthy adults (aSN max 0.06 cm^2 vs. 0.13 cm^2 [p=1.0*10-9], aSN mean 0.04 cm^2 vs. 0.10 cm^2 [p=7.8*10-10]).

Conclusions: We provide data on SN hyperechogenicity systematically obtained from a large cohort of healthy individuals ranging from newborns to the elderly, which may also serve as reference source for future studies Age-matched healthy controls are needed for a meaningful interpretation of transcranial ultrasound data obtained from patients of different age groups.

Mo-131

Basal ganglia volume and psychometric intelligence

M.L. Bringas, G.A. Hernandez, Y. Lorenzo, A. Lage, P. Valdes, M. Sanchez (Havana, Cuba)

Objective: To evaluate the relationship between BG volume using MRI automatic segmentation and intelligence assessed with validate psychometric tools

Background: Positive correlation between brain cortical volume and intelligence is well documented but the influence of subcortical morphometry, particularly BG is unknown.

Methods: The Wechsler Adult Intelligence Scale III was individually administered to 190 healthy subjects, (age range 20-69, education 7-17 years) 74 females, 93% right handed. T1 MR images were acquired using a 1.5T Vision Siemens, segmented into white, gray matter and cerebrospinal fluid using IBASPM to the Montreal Neurological Institute MNI space. The ICBM template was the reference image to parcel the anatomical images into 116 different gray matter structures grouped into 19 ROIs using MNI atlas. ROI in the BG were defined as the caudate, putamen and pallidum. Multiple regression analyzes were performed between the 116 brain structures and ROIs with the IQ scores, indexes and subtests of the WAIS III with sex and age as additional covariables. Statistical significance was assessed using false discovery rate (FDR) to control the percentage of false positives findings due to multiple comparisons.

Results: BG was the ROI with the most significant regression coefficient with Full Scale IQ: (BG left (p= 0.000353) BG right (p=0.000535)) and Performance IQ, ((BG left (p=0.010335) and BG right (p=0.019573)). Verbal IQ showed the most significant correlation with left BG (p=8,25E-05) and right BG (p=6,44E-05) and other structures such as temporal, limbic, occipital areas of the left hemisphere (p=0.003) and cerebellum bilaterally (p=0.005) all corrected by FDR. From the 116 gray matter structures bilateral caudate showed the most significant association with the three IQ scores (p<0.01), while the amygdale and left putamen were associated only with Verbal IQ. Association with pallidum did not reach significance. Letter-number sequencing, arithmetic, similarities, vocabulary, matrix and blocks were the best subtests.

Conclusions: Regression analysis showed robust associations between BG volume and global and fluid intelligence scales, which is almost unique, shared only with cerebellum. BG volume was also associated with verbal IQ and working memory. Caudate had the most extensive and significant individual relationship with IQ.

Mo-132

Aging and striatum

M.L. Bringas, G.A. Hernandez, Y. Lorenzo, M. Sanchez-Bornot, P.A. Valdes-Sosa, A. Lage (Havana, Havana City, Cuba)

Objective: To evaluate the relationship between striatum nuclei volume and age.

Background: Age-related changes in the human striatum comes from cross-sectional and longitudinal studies which revealed reduced volume in the neostriatum (caudate nucleus and putamen) whereas age differences in the volume of paleostriatum (globus pallidum) are significantly smaller. The restricted age ranges, small samples (10-53) and methodological limitations influenced the scope of previous results.

Methods: We measured the volumes of the caudate nucleus, the putamen, and the globus pallidus on MR images of 176 healthy right handed adults recruited as part of the Cuban Human Brain Mapping Project. Ages ranged between 18 and 69 years, 70 females and 106 males, mean years of education of 11.9 and MMSE scores >24. T1 MR images were acquired using a 1.5T Vision Siemens and automatically segmented into white, gray matter and cerebro spinal fluid using IBASPM to the Montreal Neurological Institute (MNI) common space. The ICBM template was the reference image to parcel the anatomical images into 116 different gray matter structures of the MNI atlas. Left and right caudate, putamen and pallidum were correlated with age using Pearson coefficients using p value <0.01.

Results: The whole volume of striatum had a strong negative correlation with age (r=-0.46, p=0.00001). The volume of the neostriatal nuclei (caudate (r=-0.43,p:0.00001), putamen (r=-0.41, p=0.00001) correlated negatively with age. The left globus pallidus (r=-0.25, p=0.001) had a significant but less robust correlation with age but not the right GP (r=-0.09).

Conclusions: Our results demonstrated robust and negative relationships between neostriatum with age. Contrary to expectation pallidum showed a specific left shrinkage with age whereas the right pallidum remained stable. In psychometric studies, we found that caudate volume had the most significant correlation with IQ and working memory, and for that reason, should be a suitable candidate for explaining age-related changes in behavior and cognition.

Mo-133

MR volumetric study of posterior fossa in hemifacial spasm

L.L. Chan, K. Ng, E.K. Tan (Singapore, Singapore)

Objective: Utilizing Magnetic Resonance techniques, we investigated the cerebrospinal space (CSF) in the posterior fossa in patients with hemifacial spasm (HFS) and control subjects to determine if there are any narrowing of CSF space in HFS patients and its associated clinical factors.

Background: HFS is a facial movement disorder that impacts on quality of life. While it is recognized that neurovascular compression (NVC) is the most common etiology, the predisposing factors for NVC have not been elucidated. A previous hypothesis has suggested that a small posterior fossa may increase the risk of HFS and this may explain the higher prevalence among Asians compared to Caucasians.

Methods: We recruited consecutive patients clinically diagnosed with HFS and age- and gender-matched control subjects and who underwent MR imaging using a standardized protocol. The volume of the cerebrospinal fluid space anterolateral to the brainstem and cerebellar peduncles within the posterior fossa on a 3D constructive interference-in-steady state (CISS) MR dataset was measured on the volume render function of the Analyze 8.1 (Mayo Clinic) program.

Results: A total of 80 subjects including 40 HFS and 40 controls were included. The mean CSF volume anterior to the brainstem in HFS and controls was not significantly different between cases and controls. Age was significantly correlated with the CSF volume measured ($p < 0.05$) in the patient group, but not in the control group. In the multivariate analysis, the CSF volume measured did not predict for HFS.

Conclusions: We showed that the posterior fossa space anterior to the brainstem was not significantly different between HFS and controls. Our data suggest that posterior fossa volume is not a major risk factor for HFS in our cohort.

Mo-134

Case control MRI study of leukoaraiosis in vascular parkinsonism

L.L. Chan, K. Ng, E.K. Tan (Singapore, Singapore)

Objective: To compare the distribution and extent of leukoaraiosis on 3 telsa MRI Imaging in patients with Vascular parkinsonism (VP), Parkinson's disease (PD) and healthy controls.

Background: Leukoaraiosis and white matter changes are frequent incidental findings on brain imaging. Patients with VP, PD and healthy controls can have leukoaraiosis on brain imaging.

Methods: We recruited patients with predominant lower body parkinsonism from a tertiary referral center. These patients were classified into VP and PD based on their levodopa response and other clinical features. Together with a group of healthy controls, all of them underwent a standardized 3-Telsa MR imaging. A neuroradiologist blinded to the clinical data analyzed the images and classified the presence of leukoaraiosis in the different brain regions and corticospinal tracts. All subjects were assessed using the Tinetti Gait Scale.

Results: 18 subjects comprising VP, PD and controls were included with mean age of about 65 years, and with equal gender ratio. VP patients had much worse Tinetti gait scores than PD and controls. Leukoaraiosis were present in the frontal, temporal, parietooccipital and subcortical regions. Patients with VP had more severe leukoaraiosis in the frontal and subcortical regions compared to controls and PD patients and this correlated with a more severe gait score ($p<0.05$).

Conclusions: Utilizing high field MRI imaging, we showed that leukoaraiosis in the frontal and subcortical regions was more common in VP patients compared to PD and controls. This may explain the predominant and more severe gait abnormality observed for VP patients.

Mo-135

Eye of the tiger-like MRI in parkinsonian variant of multiple system atrophy

M.-H. Chang (Taichung, Taiwan)

Objective: To describe a new image finding of parkinsonian variant of multiple system atrophy (MSA-P) presenting disturbance of axial motor function.

Background: Parkinsonian variant of multiple system atrophy (MSA-P) clinically presents with autonomic dysfunction and parkinsonian features. The target of magnetic resonance imaging (MRI) is focused on signal changes or volume reduction on putmen, including putaminal slit, gliosis by diffusion studies and reduction of putaminal volume.

Methods: Four patients with typical MSA-P presenting with autonomic dysfunction, rapid progression, disturbances of axial motor function and early falls with minimal appendicular symptoms. For a differential diagnosis, they received conventional magnetic resonance imaging (MRI) studies and dopamine transporter scans, focus on the signal or uptake changes over the basal ganglia.

Results: MRI scans showed symmetrical hyperintensity over the center of globus pallidus surrounded by a mildly low signal rims at T2-weighted image, which was similar to that of eye of the tiger sign except for the extremely hypointense rims that occurred at pantothenate kinase-associated neurodegeneration (PKAN). In addition, dopamine transporter scanning showed a symmetric reduction in uptake bilaterally over basal ganglia.

Conclusions: This is the first report of these unusual imaging findings in MSA-P patients. We believe this is a new findings in MSA-P characterized by a clinical presentation of axial impairment and symmetrically abnormal MRI signal changes in globus pallidus, with the eye of the tiger-like sign.

Mo-136

Midbrain atrophy in vascular parkinsonism

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Objective: Midbrain atrophy is a well-known feature of progressive supranuclear palsy (PSP), and some reports have shown that patients with vascular dementia (VaD) also showed midbrain atrophy. Because VP patients frequently had VaD, the aim of this study is to assess the midbrain atrophy through morphometric measurement of MRI in patients with clinically diagnosed VP.

Background: Vascular parkinsonism (VP) is a distinct clinical entity in parkinsonian syndromes, but clinical features of VP are various and brain imaging for the diagnosis of VP are not clearly established.

Methods: We measured midbrain and pons area in 20 patients with VP, 15 patients with probable PSP and 30 patients with idiopathic Parkinson's disease (IPD). The areas of midbrain (Amd) and pons (Apn) were measured on mid-sagittal T1-weighted MRI scans using computerized image analysing system, MIDAS (Multimodal Image Data Analysis System). We compared the Amd, the Apn and the Amd/Apn ratio among the three groups.

Results: In the Amd, the patients with VP (137.3 ± 18.3 mm^2) and PSP (120.0 ± 24.4 mm^2) had significantly smaller area than the patients with IPD (179.4 ± 24.6 mm^2). In the Apn, there was a significanct difference only between VP (559.9 ± 50.3 mm^2) and IPD (611.9 ± 62.6 mm^2). The Amd/Apn ratios of the patients with VP (0.245 ± 0.03) and PSP (0.208 ± 0.05) were significantly smaller than that in those with IPD (0.292 ± 0.05; $p<0.001$).

Conclusions: Our study shows that brainstem atrophies often occur in patients with VP and midbrain is more vulnerable than pons in this atrophic change. The Amd/Apn ratio on mid-sagittal MRI can differentiate VP from IPD and PSP.

Mo-137

Test-retest reliability of 18F-AV-133 PET imaging to assess striatal dopaminergic neuron integrity

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Objective: To evaluate the test-retest reproducibility of 18F-AV133 PET imaging of dopamine/vesicular monoamine transporter deficiency in 14 Parkinson's disease (PD) patients and 7 control (HC) subjects.

Background: The detection of reduced striatial dompaminergic neuron integrity may provide an early biomarker of PD pathology. The binding of tetrabenazine (TBZ) derivatives to presynaptic vesicular monoamine transporters (VMAT2) appears to be unaffected by drugs that modify dopamine thus providing a reliable measure of striatial dopaminergic neuron integrity.

Methods: PET images have been obtained in 6 patients with mild PD and 3 HC.

Sixty minutes after iv injection of 370 MBq (10 mCi) of 18F-AV-133 participants received a 30 minute dynamic brain image. The imaging protocol was repeated 24 hours to 4 weeks (average 8 days) after obtaining the first image. Ligand retention (SUV) in the posterior putamen was compared to retention in the occipital cortex (single bilateral region of interest) and expressed as a ratio (SUVr).

Table (Mo-137). Subject clinical characteristics

	PD	HC
Age*	63 (56-70)	66 (50-81)
UPDRS motor*	19 (6-35)	NA
Hoehn & Yahr*	1.4 (1-2)	NA

*mean, range (UPDRS done when >12 hours off medications).

Results: Posterior putamen (average of left + right) SUVr test-retest variability measured by absolute differences (test–retest)/test) ranged from 2.4 to 10.5% (mean 7.0%) in PD and 2.1 to 12.21% (mean 5.6%) in HC. There was no difference between PD and HC in posterior putamen ligand retention symmetry. There was no overlap in posterior putamen SUVr values (unilateral or bilateral), when PD patients (bilateral mean 1.6, range 1.2-2.1) were compared to HC (bilateral mean 3.1, range 2.8-

Conclusions: 18F-AV-133 SUVr values definitively separated PD patients from controls and demonstrated good test-retest reliability, indicating this PET VMAT2 ligand can be a valid measure of dopaminergic neuron integrity. These results support the use of 18F-AV-133 PET VMAT2 imaging when evaluating individuals with new onset tremor and/or mild extrapyramidal impairment.

Mo-138

Ventricular enlargement and mild cognitive impairment in incident Parkinson's disease. A case-control study

T.O. Dalaker, R. Zivadinov, D.P. Ramasamy, M.K. Beyer, G. Alves, K.S. Bronnick, O.-B. Tysnes, D. Aarsland, J.P. Larsen (Stavanger, Norway)

Objective: To examine the extent of subcortical brain atrophy and ventricular enlargement in early Parkinson's disease (PD) with and without mild cognitive impairment (MCI) compared to age and sex-matched normal controls (NC).

Background: MCI is found even in early stage of PD and might predict future dementia. Previous MRI studies have found possible brain atrophy in relation to MCI in more advanced PD. (Beyer MK, Janvin CC, Larsen JP, Aarsland D. A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry. J Neurol Neurosurg Psychiatry 2007;78(3):254-259.)

Methods: Participating in this study were 43 early PD patients and 41 age, sex and education matched NC. In the PD group 11 patients (MCI PD) (age 67.5 ± 9.3 years, disease duration 28.4 ± 18.8 months) were classified with MCI and 32 patients (non-MCI PD) were not (age 63.3 ± 10.2 years, disease duration 32.7 ± 23.5 months). Cognitive testing was done on all participants using well established tests examining attention-executive, visuospatial and memory skills. Using Freesurfer software, volumetric segmentation was performed on 3D-T1-weighted images in a number of subcortical brain structures, including basal ganglia, structures in medial temporal lobe, cerebellum and brainstem. In addition volumes of inferior lateral, third and fourth ventricle were calculated. Group differences were examined by statistical ANCOVA models controlling for total intracranial volume.

Results: The analysis showed significantly larger fourth ventricle in MCI PD (2.52 ± 0.86 ml) than in NC (2.07 ± 0.70 ml). No other significant MRI group volume differences were found.

Conclusions: This study suggests that early cognitive impairment in PD might be a result of degeneration of infratentorial structures leading to larger fourth ventricular volume. This finding is thus in

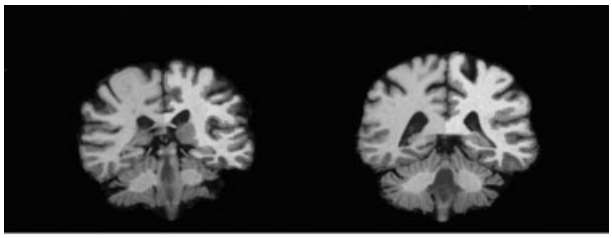

FIG. 1 (Mo-138).

line with studies reporting that early PD and its cognitive impairment is associated with involvement of brainstem structures.(Baloyannis SJ, Costa V, Baloyannis IS. Morphological alterations of the synapses in the locus coeruleus in Parkinson's disease. J Neurol Sci 2006;248(1-2):35-41.)

Mo-139

Hippocampals volume in patients with Parkinson's disease (PD)

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Objective: Comparison of hippocampal volume at different clinical stages of PD to age-matched normal subjects.

Background: Parkinson's disease (PD) is a slow progressive disease. Based on Barak pathological staging the lesions become increasingly severe and have a predictable change in their distribution pattern. We hypothesize that these pathological degenerative changes will be decreased in the relevant parts of the central nervous system and that these changes are measurable and detectable by magnetic resonance imaging (MRI). To accomplish these goals required techniques that are non-invasive but precise. Using 3D reconstruction software (Amira, Mercury Computer Systems) to visualize data objects and for computational operations such as measurement of the volumes of subcortical structures. In this pilot study we compared the volume of the hippocampus in PD patients with age-matched normal subjects, and correlated the results to the clinical stage of the patients.

Methods: The MRI of five patients with clinical criteria for typical PD (stages I-III) and five matched normal controls were obtained for this study. MRIs were performed at the Loma Linda University Medical Center on a 3T Siemens TIM Trio MRI. Sagittal 3D T1 weighted images were acquire with 1 mm slice thickness, transferred for reconstruction; segmentation; and cerebral volume calculations (Amira 4.1). Hippocampal volume was measured bilaterally and their ratio to the estimated cerebral volume calculated.

Results: The results confirmed that the two populations were not significantly different from each other ($p>0.05$).

Conclusions: Our neuroimaging pilot study demonstrated that 3D volumetric measures of subcortical structures of the brain, including hippocampus in patients with PD could be consistently obtained. The low power of this pilot study, small sample size, and the low progression stage of the PD patient data are are consistent with those reported in the literature. This study is part of a larger morphometrical longitudinal 3D volumetric analysis of PD patients using MRI.

Mo-140

Basal ganglia volume decrease in writer's cramp

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Objective: To determine whether the volume of the striatum and the pallidum is abnormal in patients with idiopathic focal hand dystonia using MRI manual segmentation.

Background: The cause of adult-onset focal dystonia is unknown, but substantial evidence suggests that the putamen may be abnormal in this condition. Morphologic and structural abnormalities (e.g. cell loss, gliosis) have been suspected but conventional MR imaging was unsuccessful in showing abnormalities in putamen in primary dystonia. However, VBM analysis revealed decreased gray matter in the putamen (Obermann et al, Mov Dis 2007).

Methods: The study included 53 patients with writer's cramp and 54 controls matched for gender and age cramp. MRI examination was performed using a 1.5 Tesla system. Anatomical high resolution scans were acquired using axial three-dimensional inversion recovery fast SPGR acquisitions. Caudate nucleus, putamen and pallidum were traced manually for each patient. Intracranial volumes for each subject were obtained using VBM optimized procedure and statistical parametric mapping software (SPM2) (Delmaire et al, Neurology 2007). Volumes were standardized by dividing them by the total brain volume. Groups were compared using generalized estimating equations models to take into account the lack of independence of the two sides for each subject; analyses were all adjusted for age, sex and side.

Results: Patients with focal hand dystonia showed lower adjusted means [SE] of the standardized volumes of the putamen (0.0028 [0,00004]) and pallidum (0,00095 [0,00002]) compared to controls (putamen, 0.0030 [0,00004], $p=0.028$; pallidum, 0,0010 [0,00002], $p=0.003$). When both volumes were included in a logistic model as independent variables, they both remained associated with writer's cramp (putamen, $p=0.05$; pallidum, $p=0.007$). No association was found between writer's cramp and caudate nucleus volume.

Conclusions: In patients with writer's cramp, volumes of the putamen and the pallidum were bilaterally decreased compared to controls. Decreased volume could reflect cell loss in these structures and could underlie the functional abnormalities that have been described in the basal ganglia in both physiological and functional imaging studies in primary dystonia.

Mo-141

Evidence for increased upper brain stem activity following STN-DBS in Parkinson's disease: An ^{18}FDG-PET study

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Objective: To study the neural correlates of gait improvement following deep brain stimulation of the subthalamic nucleus (STN-DBS) in Parkinson's disease.

Background: STN-DBS improves gait disturbances in PD (1) but the underlying, mechanisms remain unclear (2).

Methods: We studied resting state brain activity using ^{18}FDG-PET in 8 PD patients (mean age= 63 years) who underwent bilateral STN-DBS. UPDRS scores and brain metabolism were assessed off-medication under two experimental conditions: DBS-on and DBS-off. We also computed a gait-specific composite score (gait score) which corresponded to the sum of scores obtained for item 30 (gait) of UPDRS part III and items 14 (freezing when walking) and 15 (walking) of UPDRS part II. Imaging data analysis was restricted to 3 regions of interest centered on the STN, bilaterally, and upper brainstem (BS), where are located nuclei that may play an important pathogenic role in gait disturbances observed in PD (i.e., pedonculopontine nuclei).

Results: We observed a highly significant improvement in both the mean UPDRS III score (51.88%; $p=0.0009$) and mean gait score (70.49%; $p=0.001$) during DBS-on compared with DBS-off. Glucose metabolism significantly increased in the left STN during DBS-on as compared with DBS-off (9.57%; $p=0.008$). In addition, BS FDG uptake was significantly higher during DBS-on compared with DBS-off (11.17%; $p=0.0007$). No significant difference was observed in the right STN area. Finally, a correlation analysis failed to show any significant relationship between the degree of activity changes in

these areas and the level of improvement in clinical scores as measured using the UPDRS III and gait score.

Conclusions: In our PD population, bilateral STN-DBS significantly increased activity in the left STN and upper BS areas. Increased activity in upper BS may contribute to gait improvement following STN DBS. We are trying to improve our approach by combining the present data with high-resolution anatomical MRI data obtained after surgery.

Mo-142

Striatal dopaminergic dysfunction in autosomal recessive familial parkinsonism associated with PINK1 mutations

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Objective: To determine the integrity of the nigrostriatal dopaminergic system, positron emission tomography (PET) with 18-Fluorodopa (FDOPA) was performed in a family with hereditary autosomal recessive parkinsonism due to homozygous and heterozygous mutations in the PINK1 gene.

Background: Many cases of early onset parkinsonism (EOP) have a genetic background with an autosomal recessive mode of inheritance, the second most common cause are mutations in the PINK1 gene. The pathophysiological impact of this genetic defect on the neuronal basal ganglia circuitry is currently unknown.

Methods: Fifteen members of a large family carried PINK1 mutations in the homozygous (definite parkinsonism; 1 man, 3 women; mean age of onset: 50 years) or in the heterozygous state (7 men, 2 women; mean age: 44 years). While the 9 heterozygous mutation carriers did not report any symptoms related to parkinsonism, 7 of them showed subtle but unequivocal signs of parkinsonism upon careful neurological examination. We used FDOPA PET to measure striatal FDOPA uptake. The PET data were compared with those of 15 healthy controls (12 men, 3 women, mean age 54 years).

Results: Carriers of two mutant PINK1 alleles showed a significant decrease of caudate (40%) and putaminal (60%) FDOPA uptake compared to healthy controls ($p < 0.01$, ANOVA). Asymptomatic carriers of heterozygous PINK1 mutations also had significant, but less lowered putaminal FDOPA uptake in the putamen (20%) and caudate nucleus (18%) compared to controls ($p < 0.05$).

Conclusions: In subjects with proven PINK1 mutations, a reduction of the striatal FDOPA uptake correlated with the number of mutated alleles and was also obvious in asymptomatic mutation carriers. This finding supports a relationship between the proportion of mutated and intact alleles in the PINK1 mutation and the clinical outcome. Furthermore these results indicate a possible role of heterozygous PINK1 mutations as a susceptibility factor for parkinsonism.

Mo-143

A systems perspective on the effective connectivity of overt speech production

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Objective: To provide a model of effective connectivity in the human brain underlying overt speech production.

Background: In spite of its relevance to quality of life, the motor act of overt speech has received considerably less attention than cognitive components of language. Clinical observations, however, have motivated the distinction between at least two types of speech production impairment, apraxia of speech and dysarthria.

Methods: Meta-analysis of neuroimaging studies and fMRI data acquired during a verbal fluency task revealed a core network consisting of BA 44 in Broca's region, anterior insula, basal ganglia, cerebellum, premotor (PMC, BA 6) and primary motor cortex (M1, areas 4a/4p). The effective connectivity between these regions was then assessed using Dynamic Causal Modelling (DCM). The architecture of the human vocalisation network was identified using Bayesian model comparison across alternative models reflecting competing hypotheses on serial and/or parallel processing.

Results: Analysis indicated highest evidence for a system architecture featuring the insula in a serial position between BA 44 and two parallel nodes (cerebellum/basal ganglia), from which information converge onto the PMC and finally M1. Inference on the model's coupling parameters revealed that effective connectivity from the insular relay into the cerebellum/basal ganglia is primarily task driven and may hence be ascribed a preparatory role. In contrast, their output into the cortical motor system as well as the OMC-M1 coupling were less strongly modulated by the task *per se*. Only the latter coupling parameters, however, were significantly correlated with word production rate, pointing towards a primarily executive role.

Conclusions: DCM allowed not only a quantitative characterisation of the human speech production network, but also the distinction of a preparatory and an executive subsystem within it. This differentiation demonstrates the potential of system-based modelling of functional integration over a purely localising approach to brain mapping, as all areas would be deemed activated in a contrast-based analysis. The proposed model of physiological integration during speech production may now serve as a reference for investigations into the neurobiology of pathological states as encountered as an important clinical feature in disorders such as Parkinsons or MS.

Mo-144

Dopamine transporter imaging in Parkinson's disease patients with and without depression

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Objective: To evaluate the Striatal Dopamine Transporter (DAT) using TRODAT-1 and SPECT in Parkinson's disease (PD) patients with (dPD) and without (ndPD) depression.

Background: Depression is a frequent psychiatric disorder in PD patients and correlates with laterality (right-sided symtoms: left hemisphere dysfunction). There are few data however on DAT imaging in PD patients with and without depression.

Methods: Nineteen PD patients (n=13 ndPD; n=6 dPD) were matched for demographic data and clinical variables. SPECT imaging was performed using TRODAT-1 kits and data (Binding potentials=BP) was compared to age and gender matched controls. The Asymmetry index (AI) of the STR was calculated using the formula: (ipsilateral-contralateral)/(ipsilateral+contralateral)x100. Depression was defined according to Beck Depression Inventory (BDI) using a cut-off point of 18. Comparisons between groups were carried out using unpaired t test for parametric data and Mann Whitney test for non-parametric data. We also looked for correlations using the Pearson parametric correlation test. Significant values were considered if $p<0.05$.

Results: There was very good matching within the two PD groups regarding mean age at first evaluation (67.7 dPD *vs.* 65.5 ndPD), mean disease duration, gender, levodopa use and disease severity. The BP from right (R) and left (L) STR and the STR AI were as follows 1) **dPD** group: R STR BP=0.53, L STR BP=0.57, and STR AI 3.30; 2) **ndPD** group: R STR BP=0.49, L STR BP=0.50, and STR AI 0.57. We did not find any significant difference between groups. There was also no significant correlation between DAT BP and STR AI vs. BDI scores within both PD groups.

Conclusions: In this sample of PD patients with and without depression there was no correlation between DAT imaging and depression or significant differences within groups. We speculate that our results were possibly biased by the small sample size and the fact that the majority of patients had early PD (short disease duration).

Mo-145

Striatal dopamine transporter SPECT study in patients with tremor-dominant, akinetic-rigid, and mixed type Parkinson's disease

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Objective: To evaluate the Striatal Dopamine Transporter (DAT) in patients with different subtypes of Parkinson's disease (PD): tremor-dominant(Td), akinetic-rigid(AR), and mixed type(Mt).

Background: There are few studies however presenting DAT imaging results on patients with different clinical PD subtypes (Td vs. AR vs. Mt). Since Td patients demonstrate slower rates of disease progression, we hypothesized that DAT imaging would show higher uptake values in these patients than AR ones.

Methods: Twenty-five PD patients (n=9 Td; n=9 AR; n=7 Mt) were matched for demographic data and clinical variables. SPECT imaging was performed using TRODAT-1 kits and data (Binding potentials=BP) was compared to age and gender matched controls. The Asymmetry index (AI) of the striatum (STR) was calculated using the formula: (ipsilateral-contralateral)/(ipsilateral+contralateral) x100. Comparisons between groups were carried out using ANOVA and Newman-Keuls post-hoc test for parametric data. Significant values were considered if $p<0.05$.

Results: There was very good matching within the three PD groups and the controls regarding mean age at first evaluation (64.9 Td *vs.* 57.8 RA *vs.* 63.3 Mt *vs.* 63.4 controls; $p>0.05$), mean disease duration (<6years), gender, levodopa use and disease severity. The BP from right (R) and left (L) STR and the STR AI were as follows 1) **Td** group: R STR BP=0.53, L STR BP=0.51, and STR AI 1.61; 2) **RA** group: R STR BP=0.47, L STR BP=0.58, and STR AI 9.58; 3) **Mt** group: R STR BP=0.54, L STR BP=0.44, and STR AI 9.71; 4) **Control** group: R STR BP=0.95, L STR BP=0.95, and STR AI 0,45. There was significant differences between control R and L striatal BP values and the three PD groups (Control>Td,RA,Mt), and another significant difference in the STR AI (Td=control; Td<RA; $p<0.05$). No differences were found between DAT BP within the PD groups.

Conclusions: According to our data it is possible to assume that although there is a missing correlation between R and L striatal DAT results in the three PD groups evaluated (Td *vs.* RA *vs.* Mt), the significant higher STR AI in the RA group suggests a widespread degenerative involvement in the striatal region of these individuals perhaps implicating in the faster rate of disease progression.

Mo-146

Parkinsonism-myotonia complex: A TRODAT-1 SPECT study

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Objective: To present further data supporting that the parkinsonian features encountered in patients with parkinsonism-myotonia complex might be related to a degenerative process at the striatum level.

Background: "Parkinsonism-myotonia myopathy complex" is a very rare disorder with six cases described on the literature until today. Its pathophysiology remains elusive, and one case report showed that neuropathological changes might include nigro-striatal cell loss alongside with several Lewy bodies, suggesting an undergoing degenerative process.

Methods: An in vivo study with Single-Photon Computer Tomography (SPECT) was carried out in a 72-year-old subject using TRODAT-1, a radiotracer that binds on the Dopamine Transporter (DAT) at the pre-synaptic level of the striatum. The values for binding potentials were compared with three healthy control subjects matched for age and gender.

Results: The results of DAT-SPECT showed bilateral, but asymmetric reduced binding potential (BP) on both striatum. This reduction was ~24% lower than BP from control group (n=3) matched for age and gender. Additionally, the parkinsonian features did not respond to levodopa therapy.

Conclusions: This case report shows that parkinsonian features in parkinsonism-myotonia complex can be related to an underlying degenerative process at the striatum level. Our data is in line with a previous study that showed in a patient with myotonia and parkinsonism depigmentation of the substantia nigra and locus ceruleus alongside with moderate cell loss and several Lewy bodies. Further studies are needed to address this issue.

Mo-147

FMRI correlates of limb-kinetic apraxia in Parkinson's disease

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(Vienna, Austria)

Objective: To evaluate whether early PD patients relative to healthy controls show specific brain activation patterns when contrasting coin rotation with simple finger tapping using fMRI.

Background: Patients with PD show a deficit for hand and finger dexterity which may clinically be evaluated by the coin rotation test. Although controversial, this specific motor deficit has also been labelled as limb-kinetic apraxia (LKA). According to recent literature, coin rotation performance in patients with PD does not respond to dopaminergic treatment, whereas simple finger tapping performance does.

Methods: 8 right-handed patients with right-dominant PD were compared to 6 healthy subjects. Patients' scans were performed in an off state, no significant apractic disorder, MMSE-score above 25. The rotation of a wooden coin-like ring with the first three fingers of the right hand served as the target task. Right finger tapping with a practiced frequency of 1/sec was the reference task. Alternating periods of 20 secs composed a blocked design. (Siemens 3 Tesla). A group analysis (SPM5) comparing patients and subjects was performed.

Results: Patients performed less coin turns per target period than subjects (mean of 15 vs. 26). As reported for patients with LKA, the perirolandic area was strongly activated in both groups. Subjects showed significantly stronger activation of various sensorimotor network components: sensorimotor striatum (posterior Putamen), left perirolandic area. Additionally, stronger activations were found in posterior temporal areas implicated in the manipulation of tools and in the associative striatum (anterior Putamen) (Fig. 1). In contrast, patients activated more strongly in bilateral parietal cortex (Fig. 2).

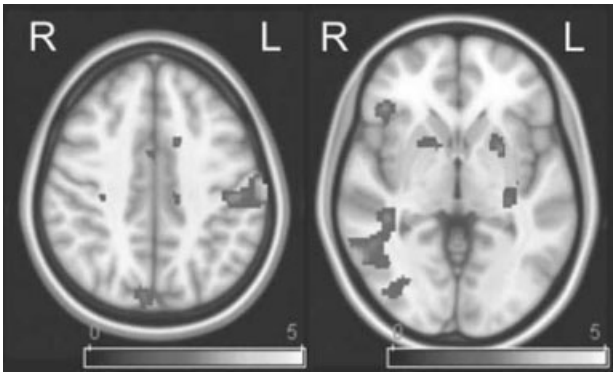

FIG. 1 (Mo-147).

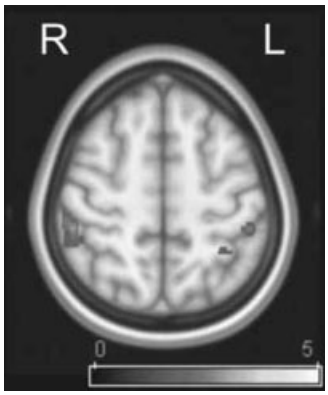

FIG. 2 (Mo-147).

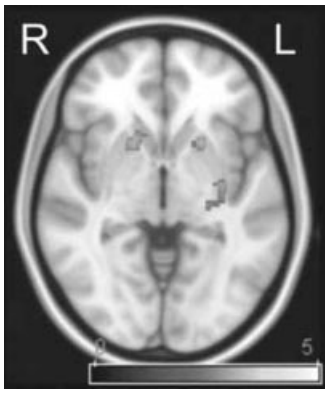

FIG. 1 (Mo-148).

Conclusions: Patients' decreased activation level in the striatum is an indication of local neuronal pathology with consequences for functional activation of the sensorimotor network. In contrast, increased activation of bilateral parietal cortex may correspond to compensatory efforts to maintain coin rotation performance. Parietal involvement in "apraxia tasks" has been demonstrated in patients with cortico-basal degeneration and LKA.

Mo-148

FMRI correlates of ideomotor apraxia in Parkinson's disease

T. Foki, N. Klinger, A. Geissler, J. Rath, T. Steinkellner, I. Hoellinger, S. Gruber, D. Haubenberger, J. Lehrner, G. Pusswald, G. Grabner, S. Trattnig, W. Pirker, E. Auff, R. Beisteiner (Vienna, Austria)

Objective: To evaluate whether early PD patients relative to healthy controls show specific brain activation patterns when contrasting symbolic object use with simple finger tapping using fMRI.

Background: Recent neuropsychological literature has demonstrated the occurrence of apractic disorders in the course of PD. In PD patients, the phenomenon of ideomotor apraxia manifests itself most frequently as impairment during the performance of transitive gestures.

Methods: 8 right-handed patients with right-dominant PD were compared to 6 healthy subjects. Patients' scans were performed in an off state, they did not suffer from any significant apractic disorder, the MMSE-score was above 25. The target task was to use the right hand to imitate the use of a visually presented object. Right finger tapping with a practiced frequency of 1/sec was used as the reference task. Data were acquired using a blocked design, with alternating periods of 20 secs. Temporal resolution was 2.5 seconds, spatial resolution was 1.8x.1.8x3mm. (Siemens 3 Tesla). A standard group analysis (SPM5) comparing patients and subjects was performed.

Results: Subjects relative to patients indicated larger activation of basal ganglia structures. Namely, the left posterior part (sensorimotor striatum) as well as the anterior parts of the Putamen and caudate nucleus in both hemispheres (associative striatum) were activated. (Fig. 1). Patients relative to subjects showed an increased level of activation of left frontal (part of the associative basal ganglia loop) and right parietal areas (Fig. 2). Detailed analysis revealed that both groups of participants showed strong activations of left parietal areas (stronger than right parietal areas). Due to a similar level of activation in both groups, no between-group difference could be determined in this area.

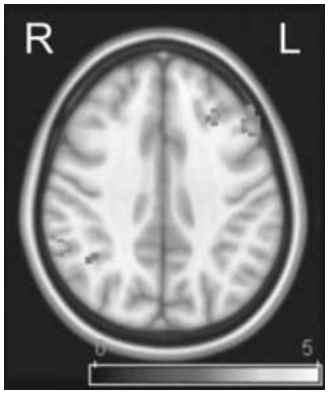

FIG. 2 (Mo-148).

Conclusions: We interpret the patients' decreased activation level in the basal ganglia as an indication for local neuronal pathology. In contrast, the increased activation level in frontal and parietal areas might correspond to compensatory efforts of yet functionally competent tissue to maintain symbolic object use performance.

Mo-149

Parkinson's disease and pathological gambling: Preliminary results from an fMRI study investigating cue induced brain activity

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Objective: To evaluate if PD/PG patients show different brain activation compared with PG patients when exposed to visual gambling cue during Fmri registration.

Background: Pathological gambling (PG) is classified as an impulse control disorder and may develop during Parkinson's disease (PD) while on dopaminergic therapy. Previous evidences have shown a dysregulation on the pre-frontal and limbic areas in PG while there are no evidences about the neural correlates of PG in PD.

Methods: Six PD patients with PG according to DSM IV criteria and 5 PD patients matched for age, sex, disease duration, severity and therapy. All patients were on dopaminergic therapy (dopamine agonists or Levodopa and dopamine agonists). Echoplanar functional magnetic resonance imaging were performed at 1.5 T by block-

design experiments with gambling-related visual cues (bingo scenes) alterned to neutral stimuli and rest periods. Within-group statistical analysis was performed by a General Linear Model approach with distinct predictor for gambling-related and neutral stimuli. The between-group differences were investigated through a T-test.

Results: PG/PD subjects and PD patients exhibited overlap in areas of brain activity in response to visual gambling cues: dorsolateral and mesial prefrontal cortices, cingulated cortex, inferior parietal lobule and cuneus (pBonf$<$0.05). However, compared to PD patients, PD/PG patients exhibited significantly increased cue-related BOLD-response in the anterior cingulated cortex bilaterally, right mesial-prefrontal cortex, right precuneus. A reduced activation has been observed in the right dorsolateral prefrontal cortex and right inferior parietal lobule ($p<0.05$).

Conclusions: The evidences of this preliminary study suggest that PG in PD patients is associated with dysfunction in pre-frontal cortex as previously observed in idiopathic PG. However in idiopathic PG a reduced frontal activation after the gambling related scenarios has been usually reported. The cue-induced activation pattern, mainly in cingulated cortex, observed in our PG PD patients is similar to that reported in drugs addicted patients. Further studies will clarify whether PG in PD should be considered an impulsive or addictive behaviour.

Mo-150

Functional imaging of presynaptic part of nigrostriatal system with ^{123}I ioflupane (DaTSCAN) in differential diagnosis of parkinsonian syndromes

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Objective: To evaluate the usefulness of single-photon emission computed tomography (SPECT) with ^{123}I ioflupane (DaTSCAN) in diagnosis of uncertain parkinsonian syndromes.

Background: The diagnosis of majority of movement disorders is based on clinical signs and symptoms as biological markers are not available and imaging studies do not reveal any structural abnormalities. The use of dopamine transporter (DAT) tracers allows to identify the disorders with the lesion of presynaptic part of dopaminergic nigrostriatal system.

Methods: In 20 patients SPECT with DaTSCAN was performed to differentiate Parkinson's disease with essential tremor (9 patients), vascular parkinsonism (3), drug induced parkinsonism (1) and psychogenic parkinsonism (2). In 5 cases more than two etiologies of parkinsonian syndrome were considered in differential diagnosis (PD, progressive supranuclear palsy as well as vascular, drug induced and psychogenic parkinsonism).

Results: Imaging with DaTSCAN SPECT revealed the lesion of the presynaptic part of nigrostriatal system in 17 (85%) patients; in 2 cases the uptake of the tracer in striatum was virtually absent. In 3 (15%) patients the study excluded abnormalities in the dopaminergic system and in these cases the diagnosis of essential tremor was finally established leading to the modification of therapy.

Conclusions: Our results confirmed the usefulness of DaTSCAN in routine management of uncertain parkinsonian syndromes. Neuroimaging studies improved accuracy of diagnosis and had significant impact on therapeutic decisions.

Mo-413

Cerebellar pathology and the triangle of Mollaret in cerebrotendinous xanthomatosis assessed by modern neuroimaging

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Objective: To characterize the chemical and microstructural abnormalities in a patient with cerebrotendinous xanthomatosis (CTX) using multimodal MR-techniques.

Background: CTX is an autosomal recessive disease due to defective activity of the mitochondrial enzyme sterol 27-hydroxylase, which is characterized by formation of xanthomatous lesions in various tissues. T2/FLAIR hyperintense magnetic resonance (MR) signals in dentate nuclei and the surrounding cerebellar white matter have been proposed as a characteristic feature of CTX.

Methods: Multimodal 3T MR imaging, including multivoxel H_1 spectroscopy with intermediate (TE=135) and long echo times (TE=270), and single voxel spectroscopy with short echo time (TE=30) as well as diffusion tensor imaging, was applied in this study. An age- and sex-matched healthy control was used for comparison purposes.

Results: We describe the case of a 34-year-old man who presented with bilateral juvenile cataracts, frequent diarrhea during childhood, presenile osteoporosis and progressive ataxic gait disturbance. The diagnosis of CTX was confirmed by molecular testing. Clinical high field (3T) MR-Imaging demonstrated T2-hyperintensities of the cerebellar white matter (CWM) as well as signal abnormalities of both dentate nuclei (DN). MR spectroscopy located abnormal asymmetric lipid accumulation within CWM and lactate peaks of the dentate nuclei. In addition, morphologically, the second stage of hypertrophic olivary degeneration (HOD) was detected without clinical evidence of palatal tremor. Diffusion tensor imaging visualized intact axonal connectivity of the triangle of Mollaret and decreased FA values of the CWM and superior cerebellar peduncles compared to the healthy control.

Conclusions: Several anatomical features of this rare condition are documented for the first time: (1) Integrity of axonal connectivity of the triangle of Mollaret, explaining the absence of palatal tremor (2) the topographic visualization of an abnormal metabolite distribution and (3) hypertrophic olivary degeneration. Our data show that multimodal MR techniques may characterize this movement disorder of metabolic origin by demonstrating biochemical and (micro) structural abnormalities. Studying connectivity in such cases may explain absence/presence of certain clinical signs.

Tu-120

Differential effect of motor coordination and visual constraints on basal ganglia connectivity

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Objective: We aim to study connectivity changes in the putamen and the caudate depending on the coordination mode between two fingers and on the visuo-motor integration demands.

Background: The performance of individuated finger movements requires selective activations of finger muscles and high sensorimotor integration demands. Individuated finger movements and visuomotor integration are respectively impaired in focal hand dystonia and Parkinson's disease, possibly due to dysfunction of basal ganglia circuits.

Methods: 15 healthy volunteers performed four visuomotor tasks (2X2 factorial design) using a force sensitive device with two buttons (one for each finger). They tracked a basic shape presented on a visual scene with a cursor. The cursor position was controlled with the force produced by the right index and the middle fingers. The shape A required that both fingers produced the same force at the same time (coupled condition) whereas the shape B required that the index finger produce a force independent to the middle finger (individuated condition). Each shape was presented in two visual modalities: with lines continuously constraining the cursor trajectories, with dots representing the direction changes of the cursor. Each condition lasted 20 s with 12 s of rest in between. Blood Oxygenation Level Dependent signal was recorded using fMRI. Cortical activation and connectivity maps were calculated using SPM5.

Results: Brain activation maps showed an activity increase in the basal ganglia during each condition compared to rest, but no effect of the coordination mode or of the visuomotor integration demands on the activity amplitude in these areas. We observe no connectivity

change in the left caudate for any of the conditions. We observe an increase of coupling between the left putamen, the right inferior parietal cortex and the right cerebellum in the individuated compared to the coupled condition, but no effect of the visuomotor integration demands.

Conclusions: There are important functional relationships between the left putamen, the right cerebellum and the right parietal cortex that may partly explain inabilities to perform individuated finger movements in patients with basal ganglia dysfunction. The interaction between these areas is independent from the visual constraints driving the motor control.

Tu-121

Dopaminergic imaging (DaTSCAN) in a French general hospital: A four years prospective study

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Objective: To present a prospective study of DaTSCAN exams prescribed by our neurological team of Aix en Provence, from November 2004 to December 2008, in the respect of official guidelines and to analyse the real impact on diagnosis.

Background: Since 2004, I123 Ioflupane (DaTSCAN), available for SPECT imaging study of dopaminergic neurons, obtained official agreement of French health authorities for differential diagnosis of tremor (Essential versus parkinsonian).

Methods: On 129 exams (126 cases), 120 exams (117 cases) according to the official rule were selected within 3 Groups: Group I (59 cases): mixed tremor (rest and posture) asymmetric with or without akineto-rigid syndrome and a positive response to L-dopa, Group II (52 cases): typical rest tremor but atypical psychological or evolutive data, Group III (6 cases): typically essential tremor but asymmetrical and/or positive response to L-dopa. Visual analysis was used to consider the dopaminergic denervation in the striatum, especially in its putaminal part.

Results: In the Group I, 35 cases were abnormal (59 %) and 24 normal (41 %). In the Group II, 46 cases were pathological (88 %) and 6 normal (12 %): 1 case normal at the 1st examination showed pathological results in the second 24 months later. In the Group III, 5 cases were normal (83 %) and 1 pathological (17 %): 2 normal cases in the 1st examination remained normal in the 2nd about 36 months later. In both Groups II and III, well clinically differentiated in spite of a positive L-dopa response in both, the diagnostic impact of the result was a confirmation of the initial clinical hypothesis in the majority of cases: indeed, the DaTSCAN examination invalidates the clinical hypothesis only in less than 20 % of cases. The group I constituted by unclassifiable cases showed a distribution close to 50 %.

Conclusions: The diagnostic impact of in vivo dopaminergic imaging is especially useful in the unclassifiable cases after a rigorous clinical analysis (about half cases of the present register).

Tu-122

Significant improvement in magnetic resonance imaging brain of a Wilson's disease patient with psychiatric onset after beginning chelanting therapy

M. Gennuso, M. Crispino (Crema, Cremona, Italy)

Objective: We report a case of WD patient with psychiatric onset who showed a rapid clinical and radiologically improvement after the beginning of the chelantig theraphy with penicillamine.

Background: Wilson's disease (WD) is an autosomal recessive inherited disorder of copper metabolism (at chromosome 13q14.3). A defective trasport of copper across membranes leads to accumulation of excess of copper in various organs, particularly liver and brain. Clinical presentation of WD includes hepatic, psychiatric and neurological manifestations. One third of patients with WD may initially presents with psychiatric symptomps as behavioral abnormalities, anxiety, depression; and failure to recognize these may lead to misdiagnosis. In this case, early WD diagnosis and a prompt treatment with chelanting therapy have favorable outcome.

Methods: A 23 years old Roumanian man developed psychiatric symptoms one year ago that required his admission to hospital. He showed behavioral abnormalities: apathy, social withdrawal and cognitive impairment. Then he showed a psycotic symptoms and he received antipsycotic drugs. After some months he developed extrapyramidal symptoms and stopped medications. He was examined by the neurological department and detected to have low serum ceruloplasmin (3 mg/dl, normal 20-50); low serum copper (20 mcg/dl (normal 70-140) and incresed levels at 24h urinary copper (213 microg/l, normal < 60). Brain MRI imaging study showed basal ganglia and cortex atrophy, bilaterally symmetric high signal intensity in the putamen on Spin Echo T2-weighted and FLAIR images; hyperintensity has been seen bilaterally in gray and white matter of the superiort frontal gyrus particularly on the right side. He started oral therapy with penicillamine.

Results: The young WD patient had a progressive disappearance of the psychiatric symptoms and the following MRI Brain showed a significant improvement in pathological changes.

Conclusions: Early diagnosis and prompt treatment of the WD patient whith psychiatric onset, have favorable clinical outcome and radiological too.

Tu-123

Training induced motor network plasticity in Parkinson's disease

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Objective: To assess whether motor training in Parkinson's disease (PD) is associated with structural motor network plasticity of the neurodegeneratively diseased brain as measured by MRI.

Background: Physical training can improve motor abilities in PD. Positive effects may outlast the training period for up to 6 weeks. The underlying mechansisms are unclear, though we hypothesize that changes in brain structure may account for this observation.

Methods: 21 PD patients (Hoehn & Yahr stage 2.0) participating in a 12-week training study received clinical examination (UPDRS motor score) and additional MR imaging (1.5 Tesla, 3D-T1mprage, 0.9x0.9x1.0 mm^3) before and after the training period. Training was performed in two matched groups: (1: conventional PD motor training, 2: newly designed continous motor learning). Image analysis was performed using voxel based morphometry (VBM).

Results: UPDRS motor scores improved after training ($p=0.007$), without significant group differences ($p=0.35$). VBM analysis without respect to the training group revealed increased grey matter volume after training in the cerebellum (figure 1B) and to a lesser extent in the right striatum and insula (1A), as well as an increased white

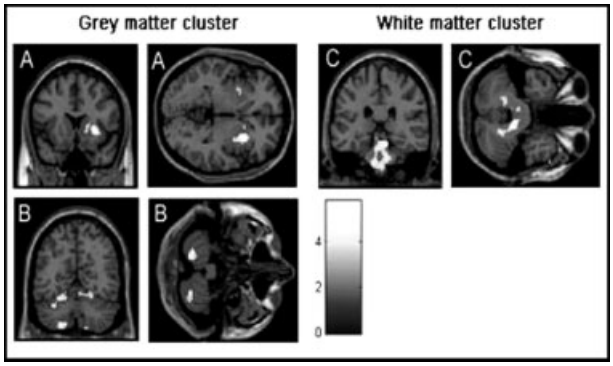

FIG. 1 (Tu-123). Voxel based morphometry. Paired *t*-test for the whole cohort without respect to the training group. All significant clusters are shown.

matter volume within the brainstem and the middle cerebellar peduncle (1C). Increased cerebellar grey and brainstem and cerebellar white matter volume were associated with greater improvement of UPDRS motor scores (p=0.009-0.03). Subgroup analysis replicated the clusters for the motor learning group but not for the motor training group when applying a stringent threshold. Moreover, there was increased grey matter volume in the left precentral gyrus in the motor learning group.

Conclusions: In conclusion, training of motor function in PD patients seems to be associated with structural motor network plasticity comprising not only the nigrostriatal circuit, but also and even more pronounced the olivo-ponto-cerebellar pathway. This may indicate a potential of the cerebellum to compensate for the already diminished basal ganglia function in PD, which may be induced predominantly by learning of new motor tasks.

Tu-124

Mismatch between FP-CIT results and the clinical scenario: A retrospective clinical audit

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Objective: To report a mismatch between FP-CIT and clinical scenario.

Background: FP-CIT SPECT is a well validated technique for establishing the presence of a pre-synaptic dopaminergic deficit in patients presenting with parkinsonism. Cases where there is a mismatch between clinical and FP-CIT scan findings are of significant interest and may be in the range 1-5%. Conditions resembling Parkinson's disease but having normal FP-CIT are referred to as SWEDDs (subjects without evidence of dopaminergic deficit). Cases of 4 repeat tauopathy (cortico-basal degeneration or progressive supranuclear gaze palsy) or multiple-system atrophy are usually reported to have abnormal FP-CIT although the pattern of abnormality is usually not distinct from PD. As 60-80% of dopaminergic neurones may be lost in PD at onset of motor symptoms, FP-CIT is usually clearly abnormal in symptomatic PD cases.

Methods: We have performed an audit of all FP-CIT carried out in our institution between 2004-2008. From this cohort of 354 we have identified 3 patients where scans show negative or borderline findings not in keeping with the clinical scenario.

Results: Three cases were identified where the patient was felt to have clinical parkinsonism and the DATSCAN was initially normal or only mildly abnormal. This does not include cases of SWEDD where the clinical diagnosis was refined in light of the FP-CIT result (mostly to dystonic tremor) Case 1: Presented with 6 month gait deterioration and falls. Initial FP-CIT was normal and MRI imaging showed extensive leukoaraiosis. There was no response to therapeutic doses of levodopa. A diagnosis of vascular parkinsonism was made. Within 15 months of this initial diagnosis, the patient showed a rapid deterioration in mobility and developed supranuclear gaze palsy. Second FP-CIT within 14 months of the first normal scan showed clearly abnormal pattern. A final diagnosis of PSP was made. Case 2 & 3: Both cases presented with signs and symptoms consistent with PD. FP-CIT in both cases was borderline abnormality. Both evolved a Parkinson's disease dementia phenotype within 6 months of the FP-CIT scan.

Conclusions: Further work is required to evaluate the negative long term predictive value of FP-CIT. FP-CIT in two cases of PDD has only shown borderline rather than clearly defined abnormality.

Tu-125

Increased striatal metabolism on PET imaging in antiphospholipid antibody – Associated chorea

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Objective: To report the case of a 23 years-old woman with antiphospholipid antibody – associated chorea (right hemichorea). PET imaging showed increased uptake of fluoro-18-deoxyglucose in both striatal regions, higher at the controlateral side of the choreic movements, despite normal MRI.

Background: Chorea is a well known but rare manifestation in patients with anthiphospholipid antibodies (APL). The mechanism of chorea in relation to the presence of APL remains unknown with two major historical hypotheses: ischemic and immunological mechanisms.

Methods: Case study.

Results: A 23 years-old woman presented with subacute onset involuntary movements of right arm. She had no prior medical history and took a contraceptive pill. The neurological examination disclosed chaotic, nonrhythmic movements of the right arm, of moderate amplitude, with no volitional control, slightly increased by action and posture. General examination revealed obesity (IMC=38,2) with no cardiac, joint or dermatological abnormalities.CBC, streptococcal antibodies titers (anti-streptolysin O) were normal. Urinalysis showed no blood or protein. The ESR was elevated (58mm) as was CRP (27,2 mg/L). Spontaneous prolongation of APTT (76 seconds) was observed as well as prolongation of dilute Russell's Viper Venom Time (dRVVT). Mixing and confirmation tests revealed the presence of a lupus anticoagulant. There were high titers of anticardiolipin IgG (84 GPLU). The complement profile was normal, the tests for antinuclear antibodies and antidouble stranded DNA antibodies were negative. Brain MRI was normal. FDG PET imaging showed bilateral striatal hypermetabolism, higher at the controlateral side of the choreic movements. The echocardiogram showed Libman-Sacks type vegetations in the mitral valve. Since MRI did not demonstrate ischemic lesions, the patient did not fulfill clinical criteria for SLE or definite APL syndrome, but isolated APL associated chorea. There was improvement of chorea with Prednisone, Tetrabenazine and Aspirine.

Conclusions: Alterations in striatal metabolism could be demonstrated in this patient on PET imaging in the absence of ischemic changes on MRI, suggesting an immune-mediated mechanism for APL-associated chorea. PET imaging may have a role for monitoring treatment efficacy in such patients.

Tu-126

Quantitative ^{1}H magnetic resonance spectroscopic imaging of normal basal ganglia and thalamus

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Objective: Goal of the study was to determine normal levels of N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), creatine (Cr), glycerophosphorylcholine (GPC), phosphocholine (PC), *myo*-inositol (mI), glutamine (Gln), and glutamate (Glu) in regions of basal ganglia and thalamus using quantitative ^{1}H-MRSI in 32 healthy subjects.

Background: Magnetic resonance spectroscopic imaging (MRSI) offers unique possibilities for non-invasive studies of biochemistry in brain *in vivo*. For evaluation of MRSI on different brain pathologies it is essential to determine the normal levels of typical brain metabolites.

Methods: Thirty-two neurologically healthy individuals (13 women, 19 men, 29-78 years) received MR examination (2D T_2-weighted turbo spin echo (TSE) and point resolved spectroscopy sequences) on a 1.5 T whole-body MR scanner (Avanto, Siemens Erlangen) using the standard head coil. Slice positions for MRSI on basal ganglia and thalamus were chosen in 2D TSE. After grid shift function with CULICH (F. Jiru, Prague) for exact voxel position inside the investigated regions, quantification of MRSI spectra were carried out by LCModel (S. W. Provencher) as a non-interactive method with automatic phasing and fitting for user-independent results. Absolute concentrations and metabolite/Cr ratios were determined for all spectra which could be fitted with good quality (standard deviation (SD) between fit and spectrum smaller than 20% for each metabolite).

Results: In this way, we found high quality spectra (SD<10%) of thalamus and splenium of corpus callosum in all subjects with reproducible quantitative results for all absolute concentrations and ratios except for Glu and Glu+Gln, which might have been difficult because of J-coupling phenomena. In putamen, only in half of subjects high quality spectra could be evaluated. In caudate nucleus low quality spectra were found, which may be attributed to its small size compared to voxel size. In voxel position corrected MRSI data no sex/age dependent variations could be observed in our group for Cr, GPC, mI, NAA, GPC+PC, NAA+NAAG, Glu, and Glu+Gln.

Conclusions: In this study we could show that valid and reproducible data can be obtained in different basal ganglia regions by MRSI. This new technique may therefore provide a promising tool to further investigate pathophysiology and diagnosis of basal ganglia disorders.

Tu-127

Brain dopaminergic modulation associated to executive function in Parkinson's disease

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Objective: In the present study, we used fMRI to examine the functional influence of dopatherapy on neural activity in parkinsonian patients candidate for deep brain stimulation.

Background: Progressive development of deficits in executive functions, including action planning, is a well known complication of Parkinson's disease. Because prefrontal areas play a critical role in the control of inhibitory processes, it is tempting to hypothesize that the difficulties in initiating behavior or inhibiting ongoing actions in PD-patients could be related to a prefrontal lobe dysfunction. The strong dopaminergic innervation of the prefrontal cortex raises questions about the putative effect of dopatherapy on this cognitive impairment.

Methods: Brain activity associated with go/nogo task was examined in 9 PD patients with and without L-DOPA treatment and in matched controls using a block-designed fMRI. All scans were performed on a 1.5 Tesla Philips Gyroscan-NT-Scanner Power track/6000.

Results: To achieve the same level of performance, different patterns of brain activations were observed depending on dopaminergic status. Drug-off state was characterized by wider brain activity, mainly in the bilateral caudate. L-dopa did not fully restore normal brain activation and induced a shift in activity from the rostral to the caudal part of the cingulate cortex.

Conclusions: These results support the idea of a critical role for dopamine in the control of executive functions in PD-patients.

Tu-128

Clinical features and [^{11}C]-CFT PET analysis of PARK2, PARK6, PARK7-linked autosomal recessive early-onset parkinsonism

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Objective: To characterize the neurochemical phenotype of clinically and asymptomatic heterozygotes from three AREP families with mutations in *Parkin*, *PINK1* and *DJ-1* genes, respectively.

Background: Mutations in *Parkin*, *PINK1*, and *DJ-1* genes can cause autosomal recessive early-onset parkinsonism(AREP). Neuropathology of cases with AREP is limited. Positron emission tomographic (PET), by providing quantitative information on dopaminergic function, is useful for the in vivo investigation of PD.

Methods: Three families with the mutations of *Parkin*, *PINK1* and *DJ-1* gene respectively, were studied with a dopamine transporter ligand [^{11}C]-CFT PET. The simple ratios of the radioactivity of the caudate nucleus and the putamen, respective to that of the cerebellum, were calculated.

Results: A marked bilaterally and dyssymmetrically decrement of [^{11}C]-CFT uptake was found in all these patients, and putamen as well as caudate nucleus was affected. We also found asymptomatic *Parkin* and *PINK1* heterozygotes showed a mild but significant decreae in [^{11}C]-CFT uptake, but this phenomenon was not found in the *DJ-1*-heterozygotes.

Conclusions: Our results suggested the three autosomal recessive forms of early onset are similar to each other on pathophysiological grounds, a sub-clinical disease process in *Parkin* and *PINK1*-heterozygotes, but not in *DJ-1*-heterozygotes.

Tu-129

Mechanisms underlying motor and cognitive slowing in Parkinson's disease

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Objective: To clarify if (1) dysfunction of the basal ganglia (BG)-cortical loops underlies motor and cognitive impairment in patients with Parkinson's disease (PD) and (2) different BG-cortical subloops are responsible for cognitive and motor impairment in patients with PD.

Background: Patients with PD show not only motor slowing but also cognitive slowing, or bradyphrenia. However, no behavioral or imaging studies have directly examined the mechanisms underlying motor and cognitive slowing, by using the same experimental framework.

Methods: Fifteen patients with PD (mean age, 63 years old) and 18 matched control subjects (mean age, 62 years old) were enrolled in the present functional magnetic resonance imaging (fMRI) study after giving written informed consent. The subjects performed actual finger tapping, imagery finger tapping, and mental calculation tasks in 30-s blocks with 4 different speeds (0.25, 0.5, 0.75 and 1 Hz). All 3 tasks were paced by visual presentation of number stimuli, and task performance was reported only after each task block. Different tasks were prescribed in different fMRI runs. Blood-oxygenation level-dependent signals were measured with a 3-T MRI. Brain activity related to each task (task-related activity) and that modulated by task speeds (speed-dependent activity) were analyzed with statistical parametric mapping.

Results: In healthy controls, speed-dependent activity was observed in the posterior frontal cortices and BG in a spatially segregated fashion. The speed-dependent activity was observed in the anterior putamen during the mental calculation task, in the posterolateral putamen during the finger tapping task, and in the middle part of the putamen during the imagery finger tapping task. Patients with PD showed decreased speed-dependent activity in the corresponding part of BG during each task.

Conclusions: The present results lend support for the hypothesis that dysfunctions of different BG-cortical subloops are responsible for cognitive and motor slowing in patients with PD.

Tu-130

A novel MRI sequence, the fast gray matter acquisition T1 inversion recovery (FGATIR), is superior to fluid attenuated inversion recovery (FLAIR) for the resolution of white matter lesions (WMLs)

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Objective: To compare FGATIR and FLAIR MRI sequences for the evaluation of white matter lesions (WMLs).

Background: Improvements in imaging have greatly enhanced our understanding of brain anatomy. Associated primarily with multiple sclerosis (MS) and stroke, WMLs have also been tied to hypertension, migraines, and dementia. Multiple diagnostic criteria depend on the accurate counting of WMLs. We developed an MRI sequence that provides high resolution slices with greater sensitivity than FLAIR, the standard imaging modality for WML evaluation.

Methods: Two sequences were acquired on a 3T Siemens Allegra MRI: a T2 FLAIR and a T1-weighted MRI protocol, the FGATIR. The FGATIR was created by attenuating the white matter signal of a standard magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence. Image acquisition was rapid for both: 12m for FLAIR and 11m for FGATIR. A brain MRI of a 35 year old man with severe MS was acquired under both protocols. We compared the scans' performance via two measures: a WML count and the intensity difference at WML boundaries. In method one, a neurologist, neurosurgeon, and medical physicist each manually counted and compared WMLs in sagittal FLAIR and FGATIR slices every five millimeters from midline to 35mm. In method two, lesions were contoured and intensity histograms generated for those pixels at the contour boundary.

Results: The FGATIR was superior on both measures of image resolution. An average of 129 WMLs (standard deviation = 15.4) was found on FGATIR versus 85 (standard dev = 23.2) on FLAIR. The FGATIR had a superior contrast ratio when compared to FLAIR: the lesion to surrounding tissue/white matter ratio was 250:50 with FGATIR and 225:125 with T2 FLAIR. These two figures show the patient's brain 10mm left of midline using both modalities. Lesions that are difficult to distinguish from background with T2 FLAIR: Are relatively easily seen via FGATIR:

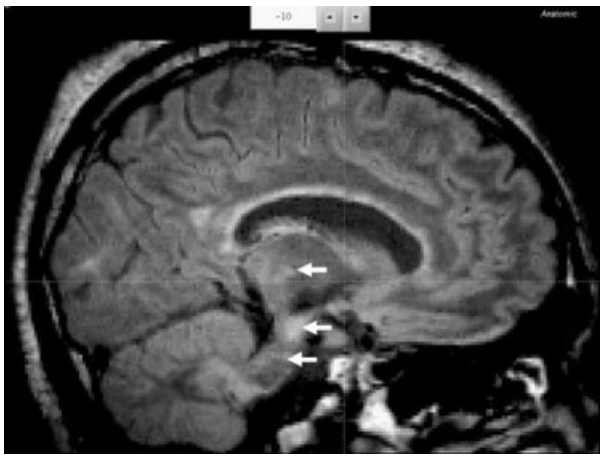

FIG. 1 (Tu-130).

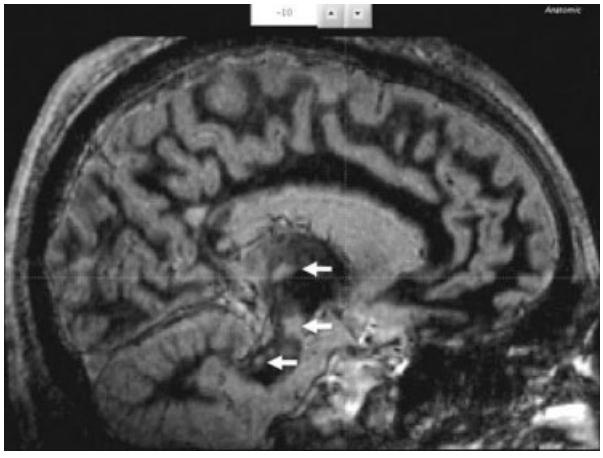

FIG. 2 (Tu-130).

Conclusions: Our results suggest the FGATIR is more sensitive for detecting WMLs than FLAIR. Though this may give rise to an increase in false positive detections, we expect this rapid and high resolution sequence to improve our understanding of the anatomy of a variety of white-matter pathologies.

Tu-131

Longitudinal MRI changes in Parkinson's disease patients with visual hallucinations

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Objective: To assess the progression of regional cortical atrophy and cognitive deficits in PD with VH patients.

Background: Longitudinal studies in Parkinson's disease (PD) have pointed the presence of visual hallucinations (VH) as a clinical predictor of cognitive decline and dementia. However, no study to date has focused on the brain atrophy progression in these patients.

Methods: Magnetic resonance imaging (MRI) and neuropsychological evaluations were obtained both at base-line and at follow-up (mean ± SD= 29.91 ± 5.74 months) on a sample composed of: 12 PD patients with VH, 14 PD patients without VH and 12 matched controls. We used voxel-based morphometry technique to assess gray matter loss from base-line to follow-up in the different groups.

Results: PD patients with VH showed a marked gray matter loss in limbic, paralimbic and neocortical areas and presented a high rate of progression to dementia. PD patients without VH did not meet criteria for dementia and only showed slight reduction in frontal areas and the cerebellum. Controls did not show dementia or any areas of brain atrophy over time.

Conclusions: The presence of VH in PD implies a rapid development of dementia which is accompanied by progressive widespread cortical atrophy.

Tu-132

^{1}H-MRS finding of substantia nigra in patients with Parkinson's disease

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Objective: To estimate the activity of neurons in substantia nigra(SN) in patients with Parkinson's disease(PD), multi-voxel 1H-MRS examination of SN in PD patients was performed and compared to SN of non-parkinsonian control.

Background: PD is characterized by neuronal loss of SN and symptomatic phase in this disaesa 50-70% neuronal loss had been estimated by morphometric studies. There had been few such studies *in vivo*.

Methods: From August 2007 to December 2008, totally 111 patients with PD(69 women and 42 men, mean age 69.4 years old) and 23 control patients(14 women and 9 men, mean age 64.5 years old) were investigated. 21 PD patients(15 women and 6 men, mean age 67.3 years old) were before treatment of dopaminergic drugs. Control were 12 tremor(including 7 essential tremor, 5 mental stress induced), 8 localized cerebellar lesion(4 CCA, 2 SCA, 1 paraneoplastic CA and 1 post EB cerebellitis) and 3 multiple sclerosis patients. Multi-voxel 1H-MRS(GE Signa Twin Speed 1.5T) was performed at the plane similar to trnscranial ultrasonography examination. After obtained metabolite spectra, NAA/Cr ratio was calculated. The difference of NAA/Cr ratio between PD and control was analyzed using Student's *t*-test.

Results: The NAA/Cr ratio of SN between PD and control showed statistically significant difference as shown in Table.

Relation between the decrease of NAA/Cr and the duration from onset was found in tremor predominant patients but no futher decrease in rigidity predominant patients was seen. The decrease of SN NAA/Cr with age was prominant in patients with untreated PD compared to that of control, i.e., the regression line was

Table (Tu-132). NAA/Cr obtained from SN

All PD Examined (N=111)	1.59±0.36•
Rigidity (N=58)	1.51±0.34
Tremor (N=46)	1.69±0.37
Untreated PD (N=21)	1.59±0.41•
Rigidity (N=10)	1.5±0.39
Tremor (N=7)	1.78±0.32
Control	1.95±0.23•
	•p<0.000001

y=-0.043x+1.88 and y=-0.0019x+2.08, respectively (where y is SN NAA/Cr and x is age).

Conclusions: The results obtained in this study seemed to be compatible with findings of previously reported morphometric studies. Whether the decrease of NAA/Cr in SN means change of neuronal activity or neuronal loss remains to be elucidated, however, it can be said that SN neurons may active approximately 80 % in function or still remaining in number even at symptomatic phase of PD.

Tu-133

Cortico-striatal activation during implicit sequence learning in Parkinson's disease with deep brain stimulation of the subthalamic nucleus

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Objective: To investigate the effect of deep brain stimulation (DBS) of the subthalamic nucleus (STN) on implicit sequence learning in Parkinson's disease (PD) and on associated patterns of brain activation.

Background: Implicit sequence learning during the serial reaction time task (SRTT) has been shown to activate the cortico-striatal circuits. Patients with PD show attenuated learning on the SRTT, which is completely abolished following surgical lesioning of the internal segment of the globus pallidus (Brown et al, 2003).

Methods: 7 PD patients with DBS of the STN were assessed after overnight withdrawal of dopaminergic medication with a H_20^{15} PET. PD patients completed five blocks of a probabilistic serial reaction time task (5 scans) followed by a control random sequence (1 scan) with DBS on and off, with order counterbalanced, using parallel sequences.

Results: With DBS on, PD patients showed significantly greater learning-related activation in the cortico-striatal circuits, than with DBS off.

Conclusions: The results provide evidence for the modulation of the cortico-striatal circuits involved in implicit sequence learning by DBS of the STN in PD. The differing effects of DBS of the STN and pallidotomy on implicit learning on the SRTT in PD suggest that the mechanisms of action of these surgical procedures are different. References Brown RG et al (2003) *NeuroReport,* **14**, 21-4.

Tu-134

Selective brain atrophy in Parkinson's disease treated with STN DBS

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Objective: In our study, we searched for any longitudinal morphological changes of the brain related to deep brain stimulation of the subthalamic nucleus (STN DBS) in patients with Parkinson's disease (PD).

Background: Bilateral STN DBS has become a routine method in long-term management of PD. Therefore we tested if STN DBS may affect morphometry of the brain manifested in change of the local intensity of gray and/or white matter.

Methods: T1–weighted brain images were obtained from 33 PD patients (age 42-76 years, PD duration: 8-24 years) using 1.5 T MRI during 2 weeks before and 1 week after the implantation of intracerebral electrodes to the STN bilaterally. The MRI was then repeated during period 1–4.5 years. The local gray and white matter intensity was analyzed with Voxel–based morfometry in SPM5 software using an optimized protocol. The statistics were compensated for the total gray matter volume, age, the between–scan interval, and PD duration. Five patients were excluded for poor–quality or incomplete data.

Results: Brain of the STN DBS treated patients developed significant atrophy of the caudate nuclei during the period under study ($P<0.001$ corrected). In addition, a gray matter atrophy was found in the inferolateral prefrontal cortex of both hemispheres and in the left planum temporale which positively correlated with the period of time interval from surgery ($P<0.05$ corrected). The white matter atrophy observed in the anterior arm of the internal capsule bilaterally correlated with the same time interval as well ($P<0.001$ uncorrected).

Conclusions: This is the first study showing selective gray and white matter atrophy in PD patients treated with STN DBS. As previous morphometric studies of pharmacologically treated PD described different pattern of brain atrophy, we believe that atrophy involving mainly the frontal lobes might be related selectively to STN DBS procedure. This seems to be consistent with cognitive decline reported in PD patients after STN DBS. *Supported from research project MŠM 0021620849 and grants IGA MZCR 1A8629-5 and GACR 309/09/1145*

Tu-135

Scans without evidence of dopaminergic deficit. Long-term follow-up in a clinical cohort

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Objective: To describe clinical characteristics and final diagnosis after two-year follow-up in 16 parkinonian subjects without evidence of dopaminergic deficit.

Background: Presynaptic dopamine transporter imaging using radioligands such as ^{123}I-FP-CIT and SPECT is generally abnormal when parkinsonism is degenerative (such as Parkinson's disease) and normal in non-degenerative movement disorders (such as essential tremor). Some patients diagnosed as degeneretive parkinsonism show normal presynaptic imaging. Follow-up of such patients could help determine whether these subjects truly have degenerative parkinsonism or represent other alternative diagnoses.

Methods: 246 patients with clinical diagnosis of parkinsonism according to United Kingdom Brain Bank Criteria (step one) underwent dopamine transporter imaging using ^{123I}I-FP-CIT SPECT in a single center from July 2003 to December 2006. General and neurological examination was performed in all patients, UPDRS and Hoehn-Yahr staging included. SPECT results were evaluated qualitatively by two nuclear medicine specialist, blinded to diagnosis and clinical data. Evaluations, including clinical features, progression of pakinsonian symptoms, response to anti-parkinsonian agents and clinical diagnosis were recorded during two-year after SPECT.

Results: 16 patients (6,5%) with normal imaging were identified. Initial diagnoses were as follows; 13(81.25%) were diagnosed as having Parkinson's Disease and 3 (18.75%) as having atypical parkinsonian syndrome. The predominant clinical feature was tremor in 10 (62.5%) and bradikinesia in 3 (18.75%); the remaining cases had mixed features. The diagnosis after follow- up was essential tremor in 8 cases (50%), drug induced parkinsonism in 2 cases (12.5%), non-degenerative parkinsonism in 3 cases (18,75%) and atypical parkinsonism in 3 cases (18.75%), due to clinical progression, no response to dopaminergic therapy and abnormal IBZM SPECT. The initial congruence between clinical diagnosis and dopamine imaging increased from 93.45% to 98,78%.

Conclusions: The clinical profile during follow-up of patients without evidence of dopaminergic deficit supports alternative diagno-

sis in nearly all cases. Besides, congruence between working diagnosis and dopamine imaging increases over time in favour of initial imaging results.

Tu-136

Reduction of the motor cortex thickness in Parkinson's disease

T. Jubault, L. Monetta, A.-L. Lafontaine, A.P. Strafella, A.C. Evans, S. Chouinard, O. Monchi (Montreal, QC, Canada)

Objective: To charaterize morphological changes in the cortical surface associated with Parkinson's disease.

Background: Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder characterized by the destruction of dopaminergic neurons in the substantia nigra and by motor symptoms (tremors and/or rigidity and bradykinesia). Neurodegeneration is known to affect cortical structure (Braak & Braak, 2000) in advanced stages of the disease. To date, anatomical scans non-demented idiopathic PD patients have show little to no differences when compared to healthy individuals with volumetric or voxel based morphometry methods. We hypothesized that, even at early stages of the disease, the neurodegenerative processs of PD could have an impact on specif cortical regions, and could be detected by cortical thickness analysis.

Methods: To assess the presence of cortical changes common to all PD patients at an early stage of the disease, we acquired high-resolution T1-weighted scans (1*1*1 mm3 MPRAGE) of 19 PD patients (Hoen and Yahr stages I to II) and 14 healthy controls (HC) matched for age and gender. We used the CIVET family of softwares (Ad-Dab'bagh et al., 2006) to extract cortical thickness in native space. Locally registered cortical thickness was analyzed with Surfstat (http://www.math.mcgill.ca/keith/surfstat/).

Results: We observed that global average cortical thickness was significantly lower in the PD group than in the control group when factoring out the effect of age. Moreover, a critical area of thinning was localized in the right motor cortex (talairach coordinates of the peak: 42, -18, 50, $P<0.05$, 54 vertex, $P<0.003$ at cluster level). A subthreshold region of cortical thinning was also detected in the left counterpart, positively correlated to the right peak.

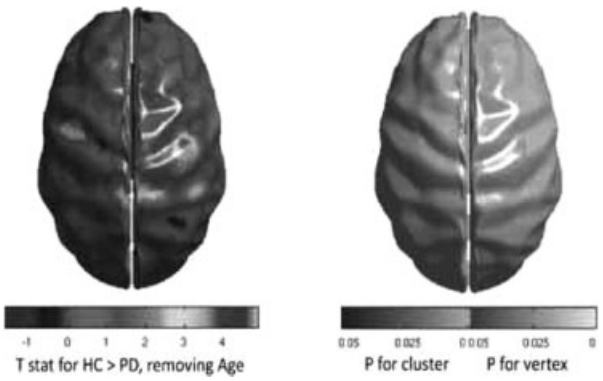

FIG. 1 (Tu-136).

Conclusions: Although cortical changes are supposed to occur at later stages, we detected a global cortical thinning in the PD group, and one specific region of thinning in the motor cortex. This result is consistant with the neurodegenerative pattern of PD and the motor symptomatology and demonstrates the sensitivity of this method to PD. Further studies would be necessary to determine the anatomical connections linking the thinning pattern of regions to the basal ganglia, and if these morphological changes are linked to functional anomalies.

Tu-137

Brain stem volume reduction in idiopathic Parkinson's disease assessed by anatomical MRI

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Objective: To detect primary damages to the brain stem in Parkinson's disease, according to Braak & Braak stages, with conventional MRI.

Background: Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder characterized by the dysfunction of dopaminergic dependant cortico-basal loops and a motor symptomatology (tremors/rigidity/bradykinesia). Recent post mortem studies of PD tend to show that the destruction of dopaminergic neurons in the substantia nigra is an intermediate step in a broader pattern of neurodegeneration linked to Lewy bodies inclusion. According to these observations, PD would start in the medulla oblongata/pontine tegmentum, and reach neo-cortical territories in late stages. To date, neuroimaging techniques have been unable to characterize the pre-symptomatic stages of PD. However, if such a regular neurodegenerative pattern were to exist, consistent damages would be found in the brain stem, even at early stages of the disease.

Methods: 19 PD patients at Hoenn and Yahr stages I to II of the disease were recruited, as well as 14 healthy controls (HC) matched for age and gender. High-resolution T1-weighted anatomical scans were acquired (MPRAGE, 1*1*1 mm3). Images were analyzed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/software/spm2/), and an optimized voxel based morphometry (VBM) protocol (Ashburner and Friston, 2000) was performed to detect white matter volume and/or density reduction.

Results: When the PD group was compared to the HC group, only one cluster showed statistical difference ($p<0.05$ corrected for false detection rate) in the white matter. This cluster ovelapped medulla oblongata and pontine tegmentum.

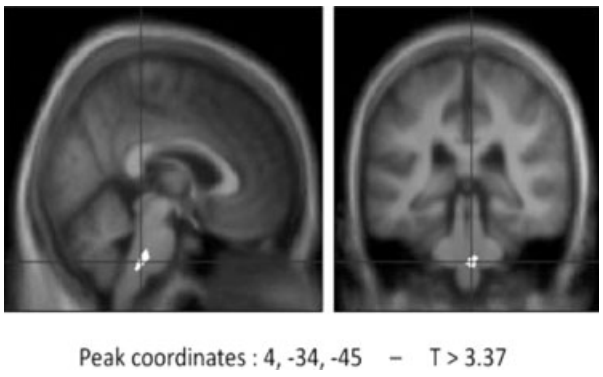

FIG. 1 (Tu-137).

Conclusions: This result is consistent with a starting point of the neuropathology common to all idiopathic PD patients, in spite of the symptomatology. It is interesting to note that only this cluster was observed significantly. We postulate that damage in this region is common to all patients while the regional evolution of the neurodegenerative process may be more variable, and hence lowers the sensibility of white matter VBM. In conclusion the present study provides evidence that the the neuropathology of PD may start in the brain stem, and promising clues for a future diagnosis method relying on conventional MRI.

Tu-138

Reduced volume of the substantia nigra pars compacta determined by neuromelanin magnetic resonance imaging in patients with Parkinson's disease

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Objective: To elucidate the volumetric changes in the substantia nigra of Parkinson's disease, we determined the volume of melanin containing substantia nigra pars compacta determined by neuromelanin images by a 3-T scanning.

Background: Parkinson's disease is characterized by a progressive degeneration of melanin-containing neurons in the substantia nigra pars compacta. The pathological change has hardly been detected by neuroimaging technique so far. The neuromelanin magnetic resonance imaging of substantia nigra reportedly detected reduced signal intensity in Parkinson's disease.

Methods: We examined 51 patients with Parkinson's disease (20 men, 31 women) (PD group) and control group consisted of 34 patients with acute cerebrovascular attacks (CVA) (16 men, 18 women) who previously had no event of CVA or other diseases in the central nervous system. The mean ages±SD were 71.4±7.5 for the PD group and 72.5±10.6 for the control group. Axial T1-weighted (T1W) images were acquired on a 3-T MRI scanner. The substantia nigra borders were traced manually with a pentablet pointing device on axial T1W images. Both the left and right substantia nigra of each subject were measured by a skilled rater. The mean volumes of left and right substantia nigra were used for statistical analysis.

Results: There was no difference of age between two groups (Figure 1). The volume of substantia nigra determined by neuromelanin imaging was significantly reduced in PD group when compared with control. The volume reduction was more marked patients with advanced stage (Figure 1).

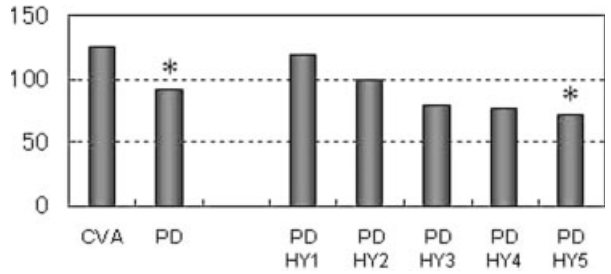

FIG. 1 (Tu-138).

Conclusions: Reduced volume of melanin containing cells in the substantia nigra pars compacta was elucidated by neuromelanin magnetic resonance imaging in patients with Parkinson's disease. Volmetric evaluation of neuromelanin MR imaging may detect the neurodegenerative change in Parkinson's disease.

Tu-139

Susceptibility weighted MR imaging can differentiate progressive supranuclear palsy from multiple system atrophy and Parkinson's disease

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Objective: To differentiate Parkinson's disease (PD), progressive supranuclear palsy (PSP) and Parkinson variant of multiple system atrophy (MSA-P) using susceptibility weighted imaging (SWI).

Background: Neuropathological studies report varying patterns of mineralization in PD, PSP and the MSA-P. SWI is the ideal MRI sequence to detect mineralization of brain.

Methods: Eleven patients with PD, 12 with PSP, 12 with MSA diagnosed by a movement disorder specialist and 11 healthy controls underwent SWI of brain. Hypointensity of putamen, red nucleus, substantia nigra and dentate nucleus in all groups was assessed according to a visual grading scale and scored from 0-3 (0 being least and 3 being most hypointense). The hypointensity of the single largest view of each of the four regions was selected for scoring them. Two radiologists who were blinded to the clinical diagnosis independently rated the scans.

Results: In PSP, the red nucleus hypointensity score was higher when compared to MSA-P ($p = 0.008$), PD ($p = 0.002$) and controls ($p = 0.004$). The putaminal hypointensity score was also higher in PSP compared to PD ($p = 0.004$). There were no significant group differences in hypointensity scores of other deep gray nuclei. For the red nucleus, the intraclass correlation coefficient (ICC) of intrarater reliability was 0.7 and of interrater reliability was 0.6. For putamen, ICC of intrarater reliability was 0.7 and of interrater reliability was 0.8. There was no correlation between red nucleus and putaminal hypointensity scores and age, severity of disease or duration of disease.

Conclusions: SWI detects differences in the degree of mineralization of red nucleus that can discriminate PSP from MSA-P and PD. Similarly, the extent of putaminal mineralization in SWI can differentiate PSP from PD. SWI should be a part of advanced MRI protocols applied in the differentiation of atypical parkinsonism from PD.

Tu-140

Simple & complex kinesia in Parkinson's disease: Functional MRI study

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Objective: To gain a better understanding of neural basis of motor performance of Parkinson's disease (PD), we compared motor activation in normal subjects and in PD patients with two different motor tasks (simple and complex).

Background: Blood oxygen level dependent (BOLD) functional MRI (fMRI) measurements of regional cerebral blood flow (rCBF) provideis a sensitive assay for localization of task-related activity in the human brain. Using fMRI offers the opportunity to study how motor pathways of the parkinsonian brain are disorganized in response to the degeneration of the nigrostriatal dopamine projections.

Methods: We recruited normal subjects and de novo PD patients. Simple motor task (finger tapping) and complex motor task (coin rotation) were performed in de novo PD patients and normal subjects. Imaging was performed on a Siemens Trio scanner operating at 3.0 T and equipped with echoplannar imaging hardware. The subjects lay in the scanner with their eye closed. T1-weighted images were also acquired to obtain structural three-dimensional volume. The fMRI data were analyzed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK) and MATLAB (The Mathworks Inc.,Natick, USA). The functional images of each subject were realigned to the first volume and normalized to the Montreal Neurological Institute template. Normalized images were smoothed with an isotropic Gaussian Kernel. To reduce the effect of low-frequency drifts arising from respiratory motion or scanner equipment, grand normalization to the grand mean was used.

Results: In PD and normal subjects, contralateral motor cortex activation was observed in finger tapping and bilateral cortical activation accompanying with activation of basal ganglia and cerebellum was observed in coin rotation. In PD, the patterns of cortical and subcortical activation were widespread compared to normal subjects.

In the group comparison study of coin rotation task, we found the reduced activation of cerebellum in PD patients.

Conclusions: These findings may suggest increased fMRI signals indicate attempt to overcome the functional deficit of the striatocortical motor loops in the dopamine-denervated brain by recruiting parallel motor circuits. We thought that in Parkinson's disease there is a failure of activation of cerebellum in complex kinesia.

Tu-141

Diffusion tensor imaging and tractography of the nigrostriatal and mesolimbic pathways on 3 Tesla MRI: Comparison of Parkinson's disease with normal controls

R. Kumari, S. Khushwaha, R. Gupta (Delhi, India)

Objective: To evaluate the nigrostriatal and mesolimbic pathways of Parkinson's disease (PD) patients and normal controls using diffusion tensor imaging (DTI) and diffusion tensor tractography (DTT) on 3 Tesla MRI. To determine whether there are detectable abnormalities of these tracts in PD patients as compared with controls.

Background: PD is a progressive neurodegenerative disease involving the loss of dopaminergic neurons primarily in the nigrostriatal and mesolimbic pathways. These pathways are particularly involved in the production of movement, as part of a system called the basal ganglia motor loop. Using quantitative DTI on a 3 T MR scanner, it is possible to detect the early micro structural changes within these pathways not appreciated on conventional MR sequences. Tractography offers a glimpse into the connecting pathways between different regions of the brain improving the detection and characterization of white matter abnormalities in PD. To the best of our knowledge, no study has so far demonstrated these tracts in PD using 3 T MRI.

Methods: Ten patients with dopamine-responsive PD and ten age matched normal controls were scanned on a 3.0 T MR scanner. DTI data was acquired using a single-shot EPI sequence with diffusion encoding in 32 directions and a voxel size of $2\times2\times2$ mm^3. DTI data were analyzed and DTT was performed using the SPM2 analysis software. The fractional anisotropy (FA) and apparent diffusion coefficient (ADC) within each tract were determined. Voxel-based analysis was used to compare ADC and FA maps in the white matter of the two groups.

Results: DTI and DTT images in patients with PD demonstrated degeneration of the nigrostriatal and mesolimbic tracts, with decreased FA and increased ADC. This accounted for loss of dopaminergic neurons characteristic of this disease. Three-dimensional images of these white matter tracts using DTT demonstrated a reduction in fiber density in patients with PD as compared with normal controls.

Conclusions: Visualization of the selective degeneration of individual fiber tracts, using DTI and DTT on 3 Tesla adds qualitative data facilitating the early diagnosis of PD. Measurements of FA and ADC values in dopaminergic fiber tracts might be used for monitoring disease progression and assessing the effect of treatment.

Tu-142

T2 relaxometry and quantitative diffusion tensor Imaging of the basal ganglia in tardive dyskinesia on 3 Tesla MRI

R. Kumari, R. Gupta, S. Khushwaha (Delhi, India)

Objective: Our aim was to determine whether there are detectable abnormalities in the basal ganglia of patients with tardive dyskinesia (TD) as compared with normal controls using T2 relaxometry and quantitative diffusion tensor imaging (DTI) on 3T MRI.

Background: TD refers to a wide variety of involuntary, repetitive, persistent movements caused by the use of dopamine receptor antagonists. It has been hypothesized that the condition is due to a neurochemical abnormality of the striatum. T2 relaxometry and diffusion imaging are non invasive quantitative means for assessing abnormalities in normal appearing brain parenchyma on conventional MR pulse sequences.

Methods: Nine drug treated patients with TD, five drug treated patients without TD and 10 control subjects were recruited and examined by T2 Relaxometry and DTI on a 3 T MR scanner. T2 mapping of basal ganglia was performed using a multiecho FRFSE sequence. DTI data was acquired using a single shot EPI sequence with diffusion encoding in 32 directions. Measurements of T2 and apparent diffusion coefficient (ADC) values in the caudate nucleus, putamen and globus pallidus were obtained in the three patient groups and the values were compared.

Results: Patients with TD had significantly shortened T2 relaxation times in the caudate nuclei when compared to patients without TD, the group of drug treated patients without TD demonstrated significant variability of the T2 values. Measurements of ADC values showed no significant differences between drug treated patients with TD and control subjects.

Conclusions: High resolution 3T MR imaging of the brain with T2 relaxometry can detect possible neuropathological abnormalities in the basal ganglia in patients with TD. Shortening of the T2 relaxation times in the caudate nuclei may be related to iron levels and may have predictive values in evaluating the risk of developing TD in patients on neuroleptics drug treatment. The discrimination between dyskinetic patients and control subjects offered by ADC values was not significant.

Tu-143

The effect of levodopa on motor pathways in healthy subjects: A functional MRI (fMRI) study

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Objective: To understand the *in vivo* effects of levodopa in motor and related pathways in healthy human subjects.

Background: Levodopa, the precursor to dopamine, dramatically improves the motor function of PD subjects. A number of functional imaging studies have shown that levodopa changes the brain activation patterns in motor and related pathways of PD subjects**.** Although it is suspected that levodopa neither affects motor performance nor alters motor pathway activation in normal subjects, there is no study yet to empirically support this assumption.

Methods: FMRI data from 15 healthy subjects performing either externally- (EG) or internally-guided (IG) sequential finger movements (SFM) were collected. All subjects were right handed and were scanned twice: before and after orally taking one tablet of carbidopa/levodopa (25/100). FMRI activation patterns were generated by contrasting pre- and post-levodopa scans for each of four task conditions (right EG, right IG, left EG, and left IG). A mask (generated using the Wake Forest University PickAtlas software) that included only motor areas was used to reduce the number of voxels included in the comparisons as a way of increasing the likelihood of finding significant differences. Significance (pre- vs post-levodopa comparisons) was defined as $p<0.05$ corrected with a cluster size >10.

Results: There were no clusters of voxels that were significantly changed by levodopa in healthy subjects for all tasks performed by either hand.

Conclusions: This study supported the hypothesis that levodopa does not have significant fMRI amplitude effects (the most commonly assessed measure) on motor and motor associated pathways in healthy subjects. Future studies are needed to investigate if there are other effects of levodopa, possibly relating to the spatial extent of activation or alterations in connectivity.

Tu-144

Differential effects of age and disease duration on the neurocognitive deficits and cerebral glucose metabolism in PD

C.H. Lyoo, W.C. Kim, M.S. Lee (Seoul, Korea)

Objective: To determine differential effects of age and disease duration on the deterioration of clinical deficits and distribution of dysfunctional brain areas in PD.

Background: Neurodegeneration associated with age is superimposed on pathological changes specific for PD. Therefore, role of aging in the progression of PD must be determined to develop strategies effective for the prevention and management of progressive deterioration of PD.

Methods: This study included 128 non-demented PD patients (means ± SD: age = 64.6 ± 8.1 years, disease duration = 49.3 ± 49.7 months and UPDRS motor score = 28 ± 13.6). UPSRS motor scores were grouped into items representing severities of tremor, rigidity, bradykinesia, and axial symptoms. Neuropsychological tests (Seoul verbal learning test, Korean-Boston naming test, Korean-color word stroop test, and Rey-Osterrieth complex figure test) were done in 111 patients. All the 128 patients underwent brain MRI and quantitative FDG PET studies.

Results: Age of patients, controlled for disease duration, correlated with H&Y stage, total UPSRS motor scores, and UPDRS scores representing severities of bradykinesia and axial deficits. Disease duration, controlled for age, correlated with H&Y stage, total UPSRS motor scores and UPDRS scores representing severities of rigidity, tremor, bradykinesia and axial deficits. Except visuospatial function, age correlated with deficits on all the cognitive functions examined. In contrast, disease duration did not correlate with any neuropsychological tests. Age of patients correlated inversely with cerebral glucose metabolism rates (CMRglu) of whole brain, prefrontal, orbitofrontal, anterior cingulate, insular and temporal cortices, caudate, thalamus and cerebellar cortex. In contrast, disease duration inversely correlated only with CMRglu of occipital cortex.

Conclusions: In PD, age of patients and disease duration have detrimental effect on worsening of bradykinesia and axial deficits, but only disease duration has deleterious influence on positive parkinsonian motor deficits. Age related neurodegeneration causes widespread cerebral hypometabolism and decline in many cognitive domains. PD related pathologies result in hypometabolism localized to occipital cortex and had no influence on cognitive decline.

Tu-145

Sparing of serotonin and norepinephrine transporter uptake compared to dopamine transporter uptake in early Parkinson's disease

K. Marek, D. Jennings, D. Russell, J. Batis, G. Tamagnan, J. Seibyl (New Haven, Connecticut)

Objective: To assess in vivo imaging radioligands targeting the norepinephrine (NET) transporter and serotonin (SERT) transporter in PD to compare NET and SERT uptake with dopamine transporter uptake (DAT).

Background: Both recent studies of PD post-mortem tissue describing early widespread synuclein pathology and increased recognition of non-dopaminergic PD clinical symptoms have spurred the search for tools to identify and monitor non-dopaminergic PD pathology. Prior studies in non-human primates and in healthy subjects have demonstrated that 123-I INER and 123-I mZIENT bind with high affinity and selectivity to NET and SERT.

Methods: Early PD patients and healthy controls (HC) underwent 123-I INER (n=32) and/or 123-I mZIENT (n=36) SPECT imaging. The primary imaging outcome was a regional equilibrium tissue distribution volume measurements assessed in thalamus, midbrain, brainstem, cortex and striatum. The ratio of target to reference region (white matter for 123-I INER and cerebellum for 123-I mZIENT) was compared in PD and HC. Subjects were also evaluated with UPDRS 12 hours off any PD medications and MMSE. Dopamine transporter imaging with 123-I ß-CIT was acquired in the majority of the PD subjects.

Results: 123-I INER, 123-I mZIENT imaging in 12, 16 HC (age range 20-62) and 20 PD subjects (age range 51-70, PD duration 0.5-9 yrs) was acquired. Comparison of PD and HS 123-I INER target to white matter ratio demonstrated no difference in midbrain or thalamus regions. Comparison of PD and HS 123-I mZIENT target to cerebellar ratio showed approximately 10% reduction in temporal cortex and striatum in PD subjects but no change in brainstem or midbrain regions. 123-I INER and123-I mZIENT imaging did not correlate with PD disease duration. PD subjects who had undergone prior DAT imaging showed a mean 62% reduction in ß-CIT uptake.

Conclusions: Both 123-I INER and 123-I mZIENT demonstrate reliable quantitative outcomes in HC and PD. There was no or little change in 123-I INER or 123-I mZIENT in PD patients compared to healthy subjects despite marked reduction in 123-I ß-CIT. These data suggest that sub-cortical norepinephrine and serotonin systems may remain functional long after PD diagnosis.

Tu-146

A systematic, comprehensive, blinded radiological study of MR findings in pathologically confirmed PSP, MSA and PD

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Objective: To describe the accuracy of MRI diagnosis and specific findings in pathologically confirmed progressive supranuclear palsy (PSP) Parkinson's disease (PD) and multiple system atrophy (MSA).

Table(Tu-146). Sensitivity and Specificity (%) of MR abnormalities in pathologically proven PSP and MSA

		PSP		MSA	
Region	MRI Abnormality	Sensitivity	Specificity	Sensitivity	Specificity
Substantia Nigra	Atrophy	43	89	14	71
	Smudging	21	89	29	86
	Hyperintensity	21	100	–	–
	Restoration of lateral signal	14	100	–	–
Putamen	Atrophy	50	74	43	63
	Hypointensity	36	84	14	71
	Hyperintensity	–	–	14	100
	Hyperintense putaminal rim	29	84	14	75
Midbrain	Axial atrophy	93	74	29	38
	Hummingbird / Giant Penguin	64	100	–	–
	Morning Glory Flower	43	95	–	–
	Periaqueductal hyperintensity	29	68	29	67
	Tectal hyperintensity	–	–	–	–
	Thinning of quadrigeminal plate	86	68	29	38
	Third ventricle dilatation	93	63	43	35
	Mickey Mouse Sign	7	100	–	–
	Superior cerebellar peduncle hyperintensity	14	95	–	–
	Superior cerebellar peduncle atrophy	43	95	–	–
	Dentate nucleus hypointensity	7	95	14	96
	Decussation of superior cerebellar peduncle hyperintensity	14	100	–	–
Pons and Cerebellum	Pontine atrophy	14	89	29	92
	Cerebellar atrophy	43	68	57	69
	Middle cerebellar peduncle atrophy	21	89	29	88
	Medullary atrophy	14	100	–	–
	Inferior Olive Atrophy	29	95	14	85
	Pontocerebellar fibre signal change	7	95	14	96
	Middle cerebellar peduncle hyperintensity	–	–	43	100
	Pontine hyperintensity	7	95	14	96
	Cerebellar hyperintensity	–	–	–	–
	Inferior olive hyperintensity	–	–	–	–
	Hot Cross Bun Sign	–	–	29	100
Cortex	Atrophy	71	68	29	46
	Ventricular dilatation	36	100	–	–
	Frontal atrophy	29	89	29	80
	Parietal atrophy	43	79	29	64
	Temporal atrophy	21	89	29	84

Specificity for MRI abnormalities seen in PSP or MSA vs other disease entities in the study (ie Specificity of a MR sign for PSP vs MSA, PD and Control, or MSA vs PSP, PD or Control); PD excluded from table due to small numbers.

Background: Clinicopathological studies in PSP, MSA and PD indicate a significant misdiagnosis rate. Few MR studies are published with pathological confirmation of the clinical diagnosis. Here we examine the accuracy of blinded radiological assessment in a pathologically confirmed cohort.

Methods: 1.5T MR images were available in 25 donors to the Queen Square Brain Bank (14 PSP, 7 MSA, 3 PD and 1 CBD) and 9 living controls. Images were blindly and systematically rated for 37 abnormalities reported in the literature by a single neuroradiologist. The final clinical diagnosis was retrieved from the medical records. All QSBB cases had histopathological diagnosis according to consensus criteria.

Results: 12/25 cases were correctly identified with MR findings alone (8/14 PSP, 4/7 MSA, 0/3 PD, 0/1 CBD); 19/25 cases were correctly identified clinically. The hummingbird sign had 100% specificity/64% sensitivity for PSP; the morning glory sign 95% specificity/43% sensitivity. In MSA middle cerebellar peduncle hyperintensity on T2 weighted images had 100% specificity/43% sensitivity; the 'hot cross bun' 100% specificity/29% sensitivity. MR abnormalities with high specificity were associated with lower sensitivity and vice versa.

Conclusions: We report the sensitivity and specificity of MR abnormalities in a pathologically confirmed cohort of PSP, MSA and PD. Differences in regional atrophy form the basis for conventional MRI abnormalities in these illnesses but typical changes are not always found even at postmortem. The correlation between macroscopic pathological abnormalities and MR findings is not well studied and key nuclei including the substantia nigra (SN), subthalamic nucleus (STN) are poorly visualized on MRI. There is an unmet need to detect specific changes in the brain occurring before regional atrophy and in small nuclei including the SN and STN.

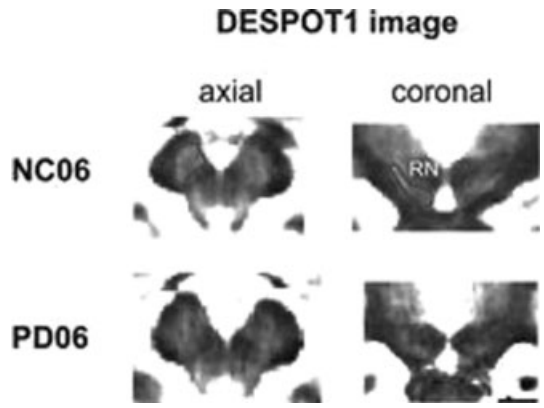

FIG. 1 (Tu-147). The substantia nigra in the DESPOT1 map of a PD patient (PD06) and an age-matched control (NC06). RN = red nucleus.

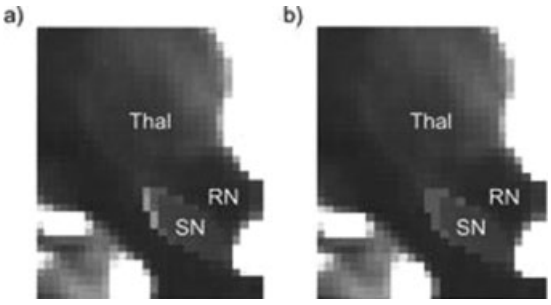

FIG. 2 (Tu-147). Principle of segmentation of the right substantia nigra (SN) based on its connectivity with the right thalamus (Thal) in a single healthy control subject (NC06) illustrated in coronal view a) The higher the connectivity with the right thalamus, the brighter the colour of a certain voxel within the SN mask. b) The voxels exceeding 10% of the individual maximum number of samples are displayed in red colour. RN=red nucleus.

Tu-147

Discrimination of patients with Parkinson's disease and healthy control subjects using MRI

R.A. Menke, J. Scholz, K.L. Miller, M. Zarei (Oxford, United Kingdom)

Objective: To evaluate the potential of the driven equilibrium single pulse observation of T1 (DESPOT1) method in visualisation of the substantia nigra (SN), whether SN volumetry can differentiate Parkinson's disease patients (PD) from controls (NC), and whether diffusion tensor imaging (DTI) measures can enhance the discrimination between PD and NC.

Background: The SN contains dopaminergic cells that project to the striatum and degenerate in PD. For differential diagnosis and unbiased monitoring of the disease progression, a non-invasive and inexpensive biomarker is highly warranted.

Methods: Ten PD patients and ten matched controls were studied. Spoiled gradient recalled images were acquired on a 3T MR scanner to create whole-brain T1 maps. Also, diffusion-data were obtained (60 directions). The SN was manually outlined on the DESPOT1 maps. SN volumes were compared between PD and NC (two-independent samples t-tests). For each subject, the connection probability between each voxel in the left/right SN and ipsilateral target masks (putamen, caudate, pallidum, thalamus, frontal lobe, cerebellum) was calculated using FMRIB's Diffusion Toolbox. Voxels were thresholded by 10% of the maximum connectivity for each target in each individual mask. The volumes of the resulting subregions were compared between groups. Discriminant analysis (DA) was used (leave-one-out classification) to determine the best model to discriminate PD from NC.

Results: DESPOT1 enables clear visualisation of the SN (Figure 1). Left/right SN volumes as well as the number of voxels in the left SN with a connectivity >10% of the maximum connection probability connected with the ipsilateral putamen, pallidum, caudate, thalamus, and frontal cortex (cf. Figure 2) were significantly lower in PD than in NC. Patients also showed reduced connectivity of right SN with the ipsilateral putamen, pallidum, and thalamus. DA revealed 60% accurate classification of PD and NC when the left and right SN volumes were considered as independent variables. Adding the volumes of the nigral subregions defined by their connectivity with the ipsilateral thalamus improved the accuracy to 80%.

Conclusions: Our results may offer a method that allows for precise segmentation of the SN and differentiation of PD from NC. Larger clinical study and pathological validation will be necessary to confirm the findings.

Tu-148

Lasting visual hallucinations in Charles Bonnet like syndrome; fMRI correlates and the influence of rTMS

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Objective: To influence visual hallucinations (VH) using repetitive transcranial magnetic stimulation (rTMS).

Background: VH can occur in a wide range of disorders, including Parkinson's disease (PD), schizophrenia, stroke and eye disease. Charles Bonnet's Syndrome (CBS) is characterized by complex VH following visual impairment in psychologically normal people. We

report a blind patient with a CBS-like syndrome, experiencing simple VH of color and visual motion. The VH showed a regular cyclic pattern; changing direction every 2 days, being slow when directed to the right and fast and disturbing when directed to the left.

Methods: Using fMRI, we localized brain regions specifically involved in either visual motion or color perception, by instructing the patient to focus attention to either color or movement. In a control condition, she counted internally. The conditions and a resting condition were balanced and presented in a block design, during 3T fMRI. The fMRI contrast motion>counting was loaded into Brainlab. The nearest skull point to the left V5/MT was determined using neuronavigation. rTMS or sham rTMS was applied single-blinded at V5/MT at 1 Hz during 10 minutes. Three weeks later rTMS was repeated at 3 consecutive days.

Results: Increased activations related to visual motion- and color conditions were found in respectively extrastriate visual area V5/MT and the fusiform gyrus. After the first rTMS session the patient reported an almost complete disappearance of her slow phase, while a shaking visual motion sensation emerged. A mild fast phase reduction and a slight shortening of the cycle duration was reported after the second rTMS session at three consecutive days.

Conclusions: Although rTMS at V5/MT slightly suppressed perceived visual motion, no lasting effect was induced. Finally we applied rTMS at V1, but no effect was obtained here either. Maybe rTMS should be applied more frequently, because long-lasting VH may require bigger changes in neuronal circuitry. Future rTMS strategies might also combine V5/MT with frontal regions. Our data nevertheless demonstrated logical patterns of increased activations associated with the nature of the VH. This procedure provides good targeting for rTMS, which seems to be a promising treatment to improve VH, as an alternative or as additional treatment besides drug therapy.

Tu-413

A fast gray matter acquisition T1 inversion recovery (FGATIR) magnetic resonance imaging (MRI) sequence for direct high resolution visualization of subcortical structures

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Objective: To develop and validate a fast high resolution MRI sequence for direct targeting of subcortical structures in DBS.

Background: There are several imaging sequences that are used for DBS targeting, but all are limited in the resolution, minimum attainable slice thickness, and/or contrast attainable. There is a need to develop a high contrast rapid MRI sequence that can provide thin high resolution slices to improve and augment direct stereotactic targeting of subcortical structures.

Methods: Using a Siemens Allegra 3T MRI, we designed and employed a high contrast rapid thin slice (1mm slice thickness) T1-weighted MRI protocol, the FGATIR, to localize the ventral lateral (VL) nuclei of the thalamus, the subthalamic nucleus (STN), and the globus pallidus interna (GPi) in essential tremor (n=1) and Parkinson's disease (n=2) on three pilot patients. The scan was created by modifying a standard magnetization prepared rapid acquisition gradient echo (MP-RAGE) sequence to attenuate the white matter signal. FGATIR scans were compared with standard T1-weighted scans and T2 fluid attenuated inversion recovery (FLAIR) scans for their ability to differentiate the neuroanatomy using both qualitative and quantitative methods.

Results: The enhanced contrast FGATIR scans more clearly defined the boundaries of the basal ganglia nuclei (as seen in Figure 1). Figure 1 shows sagittal images of the (A) standard T1, (B) T2 FLAIR, (C) FGATIR, (D) FGATIR with an atlas overlay of subcortical structures. These boundaries correlated well with atlas boundaries as well as microelectrode maps acquired intraoperatively. The quantitative measures, contrast ratio and contrast to noise ratio (CNR), for

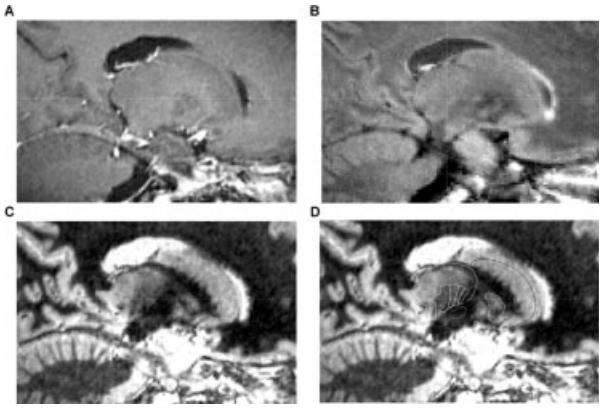
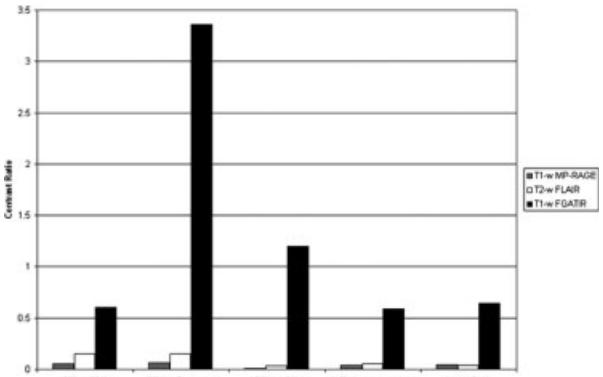


FIG. 1 (Tu-413).



		T1-w MP-RAGE	T2-w FLAIR	T1-w FGATIR
GPi to PUC	CNR	1.88	3.49	**5.96**
	Contrast Ratio	0.055	0.15	0.60
STN to Thalamus	CNR	3.86	7.85	**17.02**
	Contrast	0.067	0.15	3.36
STN to SNr	CNR	0.56	1.76	**6.06**
	Contrast Ratio	0.0097	0.034	1.20
VL Thalamus to non-VL Thalamus	CNR	2.19	2.81	**7.27**
	Contrast Ratio	0.041	0.053	0.69
VL to PUC	CNR	2.35	1.94	**7.92**
	Contrast Ratio	0.044	0.037	0.64

FIG. 2 (Tu-413).

regions of interest versus neighboring structures are summarized in Figure 2.

Conclusions: This novel MRI sequence can provide better differentiation of the brain targets utilized for DBS in movement disorders. Our results show that the contrast difference for the FGATIR scan is significantly higher than either a standard T1 MP-RAGE or T2 FLAIR scan for the subcortical structures of interest. This rapid (11 minute) high resolution sequence should augment stereotactic targeting by providing contrast superior to standard T1 and T2 FLAIR scans.

We-122

Metabolic abnormalities in human primary dystonia: A magnetic resonance spectroscopy study

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Objective: To determine whether metabolism of γ-aminobutyric acid (GABA), glutamate (Glu) and glutamine (Gln) is altered in

patients with primary dystonia, their concentrations were measured *in vivo* using ^{1}H Magnetic Resonance Spectroscopy (MRS) at 3 T.

Background: Neurochemical bases of human idiopathic dystonia are unknown. TMS studies suggest that GABAergic intracortical inhibition is decreased in dystonia. A single MRS study at 1.5T revealed decreased GABA levels in the sensorimotor (SM) cortex and the lentiform nuclei contralateral to the affected hand in 7 patients with task specific dystonia (Levy & Hallett 2002).

Methods: 18 healthy volunteers and 16 not treated patients with a primary upper limb dystonia participated in the study. *In vivo* spectra were acquired using a 3 T whole-body Siemens TIM system. Radiofrequency excitation was accomplished using body coil and signal was received using 12-channel coil. GABA-edited spectra were acquired using a MEGA-PRESS sequence (Mescher et al 1998) with VAPOR water suppression. Spectra were obtained in the SM cortex, the striatum, the cerebellum bilaterally and the occipital cortex (T_R = 3 s, T_E = 68 ms, 128 scans with editing pulse at 1.9 ppm and 128 scans with editing pulse at 7.5 ppm). Edited metabolite-nulled spectra were acquired from the occipital lobe to assess the contribution of macromolecules to the GABA peak at 3 ppm. The edited spectra were analyzed using LCModel. The basis set was built from MEGA-PRESS edited spectra measured using GABA, NAA, Glu phantoms and from sum of measured macromolecules spectra.

Results: Distinct peaks of GABA and Gln/Glu were obtained in the SM cortex, the striatum and the cerebellum. GABA and Glu+Gln concentrations quantified relative to NAA were not significantly different between dystonic patients and controls. Absolute quantification based on water will be obtained.

Conclusions: Contrasting with previous results, we did not find any differences in GABA, NAA, and Glu/Gln profiles in patients with focal dystonia despite using a larger group (n = 16) and higher magnetic field (3T MRS).

We-123

Aging effect on adenosine A_{2A} receptors in putamen – A ^{11}C-TMSX PET study

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Objective: To investigate the aging effect on adenosine A_{2A} receptors (A2ARs) in the putamen of healthy subjects using ^{11}C-TMSX and positron emission tomography (PET).

Background: A2ARs are abundant in dopamine-rich areas of the brain, and are known to interact negatively with dopamine D_2 receptors (D2Rs) at the level of second messengers and beyond. A2AR antagonists have recently attracted attention as the nondopaminergic treatment of Parkinson's disease (PD), and its alteration of the putamen in PD was reported (1,2). However, no data are available on aging effect on human A2AR. For mapping the A2AR, a PET radioligand of ^{11}C-TMSX (3) was utilized.

Methods: We studied five young healthy volunteers (23.0±3.3 y.o., 20 to 28) and six elderly volunteers (61.7±8.8 y.o., 51 to 73). A dynamic series of decay-corrected PET scans was performed for 60 minutes starting at the time of the injection of 700 MBq of ^{11}C-TMSX without arterial blood sampling. Circular ROIs of 10-mm diameter were placed in the PET images over putamen for each subject. The binding potentials (BP_{ND}) in these regions were calculated using an averaged time activity curve for tissue and the Logan graphical analysis (LGA) and EPICA (4), where the centrum semiovale was a reference region.

Results: In the putamen, BP_{ND} had no significant difference between in young (1.03±0.06) and in elderly subjects (1.06±0.18, p=0.67; Welch's t-test), and the variance was larger in elderly than in young subjects (p=0.055; Bartlett's test, Fig 1). There was no correlation between age and BP_{ND} (R^2=0.065, p=0.449, Fig 2).

Conclusions: We could not find the aging effect on A2ARs, although many studies reported that D2Rs decreased with age in the human putamen.

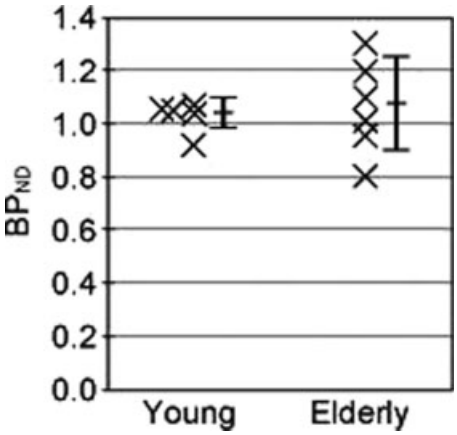

FIG. 1 (We-123). BP_{ND} for ^{11}C-TMSX in the putamen of young and elderly subjects.

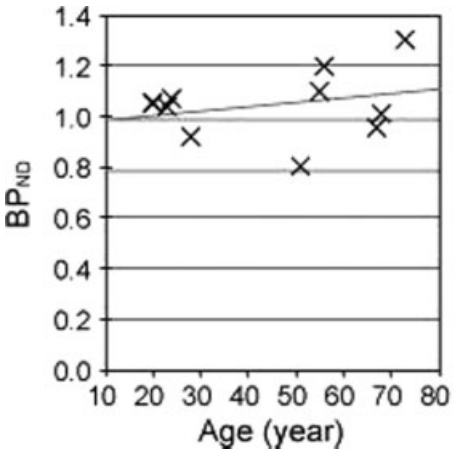

FIG. 2 (We-123). Relationship between age and BP_{ND} for ^{11}C-TMSX in the putamen of healthy subjects.

References:

1. Mishina M, et al., Synapse 61, 778-784, 2007
2. Mishina M, et al., Mov Dis 21, S622, 2006
3. Mishina M, et al., Mov Dis 23, S68, 2008
4. Naganawa M et al., IEEE Trans Bio Med, 2005 Funded by Grants-in-Aid for Scientific Research (B) No. 16390348, (B) No. 20390334, (C) No. 17590901 and (C) No. 20591033 from Japan Society for the Promotion of Science.

We-124

Usefulness of cardiac ^{123}I-MIBG scintigraphy in the differential diagnosis of parkinsonism

R. Miyamoto, H. Shibayama, F. Katada, S. Sato, T. Fukutake (Kamogawa City, Chiba, Japan)

Objective: To evaluate the usefulness of cardiac ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) scintigraphy, the only objective diagnostic tool available in Japan, in the differential diagnosis of parkinsonism (PS) from a practical point of view.

Background: Increasing evidence has been accumulated about the usefulness of cardiac ^{123}I-MIBG scintigraphy for the differential diagnosis of PS, mainly from research settings. It has been shown that

there is decreased cardiac uptake in Parkinson's disease (PD) and dementia with Lewy bodies (DLB), with approximately 80% sensitivity and specificity.

Methods: Heart/mediastinum (H/M) ratio was obtained at 20 minutes and 2 or 3 hours after injection of ^{123}I-MIBG. Decreased cardiac uptake was defined based on decreased H/M ratio (<2.0) in delayed (2 or 3 hours) phase. Clinical diagnosis was determined by the published diagnostic criteria of each disease.

Results: The subjects comprised of 67 patients with PS (33 men, 34 women, age 67.2±10.1 years, range from 40 to 84 years) who had cardiac I-MIBG scintigraphy between March 2005 and October 2008. Thirty-two of 67 patients were finally diagnosed as PD (disease duration of 1 to 12 years [4.7±3.3], Hoehn-Yahr stage of 1 to 5 [3.2±0.8]), 3 DLB, and 32 others. H/M ratio was decreased in 36 patients: 26 PD, 3 DLB, 3 unclassified PS (no progression), 1 progressive supranuclear palsy (PSP), 1 drug-induced PS, 1 vascular PS, and 1 depression. H/M ratio was preserved in 31 patients: 6 PD (3 of 6 patients age<50), 4 drug-induced PS, 3 multiple system atrophy, 3 PSP, 3 depression, 2 corticobasal degeneration, 2 essential tremor, 1 frontotemporal dementia, 1 juvenile PS, and 6 unclassified PS. Of 32 patients with PD, no significant differences were found between the decreased H/M ratio group and preserved H/M ratio group with respect to disease duration, Hoehn-Yahr stage, use of selegiline, and disease phenotype (tremor or akinesia dominant). The sensitivity and specificity for discriminating PD/DLB from other forms of PS is 83% and 78%, respectively.

Conclusions: ^{123}I-MIBG scintigraphy is acceptably useful for differentiation of PS in routine clinical settings. However, it doesn't obviate the necessity of meticulous neurological examination and follow up, and should be considered as only one of the tools of clinical characterization at present.

We-125

Changes of sensori-motor network in focal dystonia and its partial recovery under treatment with botulinum toxin

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Objective: To study changes of functional connectivity in patients with focal dystonia (FD) and the role of Botulinum toxin (BTX) treatment.

Background: The most important feature of dystonia are involuntary muscle contractions, resulting in abnormal posture. Previous studies showed distinct alterations in cortical activity concerning motor and sensory system.

Methods: Here we employed a novel functional imaging approach, the analysis of resting state activity, followed by the definition of functionally connected brain networks by independent component analysis (ICA) to assess differences between FD patients (n=18) and healthy controls (n=18). The FD patients included 10 patients with cervical dystonia and 8 patients with writer's cramp.

Results: ICA analysis revealed default mode network and the sensori-motor network. The last one showed distinct differences between patients and controls. In FD patients the functional connectivity of pre- and postcentral areas was absent and that of premotor area was significantly reduced. This reduction was partially recovered under treatment of BTX.

Conclusions: A task related reduction of activation of primary motor areas is reported in previous studies which are in line with our results. However, a decisive advantage of our method is that no task is demanded from the subjects and, thus, the problem of differential task difficulty and effort between groups is circumvented. Here we show for the first time a significant reduction of functional connectivity in sensori-motor network in FD patients and its partial recovery after treatment with BTX.

We-126

Paraspinal muscle changes in Parkinson's disease patients with scoliosis

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Objective: The aim of this study was to identify features of parkinsonian scoliosis and to clarify the main physiological mechanism for the development of scoliosis in patients with Parkinson's disease.

Background: Scoliosis is observed often in elderly people, and seems to be prevalent in Parkinson's disease patients. Although scoliosis may disturb activities of daily living (ADL), few studies have examined scoliosis in Parkinson's disease patients.

Methods: Clinical, biochemical and imaging data of 34 patients with Parkinson's disease with or without scoliosis were obtained. We analyzed the volume and degree of fatty infiltration of the paraspinal muscles using magnetic resonance imaging (MRI). In addition, aged-matched controls were analyzed using the same MRI methods.

Results: Approximately 70% of the Parkinson's disease patients showed scoliosis, and fat infiltration of the erector spinae muscles was observed in 75% of these scoliosis patients. Fat in the erector spinae muscles were diffusely infiltrated in the half of the scoliosis patients, and the rest of patients showed local fat infiltration especially in the longissimus or iliocostalis muscle on a convex side of the scoliosis. Edematous changes were also observed in the fat infiltration area. Paraspinal muscle atrophy, in the middle portion of the longissimus muscles, was remarkable in Parkinson's disease patients with scoliosis. The degree of fat infiltration and atrophy of the paraspinal muscles correlated with the severity of ADL disturbance in Parkinson's disease patients with scoliosis.

Conclusions: Various mechanisms may contribute to the development of parkinsonian scoliosis. Dopaminergic depletion in Parkinson's disease may induce functional changes in the organization of the corticospinal and reticulospinal tracts, and dysfunction may contribute to axial rigidity. Furthermore, rigidity of the paraspinal muscles may induce to muscle hypoxic conditions, which lead to progressive muscle atrophy and fatty infiltrations. To prevent the scoliosis, treatment interventions such as an appropriate pharmacotherapy and rehabilitation at the early stage of Parkinson's disease is very important.

We-127

Functional MRI of the inferior olive in essential tremor

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Objective: To evaluate functional magnetic resonance imaging (fMRI) activation patterns of the inferior olive (IO) in response to sensory stimulation in patients with essential tremor (ET) and normal controls.

Background: The pathophysiology of ET remains unknown. One of the most prevalent hypotheses is that ET is due to a defective mechanism that normally dampens the activity of a central rhythmic movement generator. The proposed site for such a central generator is the IO. However, direct evidence for IO dysfunction in ET in humans remains lacking. In an fMRI study of normal subjects, we have shown reliable activation of the IO using visual and tactile stimulation. The IO was activated when subjects perceived sequences of sensory stimuli but not during the motor performance of these sequences; a finding consistent with animal studies showing that the responsiveness of IO neurons to sensory input is in fact inhibited by movement. This may explain the failure of prior imaging studies to detect IO activity.

Methods: Six normal subjects (37±20 years) and 6 ET patients (45±18 years) were studied with an fMRI protocol with two separate conditions: tactile stimulation (using an MRI compatible piezo transducers applied to the tips of right thumb and index finger) and visual stimulation both delivered in a simple block design. Three runs were obtained with each run lasting 5 minutes consisting of 6 blocks (each

32 sec) of stimulation with 6 different interstimulus intervals interleaved with 6 blocks of rest (each 18 seconds). fMRI data were analyzed using the general linear model (GLM) and the theory of Gaussian fields as implemented in SPM5.

Results: Significant activation of the IO and cerebellar hemispheres was detected during both visual and tactile stimulations in both ET patients and controls.

Conclusions: Our preliminary data demonstrate the feasibility of utilizing fMRI and passive sensory stimulation paradigms to investigate the role of the olivocerebellar system in ET pathophysiology. *Supported by the International Essential Tremor Foundation (IETF) and The Department of Veterans Affairs.*

We-128

Use of DatScan in the Uuniversity Hospitals Leicester neurology department. A retrospective study

E. Nikfekr, R.J. Abbott (Leicester, United Kingdom)

Objective: The aim was to evaluate the impact of DatScan on our practice in terms of diagnostic and therapeutic points of view.

Background: Patients with clinically uncertain extrapyramidal features are not uncommon in clinical practice. DatScan targets the presynaptic dopamine transporters and can help differentiation between parkinsonism with and without nigrostriatal degeneration.

Methods: Case notes for all patients who were considered difficult to make a diagnosis were studied. DatScans had been performed using [123I]FP-CIT tracer, and evaluated in Nuclear Medicine Department at Unversity Hospitals of Leicester,UK.

Results: 58 patients underwent DatScan, 35 male (mean age 53) and 23 females (mean age 66). Inconclusive diagnosis of Parkinson's disease (20 cases) and uncertinity between parkinsonism and Essential Tremor (22 cases) were the main reasons for performing the scans. 15 out of 20 patients with early parkinsonism showed abnormal scans confirming parkinsonism. 16 out of 22 scans to differentiate Essential Tremor from parkinsonism were normal favouring Essential Tremor. To differentiate between drug-induced parkinsonism and Parkinson's disease, 7 patients had DatScan. 3 showed abnormal scans in favour of Parkinson's disease and 4 scans were normal indicating drug-induced parkinsonism. The remaining cases had the scans for following indications: 1) Dementia of Lewy Body and Alzheimer's dementia: 5 patients in total, 2 scans were normal and 3 patients had abnormal scans confirming Dementia of Lewy Body. 2) Normal Pressure Hydrocephalus and parkinsonism: two patients required DatScan and both scans were abnormal indicating parkinsonism.3) there were 2 patients suspicious of psychogenic movement disorder resembling parkinsonism who required scanning. Both were normal excluding parkinsonian syndromes.4) In one case it was difficult to make a diagnosis between depression and Parkinson's disease and the scan was abnormal clarifying the matter.

Conclusions: DatScan is helpful to differentiate between clinically difficult extrapyramidal cases and facilitates makeing an accurate diagnosis in patients with early parkinsonism, essential tremor, drug-induced parkinsonism, psychogenic cases, and dementia when associated with parkinsonism. Correct diagnosis added confidence and allowed initiation of appropriate treatment and withdrawal of unnecessary drugs.

We-129

Diffusion weighted imaging of the olfactory tract and its association with hyposmia in PD

M. Nocker, K. Seppi, M. Schocke, R. Esterhammer, I. Virgolini, S. Boesch, W. Poewe, C. Scherfler (Innsbruck, Austria)

Objective: To investigate whether olfactory dysfunction in patients with mild to severe Parkinson's disease (PD) is associated with the extent of Diffusion-weighted MR imaging (DWI) signal alteration in the olfactory tract.

Background: DWI and the trace of diffusion tensor (Trace (D)), a marker of water molecule diffusivity, revealed structural lesions of olfactory tract fibers in patients with PD.

Methods: 14 patients with Parkinson's disease (mean±sd: age: 67.4±6.8; disease duration: 4.4±4 range: 0.2-15.6; UPDRS motor score: 19.6±10.7; H&Y-stage: 2.4±1) were studied with DWI and olfactory testing using the validated sniffin' stick test comprising odor threshold, identification and discrimination. Only patients were included with disease specific reduction of putaminal ^{18}F dopa Ki values measured with PET. Clusters of DWI signal alterations within the olfactory tract have been previously identified in a different cohort of PD patients by statistical parametric mapping and where applied to this novel set of PD patients.

Results: Trace (D) of the olfactory tract in patients with PD was significantly correlated with disease duration ($p<0.002$; $r=0.758$). When controlling for age and disease duration DWI signal changes within the olfactory tract were further correlated with odor threshold ($p<0.03$; $r^2=0.335$), identification ($p<0.013$; $r^2=0.413$) and discrimination ($p<0.005$; $r^2=0.5$).

Conclusions: Increased diffusivity identified in mild to severe disease stages appears consistent with structural damage in the olfactory tract of patients with Parkinson's disease as shown in neuropathological studies. The correlation between the severity of DWI signal changes and clinical measures of olfactory dysfunction supports the validity of this MR feature as a biomaker for pathology in the olfactory tract in Parkinson's disease.

We-130

Quantitative comparison of MRI methods for pre-surgical localisation of the globus pallidus

R. O'Gorman, M. Footman, D. Lythgoe, M. Samuel, R. Selway, K. Ashkan, J. Jarosz (London, United Kingdom)

Objective: To quantitatively compare the visibility of the GPi with various MRI methods and assess the suitability of each method for stereotactic targeting.

Background: Deep brain stimulation (DBS) has become the surgical treatment of choice for various movement disorders including Parkinson's disease and dystonia, but the success of DBS depends heavily on the accuracy by which the target structures are reached. The globus pallidus interna (GPi) can be localised directly from preoperative MRI or indirectly from atlas coordinates, but given the anatomical variability in position[1], the direct targeting method is arguably more accurate. However, the limited contrast of the GPi and internal medullary lamina on standard MRI can hamper the application of this technique. Target coordinates are typically calculated from pre-operative proton density (PD) weighted fast spin echo (FSE)[1] or phase sensitive inversion recovery (PSIR) images, but the visibility of the GPi may be improved with alternative MRI methods including quantitative T1, T2, or T2* mapping or susceptibility-weighted imaging (SWI).

Methods: The subject group consisted of 9 healthy adult volunteers, (4 male, age range 24-43). Images were acquired with PD-weighted FSE, SWI, PSIR, T1, T2, and T2* mapping sequences using a 1.5T GE HD.x MRI scanner. Contrast to noise ratios (CNR) for the GPi were measured for all sequences. Levels of distortion were assessed with a standard MRI quality assurance test object.

Results: The GPi is clearly visible on the SWI, T2* maps and T2*-weighted gradient echo images, but the standard PD FSE demonstrates the highest CNR both between the GPi and internal capsule and between the GPi and the internal medullary lamina. Levels of geometric distortion were less than 1% (maximum deviation of 1mm over 180mm), but further studies will be needed to establish the extent of any positional shifts in the SWI, resulting from non-local phase changes.

Conclusions: Although the GPi is well visualised on SWI, T2* maps, and T2*-weighted gradient echo images, the standard PD FSE provides the best contrast between the GPi and internal capsule and

between the GPi and the internal medullary lamina. However, the optimal MRI modality for other DBS targets may differ.
Reference:
1. Hirabayashi et al. *Mov Disord* 17 Suppl 3:S130-4 (2002).

We-131

MRI magnetic susceptibility mapping of target structures for deep brain stimulation (DBS)

K. Shmueli, R. O'Gorman, D. Lythgoe, M. Samuel, R. Selway, K. Ashkan, J. Jarosz (London, United Kingdom)

Objective: To investigate the potential of susceptibility mapping for pre-surgical localisation of the subthalamic nucleus (STN) and globus pallidus (GP).

Background: Susceptibility-weighted imaging (SWI) shows potential to improve the visibility of iron-rich structures like the STN and GP on MRI but standard SWI may contain subtle artefacts in the position of these structures which may restrict its applicability for stereotactic targeting. Such artefacts may occur because the SWI contrast near the high-susceptibility iron-rich target structures arises from phase changes which are non-local and orientation-dependent. The extent of these artefacts must be determined before standard SWI can be used for stereotactic targeting. A potential solution is to calculate the tissue susceptibility from the phase images acquired for SWI. This has shown promise for overcoming the orientation-dependence and non-locality of the phase contrast at high-resolution and high field[1] (7T). Here we investigate whether susceptibility maps can be calculated from standard clinical 1.5T MRI phase data and compare susceptibility maps with standard SWI to evaluate their potential for DBS targeting.

Methods: Standard SWI was performed in 9 healthy adult volunteers, (4 male, ages 24-43) with a 1.5T GE MRI scanner using a standard head coil. Phase images were used to derive susceptibility maps using newly developed methods[1].

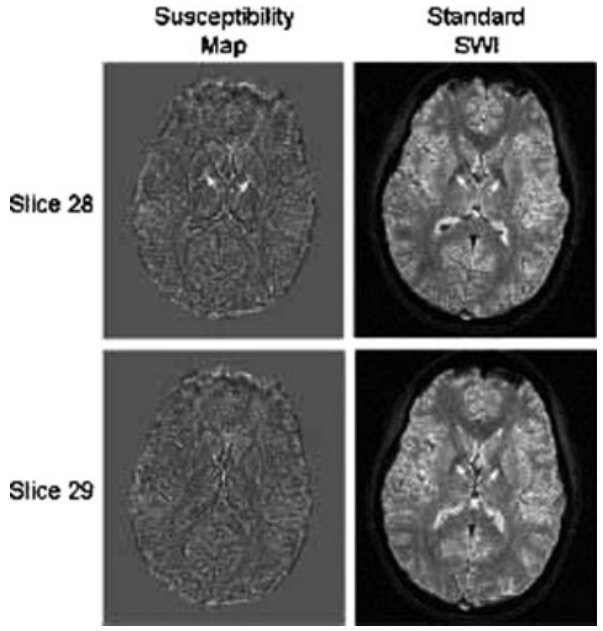

FIG. 1 (We-131). An example of a through-plane position error for the Globus pallidus (GP: see arrows) In the standard SWI related to the susceptibility map. In the standard SWI the most superior slice in which the GP is visible is 29; However, the most superior slice that clearly shows the GP in the Susceptibility Map is slice 28.

Results: Susceptibility maps were broadly similar to the original SWI but showed important differences. No shifts in position were apparent for the STN, but the superior margins of the red nuclei and GP appeared shifted superiorly by up to 2mm in the SWI for some subjects (For an example see Fig. 1). Therefore susceptibility mapping seems to reduce non-local phase changes near iron-rich target structures, and may thus reduce errors in their position.

Conclusions: Susceptibility maps were successfully calculated using standard clinical 1.5T MRI phase data. They show potential for overcoming position artefacts when using standard SWI for pre-surgical localisation of DBS target structures.

Reference:
1. K. Shmueli et al, Proceedings of the 16th Annual meeting of the ISMRM, 2008; 642

We-132

Quantitative comparison of MRI methods for pre-surgical localisation of the subthalamic nucleus

R. O'Gorman, S. Wastling, D. Lythgoe, M. Samuel, R. Selway, K. Ashkan, J. Jarosz (London, United Kingdom)

Objective: To quantitatively compare the visibility of the subthalamic nucleus (STN) with various MRI methods and assess the suitability of each method for stereotactic targeting.

Background: Deep brain stimulation (DBS) has become the surgical treatment of choice for various movement disorders including Parkinson's disease and dystonia, but the success of DBS depends heavily on the accuracy by which the target structures are reached. The STN can be localised directly from pre-operative MRI or indirectly from atlas coordinates, but given the anatomical variability in position, the direct targeting method is arguably more accurate.[1] However, the limited contrast and low visibility of the STN on standard MRI can hamper the application of this technique. STN target coordinates are typically calculated from pre-operative T2 weighted fast spin echo (FSE) images, but the visibility of the STN may be improved with alternative MRI methods including phase sensitive inversion recovery (PSIR), IR-FSE, quantitative T1, T2, or T2* mapping, or susceptibility-weighted imaging (SWI).

Methods: The subject group consisted of 9 healthy adult volunteers, (4 male, age range 24-43). Images were acquired with T2-weighted FSE, SWI, PSIR, T1, T2, and T2* mapping sequences using a 1.5T GE HDx MRI scanner. Contrast to noise ratios (CNR) for the STN were measured for all sequences. Levels of distortion were assessed with a standard MRI quality assurance test object.

Results: The SWI, T2* maps, and late echo (40ms) gradient echo images demonstrate comparable or better CNR relative to the standard T2 FSE, (figure 1 (L to R): T2 FSE, SWI, T2* map, TE=40 GRE). Levels of geometric distortion were less than 1% (maximum deviation of 1mm over 180mm) for all sequences, but further studies will be needed to establish the extent of any positional shifts in the SWI, resulting from non-local phase changes.

Conclusions: Susceptibility weighted imaging (SWI), T2* mapping, and T2*-weighted gradient echo imaging sequences may offer improved visibility of the subthalamic nucleus on pre-operative MRI relative to T2 FSE, potentially improving the accuracy of direct stereotactic targeting.
Reference:
[1]Ashkan et al *Br.J Neurosurgery* 21:197-200 (2007)

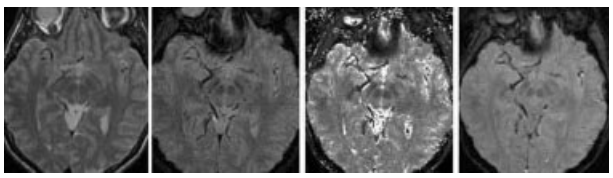

FIG. 1 (We-132).

We-133

A study of cerebral atrophy in Parkinson's disease with voxel based specific regional analysis system for Alzheimer's disease

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Objective: To clarify a relationship between structural gray matter abnormality and clinical symptoms in PD. As a preliminary study, we investigated the relationship between the gray matter atrophy and the clinical severity of motor symptoms in patients with PD using upgraded VSRAD.

Background: Voxel based specific regional analysis system for Alzheimer's disease (VSRAD) is a novel tool to detect the hippocampal atrophy for early diagnosis of Alzheimer's disease. Upgraded VSRAD can quantify gray matter volume not only in hippocampus, but also in all other Broadmann areas. An association of dementia with motor symptom in Parkinson's disease (PD) indicates that motor symptoms and cognition may share the common underlying pathology.

Methods: The subjects were 16 patients with PD (mean age ±SD;65±7), they were divided into two groups by Hoehn and Yahr classification (Group A ;II≥: 8 cases, Group B;III≤: 8 cases). Using Z-score in upgraded VSRAD, we calculated a ratio of gray matter volume of each Broadmann areas in the both PD groups to that in controls, as well as, a ratio of gray matter volume in each Broadmann area to that in whole brain within the same individual.

Results: In comparison to controls, Z-score of all areas in both PD groups were less than 2.0. In comparison to whole brain, Z-score was more than 1.3 in Broadmann 21, 23, 30 in group A and in Broadmann 1, 21, 25, 34, 47 in group B.

Conclusions: Our result suggested that cortical atrophy in patients with PD was insignificant in both groups, but the distribution of cortical atrophy changed with the progression of PD.

We-134

Efficacy of scatter correction in I-123 MIBG scintigraphy for patients with parkinsonism

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Objective: The aims of this study were to elucidate the feasibility of scatter correction in improving the quantitative accuracy of Heart-to-Mediastinum (H/M) ratio in I-123 MIBG imaging, and to clarify whether H/M ratio calculated from the scatter corrected image improves the accuracy of diagnosis in Parkinson's disease (PD).

Background: A number of investigators have reported reductions in cardiac MIBG uptake in patients with PD and Dementia with Lewy Bodies (DLB), and its relative preservation in other neurological disorders, such as multiple system atrophy (MSA). A recent study has reported considerable overlap in the values of H/M ratio between PD and non-PD patients, thus suggesting the limitation of this parameter in differentiating patients with parkinsonism.

Methods: H/M ratio was calculated using the counts from planar images processed with and without scatter correction. The triple energy window (TEW) method was used for scatter correction. In the present study, subjects comprised 142 patients suffering from PD (n = 121; mean age ± SD, 62 ± 9.0 years) or MSA (n = 21, mean age ± SD, 65 ± 7.0 years). PD patients were diagnosed using the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria, and MSA patients were diagnosed using consensus statement criteria. Planar images were obtained with a gamma camera system (GCA-9300A, Toshiba Corporation, Tokyo, Japan) equipped with a low energy, high resolution parallel hole collimator.

Results: Scatter correction increased the absolute value of H/M ratio in MSA patients ($p<0.001$), but the H/M ratio in 44% of PD patients decreased after scatter correction. H/M ratios showed no appreciable change after scatter correction in the PD group (without scatter correction: 1.42 ± 0.30, mean ± SD; with scatter correction: 1.58 ± 0.22, mean ± SD), while scatter correction yielded significantly higher H/M ratios in the MSA group ($p<0.001$) (without scatter correction: 2.18 ± 0.32, mean ± SD; with scatter correction: 3.05 ± 0.73, mean ± SD).

Conclusions: Scatter correction improved the quantitative accuracy of H/M ratio and significantly extended its diagnostic value when compared with conventional MIBG imaging. This technique may improve the sensitivity of H/M ratios in discriminating between PD and MSA patients.

We-135

Metabolic alterations during visual stimulation in 6-hydroxydopamine rat model for Parkinson's disease – in vivo small animal positron emission tomography study

N. Oishi, M. Inoue, H. Yamauchi, H. Fukuyama (Kyoto, Japan)

Objective: To evaluate the dopaminergic modulation of visual function using a well-accepted selective dopamine deficit animal model for Parkinson's disease (PD).

Background: Several stages of the visual processing system are proposed to be involved in PD, which could be related to visual dysfunction or clinical symptoms like visual hallucination. Although several studies suggest the importance of dopamine system for visual dysfunction, it's difficult to exclude effects of other neurotransmitter systems, such as cholinergic or serotonergic, which are concurrently affected in PD. The 6-hydroxydopamine (6-OHDA) rat model is suitable for evaluating the effect of dopamine system on visual function.

Methods: Fifteen adult male Sprague-Dawley rats (three unilateral 6-OHDA, twelve normal) were investigated by small animal positron emission tomography. ^{11}C-2β-carbomethoxy-3β-(4-fluorophenyl)tropane (^{11}C-CFT), a selective dopamine transporter (DAT) ligand, images were obtained in three 6-OHDA and six normal rats and parametric binding potential (BP) images were calculated. ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) images were also obtained in the same three 6-OHDA and other six normal rats during two conditions (5 Hz photic stimulation and resting condition) in the awake state. DAT BP and relative glucose metabolism images were anatomically normalized to the Paxinos stereotaxic space and analyzed on a voxel-basis using Statistical Parametric Mapping and by template-based predefined volumes-of-interests.

Results: The unilateral 6-OHDA rats showed a significant decrease of DAT BP in the ipsilateral caudate-putamen and nucleus accumbens. They also revealed a significant decrease of glucose metabolism in the ipsilateral primary visual cortex and superior colliculus and increase in the ipsilateral caudate-putamen by the photic stimulation (photic–rest) compared to the normal rats.

Conclusions: These findings suggest that dopaminergic dysfunction can induce metabolic alterations by visual stimulation not only in the subcortices but also in the cortices related to the visual system, which might be related to visual dysfunction in PD.

We-136

Reduced cardiac MIBG uptake is a potential biomarker for the presence of Lewy bodies

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Objective: To clarify clinical significance of MIBG myocardial scintigraphy, we immunohistochemically examined heart tissues and central nervous system of various neurological disorders.

Background: Reduced cardiac MIBG uptake in Parkinson's disease (PD) is due to denervation of the cardiac sympathetic nerve and is a good indicator to differentiate PD from the other parkinsonisms.

Methods: Autopsy-verified patients with PD (n=18), dementia with Lewy bodies (DLB, n=12), pure autonomic failure (PAF, n=1), incidental Lewy body disease (ILBD, n=21), multiple system atrophy (MSA, n=21), corticobasal degeneration (CBD, n=6), progressive supranuclear palsy (PSP, n=7), Alzheimer's disease (AD, n=12), vascular parkinsonism (VP, n=1), PARK2(n=3), PARK4(n=3), PARK8(n=5) and control subjects (C, n=18) were

enrolled in this study. Tissue sections of the anterior wall of the left ventricle were immunostained with antibodies against tyrosine hydroxylase (TH) and phosphorylated neurofilament (NF). The number of TH- or NF-immunoreactive axons of epicardial nerve fascicles were assessed using a semi-quantitative rating scale as follows: absent or nearly absent (0); sparse (1); moderate (2); numerous (3). If the number of TH-immunoreactive axons of epicardial nerve fascicles is 0 or 1, we defined the cardiac sympathetic nerve as being denervated.

Results: 1)All the patients with PD, DLB and PAF, and 6 of 20 patients with ILBD had denervation of the cardiac sympathetic nerves. 2)Two MSA, one CBD, all PARK4 and one PARK8 patients had denervation of the cardiac sympathetic nerve, all of whom had Lewy bodies in the nervous system.

Conclusions: We conclude that reduced cardiac MIBG uptake is a potential biomarker for the presence of Lewy bodies.

We-137

Impaired activity in basal ganglia/premotor networks preceding self-initiated sequential finger movements in writer's cramp

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Objective: To test if focal dystonia (FD) presents with abnormal activation in basal ganglia/premotor networks during the planning phase preceding a sequential movement.

Background: Pathophysiological concepts of FD assume a genuine deficit of higher order voluntary movement control, manifesting also in tasks which do not evoke dystonic posturing. In writer's cramp (WC), deficits in self-initiated as compared to externally cued tasks have been reported, as well as reduced cortical potentials preceding self-paced finger movements. Here, we characterize brain activity during the planning of self-initiated sequential finger movements using event-related fMRI at 3.0T.

Methods: 16 patients with idiopathic WC and 19 matched controls executed a pre-learned finger sequence following repeated visual instructions and variable pre-movement phases (0.3–7.6 s). According to the instructions, movement was either self-initiated or cued externally, using the right or left hand. Data were analyzed in SPM5, modeling planning (instruction and pre-movement) and movement separately.

Results: Beside slightly higher error rates in WC (5.7 vs 3.7%), groups did not differ in performance parameters. There was a remarkable resemblance of activity between groups. Planning of self-initiated movements evoked bilateral responses in frontoparietal motor regions, anterior basal ganglia, and cerebellum ($p<0.05$, FWE). During movement, activity shifted towards contralateral motor executive regions. Between-group comparisons revealed reduced activity for WC in the anterior putamen (bordering the insula) and SMA during planning ($p<0.001$, uncorrected), but no significant differences during movement.

Conclusions: The reduced activation in WC during movement planning and initiation, involving the basal ganglia (anterior putamen) and premotor network (SMA), is compatible with a genuine dysfunction of higher order voluntary movement control. Importantly, the changes observed in WC cannot be attributed to differences in task performance, which have hindered interpretation of previous studies of basal ganglia networks, yielding contradictory results.

We-138

Volume and iron content in basal ganglia and thalamus of Parkinson's disease patients: A 3T MR study

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Objective: To explore volume and iron content in subcortical entire structures in Parkinson' Disease (PD) patients using MRI.

Background: The combined imaging modality approach revealed that the normal aging induces macroscopic modifications (volume decrease) and microscopic alterations (deposition of iron proteins) with different patterns in the basal ganglia and thalamus (Peran et al., Hum Brain Mapp. 2009). Previous works showed iron pathological deposits in the substantia nigra pars compacta in PD patients. However, results about iron accumulation in basal ganglia nuclei have often been inconsistent.

Methods: 16 PD patients (age: 61,25 ± 9.9 years; disease duration: 4,8 ± 2.4 years; UPRDS motor score: 13,1 ±7.4; Levodopa equivalent daily doses (LEDD): 881 ± 444 mg) underwent a 3 Tesla MRI (Allegra, Siemens Medical Solutions) with the following sequences: T2* weighted and whole-brain T1-weighted scans. Mean R2 * values (iron-related MR values) and volumes were calculated for pallidum, putamen, thalamus and caudate nucleus. We performed Spearman rank correlations between clinical data and MR values.

Results: Considering volume analysis, the results showed significant negative correlations between disease duration and right thalamus volume ($p<.05$), and between age and left putamen volume ($p<.05$). Considering iron content, we found a positive correlation between LEDD and iron content in putamen (left:$p=0.51$ and right:$p=0.56$), and between LEDD and iron content in right pallidum ($p<.05$).

Conclusions: Even if the size of our population is still limited, our preliminary results showed that the macroscopic and microscopic values from the subcortical structures did not seem sensitive to the same PD clinical indicators. The relationship between LEDD and iron content in putamen and pallidum needs to be confirmed. However, apart from the role in oxidative stress, iron plays a role in normal metabolism, in particular in dopamine synthesis and transport (Bianco et al., J Neurochem. 2008). This relationship between dopamine and iron could explain in part our preliminary results.

We-139

Reductions in sulcal volume in Parkinson's disease without dementia

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Objective: To investigate whether sulcal volume is a sensitive measure to detect neocortical atrophy in Parkinson's disease (PD) patients without dementia.

Background: According to the stages of brain pathology in PD by Braak et al. (2003), symptomatic patients without dementia may have alterations in neocortical areas. These changes have been demonstrated by previous voxel-based morphometry (VBM) studies.

Methods: We studied MRI volume changes in 5 sulci located in neocortical areas that are known to be altered in PD patients. For sulcal measurement we applied a quantitative method (BrainVisa) to a sample of 22 non-demented PD patients (n [men/women]: 14/8, age [mean±SD]: 63.9±10.6) and 21 age-matched controls (12/9, 62.14±12.8).

Results: We found significantly lower volumes in the bilateral anterior cingulate sulcus ($p<0.0002$), in the left anterior sylvian fissure ($p<0.002$) and left anterior ascendant superior temporal sulcus ($p<0.03$) in PD patients compared to controls. The posterior cingulate sulcus and the posterior sylvian fissure did not differ between the groups. Furthermore, in PD patients, sulcal volume showed a significant correlation with age (right anterior cingulate sulcus: $r=-.33$, $p < 0.03$, left anterior sylvian fissure: $r=-.38$, $p<0.01$), Hoehn and Yahr stage (right anterior cingulate sulcus: $r=-.44$, $p<0.04$; left anterior sylvian fissure: $r=-.58$, $p<0.004$) and general cognitive functions assessed by MMSE (right anterior cingulate sulcus: $r=.53$, $p<0.0001$; bilateral anterior sylvian fissure: $r=.45$, $p < 0.002$).

Conclusions: Non-demented PD patients have reduced sulcus volume involving mainly anterior cingulate and insular regions and this reduction correlates with age, illness severity and cognitive status.

The reported reductions in sulcal volume show agreement with neocortical decreases found by previous VBM studies in PD.

We-140

Corticospinal and thalamofrontal pathways in Parkinson's disease. A diffusion tensor imaging study

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Objective: The purpose of this study was to evaluate corticospinal (CST) and thalamofrontal (TFT) pathways in PD by means of Diffusion Tensor Imaging (DTI).

Background: DTI is an MRI method for visualizing white matter tracts. An increased sensitivity in demonstrating white matter pathology has been shown in different neurodegenerative disorders. However there are few studies of DTI application in Parkinson's disease (PD).

Methods: Thirty five PD patients and 15 matched for age healthy subjects (NC) were examined by DTI-Fractional anisotropy (FA) and DTI-Tractography. For measuring the FA-values first we performed the fiber tracking of CST and TFT and then we evaluated the FA-Values upon the fibers that had appeared on the 2D-Anisotropy color map using four regions of interest (ROIs) for the CTS at the posterior limb of internal capsule (ICCTS) and pons (PCST), bilaterally and two ROIs for the TFT. Patients were clinically evaluated by means of the Unified Parkinson's Disease Rating Scale (UPDRS) and classified into Hoehn and Yahr stages.

Results: Mean FA values of ICCTS were 0.58 ± 0.04 in PD patients and 0.60±0.04 in NC ($p=0.17$, not significant), Mean FA values of PCTS were found decreased in PD patients (0.45 ± 0.06) compared to NC (0.48 ± 0.04; $p=0.046$). TFT mean FA values were not significantly different (0.44 ±0.10 in PD patients vs. 0.42 ±0.04 in NC; $p=0.78$). Correlations between all FA values and clinical parameters were not significant, but TFT was inversely associated to age (rho=-.418, $p=0.013$).

Conclusions: Our findings indicate that there are subtle FA changes in CST at pontine level in PD patients compared to healthy subjects, but this is not related to disease severity. Further studies are needed to elucidate the diagnostic validity of FA measurements in PD.

We-141

Effects of L-dopa on manual and speech movements in parkinsonian patients: A dual-task approach using fMRI

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Objective: To highlight the neuronal circuits involved in speech production and limb movement controls in Parkinson's disease (PD) and their modulation by L-dopa.

Background: L-dopa effects on cardinal and axial symptoms differ largely, often leading to therapeutical challenges. In this context, we studied the cerebral activation profiles associated with three motor tasks: unilateral hand movement (HM), speech production (SP) and a combined task (HM+SP) gathering both of them.

Methods: Twelve PD patients underwent two fMRI runs, consecutively without (after an overnight fast) and with (1 hour after medication administration) L-dopa. Scans were obtained using a 3T MRI scanner (MedSpec S300, Bruker). Each externally-cued task (HM, SP, HM+SP) was compared to rest. During HM, the patient was asked to move a joystick with the right hand in a self-selected direction (forwards, backwards, left or right). During SP, a word self-selected from 4 possibilities ("up", "down", "left" or "right") had to be pronounced. HM and SP were performed simultaneously in the combined HM+SP task. The data were analysed using SPM5, with $p_{FWE\text{-}corr}<0.05$ as the significance threshold.

Results: Without medication, a strong implication of the cortico-cerebello-cortical (CCC) circuit during the simple task performances (HM (figure) or SP) has been observed, interpreted as a compensatory mechanism of the cortico-striato-cortical (CSC) dysfunction: notably, the cerebellum and primary motor cortex activations were bilaterally strong, whereas no activation within the basal ganglia has been found. The combined task displayed an activation profile close to the one related to the HM task, no brain regions associated with SP being revealed. Following L-dopa administration, HM activation profile was associated with a reduction of the CCC circuit recruitment, concomittant with a partial improvement of the CSC circuit activation. This latter point was less marked for SP. For the combined task, the cerebral activation profile added up the areas revealed during simple HM and SP tasks.

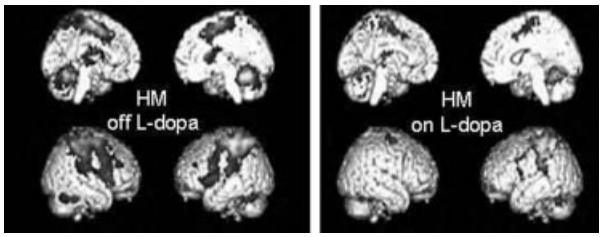

FIG. 1 (We-141).

Conclusions: Our results question the existence of task-dependant physiopathologies that may respond differently to treatments: L-dopa seems to modulate limb and speech PD symptoms in a similar way, but with a massive effect regards to HM and a mitigated one concerning SP. For the combined task, the patients' capacity of motor function additivity seemed to be restored with medication, reflecting a possible motor coordination improvement. This may be related also to a synergestic effect facilitating simultaneous task productions.

We-142

The limbic-circuitry of Huntington's disease: A combined neuroimaging approach

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Objective: This study, using a combination of imaging paradigms, aims to assess in vivo the functional and structural integrity of regions known to be involved in psychiatric aspects of Huntington's disease (HD).

Background: Many patients with HD develop psychiatric problems during the course of their illness and in some cases these can appear ahead of overt motor signs. These psychiatric problems can take the form of irritability and behavioural outburst along with depression, mood swings, schizophrenia and obsession like states. The amygdala, bed nucleus of the stria terminalis (BNST), limbic striatum (LST), orbitofrontal cortex (OFC), anterior (ACC) and posterior cingulated cortex (PCC) are all regions known to be connected with psychiatric disorders and as such we sought to investigate whether they are affected in HD patients.

Methods: The averaged brain imaging profiles of 7 premanifest HD patients (pHD; 3M/4F; 45 CAG; 41 years), and 7 symptomatic HD patients (sHD; 3M/4F; 45 CAG; 48 years; 7 years onset; UHDRS 16; TFC 6.5; IS 75) were compared using averaged normality values from 14 age-matched controls. Volume loss, D2/D3 receptor integrity and levels of activated microglia (AM) were studied using MRI-VOI, 11C-raclopride PET-ROI and 11C-PK11195 PET-ROI approaches, respectively.

Results: Significant changes were found in: AMYGDALA (pHD: 28.8% D2/D3 loss and 43.6% increases in AM; sHD: 29.9% D2/D3 loss and 45.2% increases in AM), BSTN (pHD: 34.4% D2/D3 loss and 31.2% increases in AM; sHD: 54.3% D2/D3 loss and 36.3% increases in AM), LST (sHD: 30.5% Volume loss, 40.5% D2/D3 loss

and 38.9% increases in AM), OFC (pHD: 23% Volume loss; sHD: 31.4% Volume loss) and ACC (sHD: 26.9% Volume loss and 51.1% D2/D3 loss). None of the functional changes were influenced by the effect of volume losses.

Conclusions: There are marked functional and/or structural abnormalities in the amygdala, BSTN and OFC in HD, that are present early on in the disease course and appear not to deteriorate. In contrast abnormalities in the LST and ACC appear only later on, when patients have clear manifest motor features of HD. The demonstration of abnormalities in these pathways, especially early in the disease course, may contribute to explain the prevalent and early emergence of psychiatric problems in HD.

We-143

Caudate nucleus dopamine depletion, cognitive functions and brain metabolism in early Parkinson's disease: A [^{123}I]FP-CIT SPECT and [18F]FDG PET study

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Objective: To explore the relationship between dopamine (DA) depletion severity in the caudate nucleus and 1) cognitive functions, 2) brain metabolism in early drug-naïve Parkinson's disease (PD) patients.

Background: DA depletion in the caudate nucleus is the major neuropathological substrate for early functional changes in non motor frontal striatal circuits, which in turn account for early cognitive deficits in PD patients.

Methods: 25 drug-naïve non demented PD patients (age = 65,6 ± 6,34 years; UPDRS III = 14,44 ± 5,48) underwent [123I]FP-CIT SPECT, neuropsychological assessment and [18F]FDG PET. The severity of caudate DA degeneration was measured with [123I]FP-CIT binding potential (BP), estimated with the Least-Squares (LS) method. Spearman rho was used to test for correlations between right and left caudate BP and neuropsychological data. A multiple regression analysis with Statistical Parametric Mapping (SPM) was performed to explore regions in which caudate BP correlated with regional cerebral metabolic rate of glucose (rCMRglc).

Results: As concerns cognitive functions no significant correlation was found between right and left caudate BP and neuropsychological data. As concerns brain metabolism, right caudate BP positively correlates with rCMRglc in bilateral anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), superior and middle temporal gyrus; left caudate BP correlates with rCMRglc in bilateral ACC, OFC, DLPFC and in right middle temporal gyrus.

Conclusions: In this study any significant correlation between caudate BP and neuropsychological data was found, while a significant correlation between caudate BP and rCMRglc was found in those cortical areas directly involved in the non motor fronto-striatal circuits, i.e. DLPFC, ACC, OFC. Our results suggest that neuroimaging techniques could be able to detect the early involvement of non motor networks in PD, when a direct relation between caudate DA degeneration and altered cognitive functions could not yet be identified.

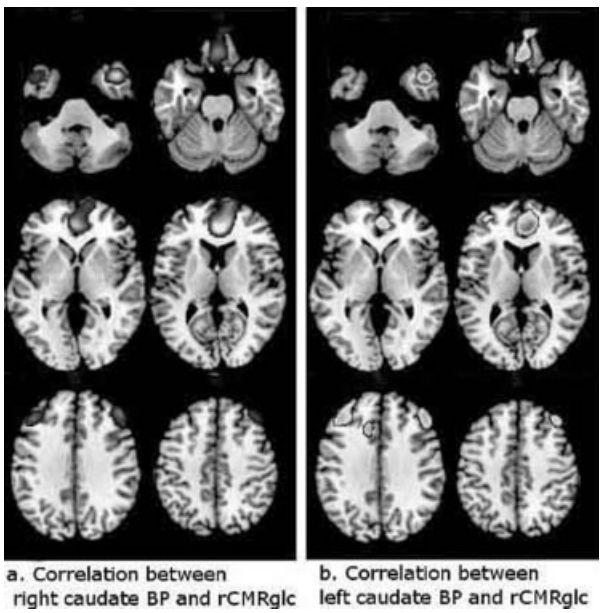

FIG. 1 (We-143).

We-144

Differential diagnosis of pathologically-proven CBGD using pattern analysis of FDG PET

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Objective: To assess the utility of FDG PET in the differential diagnosis of four patients with pathologically proven corticobasal ganglionic degeneration (CBGD).

Background: CBGD is a neurodegenerative disorder that accounts for 4-6% of parkinsonism. Diagnosis based on clinical symptoms alone is extremely difficult and only 25% of pathologically proven CBGD cases are correctly diagnosed in life. We have previously implemented a computer-guided method for the differential diagnosis of parkinsonism based on FDG PET, correctly classifying 90% of CBGD cases (Eckert et al, *NeuroImage* 2005). Nonetheless, these findings have not been validated in pathologically proven cases.

Methods: Four parkinsonian patients underwent FDG PET prior to establishment of a clinical diagnosis (followup 3±1.8yrs;mean±STD) and had postmortem findings of CBGD. Using the computer-guided method, one imaging expert reader (VD) and two non-expert readers (CE,TF), blinded to clinical diagnosis, independently assessed each patient scan by comparing it with the established metabolic templates of Parkinson's disease (IPD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and CBGD. These imaging assessments were compared to the postmortem findings.

Results: The mean age at symptom onset and time of death was 64±14.0 and 70±13.4 yrs, respectively. All patients had a diagnosis of non-specific parkinsonism at the time of PET. Using the computer-guided method, all three readers correctly classified three (75%) of the four pathologically proven CBGD cases. These patients exhibited distinctive asymmetrical metabolic reductions in multiple cortical regions. On clinical follow-up, two of these patients were determined to have probable CBGD and one to have possible MSA. The fourth pathologically proven CBGD case was correctly classified as CBGD by the expert reader, but was incorrectly classified as PSP by both non-expert readers. It was noted that the metabolic asymmetries in this patient were the least prominent of the four cases. The final clinical diagnosis of this patient was CBGD.

Conclusions: Computer-guided analysis of FDG PET can be used to accurately identify pathologically proven CBGD prior to diagnostically definitive clinical signs.

We-145

Task specific activation deficits in basal ganglia nuclei are accentuated across time: A study in early stage, drug naive Parkinson's disease

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Objective: To determine 1) whether early stage Parkinson's disease (PD) affects only specific nuclei of the basal ganglia (BG) during a motor task or whether all BG nuclei are affected, 2) how this

neural activation changes across time, and 3) if differences in neural activation exist in other brain regions in early stage PD.

Background: A clinically relevant motor feature of PD is that the performance of repetitive movements becomes progressively impaired across time. However, it is unclear how neural signals in the brain are abnormal in patients with early stage PD during the performance of such tasks. In addition, it is not clear whether deficits in BG activation are compensated for by cerebellar hyperactivity as has been suggested for patients with more advanced PD performing other tasks.

Methods: Neural activation was compared between 14 early stage drug naive patients and 14 controls during two precision grip force tasks using fMRI at 3T. A Hold task required subjects to produce six, 4s sustained isometric contractions at 15% of their maximum voluntary contraction (MVC). A Multiple Pulse task required a more vigorous switching on and off of force by producing ten, 2s contractions at 15% MVC.

Results: Voxel-wise analysis of the Hold condition revealed that PD patients were hypoactive relative to controls only in putamen and external globus pallidus. However, in the Multiple Pulse condition, hypoactivity was detected in all BG nuclei of the PD patients. Also, patients were hypoactive relative to controls in the ventrolateral thalamus, M1, and SMA. There were no differences in cerebellar activation between groups in either task. An analysis of the time-course of the blood-oxygenation-level-dependent signal change revealed that the hypoactivity observed in all BG nuclei of PD patients during the Multiple Pulse condition became significantly more pronounced over time as patients performed the task.

Conclusions: Vigorous motor tasks accentuate abnormal activity in BG nuclei in early-stage drug naive PD. In addition, abnormal BG activity becomes more pronounced across time with repeated task performance. The findings do not support compensatory cerebellar hyperactivity in early-stage drug-naive PD.

We-146

Metabolic-morphometric correlates of preclinical compensation in asymptomatic heterozygous PINK1 mutation carriers

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Objective: To evaluate striatal gray matter volume (GMV) and metabolic-structural relationship in asymptomatic heterozygous PINK1 mutation carriers (aPINK1-MC) using MRI and 18-Fluorodopa (FDOPA) PET.

Background: Recently, we reported a bilateral striatal GMV increase in asymptomatic heterozygous parkin mutation carriers (aParkin-MC), which was inversely related to a striatal decrease of FDOPA uptake and interpreted as an active compensation for the dopaminergic denervation. The striatal GMV increase was also observed aPINK1-MC. Mutations in the PINK1 gene are the second most common cause of early-onset Parkinson's disease (PD).

Methods: Nine aPINK1-MC (two females, mean age: 44.2 years) and nine matched healthy controls (two females, mean age: 45.9 years) underwent a high-resolution T1-weighted MRI and the aPINK1-MC also a FDOPA PET scan both at the University of Cologne, Germany. Clinically, the aPINK1-MC showed only mild motor signs for which they were mostly asymptomatic. MR images were analyzed with SPM5 (FIL, London, UK). Based on previous findings, we performed a ROI analysis ($p<0.005$ uncorr., $ke>20$ voxels). We further tested for a linear relationship between the individual GMV values and putaminal FDOPA uptake (Ki-values).

Results: Compared to controls, a bilateral putaminal GMV increase in aPINK1-MC was detected, which was verified with post-hoc volume analyses. The regression analyses between the individual putaminal GMV and the presynaptic FDOPA uptake revealed a negative relationship in the right putamen (Spearman rank correlation $R=0.698$) and a trend on the left side.

Conclusions: Our data confirm the previous finding of striatal hypertrophy in aParkin-MC and aPINK1-MC. We also found a similar inverse relationship between the putaminal GMV and the regional Ki-values in aPINK1-MC. The linear decrease of the presynaptic FDOPA uptake related to putaminal GMV increase in aPINK1-MC may be in keeping with a compensatory mechanism at the presymptomatic stage.

We-147

Functional neuroanatomy of vocalization in PD patients: A functional correlation study

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Objective: To study functional neuroanatomy of vocalization in PD patients and age matched controls using seed correlation analysis.

Background: It has been documented that both visceromotor (i.e. subcortical and cortical midline structures centred upon the mesencephalic periaqueducal grey matter [PAG]) and neocortical systems are co-activated during human vocalization. Parkinson's disease (PD) affects speech, including respiration, phonation and articulation.

Methods: In the previous study we measured the blood oxygen level-dependent (BOLD) response to overt sentence reading in nine treated female patients with mild to moderate PD (age; mean 66.0 $\pm$ 11.6 years, mean L-dopa equivalent 583.3 $\pm$ 397.9 mg) and eight age-matched healthy female controls (age; mean 62.2 years $\pm$ 12.3) while focusing mainly on the primary motor cortices. The quality of speech in PD patients was yet comparable to that of controls. Here we present the results of correlation analysis between the seed reference centred in PAG and the whole brain in a voxel-wise manner.

Results: In both groups, increased BOLD signal in PAG was correlated with a wide range of regions, including primary motor and premotor cortices, anterior cingulated cortex, middle occipital gyrus, temporal association areas and subcortical motor structures. In PD patients, as compared with controls, more significant positive correlations were observed between seed reference and basal ganglia, fusiform and supramarginal gyri, temporal association areas and inferior parietal lobule on the right side.

Conclusions: These results might reflect compensatory and/or treatment-dependent functional changes that seem to be hemisphere specific. Supported by Research Project of the Czech Ministry of Education: MSM 0021622404.

We-148

Position of active electrode contacts and basal ganglia activation during STN stimulation in Parkinson's disease

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Objective: To compare stimulation-related BG activation patterns of PD patients with STN DBS and intra- and extranuclear locations of active DBS poles using 18-FDG positron emission tomography (PET).

Background: Energy metabolism of the subthalamic nucleus (STN) and the basal ganglia (BG) is known to be activated by deep brain stimulation of the STN.[1] However, the optimal localization of active electrode contacts in the STN target area is under debate.

Methods: We quantified the resting cerebral metabolic rate of glucose (rCMRGlc) in 12 PD patients six months after STN-DBS in on and off-conditions. 3D-MRI datasets were co-registered to PET and the rCMRGlc was determined in STN, electrode region, pallidum, putamen, caudate and thalamus. Stereotactic coordinates of active poles were transferred from intraoperative x-ray to preoperative MRI.

Results: Active electrodes were located outside of the STN in 5/12 patients on the right side and 3/12 patients on the left side. Comparing on- versus off-DBS conditions, DBS-induced rCMRGlc increases were significantly higher in patients with extranuclear contacts (each $p < 0.05$, Mann-Whitney U test). More posteriorly posi-

tioned electrodes (higher negative y-coordinates) correlated with larger DBS-associated rCMRGlc increases in the right pallidum ($p < 0.05$, Spearman rank correlation). There were no differences of clinical outcome between patients with intra- and extranuclear electrode pole positions.

Conclusions: Metabolic BG activation under STN DBS seems to depend on the position of active electrode contacts in relation to the target nucleus. Extranuclear stimulation was associated with an increased energy metabolism in STN and pallidum, presumably explained by the proximity of the electrical field to axons and nerve fibers crossing the STN area which are tonically excited by high frequent electrical stimuli. The efficacy of STN DBS on the relief of PD motor symptoms did not depend on active electrode pole position in this study.

We-149

Differences in nigro-striatal impairment in clinical variants of early Parkinson's disease: Evidence from a FP-CIT SPECT study

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Objective: To evaluate FP-CIT uptake in different clinical phenotypes of Parkinson's disease.

Background: In idiopathic Parkinson's disease (PD) it is possible to distinguish two different clinical phenotypes: a tremor dominant variant (TD) and a rigid-akinetic type (RA). TD patients are characterized by a slower disease progression and less cognitive impairment. Striatal density of DAT, as quantified by FP-CIT SPECT correlates significantly with the UPDRS score and Hoehn&Yahr stage, in a linear way with rigidity and akinesia, but not with tremor.

Methods: We retrospectively evaluated our clinical database and selected 62 PD patients who performed an FP-CIT SPECT within 3 years from disease onset. According to UPDRS subitems, we divided patients in two subgroups: 24 tremor dominant and 38 rigid-akinetic. FP-CIT uptake has been calculated with specific (putamen and caudate) versus non specific (occipital lobe) radiotracer binding ratio.

Results: Disease duration (25.46 mts RA vs 30.52 mts TD), age at the time of SPECT scan (64.8 ys RA vs 64.3 ys TD) and disease severity as measured with UPDRS III (18.1 RA vs 15.2 TD) were not statistically different between two groups. Putamen controlateral to the most clinically affected side showed a lower FP-CIT uptake in RA patient compared to TD patients (<0.001 Mann-Whitney). No statistically significant differences emerged when considering caudate or striatal uptake bilaterally and omolateral putaminal uptake. FP-CIT controlateral striatal uptake correlated significantly with severity of rigidity and hypokinesia ($p<0.01$) but not with resting tremor ($p>0.05$, multiple regression analysis).

Conclusions: These results show a more severe putaminal impairment in RA patients compared to TD patients. These data suggest that other neurotransmitter systems apart from the nigro-striatal dopaminergic system are involved in the generation of parkinsonian tremor and they are consistent with previous evidences of lack of correlation between tremor severity and FP-CIT uptake. Putaminal relative sparing in TD patients could partially explain slower disease progression reported in this PD phenotype.

We-150

Diffusion tensor Imaging and MR-tractography for characteristic of microstructural integrity of white matter in patients with Parkinson's disease (PD)

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Objective: We study relation between white matter (WM) integrity, macrostructural changes, such as atrophy of WM, microstructural abnormalities in WM, and cognitive dysfunction in patients with PD using Diffusion Tensor Imaging (DTI) and MR-Tractography methods.

Background: We propose the quantitative indicators for the characteristics of the microstructural integrity of the WM in nondemented patients with PD and in patients with PD and cognitive dysfunction.

Methods: Two groups of patients are studied by high resolution anatomical MRI, including DTI (b=1000s/mm2, 25 directions), with 1.5T SIGNA EXCITE (GE). The 1st group includes 14 nondemented patients with PD (PDG). The 2nd group (PDCG) includes 15 patients with PD and cognitive dysfunction. Brain tissue was segmented automatically using the k-nearest neighbor classifier. The Fractional Anisotropy (FA) values and mean Apparent Diffusivity Coefficients (ADC) were measured in cortical WM and in subcortical structures that involved in cognitive dysfunction process.

Results: We assessed the association of DTI parameters with cognition using linear regression, adjusting for relevant confounders and additionally for volumes of normal appearing WM and WM with appearances of atrophy. From analysis of DTI data for two groups of patients there was a significant reduction of the FA values of temporal WM (PDG vs PDCG, 392.4+-70.3 vs 520.5+-64.7) and parietal WM (268.3+-30.3 vs 360.1+-31.2). Results of stepwise regression analysis showed the FA values of temporal and parietal WM were associated the scores of short-term memory and orientation. The higher ADC values and lower FA values in WM in subjects of PDG, and PDCG are related to worse performance on tasks assessing memory, executive function, information processing speed, global cognition and motor speed.

Conclusions: White matter integrity in temporal and parietal WM is compromised in patient with PD and cognitive dysfunction. The microstructural alterations in temporal and parietal WM may account for the more pronounced impairment of short-term memory observed in patient with PD and cognitive dysfunction relative to nondemented patients with PD.

Th-124

Diagnostic values of diffusion weighted imaging for differentiating multiple system atrophy from Parkinson's disease

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Objective: We investigated apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values using diffusion weighted imaging (DWI) MRI in multiple system atrophy (MSA) and Parkinson's disease (PD) to assess the differential diagnostic values.

Background: Differentiation of MSA from PD is clinically important because these disorders manifest dissimilar treatment response and prognosis. Characteristic MRI findings of MSA, such as dorsolateral putaminal hyperintensity or hot cross bun sign, were not always obvious especially in the early phase of the disease. Recently, quantitative analysis of DWI associated values were reported to be useful for detecting the early imaging changes of MSA.

Methods: We measured ADC and FA values in the pons, bilateral middle cerebellar peduncle and putamen comparing MSA and PD patients. We performed with 1.5 T MR scanner (Siemens, Germany) and circular shaped regions of interest (ROI) were placed in the each areas. Subjects were 10 probable MSA patients (mean age 66 years, mean disease duration 5.5 years) and 15 Parkinson's disease patients (mean age 70 years, mean disease duration 8.1 years). Normal Heart/Mediastinum ratio of cardiac MIBG scintigraphy was applied to confirm the further supporting evidence of MSA.

Results: ADC values in the all ROIs of pons, middle cerebellar peduncle, and putamen indicated significantly higher in MSA than PD. ADC values averaging all ROIs seemed best to discriminate MSA from PD. ADC values tend to be higher correlating with longer disease duration and severer clinical symptoms in MSA patients. No significant correlation with disease duration nor severity in PD patients. FA values in MSA patients showed lower in the pons and middle cerebellar peduncle, but in the putamen compared with PD. Lower FA values in the pons and middle cerebellar peduncle were detected as longer duration and severer symptoms in MSA.

Conclusions: ADC and FA values in the brainstem and putamen of MSA patients were revealed to differ from PD. The changes of these values tended to be evident in the more advanced MSA patients, suggesting these quantitative manners might reflect pathological progression in MSA. DWI appears to be a useful diagnostic tool for differential diagnosis of MSA from PD.

Th-125

Automated subcortical optimization of cerebral MRI-atlas co-registration for improved electrode localization in deep brain stimulation

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Objective: To (1) automate and (2) improve the accuracy of electrode localization on post-operative structural magnetic resonance imaging (MRI) data in patients with Parkinson's disease and dystonia treated with deep brain stimulation (DBS).

Background: The therapeutic efficacy of DBS in treating movement disorders depends critically on electrode localization, which is conventionally described using coordinates relative to the mid-commissural point. This approach lacks normalization of interindividual anatomical variances and requires manual measurement.

Methods: We have devised a scheme for automated subcortical optimization of co-registration (ASOC), which maximises patient-to-atlas normalization accuracy of MRI data into the standard Montreal Neurological Institute (MNI) space for the basal ganglia. Post-operative T2-weighted MRI data from 39 patients with Parkinson's disease (median age 66; 17 male) and 32 patients with dystonia (median age 46; 26 male) were globally affine normalised (control). The global transformations were regionally refined by two consecutive linear registration stages (ASOC-1 and 2) focusing progressively on stereotactical target sites by applying two selective brain-masks, which reference subcortical structures including ventricular cerebrospinal fluid (VCSF) at ASOC-1 and a sub-region of the basal ganglia at ASOC-2. Accuracy of the registration stages was quantified by spatial dispersion of 16 anatomical landmarks, and their root-mean-square-errors (RMSEs) with respect to pre-defined MNI-based reference points. Effects of VCSF volume, age, and sex were calculated in a general linear model.

Results: Mean RMSEs differed significantly ($p < 0.001$) between global control (4.2 ± 2.0 mm [$\mu \pm \sigma$]), ASOC-1 (1.92 ± 1.02 mm), and ASOC-2 (1.29 ± 0.78 mm). The accuracy of registration showed a significant correlation with VCSF volume at ASOC-1 ($r=0.228$; $p<0.001$) which was reduced in ASOC-2 ($r=0.091$; $p=0.002$).

Conclusions: The present method improves registration accuracy of structural MRI data into MNI space within the basal ganglia allowing for automated normalization with increased precision at stereotactic target sites and enables lead-contact localization in MNI coordinates for quantitative group analysis.

Th-126

High resolution 3T diffusion tensor imaging-based tractography for differential diagnosis of parkinsonism – A pilot study

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Objective: To show that diffusion tensor imaging (DTI)–based tractography is a reliable tool for differential diagnosis of progressive supranuclear palsy (PSP) and the parkinsonian variant of multiple system atrophy (MSA-P).

Background: Previous DTI studies with small patient samples have shown differences in the pattern of neurodegeneration in PSP and MSA-P patients. In particular the middle and the superior cerebellar peduncle as well as the transverse pontine fibers appear to be affected differently in these disorders. The present pilot study aims to demonstrate the specific changes in PSP and MSA-P in a small sample size with a standardized recording protocol.

Methods: 6 PSP and 2 MSA-P patients were included. Patients fulfilled clinical diagnostic criteria of probable PSP (NINDS-SPSP) or MSA-P (Gilman et al.). Mean age and disease duration were 72 and 4 years in MSA-P and 73 and 5 years in PSP, respectively. A 3Tesla MR-scanner was used for high resolution DTI with diffusion encoding in 32 directions and a voxel size of 2 x 2 x 2 mm, a reconstruction was performed (0,88 x 0,88 x 2 mm). The tractography was scored visually. Only imaging data without movement artifacts were used.

Results: Tractography in PSP showed a reduction of superior cerebellar peduncle connectivity, which was mild in two, moderate in one and profound in three patients (Fig.1). The PSP patient showing a moderately reduced connectivity in the superior peduncle also showed moderate fiber loss in the middle cerebellar peduncle. In MSA-P patients the trajectories of the middle cerebellar peduncle appeared mildly respectively moderately reduced in number and their cerebellar distribution. The moderately affected patient additionally showed a reduction of the ventral proportion of the transverse pontine fibers (Fig.2).

Conclusions: MSA-P and PSP present a different pattern of abnormal cerebellar and brainstem connectivity, which can be visualized using high resolutional iso-voxel tractography and DTI. By including a larger group of early and advanced patients with different parkinsonian disorders we aim at proving the clinical feasibility of this imaging method in the differential diagnosis of parkinsonism.

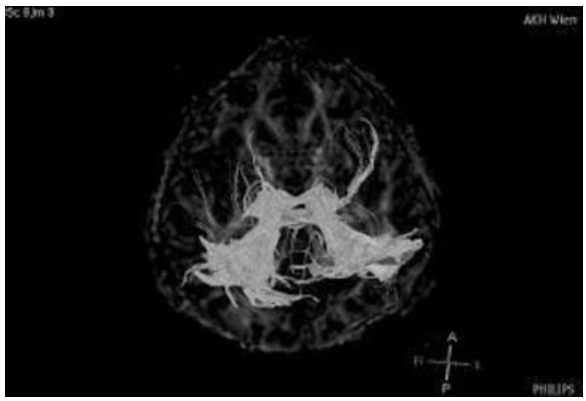

FIG. 1 (Th-126).

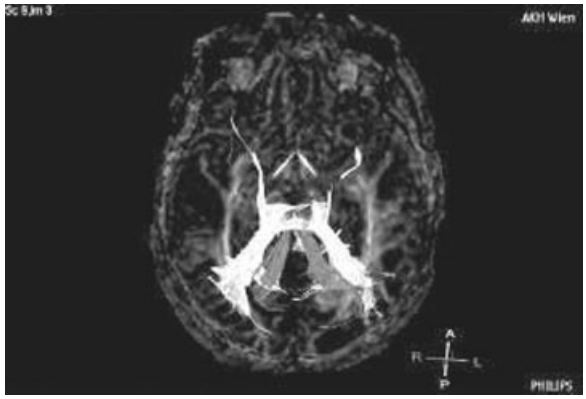

FIG. 2 (Th-126).

Th-127

N279K MAPT mutation carriers (PPND kindred) show FLAIR hyperintensity in brainstem

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Objective: MR FLAIR signal intensity might be a potential early biomarker in FTDP-17 families, including the PPND kindred carrying the N279K *MAPT* mutation.

Background: Significant atrophy of the brainstem and the superior cerebellar peduncles (SCP) in PPND patients compared to healthy controls was reported in a recent study (Slowinski et al, J Neurol in press). Another study demonstrated mesial temporal FLAIR hyperintensities (Frank et al, Neurology 2007). Our aim was to investigate if these findings occur simultaneously in *MAPT* mutation carriers. If so, this could improve diagnostic sensitivity and specificity of atypical parkinsonian syndromes.

Methods: We examined eight N279K *MAPT* mutation carriers from the PPND family [5 symptomatic women (age of onset: 41 years ± 6, age at exam: 46 y ± 4) and 3 pre-symptomatic individuals (2 women, age at exam: 41 y ± 2)]. MR FLAIR signal intensity in the brainstem and SCP were compared to 8 age and gender-matched healthy individuals. Two independent blinded raters reviewed a routine MR FLAIR sequence performed on a 1.5 T Siemens Magnetom for signal intensity of specific anatomic brainstem sites (pons, SCP, midbrain tegmentum and substantia nigra) and assigned a score between 0 and 3 points (0=normal, 3=marked FLAIR hyperintensity).

Results: MR FLAIR hyperintensity in the SCP and tegmentum (scores: 3, 2, 2, 1.5, 2) was observed in the 5 symptomatic mutation carriers. The MRI FLAIR images of the three pre-symptomatic mutation carriers showed comparable (1, 2, 2) but less intense signal abnormalities. No alterations of signal intensity were seen in the control subjects.

Conclusions: This study demonstrates that marked MR FLAIR hyperintensity is not only seen in the mesial temporal lobes but also in selected brainstem sites of symptomatic *MAPT* mutation carriers. Furthermore, the presence of similar but less prominent abnormalities in pre-symptomatic mutation carriers shows that MRI FLAIR is a valuable tool for the early detection of radiological abnormalities in FTDP-17. Further studies are needed to establish the pathological substrate of these MR findings. If similar radiological abnormalities are also present in other forms of atypical parkinsonism (e.g. PSP) remains to be seen.

Th-128

Task-specific recruitment of cerebello-thalamo-cortical motor circuitry during progression of Parkinson's disease

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Objective: To evaluate the changes in the striato- and cerebello-thalamo-cortical motor circuits during the progression of Parkinson's disease.

Background: Both basal ganglia and cerebellum are known to influence cortical motor (and motor-associated) areas via the thalamus. Only the striato-thalamo-cortical motor circuit (STC) has been implicated in the pathophysiology of Parkinson's disease (PD). The cerebello-thalamo-cortical motor circuit (CTC) also may be involved in PD, however, this pathway has not been well studied.

Methods: Longitudinal functional magnetic resonance images (fMRI, ~two years apart) were obtained from five PD (61 ± 12 yr) and five controls (57 ± 9 yr) performing either externally- (EG) or internally-guided (IG) sequential finger movements. All PD subjects had unilateral motor symptoms at baseline and developed bilateral symptoms at follow-up. Within-group analyses were performed by comparing fMRI activation patterns between baseline and follow-up scans. Between-groups comparisons were made by contrasting fMRI activation patterns generated by more-affected and less-affected hands of PD subjects with the dominant and non-dominant hands of controls, respectively.

Results: *Compared to baseline:* PD subjects had increased recruitment of cerebellar and cortical motor associated areas during both EG and IG tasks using either hand. These changes were most prominent when the task was IG. Controls showed increased recruitment of contralateral cerebellum during EG tasks by the non-dominant hand. *Compared to controls:* PD subjects demonstrated augmented recruitment of CTC circuits over time which was most prominent when the task was performed by the hand that transitioned from non-symptomatic to symptomatic ($p=0.0407$, PD vs. Control), and was specific for the IG task ($p=0.0123$, IG vs. EG).

Conclusions: This study demonstrated a task-specific increased recruitment of CTC motor circuitry during PD progression, supporting a role of the CTC pathway in PD pathophysiology, especially as a compensatory mechanism.

Th-129

Wilson's disease: Two treatment modalities. Correlations to pre and post-treatment brain MRI

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Objective: To evaluate correlations between neurological and neuroimaging features in Wilson's disease (WD), comparing treatment with zinc (Zn) and D-penicillamine (DP).

Background: Brain magnetic resonance imaging (MRI) studies on WD show disagreements and lack of correlations between neurological and neuroimaging features. Long term follow-up reports with se-

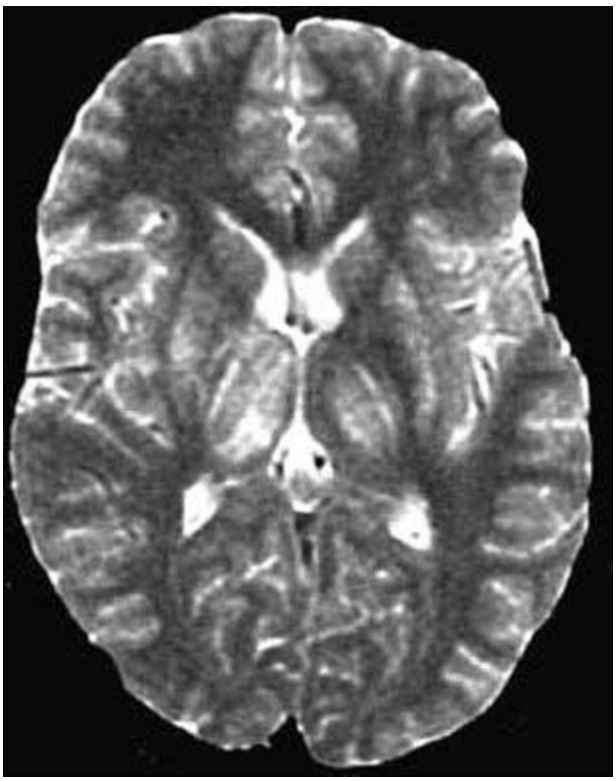

FIG. 1 (Th-129).

quential brain MRI in patients with neurological WD comparing different modalities of treatment are scarce.

Methods: This is a retrospective study of eighteen patients from a tertiary health care center with neurological WD, who underwent pre and post-treatment brain MRI scans to evaluate the range of abnormalities. All patients underwent at least two MRI scans at different intervals, up to 11 years after the beginning of treatment. MRI findings were correlated with clinical picture, clinical severity, duration of neurological symptoms and treatment with two different drugs. Patients were divided into two groups according to treatment: nine patients were treated exclusively with D-penicillamine (D-P), two patients began their treatments with zinc (Zn) and seven received Zn after the onset of severe intolerance to D-P.

Results: MRI scans before treatment showed, in all patients, hypersignal intensity lesions on T2 and proton density weighted images bilateral and symmetrically at basal ganglia, thalamus, brain stem, cerebellum, and brain cortex and white matter. The most common neurological symptoms were: dysarthria, parkinsonism, dystonia, tremor, psychiatric disturbances, dysphagia, risus sardonicus, ataxia, chorea and athethosis.

Conclusions: From the neurological point of view there was no difference on the evolution between the group treated exclusively with D-P and the one treated with Zn. Analysis of MRI scans with longer intervals after the beginning of treatment depicted a trend for neuroimaging worsening, without neurological correspondence, among patients treated with Zn. Neuroimaging pattern of evolution was more favorable for the group that received exclusively D-P.

Th-130

Differential diagnosis of Parkinson's disease and essential tremor with transcranial sonography: A population-based study

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Objective: To determine the diagnostic accuracy of midbrain hyperechogenicity as assessed by transcranial sonography (TCS) for the differential diagnosis of Parkinson's disease (PD) and essential tremor (ET) in the general population.

Background: Several studies have shown that midbrain hyperechogenicity is a common transcranial sonography finding in patients with PD.

Methods: As part of an ongoing prospective population-based study of carotid atherosclerosis and stroke risk (the Bruneck study), a total of 574 men and women aged 55-94 years underwent an examination with TCS (follow-up rate 86.2%). The diagnosis of PD and ET was based on UK Brain Bank Criteria and the MDS consensus criteria for classical ET. TCS was performed (2.5MHz transducer, Logiq 7, GE) by one experienced examiner from both sides using the temporal approach to display the butterflyshaped mesencephalon. Echogenic areas of both sides were analyzed separately. To compare areas of echogenicity and the prevalence of hyperechogenicity between groups, the side of greater value of SN echogenicity of each subject was used for statistical analysis. Based on a ROC analysis between healthy controls and patients with PD, hyperechogenicity is defined as an area of echogenic signal of 0.18 cm^2 or greater at least on one side.

Results: 5% of the study population had no sufficient acoustic bone window or had no TCS due to institutionalization (n=12). Of the subjects with sufficient acoustic bone window, 17 subjects had a diagnosis of clinical definite PD (age 79 years, SD 8; females n=7) and 16 subjects had a diagnosis of ET (age 75 years, SD 8; females n=12), respectively. 88% (n=15) of patients with PD were found to have SN hyperechogenicity as compared to 36% (n=5) of patients with ET. The sensitivity of TCS to differentiate between PD and ET was 71%, the specificity was 86%. The positive predicitive value of TCS for PD was 86%.

Conclusions: Despite different phenomenology, the differentiation of parkinsonian and essential tremor may be a diagnostic challenge. In clinically uncertain cases, TCS may be helpful to distinguish between PD and ET.

Th-131

Substantia nigra's hyperechogeneity: A mirror of Parkinsons's disease?

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Objective: Typically Parkinson's disease (PD) has unilateral onset with persistent asymmetry affecting the side of onset most. In most patients with PD hyperechogeneity of substantia nigra (SN) can be found by transcranial sonography (TCS) as a typical hallmark of disease. The symptoms of disease start on the side contralateral to the SN, which is primarely affected. Recently it could be demonstrated that iron related changes of the SN may be one important factor contributing to the hyperechogeneity typically visualized by TCS in PD.

Background: SN hyperechogeneity can be regarded as a sign for dysfunction of the nigrostriatal system. It could be hypothetised, that hyperechogeneity should be increased on the side contralateral to the more affected side and that the total area of hyperechogenicity should increase due to progression of PD or age.

Methods: We scanned 29 patients with PD, 10 male, 19 female, mean age 68 years, (range 44 to 81) and measured the area of hyperechogeneity at the largest extent on both sides. UPDRS motor score was assessed in 19 patients.

Results: Mean area of hyperechogeneity on the right was 0,55 cm^2 (range 0 – 0.78), on the left 0,50 cm^2 (range 0 – 1,26). In 15 patents the area contralateral to the more affected side was larger, in 14 patents the area ipsilateral to the more affected side was larger. The UPDRS motor score did not correlate with the size of the hyperechogenetic area in sum. The area of hyperechogeneity did not correlate with age either.

Conclusions: In our survey on 29 patients the area of hyperechogeneity did not correspond with the clinically more affected side at all. The size of the area of hyperechogeneity did not correlate with UPDRS motor score or age either. SN hyperechogeneity remains a phenomenon to be elucidated.

Th-132

Transcranial brain parenchyma sonography in Wilson's disease patients

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Objective: To investigate wheather transcranial brain parenchyma sonography (TCS) detects basal ganglia abnormalities in Wilson's disease (WD) patients and wheather these findings correlate with form of disease.

Background: It was previously reported that patients with WD had abnormalities in echogenicity of nucleus lentiformis (NL) in TCS which was possibly associated with increased copper content and was significantly correlated with disease severity.

Methods: The study comprised 45 patients (29 men) consecutive, clinically stable and treated patients with WD recruited from the WD Clinical Research Program at the University of Belgrade. Basal ganglia TCS was performed according to standardized protocol.

Results: Patients mean age was 34,7±10,2yrs, disease duration 11,3±9,3yrs, 64% of patients was continuously treated. Hepatic form of disease had 40%, neurological 51% and mixed form 9%. We found hyperechogenicity of substantia nigra in 11 patients (24.4%), 54.5% of which were neurological form. Abnormal hyperechogenicity of NL was detected in 13 patients (28.9%). Only three patients had hyperechogenicity of nucleus caudatus. Brainstem raphe echogenicity was reduced in 9 patients. There was significant difference in diameter of third ventricle in patients with neurological vs. hepatic form of disease (p=0.023).

Conclusions: Basal ganglia TCS could be usefull and promising tool for disease monitoring.

Th-133

Basal ganglia dopamine and motor subtypes of Parkinson's disease

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Objective: To investigate the patterns of basal ganglia dopamine in tremor subtype and postural-instability-gait-disturbance (PIGD) subtype of Parkinson's disease (PD) by measuring dopamine transporter availability with ^{11}C-β-CFT PET.

Background: Patients with PD may be divided into several subtypes based on clinical symptoms including tremor subtype and PIGD subtype (Jankovic 1990). The pathophysiologic basis of these different subtypes remains unknown. A previous postmortem study suggests that pallidal dopamine may be relatively preserved in tremor subtype compared with other subtypes (Rajput 2008).

Methods: We studied 12 patients with PD diagnosed according to UK PD brain bank criteria. The patients were divided into two groups based on tremor and PIGD subscales extracted from UPDRS: 1) 4 patients with tremor subtype (mean ±SD; age 55.3±17.9, disease duration 2.9±1.7year, 2 females) and 2) 8 patients with PIGD subtype (age 59.0±10.8, disease duration 2.0±1.3year, 5 females). These groups were matched for bradykinesia and rigidity scores of UPDRS. Using GE advance PET scanner, ^{11}C-β-CFT uptake was measured for 20 minutes starting at 60 minutes after injection. The specific ^{11}C-β-CFT uptake was calculated as a (region-cerebellum)/cerebellum ratio, and submitted for voxel-based analysis with statistical parametrical mapping (SPM2). For the analysis, the images of those patients whose right limbs were clinically more affected were flipped so that the major loss of dopamine function appeared in the right hemisphere in all the cases.

Results: All the patients showed decreased ^{11}C-β-CFT PET uptake in the striatum, especially in the posterior putamen. Between group comparison showed that the right pallidal uptake (contralateral to clinically more affected side of the body) in tremor subtype tended to be relatively preserved compared with PIGD subtype (threshold uncorrected $p<0.05$). Analysis on data of all the patients confirmed that this pallidal uptake correlated with neither bradykinesia nor rigidity score of UPDRS. The striatal uptake showed no significant group difference.

Conclusions: Pallidal dopamine tends to be relatively preserved in tremor subtype compared with PIGD subtype. This may contribute to the pathophysiologic basis of tremor subtype of PD patients.

Th-134

Changes in brain metabolism and dysphagia in Parkinson's disease

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Objective: The purpose of this study is to determine whether any changes in brain metabolism are related to the dysphagia in Parkinson's disease (PD).

Background: Dysphagia is one of cardinal symptoms especially related to the QOL and longevity in PD. Previous studies suggested that impaired medullary deglutition center was responsible for it. On the other hand, the higher brain function is also shown to play a role in swallowing, but it has not been assessed intensively in PD cases with dysphagia.

Methods: We evaluated the brain glucose metabolism and the swallowing ability in 29 cases with PD. Swallowing functions were assessed by measuring the time from guidance cues to the start of swallowing and the regional cerebral metabolic rate of glucose consumption (rCMRGlc) was measured by using 18F-FDG PET.

Results: The swallowing start time was significantly longer in PD patients with dysphagia. Using voxel-based FDG PET imaging technique, brain images were compared between 10 cases with dysphagia and 19 cases without dysphagia. Patients with dysphagia showed hypometabolisms in supplementary motor area, anterior cingulate cortex and primary sensoriomotor cortex.

Conclusions: These results suggest that difficulties to start the swallowing play a major role in dysphagia in PD. Hypometabolisms in these brain areas may be related to impaired motor planning and response selection, which are closely associated with motor dysfunctions in PD.

Th-135

Mechanism of mirror movements in Parkinson's disease

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Objective: This study aims to clarify the functional basis of mirrors movements (MM) during Parkinson's disease (PD), using functional magnetic resonance imaging (fMRI).

Background: MM consist in involuntary contractions of contralateral homologous muscles during voluntary unilateral movements of one limb. They are physiological during childhood, but generally disappear by the age of ten. In adults MM usually reflect an underlying pathology, which affects motor or cerebellar pathways or basal ganglia. In PD, MM are observed on the less affected side during voluntary movements of the most akinetic side. The presence of MM in PD could reflect: 1) a compensatory mechanism with abnormal activations of cortical areas including the ispilateral primary motor area (M1); 2) an insufficient activation of regions specialized in "non mirroring transformation".

Methods: Eight right-handed PD patients, with predominant right hemibody PD and MM during akinetic (right) hand movements, and 10 right-handed healthy volunteers were included. During fMRI, subjects performed index finger to thumb opposition movements with their right and then with their left hand, in alternation with a rest condition. Presence or not of MM during fMRI was assessed by a simultaneous electromyography recording. Rest and activation conditions were compared for each hand, within each group. Then comparisons between the two groups were performed.

Results: When patients performed the movement with their akinetic compared to their non akinetic hand, cerebral activation was found in the ipsilateral M1 and bilaterally in the anterior cingulate cortex and the inferior parietal lobes. Same areas were found to be overactivated in "intergroup" comparison. We did not observe any decrease of activation when MM occur.

Conclusions: These results underline the link between MM and cerebral overactivations in PD. These overactivations, including ipsilateral M1, could be interpreted as: 1) a compensatory mechanism aiming at improving the quality of the movement but leading to abnormal MM; 2) a loss of selectivity of cerebral activation in PD. On the opposite our results do not support as a mechanism for MM a default of recruitment of areas specialized in "non mirroring transformation".

Th-136

Dat scan examination – Benefit in clinical praxis

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Objective: To analysed benefit of Dat Scan examination in clinical praxis.

Background: Dat Scan method in vivo evaluate degree of loss of dopaminergic neurons in striatum. It is neuroimage technique using radio-active substance ^{123} I-Ioflupan (^{123} I-FP-CIT) that selectively bound on cells transporing dopamin (dopamin transporter – DAT) in presinaptic terminal of dopaminergic neurons in striatum.

Methods: We had analysed Dat Scan examined patients that were sent from our Department in period from 2006-2008. Patients were divided into the groups according to symptoms and according to different kind of tremors. Data were evaluated using χ^2-test with the significance of $p<0,05$.

Results: We analysed 55 patients in range from 20-78 years, average age of 62 years. There were 33 female and 22 male patients. Patients were divided in regard to symptoms on those with tremor (54,55%), those with extrapiramidal symptomatology (EPS) (36,36%), with cerebellar symptoms (3,64%) and patients with other symptoms (5,45%). Dat Scan examination was normal in 54,55% patients, and pathological in 45,45% of patients. EPS had 70% of patients with pathological finding and 30% of patients with normal finding. Tremor was present in 33,30% of patients with pathological finding, and in 66,67% patients with normal finding. Cerebellar signs were equaly present in those with pathological and normal finding (50%), and other symptoms were present only in group of the patients with normal finding (100%). There was statistical significance $p=0,027$. Dat Scan was pathological in 63,33% of patients with rest tremor and normal in 36,65% of patients. In those with action tremor finding was pathological in 33,33% and normal in 66,67% of patients, and in the group with postural tremor finding was pathological in 25% and normal in 75% of patients. There was statistical significance $p=0,032$.

Conclusions: Patients having tremor as only symptom most often had normal Dat Scan, while patients having EPS most often had pathological finding. Patients with rest tremor had most often pathological Dat Scan, while patients with action and postural tremor had most often normal finding. Dat Scan examination is not only useful in differential between Parkinson's disease (including Parkinson Plus syndrom) and other kind of tremor, but also in it's earlier detection and treatment onset.

Th-137

Inter- and intraobserver reliability of substantia nigra sonography for the diagnosis of Parkinson's disease

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Objective: Since TCS is non-invasive, commonly available, its broad implementation in the diagnostic routine is highly desirable, but requires a sufficient inter- and intra-rater reliability. Thus, we performed a multi-investigator, blinded crossed-sectional TCS reliability study in iPD and healthy controls.

Background: TCS of the substantia nigra (SN TCS) has become a widely-used method in the diagnosis of idiopathic Parkinson's disease (iPD) showing a hyperechogenic SN as the most characteristic finding.

Methods: SN TCS was performed in 22 iPD patients and 10 controls with the Sonoline Antares system (Siemens AG, Germany) by 4 experienced raters blinded for the disease status of the individuals and the results of the other examiners. Each individual was examined twice. Semiquantitative SN echogenicity rating (1-3) and SN planimetry (cm^2) were documented ipsi – and contralateral to the most affected side. After each investigation the disease status (iPD/control) was predicted.

Results: In both hemispheres, echogenicity grading and SN planimetry showed significantly higher values in iPD than in controls. In a multivariate model adjusted for age, gender and rater, a marked hyperechogenic SN (grade 3) had a significant 6.30 odds ratio for iPD (CI95% 2.67-14.84, $p<0.0001$). Global sensitivity and specificity of SN TCS for iPD detection were 86.4 % and 62.5% (0.74 AUC in ROC analysis, $p=0.0005$). For SN planimetry, the inter-observer ICC were 0.84 ipsi- and 0.89 contralateral, the intra-observer ICC (Cronbach's alpha) were 0.96 ipsi- and 0.87 contralateral. Echogenicity grading revealed investigator-dependent weighted kappa values of 0.33–0.51 (inter-observer) and 0.57 – 0.82 (intra-observer).

Conclusions: These data show that TCS of the SN has a high inter- and intra-rater reliability in skilled examiners with higher concordance rates in planimetric interval-scaled SN ratings than in the ordinal three-grade echogenicity classification. SN TCS has a high sensitivity for iPD diagnosis but a lower specificity in line with the known 10% prevalence of a hyperechogenic SN in healthy controls. We conclude that particularly planimetry of the hyperechogenic SN is a reliable imaging tool for the diagnosis of iPD and for multi-center trials assessing SN echogenicity.

Th-138

Overactivity of the left rostral putamen in asymptomatic carriers of a single mutant parkin allele in the context of a visuospatial response conflict

J.P.M. van der Vegt, M.M. Weiss, B.R. Bloem, F. Binkofski, C. Klein, H.R. Siebner (Nijmegen, Netherlands)

Objective: We examined how the presence of a mutant parkin allele influences task related activity in the basal ganglia when subjects have to select a movement in the context of competing response tendencies.

Background: Asymptomatic carriers of a single mutant parkin allele show a latent nigrostriatal dopaminergic dysfunction. We chose the Simon task because patients with Parkinson's disease are impaired at resolving the conflict induced by spatial incompatibility (Praamstra and Plat, 2001).

Methods: Asymptomatic individuals carrying a single mutant parkin allele ($n=6$) and healthy age-matched controls ($n=10$) performed a Simon task during fMRI at 3T. Responses are coded by symbolic cues in this two-choice reaction time task. The position of these cues is either spatially compatible or incompatible with the response instructed by the symbolic cue. Mean reaction times (RT) and error rates (ER) during fMRI were analyzed using ANOVA. Task-related BOLD signal changes were analysed using SPM2 software. Only correct responses were included in these analyses.

Results: Participants responded faster when the relative spatial positions of stimulus and response match. Incompatible trials were associated with higher ER in both groups. Parkin mutation carriers made significantly more errors than healthy non-carriers in compatible and incompatible trials. No significant differences in RT were found between groups. Analysis of the fMRI data revealed an increased activation of the left anterior putamen during spatially incompatible trials in parkin mutation carriers relative to non-mutation carriers. This hyperactivity was mainly present in right hand responses. No differences between groups were found during spatially compatible trials.

Conclusions: The fMRI results indicate that a mutant parkin allele is associated with overactivity of the basal ganglia when a correct action has to be selected in the context of conflicting response tendencies, due to a latent dopaminergic dysfunction. Given the overall increase in error rate, this may indicate basal ganglia dysfunction associated with latent nigrostriatal dopaminergic degeneration.

Th-139

Dopamine agonists reduce baseline activity, but boost gambling related activity in the orbitofrontal cortex. A PET activation study in PD patients

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Objective: To investigate the neurobehavioral effects of dopaminergic medication in the context of reward processing and risk-taking in PD patients.

Background: Dopamine agonists (DA) induce pathological gambling in PD. A possible underlying mechanism is an alteration of reward processing due to non-physiologic stimulation of dopamine receptors in the reward system (ventral striatum, orbitofrontal cortex, [OFC]).

Methods: 8 PD patients were studied before and after administration of DA (apomorphine) following overnight withdrawal of medi-

cation. Patients played a card game featuring either financial (gambling) or neutral (non-gambling) feedback during rCBF (regional cerebral blood flow) PET. Maps entered an ANOVA with a 2x2 factorial design (two tasks, on and off DA).

Results: DA reduced rCBF in the OFC and the ventral anterior cingulate cortex during the non-gambling task, while it increased rCBF in both areas during the gambling task.

Conclusions: Our findings suggest that non-physiologic tonic stimulation of dopamine receptors in OFC increases local synaptic reactivity to financial feedback, while at the same time reduces baseline levels of synaptic activity. This finding may advance our understanding of underlying neurobehavioural mechanisms of how DA could prime pathological gambling in PD.

Th-140

Tonic stimulation of the orbitofrontal cortex by dopamine agonists in PD wipes out reward processing and increases risk taking behaviour: Are they at risk of gambling?

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Objective: To investigate the differential neurobehavioral effects of dopaminergic medication in the context of reward processing and risk-taking in PD patients.

Background: Dopamine agonists (DA) stand accused to induce pathological gambling in PD. A possible underlying mechanism is an alteration of reward processing due to non-physiologic stimulation of dopamine receptors in the reward system (ventral striatum, [VS] orbitofrontal cortex, [OFC]).

Methods: 8 non-gambling PD patients on a combination of LD and DA were studied on 3 different days after overnight withdrawal. One session OFF medication, one session after LD (100 mg), one session after LD equivalent dose of DA. The sequence was randomized. Patients played a roulette game during fMRI (for each trial, an index of reward processing was computed using outcome, stake and probability) and performed a financial risk-taking task offline. We calculated brain maps of i) synaptic activity change at the time of outcome and ii) correlation with the index of reward processing (SPM5). Maps were entered in an ANOVA with the factor medication (OFF, LD, DA). Offline risk-taking scores were used as covariates of activation.

Results: DA specifically changed the activity in the reward system in two ways; both associated with risk-taking. First: plain outcome-induced activations in OFC were generally higher with DA compared to LD/OFF. In addition, outcome-induced OFC activations during DA positively correlated with risk-taking scores. Second: in the VS, both dopaminergic medications (LD/DA) equally diminished local reward processing compared to OFF. In OFC, however, only DA completely abolished local reward processing. More robust reward processing in OFC negatively correlated with risk-taking scores.

Conclusions: This is the first study to specifically link synaptic effects of DA in PD with impaired reward processing and increased risk-taking behaviour. We suggest non-physiologic tonic stimulation of dopamine receptors in OFC derails local synaptic reactivity and wipes out local reward processing. As both findings were associated with increased risk-taking behaviour, we provide a possible neurobehavioural model how dopamine agonists could prime pathological gambling in PD.

Th-141

Equally normalized motor activation in medicated Parkin-associated and sporadic PD

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Objective: To investigate pathophysiological differences between Parkin-associated and sporadic PD on dopaminergic medication.

Background: Patients with Parkin-associated PD often show a stable long-term response to dopaminergic therapy without developing motor fluctuations. Therefore, we reasoned that long-term dopaminergic therapy may be associated with differences in motor activation (MA) in Parkin-associated compared to sporadic PD.

Methods: To test this hypothesis, medicated patients with either Parkin-associated or sporadic PD and healthy controls underwent functional magnetic resonance imaging (fMRI) while performing externally specified or internally selected movements.

Results: Patients with Parkin-associated PD, sporadic PD, and healthy controls showed no difference in MA. Moreover, the covariates 'age' and 'disease duration' influenced MA to a comparable extent in both patient groups.

Conclusions: In previous studies with the same type of task, non-medicated sporadic PD patients consistently showed hypoactivity of frontal areas with internally selected movements. Therefore, the present finding suggests that a) dopaminergic therapy is equally effective in normalizing MA in Parkin-associated and sporadic PD and b) a stable long-term motor response in some patients with Parkin-associated PD may not be related to differences in cortical recruitment. In conclusion, our findings corroborate a substantial pathophysiologic overlap between Parkin-associated and sporadic PD and lend further support to the notion that Parkin-associated PD is a suitable genetic model for sporadic PD.

Th-142

Genotype-related changes in brain activity are influenced by the speed of task performance in non-manifesting carriers of a single mutant Parkin or PINK1 allele

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Objective: To test whether genotype related changes in motor activity in the presence of a *Parkin* or *PINK1* are influenced by task performance.

Background: The presence of a single *Parkin* or *PINK1* allele is associated with a dopaminergic nigrostriatal dysfunction and may convey an increased risk to develop Parkinson's disease throughout lifetime. Using functional magnetic resonance imaging (fMRI), we have shown previously that non-manifesting *Parkin* and *PINK1* mutation carriers displayed stronger activation of rostral premotor areas during a simple motor sequence task performed with the right hand (Van Nuenen et al, Neurol. 2008).

Methods: Here we reanalyzed the original fMRI data taking into account the speed of task performance. To this end, we divided *Parkin* and *PINK1* mutation carriers into fast and slow performers, operationally defined as being above or below the mean completion time. We examined whether slow and fast performers showed different effects of the genotype (i.e. presence of a *Parkin* or *PINK1* mutation) on movement related brain activity.

Results: Overactivity in rostral premotor areas with sequential movements was independent of the speed of performance. The left primary motor hand area showed a relative decrease in activation in fast non-mutation carriers. The left caudal putamen showed a stronger activation in slow mutation carriers during the sequential task.

Conclusions: These preliminary results suggest that the way participants perform a motor task may alter the genotype-related changes in movement related brain activity. Presumably, these differences are related to inter-individual variations in the strategies how to perform the task. This issue needs to be considered in future studies on preclinical motor reorganization in non-manifesting carriers of a PARK mutation.

Th-143

The reliability of transcranial duplex scanning in parkinsonian patients: comparison of different observers and ultrasound systems

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Objective: To establish the inter-observer and intra-transducer reliability of on- and off-line assessment of substantia nigra (SN) and Raphe nuclei (RN) by TCD in a mixed population.

Background: TCD is increasingly used in the diagnostic work-up of parkinsonian patients. The widespread use of TCD might be questioned if the results obtained vary when different examiners perform the test or when using different ultrasound systems.

Methods: In total 24 subjects were studied: Parkinson's disease 9, unclear parkinsonism 10, essential tremor 1, healthy controls 4. Each patient was assessed 4 times by 2 independent sonographers using 2 different ultrasound devices: SONOS 5500 and iU22 (Philips). The SN is evaluated qualitatively and quantitatively and the RN only qualitatively. 1) In the on-line assessment we determined: A) the inter-observer agreement of the 4 possible combinations B) the intra-observer agreement of both sonographers using 2 different ultrasound systems. 2) In the off-line assessment a third sonographer re-examined the stored images. We determined the inter-observer agreement of the third sonographer with the on-line assessment of the other 2 sonographers. Cohen's k value was used.

Results: 1A. The on-line inter-observer agreement of the 4 possible combinations was: kappa 0.23–0.39 for the qualitative SN evaluation, kappa 0.31–0.56 for the quantitative SN evaluation and kappa 0.03–0.15 for the RN evaluation. 1B. The on-line intra-observer agreement was: kappa 0.53–0.67 for the qualitative SN evaluation, kappa 0.55–0.76 for the quantitative SN evaluation and kappa 0.45–0.47 for the RN evaluation. 2. The off-line inter-observer agreement was: kappa 0.32–0.67 for the qualitative SN evaluation, kappa 0.53–0.61 for the quantitative SN evaluation and kappa 0.08–0.33 for the RN evaluation.

Conclusions: For the SN we found mediocre accordance comparing both observers on-line with each other as well as comparing an off-line observer with both on-line observers. Comparing the on-line observers with themselves, the intra-observer agreement appeared to be moderate. For RN evaluation, the concordance between the different observers was low, whereas the consistency for a single on-line observer using 2 different ultrasound systems was comparable to the SN evaluation.

Th-144

Antigen retrieval improves the immunoreactivity of cells and receptor sites of the basal ganglia on rat and human brains

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Objective: This study addresses the methodological issues of immunoreactivty of visualizing cells and receptor sites and incorporating antigen amplification methods.

Background: The neurocircuitry of the basal ganglia in humans is thought to be very similar to the rat, thus there exists many animal models for studying movement disorders. One particular component of the rat basal ganglia, the caudate/putamen, is collectively known as the neostriatum or the striatum. Subpopulations of neurons are usually identified by the use of immunofluorescence and in situ hybridization techniques. These techniques have complimented various neuropharmacological studies however, samples in such studies are usually limited to a small subsection of the striatum thus hindering a global overview of the neuronal distribution. The established immunohistochemical techniques are more effective if additional steps are taken to amplify antigen sensitivity and decrease background staining. The advancement in antigen retrieval (AR) methods has increased antigen sensitivity so that immunohistochemical methods may prove to be more instrumental in visualizing cells and receptor sites possibly resulting in a greater understanding of receptor density etc.

Methods: Our laboratory utilised large paraffin sections of whole human striatum (64x35mm) and coronal slices of rat striatum. Utilising standard immunoperoxidase techniques we compared the immunoreactivity of cells in tissue sections with and with out the application of steamed AR (pH 6.0) using anti-tyrosine hydroxylase, anti-enkephalin, anti-substance P, anti-adenosine A2A receptor, anti-D1 receptor, anti-D2 receptor and anti-calbindin.

Results: Steam antigen retrieval techniques did have any detrimental affects on the general cellular morphology. The tissue sections that were subjected to steam AR demonstrated an amplification in antigen sensitivity with a reduction of background staining thus enhancing the detection/visualisation of different cell types and receptor content.

Conclusions: The use of larger whole human striatal sections improves our spatial knowledge of distribution of such cell populations and receptors. Imporved immunohistochemical techniques could enhance research capabilities of studies looking into function and dysfunction of the basal ganglia.

Th-145

Reduced neuron integrity in cerebellar peduncle in patients of progressive supranuclear palsy

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Objective: To assess the fiber integrity by diffusion tensor imaging (DTI) in the early stage of Parkinson's disease (PD) and progressive supranuclear palsy (PSP).

Background: Efforts have been made to develop for a possible or probable diagnosis of PSP in clinics, next to neuropathological examination. The neuropathology of PSP can be attributed to neurodegeneration in subcortical regions, including the brain stem, basal ganglia, and frontal lobe. Our study proposed to use DTI to characterize the early stage of PSP such as the progressive death of neurons and to assess the fiber integrity.

Methods: Six patients with PSP, 6 patients with PD and 6 healthy age-matched controls were included. Images were acquired on a 3 T MR scanner (Trio with TIM, Siemens, Germany) in Chang Gung Hospital. DTI was acquired with imaging parameters of matrix size = 128 * 128, 64 slices of 2 mm, TR/TE = 7800msec/83msec, b factor = 1000 s/mm2 in 64 directions. Both Fractional Anisotropy (FA) and trace were calculated from the diffusion tensor.

Results: Regions of interest were located in putamen, and cerebellar peduncle. The results showed FA decreased significantly in cerebellar peduncle in both patient groups (PSP: 0.543 $\pm$ 0.179, PD: 0.609 $\pm$ 0.132) when compared to the normal (control: 0.778 $\pm$ 0.140, PSP vs control: $p < 0.005$, PD vs control: $p < 0.05$), but not in putamen. None of the difference of trace reaches statistical significance in all groups. The decrease in diffusion anisotropy in peduncle indicated changes of microstructure in patients of PSP and PD. The findings are consistent with previous pathological or radiological studies in PSP, which reported involvement of superior cerebellar peduncle. The loss of neuron integrity of cerebellar peduncle in PD suggested an extensive neuron network can be affected.

Conclusions: Diffusion Tensor Imaging can appropriately reflect the degeneration of the brain microstructure as the progress of the disease change in patients with PSP.

Th-146

Increased resting state activity in patient of progressive supranuclear palsy

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Objective: To examine the changes in the default mode network (DMN) activity during the resting state fMRI.

Background: Progressive supranuclear palsy (PSP) is an atypical parkinsonian syndrome. Conventional MR imaging is useful, though controversial, in distinguishing PSP from PD or other parkinsonian syndromes. Analyses of resting-state fMRI have demonstrated temporal correlations in BOLD signal of widely separated brain regions, which are presumed to reflect the intrinsic connectivity. The DMN, including medial prefrontal cortex, medial temporal lobe, and posterior cingulate cortex/retrosplenial cortex, typically deactivates during performance of cognitive tasks and has been implicated in episodic

memory processing. Because it was assumed the thalamo-cortical circuit was involved in the PSP disease state, the functional connectivity in DMN could be affected. The present work proposed to examine the changes in the DMN activity in patients with PSP when compared to normal control.

Methods: Six patients with PSP and 6 healthy old controls were included. All studies were performed on a 3.0 Tesla MR scanner (Trio a TIM system, Siemens, Erlangen, Germany). Images were acquired using a gradient recalled EPI sequence with the following parameters: 40 slices of thickness of 3 mm to cover the whole brain down to cerebellum; TR/TE = 3000ms/45ms, matrix size = 64×64, FOV= 192mm and 120 measurements. Subjects were prompted to remain restingly awake without performing any specific task. The resting state data were analyzed through independent component analysis.

Results: Figure 1 shows the default mode network activities in the patients (left), when compared to the controls (right). Increased activities in the DMN were found in anterior cingulate and parahipocampus in patients than the controls, as indicated by the arrows. The findings suggested that the affected neural network might require increased amount of resources to maintain a similar level of performance.

Conclusions: The resting state connectivity of the DMN would be affected by the PSP diseased state, which could be served as a potential image marker for the disease.

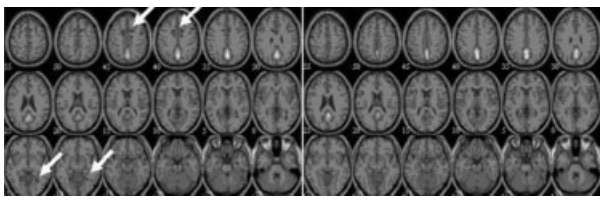

FIG. 1 (Th-146).

Th-147

Color discrimination impairment in patients with Parkinson's disease and their regional cerebral blood flow changes

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Objective: The aim of this study is to investigate possible role of visual cortices for the color discrimination impairment in patients with PD.

Background: Dysfuntions of color vision in PD could be demonstrated using the Farnsworth-Munsell 100 hue test from the early stage of the disease. The high sensitivity and dopa-responsive nature of the test is thought to be useful for the early detection of PD. Although the retina has been thought as a candidate, the causative lesion for the disorder has not yet been determined.

Methods: *Subjects:* We enrolled 58 parkinsonian subjects, mean age 67.8 years into this investigation on both color discrimination and cerebral perfusion study. A age-matched group of 29 healthy volunteers served as controls. *Farnsworth-Munsell 100Hue test (FMT):* We performed the FMT in a binocular fashion. We determined the total error score (TES) of the FMT. As Kormogorov-Smirnov test revealed some degree of skewness in the distribution of TES,we square root transformed the TES (sqTES) before performing further statistical analyses. *SPECT*: Subjects were studied with SPECT using ^{123}I-IMP as a radiotracer. Image analysis by 3D-SSP was performed using Neurological Statistical Image Analysis software. After normalization, the resulting statistical parametric maps of t statistics were transformed to Z-score maps of unit normal distribution.

Results: Mean sqTES of PD group showed significantlly higher than that of controls. The sqTES of patients were correlated with both age, duration of illness, and H&Y stage. We subdivided the cohort into two groups, namely group A and B, according to the sqTES scores (A: sqTES$<$7, B: 10$\leq$sqTES). According to 3D-SSP analysis, the rCBF in the cuneus and inferior temporal gyrus in the group B were significantly lower than those in the respective area in the control group. The rCBF in the cuneus in the group A were also lower than control, but rCBF in the inferior temporal gyrus were relatively preserved.

Conclusions: Color discrimination impairment is common among patients with PD. It appeared from early stage of the disease, but it progress successively along with the motor syndrome. Dysfunction of occipital visual cortex and temporal visual association cortex could play a role in color discrimination impairment in PD.

Th-148

Safety of a non standard protocol for postoperative MRI in DBS patients

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Objective: To evaluate the safety and to assess the incidence of adverse events using a postoperative MRI protocol with a higher specific absorption rate (SAR) value than recommended in the manufacturer's guidelines.

Background: Magnetic resonance imaging (MRI) in patients bearing a deep brain stimulation (DBS) device may lead to radiofrequency lesions due to electrode heating. In order to avoid the risk of permanent neurological deficit in association to MRI diagnostics the device manufacturer has released saftey guidelines. Prior to the release of the manufacturers guidelines we installed a postoperative MRI- protocol allowing a higher specific absorption rate (SAR) value than subsequently recommended in the manufacturer's guidelines.

Methods: Between January 2000 and May 2008 post-DBS-procedure MRI was performed with a 1,5 Tesla scanner using a head coil (send and receive). The protocol used in our institution comprised a higher SAR of up to 0,9 W/kg compared to 0,1 W/kg in the manufacturer's guidelines. A retrospective analysis of patients records and radiological records was performed to assess the incidence of new neurological deficits using our MRI protocol in DBS treated patients.

Results: A total of 208 patients underewent DBS surgery within the observed period. All patients received postoperative cranial MRI using our protocol. In 17% at least one supplementary MRI was performed during the follow up period using the same protocol for various clinical reasons. None of the patients demonstrated a new neurological deficit during or after MRI acquisition. Even after repeating MRI no neurological deficits were observed.

Conclusions: This MRI protocol using higher SAR values was safe. In view of case reports, the manufacturer's guidelines, as well as in vitro studies, post operative MRI in DBS patients have to follow a strict protocol and should only be performed in specialized centers. Our results suggest that higher energy levels of cerebral MRI may be feasible in DBS treated patients. New guidelines for 3Tesla scanners and MRI compatible devices should be developed.

Th-149

Cerebral glucose metabolism in PD patients with and without dementia

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Objective: To evaluate the relativity of the cognitive function, the dopaminergic degeneration, and the cerebral glucose metabolism in Parkinson's disease (PD) patients with and without dementia.

Background: PD is clinically characterized by motor symptoms. However, the nonmotor symptoms, including depression and dementia, are also have marked impact on the quality of life in PD patients.

The risk of developing dementia in PD is almost 6-fold that of age-matched controls. To date, there is no objective marker to predict the development of dementia in PD. We conducted this study to search for any correlation between the dopaminergic degeneration, glucose metabolism, and the risk of dementia in PD patients.

Methods: Twenty PD patients with mild dementia (CDR: 1.0) (PDD group) and 30 age- matched PD patients without dementia were enrolled. The duration of disease and the severity of motor symptoms in the two groups were similar. All the subjects received F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) and Tc-99m-TRODAT-1 single photon emission computed tomography (SPECT). The FDG PET images were normalized to a standard template. Statistical comparison was performed on a voxel-by-voxel basis using two-sample t-test. The SPECT images were normalized and automatically co-register to a MRI template. Each ratio of specific-to-nonspecific striatal Tc-99m-TRODAT-1 binding was calculated as the specific uptake ratio (UR).

Results: The striatal UR of Tc-99m-TRODAT-1 had no significant difference between the PD and PPD group. The glucose metabolism of PDD patients was significantly decreased in right precuneous gyrus, angular gyrus, and superior parietal lobe compared with those in PD patients ($p<0.005$).

Conclusions: Our results suggested that the cerebral glucose metabolism was a more sensitive marker to reflect the cognitive impairment in PD than the dopamine transporter density. FDG PET imaging may be useful in monitoring the therapeutic effects of anti-dementia drugs in PDD and the longitudinal follow-up in PD patients with mild cognitive impairment.

Th-150

Effects of dopaminergic treatment on putaminal dopamine turnover measured with ^{18}F-dopa-PET in Parkinson's disease

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Objective: To assess pharmacological effects of dopaminergic treatment (cabergoline vs. levodopa) on putaminal dopamine turnover measured with ^{18}F-Dopa-PET in Parkinson's disease (PD).

Background: Dopamine turnover as the ratio between dopamine metabolites and dopamine can be estimated as the inverse of the effective dopamine distribution volume ratio (EDVR) measured in ^{18}F-Dopa-PET. There is evidence that an increase in dopamine turnover might be an important early compensatory mechanism in PD. The aim of our study was to analyze the influence of dopaminergic compounds on putaminal dopamine turnover.

Methods: We assessed 40 *de-novo* PD patients using ^{18}F-Dopa-PET to measure the EDVR in the putamen at baseline and after three months of treatment with levodopa or cabergoline in a controlled randomized observer-blinded trial.

Results: 36 patients (19 in the levodopa, 17 in the cabergoline group) completed the study per protocol. There were no statistical significant differences between the groups with respect to demographical data. Patients in both treatment groups showed significant therapeutic benefit as measured by total UPDRS after three month treatment (levodopa group [300 mg/day]: 27.7 at baseline vs. 16.5 points at trial endpoint, $P<0.0001$; cabergoline group [3 mg/day]: 29.06 vs. 21.06 points, $P=0.002$). The EDVR significantly increased from baseline to the visit after three months of treatment in both groups with a significant difference between groups (7.77% in levodopa vs. 18.65% in cabergoline treated patients; $P=0.035$).

Conclusions: We found an increase of putaminal EDVR (decreased dopamine turnover) after three months of dopaminergic treatment in *de-novo* PD patients with significant larger influence by cabergoline compared to levodopa. These are most likely mediated through the stimulation of presynaptic dopamine D2 receptors in the putamen.

NEUROPHARMACOLOGY

Mo-151

A pharmacoeconomic evaluation of botulinum toxin A therapy in the Philippines

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Objective: To evaluate the cost of botulinum toxin A (BTX-A) treatment in the Philippines, and determine the dose, clinical response, and adverse effects to BTX-A therapy.

Background: Botulinum toxin therapy for various neurological disorders was made available in the Philippines since the late 1990's. However, since its introduction in the country, there has been no report on the burden of therapy incurred by the patient being treated with BTX.

Methods: We identified all patients injected with BTX-A from a Movement Disorders Clinic database between May 2001 and August 2007. Patients' medical records were reviewed, and demographic and clinical data using a standardized data collection form were obtained. The number of injections, dose given, response and adverse effects, and cost of treatment were determined. Positive clinical response was defined as any degree of improvement of the presenting symptoms.

Results: A total of 168 patients were included, wherein 378 BTX-A injections were done. Eighty-five (50.6%) were males. The mean age of patients was 48.0 + 16.2 years old (range: 7 – 81 years). The majority of patients have dystonia (n= 71, 42.2%), hemifacial spasms (n= 66, 39.3%) and spasticity (n=22, 13.1%). Clinical improvement was documented in 89.7% (n=87) and 90.8% (n=79) of patients given with Botox® and Dysport®, respectively. The mean duration of benefit is 3.8 + 1.3 months (range: 0 – 8 months). Adverse effects were noted in 9.5% (n=16) of patients (Dysport®:12.4%; Botox®: 8.0%). The most common adverse effect was ptosis. The overall average cost per treatment is PhP 15,524.19 +/- 13,818 ($ 328 +/- 291.95), while the overall mean cost of the BTX-A alone per injection is PhP 10,036.2 +/- 9,401 ($ 212.05 +/- 198.63). Of the disorders included, XDP had the highest mean expenditure of PhP 33, 970 +/- 29,980 ($ 717.73 +/- 633.42) per treatment.

Conclusions: Although, the cost of individual injection is high, other cost factors such as indirect and intangible costs contribute to the burden of management of these disorders. The subjective and objective relief noted after treatment, may compensate the expenditure with use of BTX-A.

Mo-152

Use of anticholinergic drugs and impact on cognition in Parkinson's disease

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Objective: To study whether the use of anticholinergic agents is an independent risk factor for cognitive decline in patients with PD.

Background: Cognitive decline is common in Parkinson's disease (PD). Although some of the etiological factors are known, it is not yet known whether drugs with anticholinergic activity (AA) contribute to this cognitive decline. Such knowledge would provide opportunities to prevent acceleration of cognitive decline in PD.

Methods: A community-based cohort of patients with PD (n=235) were included and assessed at baseline. They were followed with assessments were made four and 8 years later. Cognition was assessed using the Mini-Mental State Examination (MMSE). A detailed assessment of the AA of all drugs prescribed was made, and AA was classified according to a standardised scale. Relationships between cognitive decline and AA load and duration of treatment were assessed using bivariate and multivariate statistical analyses.

Results: More than 40% used drugs with AA at baseline. During the 8-year follow-up, the cognitive decline was higher in those who had been taking AA drugs (median decline on MMSE 8 points) com-

pared to those who had not taken such drugs (median decline 1 point); p=0.013). In linear regression analyses adjusting for age and baseline cognition, significant associations with decline on MMSE were found for total AA load (standardised Beta=0.217, p=0.036) as well as duration of using AA drugs (standardized beta 0.241, p=0.028).

Conclusions: Our findings confirm the association between cholinergic activity and cognitive decline in PD, providing an important opportunity for clinicians to avoid increasing progression of cognitive decline by avoiding drugs with AA. Increased awareness by clinicians is required about the classes of drugs that have anticholinergic properties.

Mo-153

"Espresso coffee" for the treatment of excessive daytime sleepiness in Parkinson's disease: Results of four pilot n-of-one clinical trials

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Objective: To evaluate the efficacy, tolerability, and safety of regular espresso coffee for the treatment of excessive daytime somnolence in PD patients.

Background: Daytime somnolence constitutes a relevant problem for the management of Parkinson's disease (PD), but no treatment other than the control of the precipitating factors has shown a clear therapeutic effect.

Methods: We conducted four pilot, randomised, placebo-controlled, double-blind, and multi-crossover single-patient trials. Eligibility criteria were: diagnosis of idiopathic PD according to the UK Brain Bank, aged 30 years or above, modified Hoehn and Yahr stage < 5 in the "OFF" state, stable dose of all antiparkinsonian drug treatments for at least one month, and a daytime somnolence defined as an Epworth Sleepiness Score higher than 9. The primary efficacy outcome was a 7-point Likert scale monitoring subjective "daytime somnolence". The secondary efficacy endpoints were: a 7-point scale monitoring subjective "tendency to sleep episodes", a 7-point scale monitoring daytime somnolence in the situation/activity in which he presented the higher tendency to fall asleep, a VAS of fatigue, and the Epworth Sleepiness Scale.

Results: Four n-of-one studies were conducted. Three patients completed the three pairs of treatment periods. One patient completed only two crossovers. The visual analysis of the plotted results of the 7-point scales found a pattern of response, which was suggestive of a beneficial effect in two patients. This pattern was visible for the outcomes global daytime somnolence and somnolence during specific tasks with higher tendency for somnolence. When using the Guyatt criteria, we concluded that for the primary outcome, the therapeutic intervention was classified as having a beneficial trend, in two patients. The same patients were classified as possible responders using other classifications based on the number of paired periods favorable to the active intervention.

Conclusions: It was feasible to conduct n-of-1 trials in a PD sample. Two of the four patients included in these studies were classified as responders to espresso coffee and coffee seems a potential therapeutic intervention to treat somnolence in PD and to deserve further therapeutic studies.

Mo-154

A systematic review of the incidence of fatigue as an adverse event in placebo-controlled trials for Parkinson's disease

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Objective: To quantify the risk of occurrence of fatigue as an adverse event (AE) of available antiparkinsonian drugs in comparison with placebo.

Background: Fatigue is a common complaint in Parkinson's disease (PD). It is commonly attributable to the disease itself, but is also likely to be associated with the use of the most common antiparkinsonian drugs. The contribution of either remains unclear.

Methods: Study design: Systematic review with meta-analysis. Search strategy: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Medline (1950 to December 2007) and Embase (1980 to December 2007). Inclusion criteria: Randomised placebo-controlled trials of marketed antiparkinsonian drugs for PD published in an article (or equivalent manuscript); report of AE in the original article. Outcome measures: The pre-specified outcomes were "type and incidence of a fatigue-related AE" The definition of fatigue comprehended both reports of "fatigue" or "asthenia". The risk of fatigue was defined in terms of odds-ratio taking in account its incidence both in treatment and placebo groups.

Results: Of 625 studies identified, 96 fulfilled inclusion criteria. 19 trials reported fatigue or asthenia as an AE. Overall, fatigue was significantly more common with the use of antiparkinsonian drugs than with placebo (OR 1.33, 95% CI 1.06 to 1.66). However, when a random effects analysis is conducted (due to a significant heterogeneity between trials), the reported difference was found to be statistically not significant (OR 1.41, 95% CI 0.94 to 2.11). Ropinirole was the only antiparkinsonian drug that was significantly associated with an increased risk of fatigue (OR 5.63, 95% CI 2.02 to 15.74). Rasagiline was the only antiparkinsonian drug associated with a decreased risk of fatigue when compared to placebo (OR 0.39, 95% CI 0.18 to 0.85). The remaining drugs were not different from placebo in terms of occurrence of fatigue.

Conclusions: Fatigue is frequently reported as an AE in PD clinical trials. Our results suggest that rasagiline may have an effect in control of fatigue in PD, what should be further evaluated in dedicated studies.

Mo-414

Dramatic improvement in parkinsonism after sinemet therapy in a patient with severe Wilson's disease

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Objective: Wilson's disease (WD) manifests commonly as parkinsonism and dystonia. We report a case of a patient with severe parkinsonism who exhibited dramatic improvement after Sinemet therapy.

Background: WD is an autosomal recessive inherited disorder of copper accumulation. parkinsonism and dystonia are assumed to be due to presynaptic nigrostriatal dopaminergic injury.

Methods: We present a case report of a 53-year old man who was diagnosed with WD at age 14 by liver biopsy and treated with Penicillamine for 4 years at that time. At age 49, behavioral changes were noted and Zinc and Penicillamine were restarted. Two months later he experienced imbalance and falls. Examination showed nystagmus, mild upper motor neuron left sided weakness and ataxic gait. Brain MRI demonstrated T2 and FLAIR hyperintense areas bilaterally in pons, midbrain and putamen. Three months after initiation of Penicillamine, examination showed severe parkinsonism, quadruparesis and bulbar signs. He required PEG tube and was bed ridden. Brain MRI revealed an increase of T2 hyperintensities at the striatum bilaterally, midbrain and pons. Penicillamine was discontinued and Trientene and Zinc sulfate were started. Due to minimal improvement 300 mg of levodopa was initiated two months later and shortly thereafter increased to 450 mg daily. Within 4 months he showed dramatic improvement in parkinsonism followed by near normalization of gait and speech. Repeat brain MRI showed significant reduction of T2 hyperintensities.

Conclusions: A severe case of Wilson's disease showed dramatic improvement in parkinsonism after initiation of carbidopa/ levodopa. In the past, this medication was shown to be ineffective in WD most likely because substantia nigra was not abnormal in pathological studies. Presynaptic dopaminergic abnormality in the nigrostriatal

pathway, seen in imaging studies, might explain some of our observed benefit in parkinsonism signs.

Tu-149

Zinc-induced copper deficiency in Wilson's disease

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Objective: To describe a case of treatment-induced zinc intoxication in a patient with Wilson's disease.

Background: Zinc intoxication has been reported in cases of therapeutic overdose for skin conditions, of coin ingestion and of chronic use of denture cream. Toxicity of zinc is due to copper deficiency, the former interfering with the intestinal absorption of copper, and it is responsible for hematologic abnormalities: acquired myelodysplasia with ringed sideroblasts. Neurological complications such as myelopathy and peripheral neuropathy have also been reported. No case of renal involvement has yet been published.

Methods: Case report.

Results: A 41-year-old patient had been treated by zinc-sulfate monotherapy for Wilson's disease for 10 years by 880 mg zinc-sulfate daily, and recently 1000mg/day. He presented with a distal tetraparesis and hypoesthesia progressing for several months. Electroneuromyography confirmed a severe, axonal and predominantly motor polyneuropathy. He developed anaemia with neutropenia. Bone marrow aspirates showed ringed sideroblasts and vacuolisation of hematopoietic precursors. He had severe yet asymptomatic albuminuria (8,300mg/24h) due to glomerulosclerosis with segmental hyalinosis. Urinary zinc excretion was 200 times the normal upper limit. Serum and urinary copper levels and ceruloplasmine were low. Liver biopsy showed copper depletion. Zinc treatment was interrupted, hematopoietic abnormalities normalized within a month, albuminuria decreased by 10 times within 3 months. Peripheral neuropathy, however, remained unchanged at the 6 months follow-up visit.

Conclusions: This is the first reported case of zinc intoxication due to therapy for Wilson's disease. Chronic zinc overdose, in fact, resulted in the paradoxical situation of acquired copper deficiency in a genetic condition of copper overload. Besides typical and reversible hematologic abnormalities, the patient had a massive albuminuria that improved dramatically after zinc discontinuation. The underlying glomerulonephropathy appears to be a yet unreported feature of zinc toxicity. The patient is receiving no treatment for his Wilson's disease and he is followed by repeated clinical and laboratory controls. Improvement of his motor neuropathy might occur by axonal regrowth. A chelating agent will be considered, as soon as evidence of copper re-accumulation appears.

Tu-150

L-dopa therapy increases the homocysteine concentrations in the cerebrospinal fluid from patients with Parkinson's disease

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Objective: To investigate the effect of L-DOPA therapy on homocysteine (HC) in patient with Parkinson's disease (PD), the concentrations of total HC and methionine (Met) in cerebrospinal fluid were compared between 18 untreated PD patients and was compared 16 controls.

Background: Late years with PD, a report homozygous genetic polymorphism of MTHFR in an elderl soldier, revealed elevated plasma HC levels in PD (T/T) that we significantly have many models is proved, and suggest the possibility that (T/T) is one of the genetic risk factor for PD.

Methods: Subjects were 18 untreated patients with PD (M/F, 8/10) and controls (M/F, 10/6), mean age Mean (± SD) age was 64.6+9.4 years for patients and 65.7+9.2 years for contraols. PD patients were administered L-DOPA/dopa-decarboxylase inhibitor (DCI) at mean dose of 358±72.5 (300mg/day, n =12; 450 mg/day, n = 6) for 8 weeks. The concentration of HC in CSF for PD patients was measured by high-performance liquid chromatography (HPLC) using electrochemical detector. Control subjects were neurologically normal patients who underwent lumbar spinal anesthesia for minor surgery. We used UK Brain Bank diagnostic criteria were used to define PD[2] Severity of the disease was assessed based on the Hohen & Yahr scale.

Results: Concentrations of total HC in patients were significantly higher following L-DOPA therapy than in untreated PD patients and controls. Conversely, Concentrations of total Met in PD patients were significantly lower after L-DOPA therapy than before L-DOPA therapy.

Conclusions: These results using cerebrospinal fluid sampled from living PD patients suggested that L-DOPA therapy, particularly high-dose L-DOPA for the treatment PD, may enhance intracranial methylation and elevate concentration of total homocysteine.

Tu-151

Effect of levodopa on heart rate variability in Parkinson's disease

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Objective: To assess the immediate effect of one dose of standard Levodopa (LD) on the Heart Rate Variability (HRV) in patients with Parkinson's disease (PD).

Background: Cardiac autonomic dysfunction has been reported after chronic LD treatment, and also in untreated PD. However, little is known about the immediate effects of LD on HRV.

Methods: Eleven patients of idiopathic PD (M:F=9:2, mean age=57.3±8.56 yrs, duration of illness=3.8±2.7 yrs, mean H&Ystage=2.1±0.2) on stable LD dosage, were recruited for the study. Motor part of UPDRS and resting Lead II ECG recordings were performed at baseline (12 hrs off medication) and after 2 tablets of 100/10 mg of standard Levodopa/ carbidopa. ECG was recorded continuously in the first hour (H1) followed by a 15 min recording in second (H2), third (H3) and fourth (H4) hours. An artifact free 5 min segment of the ECG in these time frames were analyzed offline to obtain the HRV parameters in Time Domain (TD) and Frequency Domain (FD). Repeated measures of ANOVA was used to ascertain the changes at the different time points.

Results: The mean motor UPDRS was 37.6±2.0 at baseline, which improved significantly to 22.6±2.1 ($p<0.001$) in the H1. The average heart rate reduced significantly in the H1 to 69.6±2.9 from a baseline of 76.8±3.1 ($p<0.01$). The improvement in the TD and FD parameters of HRV was maximal in the H1 and gradually diminished by the H4. Among the TD parameters (ms), the SDNN was 23.5±2.7 and increased significantly to 42.9±6.0 ($p<0.01$) in the H1. RMSSD increased from 16.3±2.9 to 31.5±6.5 in H1 ($p<0.01$). The NN50 increased significantly from 9.4±5.9 to 39.6±13.8 ($p<0.01$) and pNN50 increased from 2.5±1.5 to 12.6±4.7 ($p<0.05$) in the H1. Among the FD parameters (ms2), the Total Power (TP) increased significantly from 568.9±125.7 to 1961.9±478.1 ($p<0.01$) and the High Frequency Power (HF) increased from 107.4±33.9 to 454.5±157.4 ($p<0.05$) in the H1.

Conclusions: There was a transient improvement in the HRV after LD administration with peak effects in the 1st hour. Improvement was observed in SDNN and TP, which are estimates of the overall HRV and RMSSD, NN50, pNN50 and HF which are considered the best predictors of parasympathetic activity. The results are suggestive of a possible modulation of HRV by Levodopa, which may benefit the patients.

Tu-152

Valvular heart regurgitation and pergolide in Parkinson's disease: Follow-up of an observational study

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Objective: to heart valve characteristics changes during pergolide therapy in Parkinson's disease (PD).

Background: Heart valve disease (HVD) has been associated with pergolide, an ergot-derived dopamine receptor agonist used to treat PD. Studies investigating heart valve characteristics prospectively during pergolide therapy are lacking. We recently reported the results of a transversal study conducted at the Pitié-Salpétrière hospital showing a dose-dependent increased risk of HVD in PD patients treated with pergolide (Corvol et al. Arch neurol 2007). We report here the results of heart valve characteristics assessed by a second echocardiography performed during the follow-up of this cohort.

Methods: The initial cohort included 86 PD patients treated with pergolide, recruited between April 2005 and August 2006. Patients had a standardized echocardiography at baseline. A second echocardiography was performed 6-12 months after baseline. The neurologist was free to modify Antiparkinsonian therapy, including pergolide, between the two exams.

Results: Among the 86 patients of the initial cohort, 55 patients had a second echocardiography 10 +/- 3 months after baseline (23 patients lost of follow-up). Thirty patients stopped pergolide whereas 25 patients were still on pergolide. Patients who stopped pergolide had higher systolic pulomonary arterial pressure (36 +/- 7 versus 32 +/- 5 mmHg, p = 0.004) and more moderate to severe valve regurgitations (15/25 versus 0/30, p = 0.05) on the baseline echocardiography. On the second echocardiography, moderate to severe regurgitation improved in 4 patients in the pergolide withdrawal group whereas moderate to severe regurgitations occurred in 3 patients still on pergolide. Systolic pulmonary arterial pressure decreased in patients who stopped pergolide (-2.3+/- 9.1 mmHg) and increased in patients who continued pergolide (+3.2 +/- 4.7 mmHg, p = 0.02).

Conclusions: Increased pulmonary arterial pressure and heart valve regurgitation association with pergolide therapy was confirmed in this prospective echocardiogarphic study. Heart valve abnormalities may improve after pergolide withdrawal.

Tu-153

Treatment with oral iron chelation in a case of neurodegeneration with brain accumulation

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Objective: To assess the possibility of reducing brain iron accumulation with an oral iron chelator in neurodegeneration with brain iron accumulation (NBIA), and to evaluate its clinical efficiency and safety.

Background: NBIA describes a group of progressive extrapyramidal disorders characterized by brain iron overload, including mutations in the PANK2 or PLA2G6 genes, aceruleoplasminemia and neuroferritinopathy. Oral chelator have recently been used in few reported cases of neurological diseases of iron metabolism.

Methods: A 52-years-old woman who presented an idiopathic NBIA (no mutation in PANK2 or L-ferritine genes) was treated with oral iron chelation (deferiprone: 20 mg/kg bid). At the onset (47 years-old) primary clinical features included dysarthria and oro-facial dystonia. She developed a progressive cerebellar ataxia, an asymmetric dysmetria and a moderate parkinsonism. Brain MRI showed iron accumulation in the basal ganglia. We closely monitored the patient for adverse effects and efficiency, with monthly blood counts, clinical scales and repeated MRI scans. We used the mean relaxation time on the T2* (R2*) 1.5 T MRI sequence for the whole of the dentate nuclei, red nuclei and locus niger to estimate regional iron accumulation.

Results: After 10 months of therapy, iron chelator caused no apparent neurologic or hematologic side effects. Scores of ataxia scales gradually improved of 30-40%. Dysarthria and gait disorders decreased. Examination showed less marked reduction in parkinsonism. Analysis of T2* changes in MRI after 3 months of treatment revealed an increase of iron accumulation in the 3 regions of interest. After 7 months of treatment, iron accumulation decreased in dentate nuclei and left red nucleus compared with treatment onset and was unchanged in locus niger and right red nucleus compared with analysis after 3 months of deferiprone administration.

Conclusions: Oral iron chelation may be a reasonable therapeutic alternative in patients with NBIA. Long term deferiprone treatment could be efficient. T2* MRI measurements provide some objective clues to survey treatment with iron chelator.

Tu-154

Pore-forming iron-induced alpha-synuclein oligomers – A target for developing compounds against pathological protein aggregation

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Objective: To develop and characterize an *in vitro* assay for the evaluation of possible anti-aggregatory agents that inhibit pathological alpha-synuclein aggregation.

Background: Several neurodegenerative diseases including Parkinson's disease (PD) are characterized by the formation of fibrillar protein aggregates of alpha-synuclein such as Lewy bodies. Increasing evidence implicates alpha-synuclein oligomers as the principal toxic aggregate species in the neurodegenerative process. Furthermore, studies of brain tissue and epidemiologic data implicate iron ions in the disease progression in PD.

Methods: Using three independent single particle-based methods we analyzed aggregation pathways and oligomer formation of alpha-synuclein. Biophysical and structural characterization was performed by confocal single molecule fluorescence techniques and atomic force microscopy. Functional characterization included single pore electrophysiology in a lipid bilayer set-up.

Results: We characterized two different oligomer species. Organic solvents were used to trigger aggregation, which resulted in small oligomers. Under these conditions, Fe^{3+}- ions at low micromolar concentrations dramatically increased aggregation and induced formation of larger oligomers, whereas Fe^{2+}-ions failed to enhance aggregation. Notably, Fe^{3+}-induced oligomers were SDS-resistant and on-pathway to amyloid fibrils. In contrast to monomers and intermediate I oligomers, only Fe^{3+}-induced aggregates were able to bind to unilamelar lipid vesicles composed of palmitoyl-oleoyl-phosphatidylcholine. In regard to toxicity, functional characterization of these aggregates with single pore electrophysiology revealed the generation of ion-permeable membrane pores. Deferoxamine was able to dissolve the aggregates formed in presence of Fe^{3+}. Interestingly, Deferoxamine has also been reported to show positive effects in animal models of PD. Based on these results, we developed a high-throughput confocal single-particle alpha-synuclein aggregation assay and identified N'-benzylidene-benzohydrazide (NBB) derivates inhibiting oligomer formation.

Conclusions: Our results shed light on the role and biochemical properties of iron-induced toxic oligomers in neurodegenerative diseases and provide new approaches for drug-development.

We-151

The HMG-CoA reductase inhibitor simvastatin reduces severity of L-dopa-induced abnormal involuntary movements in the MPTP-macaque model of Parkinson's disease

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Objective: We aim at developing an Anti-Dyskinetic Therapy.

Background: Chronic L-3,4-dihydroxyphenylalanine (L-dopa) treatment of Parkinson's disease (PD) often leads to debilitating involuntary movements, termed L-dopa-induced dyskinesia (LID), about which the rodent analog, the abnormal involuntary movements (AIMs), has consistently been associated with an activation of the Ras-Extracellular signal-Regulated Kinase 1/2 (ERK 1/2) mitogen-activated protein kinase signalling pathway. Previous studies have shown that statins, specific inhibitors of the rate-limiting enzyme in

cholesterol biosynthesis, can also inhibit Ras isoprenylation and activity and subsequently the phosphorylation of ERK1/2.

Methods: We hypothesized and showed that statin treatment commenced prior L-dopa exposure reduces AIM incidence and severity in the 6-hydroxydopamine (6-OHDA) rat model of PD by secondarily preventing the L-dopa/Benserazide-induced increase in pERK1 levels (Schuster et al. J Neurosci 2008). We here confirm in a non-human primate model of PD and LID that simvastatin dose-dependently reduces LID.

Results: Simvastatin was preferred to other statins for its better brain penetrance. The simvastatin-L-dopa-treated MPTP macaques (n=6) displayed less severe dyskinesia without compromising the therapeutic efficacy of L-dopa upon parkinsonian symptoms.

Conclusions: Those results strongly suggest that simvastatin might represent a treatment option for managing LID in PD.

We-152

EFF0311, an antiparkinson full D_1 dopamine agonist with longer duration and possible functional selectivity

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Objective: To discover a full dopamine D_1 agonist with intermediate duration of action that would cause profound antiparkinson effects without inducing rapid tolerance, seizures, or profound hypotension.

Background: Dopamine activates both D_1- and D_2-like receptors, yet D_2 activation has been accepted as the mechanism mediating antiparkinson effects of levodopa. Since our demonstration in 1991 of profound antiparkinson effects of the first full D_1 agonist dihydrexidine, all full D_1 agonists have been shown to be effective against MPTP-induced parkinsonism, and one (ABT-431) was equieffective to levodopa in humans. Yet dihydrexidine and all subsequent D_1 agonists have failed to reach the clinic. One primary limitation has been pharmacokinetic, with most drugs having ultrashort durations of actions. A few that did not have either caused seizures or rapid tolerance.

Methods: Compounds were tested for affinity in both cell lines expressing cloned human dopamine receptors and in rat striatal tissue. Affinity was also evaluated at a wide battery of non-dopamine receptors. Functional profile was then assessed using a battery of cellular and subcellular functional assays. Finally, compounds were tested in normal rats and in rats with unilateral 6-OHDA lesions.

Results: A promising lead compound EFF0311 was found to have nanomolar affinity for the both the D_1 and D_5 receptors, yet was more D_1 selective (vs. D_2, D_3, or D_4 receptors) than its parent compound dihydrexidine. EFF0311 was a full D_1 agonist at adenylate cyclase activation, but differed from other D_1 agonists in other functional properties. Unexpectedly, EFF0311 had a duration of action in rats of 8-10 hr, versus 1-2 hr for its parent dihydrexidine or other catechols like apomorphine.

Conclusions: The full D_1 agonism of EFF0311 suggests it will have profound antiparkinson effects in primates. If the intermediate duration of action in rats is replicated in humans, then EFF0311 has the potential to avoid rapid tolerance seen with long acting compounds like A77636, or the hypotension often resulting from short-acting compounds. If EFF0311 is a functionally selective D_1 agonist, it may avoid the seizures caused by many drugs of this class. Such a drug would be effective monotherapy in any stage of PD, and could avoid induction of dyskinesias or seizures.

We-153

Overexpression of cannabinoid CB2 reecptors results in decreased behavioral and neurochemical vulnerability to intracaudate administration of 6-hydroxydopamine

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Objective: The purpose of this study was to evaluate the role of the CB2 receptor in the motor and non-motor responses induced by intracaudate administration of 6-hydroxydopamine (6-OHDA). To this aim, 6-OHDA (12μg/4μl) or its vehicle was injected under stereotaxic surgery in two sites of the caudate-putamen of transgenic mice overexpressing the CB2 receptor (CB2xP) developed in our laboratory), CB2r knockout (CB2ko) and Swiss albino mice (WT).

Methods: Motor impairment (contralateral rotations induced by apomorphine), emotional behaviors (light dark box) and cognitive alterations (step down inhibitory avoidance) were evaluated at various times between 2-7 weeks after surgery. In addition, 7 weeks after the administration of 6-OHDA mice were anesthetized, perfused and brains were sliced at 40 μm using a vibratome. Tyrosine hydroxylase (TH) was examined by immunocytochemistry.

Results: CB2xP-lesioned mice presented significantly less motor deterioration than WT-or CB2 ko-lesioned mice at 2, 4 and 6 weeks. In contrast, the 6-OHDA lesion in CB2ko showed significantly higher motor deterioration (increased contralateral rotations induced by apomorphine) than WT mice at 4 and 6 weeks. The administration of 6-OHDA resulted in anxiogenic-like behaviors in CB2xP and WT at 3 weeks. The basal anxiogenic-like behavior of Cb2ko mice was not altered by the administration of 6-OHDA. The assessment of cognitive behaviors 7 weeks after the lesion, revealed impairment in short term memory (1 and 3 hours) in CB2xP- and WT-lesioned mice and in long-term memory (24 hours) in CB2ko- and CB2xP-lesioned group. The immunocytochemical analyses of tyrosine hydroxylase TH) in the substantia nigra (SN) and caudate-putamen (CPu) revealed significant lower lesion in CB2xP than in WT and significantly higher loss of TH immunoreactivity in CB2ko than in WT mice.

Conclusions: Taken together, these results showed that increased expression of CB2r results in decreased vulnerability for motor impairment and TH immunoreactivity in SN and CPu after intracaudate administration of 6-OHDA.

We-154

The partial dopamine agonist and full serotonin ($5\text{-}HT)_{1A}$ agonist pardoprunox (SLV308) has antidepressant and anxiolytic-like properties in rats, a detailed pharmacological evaluation

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Objective: The aim of the present studies was to assess the effects of the partial dopamine agonist and full $serotonin_{1A}$ receptor agonist (pDSA) pardoprunox (SLV308) in the social interaction (SI) and forced swim test (FST) paradigms, which are preclinical screening models for anxiolytic and antidepressant drugs, respectively. Additionally, experiments were conducted to assess the role of $5\text{-}HT_{1A}$ and DA $D_{2/3}$ receptors in mediating the pharmacological actions of pardoprunox.

Background: Parkinson's disease is commonly associated with the comorbid expression of anxiety and depression which might even be of clinical relevence prior to the expression of motor symptoms. Therefore, we examined the effects of the acute administration of the novel antiparkinsonian pDSA pardoprunox (SLV308) in animal models of anxiety and depression using naive, adult, male Sprague-Dawley rats.

Methods: In preliminary studies, the effects of pardoprunox were assessed alone in the SI (0, 0.01, 0.03, 0.1 or 0.3 mg/kg po) or FST (0, 0.1, 0.3, 1 or 3 mg/kg po). Thereafter, the effects of pardoprunox were assessed alone (0.01 mg/kg for SI and 0.3 mg/kg for FST) and in combined pretreatment with the DA D_2 antagonist L741,626 (0, 0.3, 1, 3 mg/kg ip), the D_3 antagonist SB-277011A (SB; 0, 5,10 and 20 mg/kg ip) or the silent $5\text{-}HT_{1A}$ receptor antagonist WAY100635 (0, 0.1, 0.3 and 1 mg/kg ip).

Results: Pardoprunox had antidepressant effects in the FST (minimal effective dose, MED, 0.3 mg/kg) and SI tests (all doses tested). The pardoprunox-induced increase (0.01mg/kg) in SI was significantly attenuated by WAY100635 (0.1, 0.3 or 1 mg/kg; 100% antagonism), SB-277011A (5, 10 or 20 mg/kg; 7-8%), while the effects of the D_2 antagonist on the pardoprunox-increase in SI were difficult to

interpret due to an effect of L741,626 alone. The pardoprunox increase in swimming and decrease in immobility in the FST was significantly antagonized by WAY-100635 and SB-277011A.

Conclusions: These data demonstrate that the pDSA pardoprunox has significant antidepressant and anxiolytic-like properties and, for the first time, that these effects are mediated by interactions with 5-HT_{1A} receptors and partly D_3 receptors.

We-155

An environmental xenobiotic compound realise an neuroprotective effect against neurodegeneration of dopaminergic neurons from striatum nigra

A.G. Mititelu (London, United Kingdom)

Objective: the objective of the present study are represented by the increased redox activity of some components of cigarette smoke tar into animal models of Parkinson"s Disease. By inhibition of free radicals, produced during the oxidative stress, highly increased in regions of striatum nigra especially. Also the new compound might extert antiapoptotic properties which had been discussed recently as part of patophysiology process in Parkinson"s Disease.

Background: it is almost a certainty, not just an "confounding" result from clinico-epidemiological but also pharmacological numerous studies. Cigarette tar is an "incredible" chemical factory of more than 1500 chemical components.among these there is one compound-MEP-Melanin Exogenous Polymer studied extensivelly in the last decade. he has a very unstable structure,Hydroquinone and Semiquinone, and acts as real scavenger for free radicals and oxidative reactions produced by various metals-Zn,Fe,Al.

Methods: The present study had been realised using experiemntal methods but also clinico-epidemiological retrospective data from previous research. It had been used the classical animal models of Parkinson's Disease which had been treated previously with MPTP until the appearance of clinical simptoms resembling Parkinson's disease. Subsequently, the experimental models had been treated with specific compounds containing MEP. In our attempts to elucidate the negative association between Parkinson's Disease and smoking, we realise a massive thematical research.

Results: The results of the research experiments and also the database from actual literature on this area reflects the great scavenger properties, basically the redox activities of MEP. Also the experiments showed that the rate of neuronal distruction in the animal models exposed to MEP had been lower(35%) comparing with the percentage of those models unexposed to MEP.

Conclusions: The previous research together with increasing accumulating evidence in favour of some neuroprotective action from cigarette smoke towards the neurodegenerative process from substantia nigra, might reveal a new therapeutic perspective regarding the neurochemical process which underlies the destruction of dopaminergic neurons from striatum nigra. The new therapeutic action is not determined by nicotine but from different compounds of tar.

We-156

A metanalysis of neutralizing antibody conversion following a specific formulation of botulinum toxin type A (BoNTA, Allergan, Inc): An analysis of large clinical trials across five indications

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Objective: To determine the rate of neutralizing antibody (nAb) formation with botulinum toxin type A (BoNTA) across five different indications.

Background: It is important to evaluate the incidence of nAb conversion with BoNTs across indications and routes of administration. Allergan has an extensive clinical database to study immunogenicity.

Methods: This was a pooled analysis of the immunogenicity of BoNTA (Allergan) based on 16 controlled or open label trials across five studied indications (axillary hyperhidrosis, HH; glabellar lines, GL; focal post-stroke spasticity, PSS; cervical dystonia, CD; neurogenic overactive bladder, nOAB). All studies were company sponsored (Allergan/GSK) and used the current formulation of BoNTA. Some trials were designed to evaluate immunogenicity; others were safety and efficacy studies that included immunogenicity assessments. Trial durations varied from 4 months to ≥2 years. Serum samples were analyzed for nAbs using the Mouse Protection Assay (MPA). Subjects who had a negative MPA result at baseline and at least one analyzable post-baseline MPA result were included in this analysis.

Results: Subjects received 1 to 15 treatments (mean 3.8 treatments) with BoNTA at total doses per treatment cycle of 50 or 75 U per axilla in HH, 10 or 20 U in GL, 200-400 U in PSS, 20-500 U in CD, and 200 or 300 U in nOAB (mean dose across indications: 115 U). The numbers (%) of subjects who converted from an MPA negative result at baseline to an MPA positive result at any post-treatment time point were as follows: HH 4/871 (0.46%), GL 2/718 (0.28%), PSS 1/317 (0.32%), CD 4/312 (1.28%), and nOAB 0/22 (0%). Across all indications, 11/2240 subjects (0.49%) converted from MPA negative at baseline to MPA positive at 1 or more post-treatment time points. However, at study exit, 4 were MPA positive (0 GL; 2 HH, 1 CD, 1 PSS).

Conclusions: Based on this metanalysis of an extensive clinical trial database, the incidence of nAb conversion with a specific formulation of BoNTA (Allergan) though variable across indications, was consistently low at <0.5%, and not sustained in some patients.

Th-151

Resveratrol, a polyphenol found in red wine, protects against rotenone-induced apoptosis through autophagy induction

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Objective: To examine the neuroprotective effects of resveratrol on rotenone-induced apoptosis in SH-SY5Y cells.

Background: Resveratrol, an antioxidant polyphenol found in red wine, has been reported to increase the expression of mammalian Sir2 deacetylase (SIRT1). The fact that SIRT1 inhibits stress-induced apoptosis and that SIRT1 is an important autophagy regulator led us to hypothesize that resveratrol may enhance autophagy through SIRT1 and prevent neuronal death related to accumulation of aggregated/misfolded proteins, such as in Parkinson's disease (PD). Rotenone, an inhibitor of mitochondrial complex I, induces neuronal death accompanied by inhibition of proteasome activity, which, in turn, leads to an increase in aggregated/misfolded proteins associated with the pathogenesis of PD. Here, the neuroprotective effects of resveratrol on rotenone-induced injury were examined in SH-SY5Y cells.

Methods: The cells were treated with resveratrol at various concentrations for different time periods, or exposed to rotenone with or without resveratrol pretreatment. Protein levels of SIRT1, LC3, a marker of autophagy, or PARP, a marker of apoptosis, were determined by Westernblot. The induction of autophagy was verified by electron microscopy. The cells were then transfected with *SIRT1* siRNA or *Atg5* siRNA followed by addition of rotenone with or without resveratrol and the poptosis was determined by Westernblot.

Results: SIRT1 and LC3-II/I ratio were increased by resveratrol treatment indicating induction of autophagy. Electron microscopy analysis confirmed active autophagy in cells treated with resveratrol. Suppression of *SIRT1* gene blocked induction of autophagy by resveratrol. Reveratrol pretreatment attenuated the apoptosis and accumulation of aggregated proteins caused by rotenone. The neuroprotective effect of resveratrol on rotenone-induced apoptosis was partially blocked when *SIRT1* or *Atg5* gene was suppressed.

Conclusions: In addition to the induction of SIRT1, autophagy induction by resveratrol plays an important role in protecting against rotenone-induced apoptosis, which may lead to a novel therapeutic approach to neurodegenerative disorders associated with aggregation

of misfolded proteins. Further studies, including *in vivo* experiments, are needed to confirm the role of resveratrol as a putative neuroprotective agent.

Th-152

Influence of tempo-rhythmic correction of gait method on expenses for pharmacological treatment of Parkinson's disease

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Objective: To investigate if the use of tempo-rhythmic correction of gait(TRCG) decreases Drug treatment(DT) expences.

Background: The drug treatment of Parkinson's disease (PD) is high in costs. We have numerously presented fragments of our research concerning gait restoration, using TRCG method (in addition to DT), which improved gait parameters.

Methods: Experience group (EG): 30patients (64,7±6,3years) stage 3,0 PD, without significant motor fluctuations and dyskinesia, receiving TRCG and DT. Control group(CG): 30patients (63,9±7,3years) stage3,0 PD, without significant motor fluctuations and dyskinesia, receiving medications only. Medication dose was corrected during first 3weeks in both groups, later therapy remained constant (6 month), after that, if necessary, dose was corrected by "blind" doctor. At 3 weeks and 6,5 month (after drug dose adjustment) points, we have investigated an average daily dose of L-DOPHA (Madopar, sometimes Nacom) and monthly expenses for it, and, as some treatments were combined, expenses on dopamine receptors agonists (Pramipexol and Piribedil), amantadin, cholinergic antagonist, MAO- and COMT- inhibititors. The clinical impression of doctor and subjective impression of patients was the criterion of adequacy of medical regimen and drug doses.

Results: At the point of 3 weeks, the average L-DOPHA dose in EG was 529,3±154,9 mg per day, which cost 312,23 rur for person per month, total costs 1083,94 rur for person per month. In CG 551,7±127,7 mg per day, which cost 343,84 rur for person per month, total costs 1061,98 rur for person per month. Therefore, at this time, treatment expenses were similar in both groups. At the point of 6,5 month, the average L-DOPHA dose in EG was 526,7±169,5 mg per day, which cost 321,38 rur for person per month, total costs 1211,25 rur for person per month. In CG 678,3±133,0mg per day, which cost 321,38 rur for person per month, total costs 1626,02 rur for person per month. This shows, that CG uses higher doses of L-DOPHA and has 33% greater total treatment costs than EG.

Conclusions: We relate the described effect to 3 factors: DT has low effect on gait disorders, which sometimes causes unreasonable dose increase in hope for greater effect; it is possible, that physical activity increases L-DOPHA absorption efficiency; positive psychological effect on patient is also important.

Th-153

The use of dopamine agonists (DAGs) in "de novo" Parkinson's disease patients (PDpts) first diagnosed after 70years old

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Objective: To review the use of DAGs in patients diagnosed with PD after 70 year old considering their therapeutic effect and side effects profile.

Background: The use of DAGs as the primary treatment for newly diagnosed PD has been cosidered a promising strategy supported by 5 randomized controlled studies (bromocirptine, pergolide, ropinirole, cabergoline and pramipexole). Those studies showed that using first DAGs and then LD when needed, delays the occurance of dyskinesias and probably also motor fluctuations. However this was at cost of less control of motor symptomatology. By the other hand considering that psychosis and orthostatism are side effects frequently reported using DAGS, it become quite common to avoid its use in old PDpts.

Methods: In the present study we reviewed the clinical data collected during the last 8 years in our Movement Disorder Clinic in which we treated 19 "de novo" PDpts over 70 (mean age 75; 15 male,Yahr stage II:5; III:7; IV: 7; 6 demented DSM IV criteria) who received DAGS (as first drug in 2 and as a second drug in 17). Mean LD dose 560 mg ± 270 mg; mean pergolide dose (after conversion 2.1 mg (± 1.4 mg) (Pergolide 12;Ropinirole 5; Bromocriptine 2).

Results: Mean follow-up recorded 4.7 years (± 3.5). Three of them were lost for follow up. The reason patients were added DAGs to LD was lack of enough benefit. The combined treatment timproved their motor performance as reported by patients and their caregivers. Side effects: Six PDpts did not report side effects. during the observation period. Ten of them (62%) developed psychosis with frightening hallucinations and paranoidal delusions. Three of them (18.7%) reported ankle edema. Three (18.7 %) of them reported orthostatism and 4 (25%)developed dyskinesias of limbs (25%). Six of them received clozapine to treat the psychosi with good results (mean dose 12.5 mg).

Conclusions: Although there is a tendency to try aged PDpts exclusively with LD our experience showed that old PDpts may benefit of DAGs addition when necessary if carefully monitored. Clozapine in those patients is also a useful additive.

Th-154

A placebo-controlled study of the efficacy of botulinum toxin A in the treatment of nocturnal leg cramps

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Objective: This placebo controlled study was designed to the test the efficacy and safety of botulinum toxin type A in the treatment of nocturnal leg cramps (NLC).

Background: NLC, usually involving the calf muscles are common and troublesome in older people. Although NLC are generally a benign, transient problem, they can cause considerable distress for patients. Management can be difficult, and there has been considerable controversy about the safety and efficacy of medications, including quinidine and vitamin E. The pathophysiology of muscle cramps is still unclear, but mechanisms that may contribute to motor unit hyperactivity include spinal inhibition, abnormal terminal motor nerve excitability, and enhanced muscle contraction propagation through cross activation of adjacent neurons. Pain may occur as a result of accumulation of metabolites or possibly as a result of focal ischemia. Botulinum toxin A (BTX-A) can suppress motor unit hyperactivity and muscle contraction propagation, is analgesic, and has muscle relaxation effects.

Methods: Subjects (n=48) were recruited at the Jeonbuk National University Hospital in Korea, from April, 2006, to October, 2008, who reported at least six cramps per month. Of these 48 patients, 20 were excluded by exclusion criteria (12) or patient refusal (8). The 28 remaining subjects completed the study. Half of the patients received a BTX-A (Dysport 100 U/1mL) injection (1 mL) in one calf once a month for 3 months, and the other half received saline (9%) injections. Outcome measures were recorded in subject diaries: 1) Number of cramps, 2) Number of nights with cramps, 3) Severity of cramps, and 4) sleep disturbance. The data were analyzed with Mann-Whitney U test using SPSS ver 11.

Results: BTX-A treatment significantly reduced the number of cramps, numbers of nights with cramps, sleep disturbance score, and severity score.

Conclusions: BTX-A can successfully reduce the frequency and severity of NLC and decrease sleep disturbances induced by NLC.

Th-155

Does dopaminergic drugs induce a place preference in normal rat?

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Objective: The potential rewarding effect of different selective dopaminergic agonists (DA) for D1, D2, D3 receptors and Levodopa

will be assess by the conditioned place preference (CPP) test in normal rats.

Background: Hedonistic homeostatic dysregulation (HHD) is a behavioral disorder that was initially described in association with addiction and substance misuse. It is presented as spiraling cycles of misregulation of the brain reward systems, increasing progressively and resulting in compulsive drug use and loss of control over drug taking. In Parkinson's disease (PD), the equivalent of HHD is called dopamine dysregulation syndrome (DDS). It is defined by severe dopamine addiction to dopaminergic replacement therapy (DRT) and behavioral disorders such as hypersexuality, pathological gambling, compulsive buying, and psychopathological states. The high consumption of DRT could be linked to the motor improvement or could be induced by the powerfull addictive capacity of these molecules. Our hypothesis is repeated dopaminergic drugs administration in intact rats induce a place preference

Methods: The CPP test has been widely used to study the rewarding effects of various drugs. Drug induced CPP is based upon the principle that when a primary reinforcer is paired with contextual stimuli can acquire secondary reinforcing properties. These, which are presumably established due to a Pavlovian contingency, are thought to be able to elicit an operant approach response or place preference. To highlight the rewarding effects of DA and levodopa in the control rat, CPP test will be performed on 8 rats per drug and per dose. Drugs tested are R(+)-SKF-81 297 (selective D1 receptors agonists; 1.0, 3.0 and 10.0 mg/kg), Bromocriptine (selective D2 receptors agonists; 0.1, 1.0 and 10.0 mg/kg), (+)-PD 128 907 (selective D3 receptors agonists; 0.3, 1.0 and 3.0 mg/kg) and Levodopa (50, 100 and 200 mg/kg).

Results: Only 3mg/kg of SKF-81297, 1.0mg/kg of Bromocriptine and 1.0mg/kg of PD 128 907 produced a significant place preference but none dose of levodopa conduced a significant result in normal rats.

Conclusions: These results obtained with dopamine agonists and levodopa seem to corroborate our hypothesis. The next step will be to study the impact of these molecules on rat model of PD.

Th-156

Botulinum toxin type A injection as a novel treatment for kinetic tremors associated with FXTAS

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Objective: To examine the efficacy of botulinum toxin type A (BTA) in reducing arm and jaw tremors in a patient with Fragile X-associated tremor/ataxia syndrome (FXTAS).

Background: Patients with FXTAS suffer from intention and kinetic tremor, cerebellar and sensory ataxia, cognitive impairment and parkinsonism. Despite rigorous clinical testing, no effective therapeutic agents for FXTAS have been approved thus far. Symptoms of FXTAS are currently being managed on a case-by-case basis. While earlier studies have shown the clinical value of BTA in managing various neurologic conditions, including tremors, its utility in treating tremors associated with FXTAS has yet to be clinically tested. Here, we present a FXTAS patient with disabling tremor being treated with BTA injections for the first time.

Methods: After obtaining signed informed consent, a patient with FXTAS was injected with BTA for his hand and jaw tremors. A total of 150 units of BTA in a 1:2 dilution with normal saline were delivered under EMG guidance to both the arms (130U) and face (20U). The muscles targeted for injection were selected based on clinical examination and EMG signals. A detailed injection protocol will be presented with video segments for pre- and post-injection evaluations.

Results: A 70-year-old man presents with profound arm and hand tremors, rigidity of the upper extremities, and spasms involving the masseter and temporalis muscles. His tremors, however, have been most disabling and quite resistant to anti-Parkinson medications (e.g. Amantadine), significantly affecting his daily activities. Following BTA treatment, his hand and jaw tremors were markedly reduced, allowing him to carry out daily activities without assistance. The patient did not endure any side effects immediately after the injections, except for some mild, transient local pain. To date the patient reports no treatment-emerging side effects.

Conclusions: Successful treatment with BTA in our patient suggests that effective doses of the neurotoxin can significantly reduce tremors related to FXTAS with minor or no side effects. While further studies utilizing controlled conditions are certainly warranted, our study provides preliminary evidence that BTA injection may serve as a minimally invasive treatment for kinetic tremors arising from FXTAS, and thereby improve the quality of life for these patients.

NON-MOTOR ASPECTS OF MOVEMENT DISORDERS (NOT PD): DYSAUTONOMIA

Mo-155

Gustatory sweating presenting as autonomic manifestation of Parkinson's disease

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Objective: To describe focal hyperhidrosis (gustatory sweating) in a patient with Parkinson's disease(PD).

Background: Gustatory sweating is a rare disorder of focal hyperhidrosis at the face, forehead and neck in response to salivation or anticipation of food. It is typically associated with parotid lesions, and thought to be secondary to missprouting of cholinergic secretomotor fibers. Gustatory sweating can also accompany diabetes mellitus. Sweating abnormalities are common in Parkinson's disease, affecting up to two thirds of patients. Focal hyperhidrosis is especially common, typically affecting the face, head, and trunk. However, to our knowledge, gustatory sweating has not been reported in Parkinson's disease.

Methods: Retrospective chart review at a tertiary movement disorders clinic revealed one patient with gustatory sweating.

Results: The patient is a 74 year old male with a history of idiopathic Parkinson's disease, diagnosed approximately six years ago. He did not have history of parotid or facial nerve lesions or diabetes mellitus. Patient reported profuse, bothersome sweating in the nape of the neck while eating. This was so profuse that he had to use towels to control the moisture, and his wife had to change the towels several times during each meal. He also had significant drooling while eating. Patient was injected with botulinum toxin type B to the salivary glands and subcutaneous tissues at the nape of the neck. He has reported significant benefit in his symptoms, with near-complete resolution of both sialorrhea and gustatory sweating.

Conclusions: Autonomic symptoms in PD are thought to be secondary to autonomic ganglia involvement by Lewy bodies causing generalized dysautonomia. Focal dysautonomia, presenting as focal gustatory sweating, may imply more localized pathology involving the autonomic ganglia. Hyperhidrosis can cause discomfort and embarrassment, especially in social situations. Botulinum toxin may be helpful for both sialorrhea and gustatory sweating. Further studies are needed to evaluate why there may be selective involvement of certain autonomic ganglia in some patients with PD.

Tu-155

Pseudo-spinal cord transection as the initial manifestation of multiple system atrophy

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Objective: We report a case of MSA presenting with symptoms suggestive of spinal cord transection three years before onset of motor symptoms.

Background: Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder presenting with parkinsonism, cerebellar ataxia and autonomic failure in any combination. Characteristic autonomic symptoms include urinary disturbance, orthostatic hypotension, hypohidrosis, and obstipation. **Patient history:** This 57 year-old male patient presented with episodes of heaviness of limbs and sensory loss below T10 bilaterally when standing up. Spinal cord pathology was suspected, but excluded by MRI. Three years later, severe orthostatic hypotension was first noted with a fall of blood pressure by 40/22 systolic/diastolic mmHg with recurrent syncope. Further autonomic symptoms included impotence and urinary urgency. Again, several years later action tremor of the right upper limb and a slight rigidity right upper limb emerged. Four years after onset of sensory disturbance, the patient suffered from gait unsteadiness, urge incontinence, dysphagia, and anhidrosis bilaterally below T4.

Methods: On neurological examination 3 years after onset of spinal cord symptoms, the patient presented with ataxic tandem gait, ataxic finger nose test, mild bradykinesia and rigidity of the right arm, and positive Babinski sign of the right side. Cognition was intact (MMSE 30). Brain MRI showed abnormalities consistent with MSA including atrophy of the middle cerebellar peduncle and pons. DAT SPECT and IBZM SPECT were both pathological.

Results: This patient with probable MSA-C presented with postural spinal cord transection presumably as a result of undiagnosed orthostatic hypotension which became obvious only several years later when classical features such as syncope developed.

Conclusions: The spectrum of orthostatic hypotension due to MSA associated autonomic failure is broader than commonly recognized. Symptoms generally arize from postural hypoperfusion of target organs such as brain (syncope), muscle (coat hanger ache, lumbal pain), and kidney (oliguria). Similar to other rare examples in the literature our patient adds pseudo-spinal cord transection to the list of possible manifestations.

NON-MOTOR ASPECTS OF MOVEMENT DISORDERS (NOT PD): BEHAVIOR

Mo-156

Sexual Health in Parkinson's disease

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Objective: To describe and evaluate the sexual health of patients with Parkinson's disease following deep brain stimulation (DBS) of the subthalamic nucleus (STN).

Background: The changes in sexual health of patients with Parkinson's disease must be a concern to the clinicians. The effects of functional cirurgy in sexual health of Parkinson's patients are still a matter of debate.

Methods: Patients with Parkinson's disease bilaterally implanted for DBS of STN and those only pharmacologically treated, will be evaluated. Sexual functioning will be assessed using the international erectile function indices (IEFI) and the female sexual function indices (FSFI). Depression and anxiety will be evaluated using the Beck depression inventory and the brief symptom inventory.

Results: We have a control group with 23 normal volunteers matched for sex and age, a group with 19 Parkinson patients only pharmacologically treated, and a group with 20 Parkinson's patients bilaterally implanted for DBS of STN. Mean age was 61,3 years (SD 10,27), 90,3% were married and 70,0% have four years of school. The three groups have BSI scores higher than 64,8. Control group have higher somatization index ($p<0,05$), only pharmacologically treated group have higher somatization and phobic anxiety indices ($p<0,05$), cirurgy group have higher obsessive-compulsive, phobic anxiety, and psychoticism index ($p<0,05$). BDI score was 20,23 in cirurgy group ($p<0,001$). IEFI have was lowest in cirurgy group (26,3; $p<0,05$). The pharmacologically treated group have a higher orgasm score (15,7; $p<0,05$). FSFI was higher in the cirurgy group (44,0; $p<0,05$).

Conclusions: The sexual function of Parkinson patients is globally impaired. When submitted to cirurgy women suffer an improvement and men impairment. Patients submitted to functional cirurgy have a different psychopathological profile. These should take in to account in the follow up of these patients.

Mo-157

Executive functions evaluation in patients with neurological form of Wilson's disease – according to performance of Tower of London, Wisconsin Card Sorting Test and General Health Questionnaire 28

G. Chabik (Warsaw, Poland)

Objective: The aim of this study was to explore the executive function disturbances as a consequence of prefronto-subcortical loops disturbances in Wilson's disease patients.

Background: Wilson's disease (WD), is an autosomal, recessive disorder of copper metabolism. It leads to accumulation of copper mainly in liver and CNS, but also in other organs such as kidneys and skin. Most common clinical symptoms of WD is liver malfunctioning and neurological as well as neuropsychiatric disturbances. Neurological symptoms include mainly tremor, rigidity, dystonia, ataxia, and speech or gait abnormalities. Among patients with neurological symptoms also multiple neuropsychiatric/neuropsychological disturbances may coexist, such as mood, emotional and social behavior or/and executive functioning abnormalities – resembling those seen in a frontal demage. These two groups of symptoms have the same pathogenesis as they are caused mostly by disturbances of basal ganglia (BG) and their loops with frontal and prefrontal areas. The neuroanatomical basis of the existence of prefrontal symptoms in BG lesions is widely known since publication of Alexander & colleagues in 1986, in which connections of frontal motor and prefrontal areas with certain BG structures forming jointly fronto-subcortical loops were described. Different loops are responsible for different aspects of human behavior. This explains why typical frontal syndrome's features may be often present along with BG structures pathology.

Methods: 25 WD patients presenting neurological signs with BG lesions revealed in MRI were examined, in comparison to 25 healthy controls, by "classic" executive function measures such as TOL and WCST as well as with GHQ 28 – a mood, social and emotional disturbance measure.

Results: The results revealed significantly poorer performance of executive functions tasks as well as existence of profound mood, emotional and social behavior abnormalities among WD patients.

Conclusions: This is presumably the first evaluation of the executive function disturbances measured according to performance of TOL and WSCT in WD patients. Obtained data imply therefore that BG lesions seen in WD, may result in symptoms typical to prefrontal areas pathology.

Mo-158

Effects of continuos application of L-dopa/carbidopa gel on psychiatric symptoms in advanced Parkinson's disease (PD)

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Objective: A prospective non-controlled study of the effect of continuous dopaminergic stimulation (CDS), with L-dopa/Carbidopa duodenal infusion on psychiatric symptoms in patients with advanced Parkinson's disease (PD).

Background: During the last decade the non-motor and not least the psychiatric symptoms in PD have come more in focus. Depression

is often an early symptom and is found in about 35% of PD patients. The cumulative prevalence of psychotic symptoms such as hallucinations is up to 75%. The value of CDS, as achieved with continuous infusion of L-dopa/Carbidopa gel, regarding motor fluctuations is well established. There is so far limited information on the effect of CDS vs. pulsative dopaminergic stimulation regarding psychiatric symptoms.

Methods: Nine patients with advanced idiopathic Parkinson's disease were included in a prospective non-controlled study on the effect of L-dopa duodenal infusion on psychiatric symptomatology. The patients were followed for a minimum of 6 months. The following scales were used: PDQ-39, BDI, MADRS, Neuropsychiatric Inventory (NPI), Modified Minnesota Impulsive Disorder Interview (MIDI), MMSE, UPDRS.

Results: There was an improvement in several psychiatric parameters. Regarding depression mean BDI value was reduced from 15 to 9.6, the mean MADRS score was reduced from 19 to 9.3. We also noticed an improvement of anxiety and hallucinations/psychotic symptomatology in several of the domains (as reflected in NPI). Hypersexuality was improved in the only patient exhibiting such symptoms. Further we noticed an improvement of the health-related quality of life, measured with PDQ-39.

Conclusions: These experiences reflect that cds might have advantages not only for motor but also for psychiatric symptoms when treating advanced PD.

Tu-156

Probable Fahr's disease presenting as bipolar disorder

R.P. Gandhy, K.K. Appleby, B.S. Appleby, L.B. Bahroo, F.L. Pagan (Washington, District of Columbia)

Objective: Presentation of psychiatric symptoms in the setting of probable Fahr's disease.

Background: Fahr's disease, is a progressive illness characterized by bilateral calcifications in the basal ganglia. Clinical manifestations of parkinsonism, dystonia, paresis and speech impairment. About 40% of patients with Fahr's Disease can have primary cognitive and other psychiatric symptoms such as impulsivity, obsessive compulsive behavior, mood disorders, and personality changes.

Methods: A case report with relevant literature review.

Results: A 41year old female with 5 years of worsening mood swings, cognitive difficulty, impulsivity and distractibility was recently diagnosed with bipolar disorder and started on lithium, buproprion, lamotrigine. Pertinent neurological findings include executive dysfunction, impaired attention, mild cogwheel rigidity. (BSA – please input psych eval) Head CT shows dense bilateral calcifications in globus pallidus, head of the caudate, and anterior thalamus suggestive of Fahr's disease. Brain MRI demonstrated two punctuate 3mm T1 hypointense signals adjacent to the bilateral frontal horns extending along the corpus callosum.

Conclusions: This case of a patient with basal ganglia calcification, significant frontal lobe dysfunction, mild parkinsonian signs and bipolar disorder highlights the role of basal ganglia circuitry in frontal and limbic functions. Fahr's disease and co-existent bipolar disorder is rare. Only three cases studies have been documented with bipolar disorder and Fahr's disease. Studies have shown bipolar disorder has abnormalities in the orbitofrontal cortex and anterior cingulate. Unique in this case was the initial presentation of psychiatric features likely associated with the calcifications disrupting the frontal pathways and the limbic system.

Tu-157

Regulation of movement energetic costs is impaired in presymptomatic Huntington's disease (pHD) and in the early stages Parkinson's disease (PD)

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Objective: To determine whether movement energetic regulation is impaired in basal ganglia disorders.

Background: The energetic cost of a movement is highly correlated with its duration and depends on the task demands: energetic expenditure is reduced when target occurrence is predictable and anticipation possible; when time must be saved, as in reaction time tasks, energetic costs are higher (Moisello, 2008). Basal ganglia are likely involved in energy cost regulation.

Methods: 14 normal subjects (age: 28-70 years); 16 subjects with PD (stage 1-2, tested 12h without medications, age: 40-70 years); 11 subjects with pHD (CAG repeats>40; age: 30-62 years) made movements to targets appearing in synchrony with a tone, performing two tasks: RAN: A reaction time task with targets presented in random, unpredictable order; instructions were to move as soon as possible, minimizing reaction time but avoiding target anticipation. CCW: A timed-response task with targets appearing in predictable counterclockwise order; instructions were to reach targets in synchrony with the tone, anticipating their occurrence. We previously found that RAN has higher energetic costs (shorter movement time (MT), higher velocity and acceleration) than CCW.

Results: MT and spatial accuracy were higher in CCW than in RAN in all the groups ($p<0.05$). However, although the patient groups showed minimal or no motor symptoms, compared to controls, movements were faster in pHD with shorter MT and higher spatial error; and were slower in PD, with longer MT and higher accuracy. The difference between CCW and RAN MT was narrower in PD (69 ms) and pHD (64 ms) compared to controls (101 ms). However, in pHD, MT were skewed toward higher energy costs (combined CCW/RAN mean: 322 ms), while in PD, MT were skewed toward energy-saving costs (397 ms) compared to normal subjects (349 ms). In PD, these abnormalities correlated with UPDRS scores ($r=0.6$, $p=0.02$).

Conclusions: Energy regulation abnormalities are part of a general impairment in trajectory formation in both PD and pHD. Thus, basal ganglia are involved in the regulation of movement energetic expenditures. However, the several cortico-striato-cortical loops nust play different roles in such a regulation.

Tu-158

Progressive supranuclear palsy impairs emotion recognition

B.C.P. Ghosh, A.J. Calder, P. Peers, A.D. Lawrence, J. Hodges, J.M. Rowe (Cambridge, United Kingdom)

Objective: To establish whether patients with progressive supranuclear palsy (PSP) have normal emotion recognition.

Background: PSP is an akinetic, rigid syndrome with supranuclear gaze palsy. Patients also have difficulties with social interactions. This may be due to verbal or physical disability, but may also reflect abnormal cognition. Other diseases with phenotypic or pathological overlap with PSP, eg. Parkinson's disease or fronto-temporal dementia, are associated with emotion recognition deficits. PSP impairs recognition of facial emotions (Ghosh et al. in press). However, that result could be due to poor emotion recognition or impaired perception. We therefore tested emotion recognition in 2 modalities, in a new cohort.

Methods: 19 patients with probable/possible PSP and 22 matched controls were tested on 2 forced-choice emotion recognition tests. First, using morphed photographs of an actor showing varying degrees of 6 basic emotions: happy; angry; sad; surprise; disgust and fear. Second, listening to 'burst' vocalisations by actors, representing the same emotions and neutral. Control tests of face perception and hearing (250-4000Hz) were used.

Results: There was a group difference in facial emotion recognition. ANOVA showed a main effect for group($F(1,38)=39$,$p<0.001$), and a group x emotion interaction($F(4,147)=7$,$p<0.001$), ie. patients with PSP were poor at detecting facial emotions. There was no difference between patients and controls in face perception (group($F(1,38)=3$,ns), testxgroup interaction($F(2,69)=3$,ns)). A difference was also seen in the vocal emotion test, which showed a main effect for group($F(1,39)=30$,$p<0.001$), and an emotionxgroup interaction

(F(4,170)=3,p=0.01), ie. patients had a general deficit in vocal emotion recognition. There was no difference between groups in hearing thresholds (group (F<1), frequencyxgroup interaction (F(3,133) =2,ns)).

Conclusions: Patients with PSP have difficulty recognising emotions. We have replicated and extended previous findings, showing a deficit in recognising facial and vocal emotions. The presence of emotion recognition deficits in two modalities and normal control task function in patients suggests that this deficit is not the result of perceptual problems. We suggest that PSP pathology affects the emotion recognition system and that this deficit is important for management of patients and carers in the clinic.

Tu-159

Contributors to naming impairment in corticobasal syndrome

R. Goldmann Gross, D.J. Libon, P. Moore, M. Grossman (Philadelphia, Pennsylvania)

Objective: To identify contributors to naming difficulty in corticobasal syndrome (CBS).

Background: CBS is an extrapyramidal condition associated with prominent cognitive impairment. Naming difficulty is widely recognized in CBS, but the basis for this deficit remains uninvestigated.

Methods: Sixty-eight CBS patients (mean age=67.0 years, education=14.4 years, disease duration=3.6 years) completed a picture naming task (Boston Naming Test (BNT)). Other language measures (category naming fluency, word and picture portions of the Pyramids and Palm Trees (PPT) test of semantic memory), executive tasks (letter fluency, reverse digit span), and visuospatial/visuoperceptual tests (estimating the location of dots in space, identifying objects shown from an unusual view, and copying a geometric design) were performed. Stepwise regression analyses were performed separately for each cognitive domain (i.e., language, executive, and visuospatial/visuoperceptual) using BNT as the dependent variable. The variables surviving each analysis were included in a final stepwise regression model to identify those most predictive of BNT performance. For 10 CBS patients, we correlated BNT performance with cortical atrophy as identified by MRI voxel-based morphometry.

Results: Mean BNT score among CBS patients was 75% correct (Z=-3.0, p<0.005). Variables surviving the domain-specific regression analyses were PPT-pictures (r^2=0.70; p<0.001), letter fluency (r^2=0.13; p<0.01), and both geometric design copy and unusual views (r^2=0.59; p<0.05). Using these independent variables, the final stepwise regression model showed that geometric design copy and PPT-pictures predicted BNT performance (r^2=0.70; p<0.01). BNT performance correlated with right inferior parietal atrophy (Brodmann area 40; FDR-corrected p<0.05).

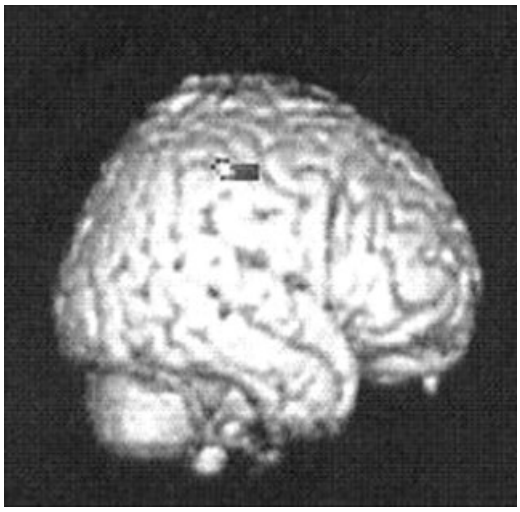

FIG. 1 (Tu-159). Correlation between cortical atrophy and BNT performance in CBS.

Table 1 (Tu-159). Coordinates for the correlation between cortical atrophy and BNT performance

Anatomic locus	Z-score	p-value (FDR-corrected)	Talairach coordinates (X,Y,Z)
R inferior parietal (40)	3.80	0.022	59,−29,46

Conclusions: Picture naming is significantly impaired in a group of CBS patients, many of whom are not aphasic clinically. Geometric design copy and PPT-pictures explain 70% of the variance in CBS naming performance. These tasks both require integration of visual material into a coherent picture. We suggest that impaired integration of visual information, related to right parietal disease, contributes to picture naming difficulty in CBS. Naming difficulty in these patients cannot be entirely attributed to language deficits.

We-158

Limitations of traditional screening tools to detect depression in Parkinson's disease

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Objective: To report on subjects with Parkinson's disease (PD) who endorsed depression during screening for a research study, yet failed to meet criteria for depression when rated with the Hamilton depression rating scale (HAM-D).

Background: Depression is a frequent co-morbid disorder in patients with PD, affecting up to 40% of such patients. Screening tools to detect depression include items three (depressed mood) and four (motivation and initiative) of the Unified Parkinson's Disease Rating Scale (UPDRS) and rating scales such as the HAM-D. Studies have suggested that the clinical characteristics of depression in patients with PD differ from depressed patients without PD. Given this, scales such as the HAM-D, which were designed for patients without PD, may not be as useful to screen for depression in patients with PD.

Methods: Our institution is conducting a randomized, double-blind placebo controlled study treating depression in PD patients with either s-adenosyl-l-methionine, (SAM-E), escitalopram, or placebo. Among 212 subjects referred to the study, 53 appeared to meet clinical criteria for PD and depression in the pre-screening process and were then formally screened for depression using the HAM-D.

Results: Of the 53 subjects screened for the study, 23 either withdrew consent or met one of the study's exclusion criteria. Of these 23 subjects, 10 (43%) were excluded for having a sub-threshold score on the HAM-D. All subjects, except one, also had a sub-threshold score on item three of the UPDRS.

Conclusions: Our experience suggests that traditional scales of depression, such as the HAM-D, may not be adequate to fully capture the spectrum of depressive symptoms in patients with PD. Our subjects regarded themselves as suffering from depression such that they were willing to enter a study of investigational medicines to treat depression. Yet, based on a standard measure of depression, these subjects were not rated as depressed. This further supports the contention that the phenotype of depression in PD patients differs from those in depressed patients without PD. It suggests that alternate measurements may be needed to fully characterize depression in patients with PD.

We-159

Cognitive impairment in essential tremor without dementia

J.-S. Kim, I.-U. Song, Y.-S. Shim, K.-S. Lee, Y.-D. Kim, H.-T. Kim (Seoul, Korea)

Objective: To evaluate cognitive functions in patients with essential tremor (ET), without dementia.

Background: Several clinical studies have demonstrated that patients with ET may have cognitive deficits; however, the results of detailed neuropsychological assessment in ET without dementia have not been reported.

Methods: Thirty-four consecutive patients with ET and the 33 age-matched controls who underwent a dementia screening questionnaire and detailed neuropsychological investigation were included and analyzed.

Results: There were severe impairments observed in most domains, including attention, a part of language function, verbal memory, and frontal executive functions in the ET group compared to the controls.

Conclusions: Our results support the finding that the subclinical cognitive deficits characterized by attention, verbal memory impairments and executive dysfunction may be a clinical feature of ET. In addition, our results can be taken to support the finding that age at examination and educational status were the most important risk factor associated with cognitive deficits in patients with ET as with other types of dementia.

We-160

Anxiety and depression in children with Tourette syndrome versus epilepsy – Impact on quality of life, a comparative study

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Objective: To compare anxiety and depression in children with Tourette syndrome versus children with epilepsy; assess quality of life.

Background: Reports suggest that comorbid anxiety and depression can be more problematic for children with Tourette syndrome and epilepsy than the severity of the tics or seizures; this impacts quality of life. Tourette syndrome characterized by the presence of motor and vocal tics is often accompanied by comorbid symptoms including obsessive-compulsive disorder, attention deficit hyperactivity disorder, sleep disturbances and depression. Psychosocial issues predominate in both patients with TS and EP. Assessment was conducted to identify and compare the the prevalence of anxiety and depression among children with Tourette syndrome and epilepsy, attending specific summer camps for one week. Although both conditions have different symptoms and rates of mood disorders, the condition was predicted to have a similar impact on quality of life.

Methods: Twenty-nine children with TS and 59 with EP were ages 8-16 years completed the Multidimensional Anxiety Scale for Children(MASC) and Child Depression Index(CDI). Children with TS and EP were rated for severity using disorder-specific scales of Yale_Brown Obsessive Compulsive Scale(YBOC),Tic Severity Scale (TSS) or Seizure Activity Scales measuring seizure frequency and types. The two groups were compared using analysis of variance (ANOVA).

Results: Higher rates of anxiety and depression were found in the two groups compared to age matched general population. Rates of anxiety and depression were 28% and 34% respectively in TS and 19% and 23% respectively in EP. No significant difference in scores between the two groups on the CDI or on the MASC domains were noted. Tic severity with co-morbidity of OCD in TS did not appear to affect anxiety or depression, nor did severity of seizures in EP. Anxiety and depression affects pediatric quality of life score (PedsQL).

Conclusions: Despite different clinical symptom-presentations, utilizing severity rating(s), our findings suggest that children with Tourette syndrome and children with epilepsy have high rates of anxiety and depression, impacting quality of life. Less commonly reported in childhood compared to adults, statistical differences may be discerned in this population.

We-161

The effects of expiratory muscle strength training (EMST) on the velar function in a patient with velopharyngeal incompetency

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Objective: To assess the outcome of Expiratory Muscle Strength Training (EMST) to functionally improve velopharyngeal closure in a patient with velopharyngeal incompetency (VPI) using maximum expiratory pressure (MEP) generated at the mouth.

Background: VPI, a common sequalae of many movement disorders, refers to the failure to achieve complete velopharyngeal closure due to reduced velar muscle strength. EMST is a rehabilitative program that is both intensive and physiologically specific, targeting the expiratory muscle group. Increased strength of the expiratory muscles improves MEP generated at the mouth. Changes in intraoral pressure are known to induce contraction of the levator veli palatini, the main muscle of velar elevation (Kuehn & Moon, 1994).

Methods: A 24 year old male with VPI was followed for 38 weeks while undergoing EMST. Weekly measurements (2 pretreatment and 38 during) of MEP were recorded, and later compared, in two conditions; nostrils closed and nostrils open. MEP improvements in the nostrils closed condition reflect strength increases in the expiratory muscles, while such improvements in the nostrils open condition reflect better closure of the velopharyngeal port. EMST is an intesive, home-based rehabilitation program which uses a pressure-threshold device that provides a consistent pressure load on expiration. The load is 75% of a person's ability to generate MEP. Participants must overcome a threshold load by generating an expiratory pressure sufficient to open the expiratory spring-loaded valve. If the participant does not generate the threshold pressure, the valve remains closed.

Results: Improvement of MEP in the nostrils closed condition was 131.6% (mean pretreatment = 88.9, post-treatment =205.8 cm H_2O). On the other hand, improvements of MEP in the nostrils open condition was 163.8% (mean pretreatment = 42.2, post-treatment = 187.8).

Conclusions: Data suggest that EMST improves the functional closure of the velopharyngeal port in patients with VPI. A full-scale investigation is warranted. Investigations of the effects this improved closure may have on speech and swallowing should also be considered.

Th-157

Alcohol pad application as a provocative test in diagnosing psychogenic movement disorders

K.H. Nawaz, V. Abbott, M.S. Siddiqui (Winston-Salem, North Carolina)

Objective: To evaluate the utility of alcohol pad application (APA) as a provocative bed side test to diagnose psychogenic movement disorders (PMD).

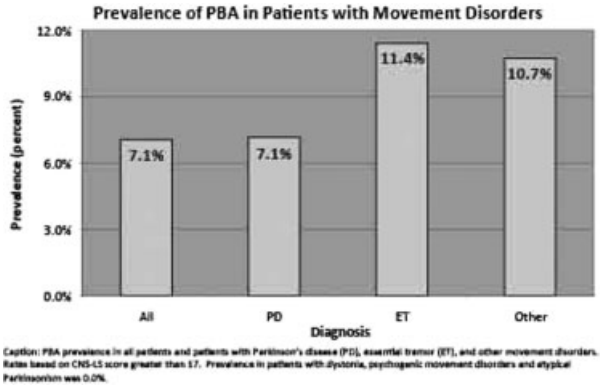
Background: PMD is a diagnostic dilemma that may result in expensive workup and incorrect treatment. Use of provocative tests in diagnosing non-epileptic seizures is widely used with a specificity approaching almost 100%.

Methods: Twenty three patients diagnosed with PMD by a movement disorder specialist, were included in the study. APA on the skin over the neck with videotaping, was used as a provocative test in 18 of these patients. In 5 of the 23 PMD patients APA was superfluous as the PMD was self evident with just verbal suggestion. APA testing followed an explanation that it could provoke their movement disorder and aid in diagnosis. Keeping in mind ethical considerations we

obtained consent and shared the findings with the patients at the conclusion of the testing.

Results: Of the 23 patients, 15 (65.2%) were females and 8 (34.8%) were males. Mean age was 53.8 (SD 14.2) and ranged from 20 to 79 years. Onset of PMD was sudden in 19 (82.6 %) patients while it was gradual or unclear in the rest. Mean duration of illness was 5.2 yrs (SD 6.28). The phenomenology for PMD was varied; tremor 14 (60.9%), nonspecific jerking 5 (21.7%), rocking movements of the trunk 3 (13%); flailing movements of limbs 1 (4.3%) hemi paresis with dystonia 1 (4.3%). Abnormal neurological findings other than PMD were present in 8 (34.8%). A precipitating stressful event could be identified in 10 (43.4%) patients. History of sexual abuse was found in 1(4.3%). Brain imaging was performed in 17 (73.9%) and was either normal or had nonspecific findings. History of depression was present in 8 (34.8%) and mean Beck Depression Inventory (BDI) score was 15.1. Mean PDQ 39 score was 48.6. APA testing was performed in 18 (78.2%) patients. Out of those tested, 13 (72.2%) showed a positive response and 5 (27.8%) showed no response.

Conclusions: Our population resembled a typical group of patients with PMD and APA testing was well tolerated. It established a concrete diagnosis in over 3/4 of the patients. If done in an ethical way, APA can be considered an extension of verbal suggestion and is a useful, cost-effective, bedside provocative test.



Caption: PBA prevalence in all patients and patients with Parkinson's disease (PD), essential tremor (ET), and other movement disorders. Rates based on CNS-LS score greater than 17. Prevalence in patients with dystonia, psychogenic movement disorders and atypical Parkinsonism was 0.0%.

FIG. 1 (Th-158).

Conclusions: PBA is common in patients with movement disorders, with a prevalence of 7.1% in this study. The self-administered CNS-LS questionnaire provides a means of screening these patients for PBA. Patients with PBA tend to have more chronic depressive symptoms, and those on antidepressants had a higher prevalence of PBA.

Th-158

Prevalence of pseudobulbar affect in movement disorders and its relationship with mood symptoms

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(Winston-Salem, North Carolina)

Objective: To calculate the prevalence of pseudobulbar affect (PBA) in movement disorders and study its relationship with mood symptoms using a validated, self-administered instrument, the Center for Neurologic Study-Lability Scale (CNS-LS).

Background: PBA is an affective disinhibition syndrome characterized by sudden, involuntary outbursts of inappropriate crying or laughing that are incongruent with a patient's underlying mood. We had previously reported the prevalence of PBA in patients with movement disorders using an invalidated, self-designed questionnaire.

Methods: We studied 584 consecutive patients presenting to our movement disorder clinic, of which 269 met inclusion criteria (gave consent, age >18 years, formal diagnosis by a movement disorder specialist, and completion of the CNS-LS). Based on previous studies of the CNS-LS in patients with multiple sclerosis, a cutoff score of 17 was used to assess prevalence rates. Additional information including patient demographics, duration of diagnosis, history of deep brain stimulation surgery, previous psychiatric diagnosis, current use of antidepressant medication, Beck Depression Inventory (BDI) score, and Parkinson's disease questionnaire (PDQ-39) emotional well-being subscore were recorded. Logistic regression analysis was used to predict associations with PBA.

Results: PBA was prevalent in 7.1% (n=19) of all patients based on a score of greater than 17 on the CNS-LS. No significant difference in prevalence was observed by patient diagnosis (p=0.587) with rates of 7.1% (12/168) in PD, 11.4% (4/35) in ET, 0% (0/13) in dystonia, 0% (0/16) in psychogenic movement disorders, 0% (0/9) in atypical parkinsonism, and 10.7% (3/28) in patients with other movement disorders. Patients with PBA had higher BDI scores (p<0.002) and PDQ-39 emotional well-being subscores (p<0.002), indicating more depressive symptoms. Patients on antidepressant medications had significantly higher PBA prevalence of 14.9% compared to 3.1% in those not on antidepressants (p<0.002).

Th-159

Mood differences between women diagnosed with psychogenic movement disorders and psychogenic seizures

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Objective: To examine possible differences in mood and psychological factors between women with psychogenic movement disorders (PMD) and psychogenic seizures (PS).

Background: As neurologists become more familiar with the phenomenological spectrum of movement disorders and seizures, they tend to refer to specialty clinics the more atypical conditions, many of which have psychogenic origin. About 5% of individuals treated in movement disorder centers are diagnosed with PMD, whereas 20-30% of patients referred to epilepsy centers for refractory seizures are ultimately diagnosed with PS. The etiopathogenesis of PMD and PS is poorly understood, but both of these conditions occur mostly in women and are frequently associated with mood disorders.

Methods: We examined 16 women with PMD and 17 age-matched women with PS. Diagnoses were based upon Fahn and Williams criteria and video-EEG monitoring in the PMD and PS groups, respectively. Participants completed the Beck Depression Inventory-second edition and the Beck Anxiety Inventory as part of their evaluation.

Results: A significant group difference was found between the PMD and the PS groups for symptoms of depression. The PMD group's symptoms were within the mild range while the PS group experienced a severe level of distress. No significant between group difference was found for anxiety scores. Furthermore, 44% of the PMD sample met criteria for a diagnosis of depression and 81% met criteria for anxiety. In contrast, 94% and 100% of the PS sample met diagnostic criteria for depression and anxiety, respectively. Moreover, only 25% of the PMD sample reported a history of abuse in comparison to 60% of the PS patients.

Conclusions: We found a significant difference between the emotional distress, specifically severity of depression, experienced by patients with PMD versus PS. We hypothesize that the constant physical symptoms expressed by the PMD group function as a coping mechanism for psychological distress, which in turn ameliorates their poor mood. In contrast, the more intermittent episodes experienced by the PS group may be less effective in reducing emotional turmoil. Further examination of psychological similarities and differences,

including dissociation tendencies and locus of control in these psychogenic disorders is warranted.

Th-160

Hemichorea-hemiballism caused by hyperglycemia associated with hypomania in acute stage: A brief report

C.-S. Su, J.-S. Liu, M.-Y. Lan, Y.-Y. Chang (Kaohsiung, Taiwan)

Objective: To analyze the non-motor part changes in patients of hemichorea-hemiballism (HCHB) caused by hyperglycemia.

Background: Hyperglycemic state in patients with type 2 DM has been reported as a major cause of HCHB. Hypomanic symptoms such as irritable, restlessness and insomnia had been mentioned in some by case reports. However, the anatomical localization of mania in this entity is still uncertain, although reports of right hemispheric lesions increased evidently. We reviewed patients of HCHB caused by hyperglycemia and focus on the non-motor part changes.

Methods: We retrospectively reviewed the patients of HCHB caused by hyperglycemia in Kaohsiung Chang Gung Memorial Hospital from November 2000 to October 2007. All the patients received brain magnetic resonance imaging (MRI). Data including age, sex, serum glucose and HbA1c, drugs for the HCHB treatment, the duration of involuntary symptoms, the latency from symptom onset to admission, and the neuroimaging characteristics were analyzed to compare the difference between the patients with and without hypomanic symptoms.

Results: A total of 22 patients were included in our study. Elated mood with more talkative, restlessness, decreased need for sleep or irritability were observed in 5 patients. There were no statistical differences in age, sex and HbA1c between hypomania and non-hypomania group. However, the latency from symptom onset to admission was shorter in hypomania group and all patients with hypomania had right-sided basal ganglia lesions.

Conclusions: Interestingly, hypomanic state were observed in 5 patients with right-sided basal ganglia lesions. Our results support the view that the secondary mania could be related to the right hemispheric lesion. Correspondingly, the striatial damage may disrupt frontal-subcortical circuits and result in mood disorder.

PARKINSON'S DISEASE: BEHAVIORAL DISORDERS

Mo-159

Neuropsychiatric disturbances in parkinsonian patients with and without freezing of gait

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Objective: The aim of this study is to determine the neuropsychiatric disorders in a cohort of parkinsonian patients with and without FOG.

Background: Freezing of gait (FOG) is a common and debilitating symptom in patients with Parkinson's disease (PD). A frontal lobe dysfunction has been proposed to explain the occurrence of FOG. In a previous study we demonstrated that PD patients with FOG scored lower at frontal tests compared with PD patients without FOG.

Methods: 12 PD patients in early stage of disease (H&Y$\leq$2.5) with freezing during on (FOG +) and 14 age-,H&Y score- and disease duration-matched PD patients without freezing (FOG-) have been investigated. All patients have been visited for a clinical and neuropsychiatric assessment. The clinical assessment included UPDRS I-IV, MMSE and FOG-Questionnaire. Psychopathology has been evaluated by means of the Neuropsychiatric Inventory (NPI-10), that has been administered to each patient's caregiver, and the Beck Depression Inventory (BDI), self administered by each patient.

Results: There were no significant differences in MMSE and BDI scores between the two groups. FOG + exhibited worse scores on both UPDRS II and III. Spearman's correlation analysis, using as variables the presence/absence of FOG and each single neuropsychiatric domain score (delusions/NPI-1, hallucinations/NPI-2, agitation/NPI-3, dysphoria/NPI-4, anxiety/NPI-5, euphoria/NPI-6, apathy/NPI-7, disinhibition/NPI-8, irritability/NPI-9, aberrant motor behavior/NPI-10), revealed significant correlations between FOG and apathy (Spearman's correlation= 0,445, $p<0.05$) and between FOG and disinhibition (Spearman's correlation rho=0,459, $p<0.05$). The absence of FOG correlated with anxiety (Spearman's correlation rho=0,453, $p<0.05$). In particular, in the group of FOG+ patients 9/12 (75%) were apathetic and 4/12 (33.3%) were disinhibited whereas in the group without FOG 4/14 (28.6%) patients exhibited pathological scores on apathy domain and none (0%) resulted disinhibited. There was no significant correlation between apathy and disinhibition in the FOG+ group.

Conclusions: FOG correlates with apathy and disinhibition in patients with PD.

Mo-160

Novelty seeking personality traits do not influence the risk of Parkinson's disease

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Objective: To study the association of novelty seeking personality traits with the subsequent risk of parkinsonism and Parkinson's disease (PD).

Background: For nearly a century, it has been suggested the existence of a distinctive "parkinsonian personality". Less novelty seeking, more morally rigid, introverted, punctual, cautious, and conventional personality type has been considered as possibly associated with the risk of Parkinson's disease (PD). The debate on the issue of a "personality at risk" for PD remains still controversial indeed. To confirm that personality traits precede PD onset and are a risk for this condition, prospective researches are required.

Methods: We established a historical cohort of 7,216 subjects who completed the Minnesota Multiphasic Personality Inventory (MMPI) at the Mayo Clinic from 1962 through 1965 for research, and who resided within a 120-mile radius centered in Rochester, MN. A total of 6,822 subjects (94.5%) were followed over four decades either actively (via a direct or proxy telephone interview) or passively (via a population-based records-linkage system, via the Mayo Clinic records archive, or by obtaining death certificates). We examined the association of novelty seeking personality traits measured using 5 MMPI scales (sensation seeking, hypomania, positive emotionality, constraint, and social introversion scales) with the risk of parkinsonism. During follow-up, 227 subjects developed parkinsonism (156 of those developed PD).

Results: Sensation seeking personality trait was not associated with an increased risk of parkinsonism and PD nor did hypomania, positive emotionality, constraint, or social introversion traits.

Conclusions: Our findings suggest that novelty seeking personality traits cannot be considered as risk factors for the later development of parkinsonism or PD.

Mo-161

Piribedil improves apathy, depression and anxiety in Parkinson's disease

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Objective: To study the effect of piribedil, a dopamine agonist drug on parkinsonian apathy.

Background: In PD patients with good motor response to subthalamic nucleus stimulation (STN DBS), dopaminergic treatment can be greatly decreased. This drug withdrawal can unmask parkinsonian

apathy accompanied or not by depression or anxiety. We took advantage of this model of parkinsonian apathy with little motor symptoms to study the effect of piribedil on apathy, mood and anxiety.

Methods: Open study of piribedil in PD patients developing postoperative apathy. Dopamine agonist drugs were arrested after surgery and the L-dopa dose was adapted to motor symptoms. Apathy was evaluated by phone every month using the Starkstein apathy scale (SAS). If patients developed apathy (score ≥ 14 on SAS), they were hospitalized for evaluation in on stimulation/off L-dopa condition, including SAS, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS III) before starting piribedil up to 300 mg/d. Evaluation was repeated 12 months after surgery (T12). Only patients who had at least three months of treatment with piribedil were included. The scores at the time of inclusion (TX) and T12 were compared using Wilcoxon's test.

Results: 12 PD patients (5 women, 7 men, age 56 ± 11 years, duration of disease 11 ± 4 years) were included. Apathy occurred 4.5 months (range 2-7) months after surgery. At that time, the L-dopa dose was 183 ± 166 mg/d, decreased by 79% in comparison with before surgery. At TX and T12, the L-dopa dose and the stimulation parameters were similar. The piribedil dose was 242 ± 85 mg/d at T12. While the motor scores were unchanged between TX and T12, the apathy, depression and anxiety scores significantly improved (table).

Table (Mo-161).

	Tx	T12	p
UPDRS III	18.9 ± 9.4	18.2 ± 10.3	ns
Apathy (SAS score)	20.9 ± 4.1	12.5 ± 5.4	<0.01
Depression (BDI score)	15.8 ± 6.5	9.6 ± 6.6	<0.05
Anxiety (BAI score)	11.3 ± 10.1	5.6 ± 5.4	<0.05

Conclusions: Piribedil improves apathy, depression and anxiety that occur after STN DBS in PD.

Mo-162

Observations on dopamine dysregulation syndrome

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Objective: To describe the characteristics of clinic patients with dopamine dysregulation syndrome.

Background: Dopamine dysregulation syndrome (DDS), formerly called homeostatic hedonistic syndrome, is a rare complication (4%) of dopaminergic therapy. It is seen typically affecting men and young onset Parkinson's disease patients. It is characterized by obsessive compulsive behavior including overmedicating with dopamine agonists and levodopa, increased impulsivity, mood disorder and punding. The neuropsychological symptoms may be due to the altered dopamine neurotransmission in the ventral striatum and the nucleus accumbens leading to maladaptive learning, impulsivity and addiction behaviors. Alterations involving the mesostriatal and mesolimbic regions are demonstrated in PET scans and fMRI studies.

Methods: Case series with literature review.

Results: 14 patients (9 males and 5 females) with an average age at time of symptoms 56 years (range 41 – 75). The average dose of pramipexole in nine patients was 3.1mg, for ropinerole in 5 patients was 12mg and for 2 patients on rotigotine was 6mg. The average dose of levodopa was 500mg. Four patients admitted to taking extra doses of dopamine agonist and 3 patients took extra doses of levodopa. Hypersexuality was seen in 5 patients, 4 had overeating, 3 experienced compulsive gambling and 2 had impulsive spending. 10 out of 14 patients have a prior predilection their behavior.

Conclusions: The pattern of impulsivity seems to be gender based, males developed hypersexuality and gambling while females developed hyperphagia or impulsive spending. Uniquely 35% of the patients were female, previous studies found the condition to predominately affect males. It is likely that dopamine dysregulation syndrome may involve both genders but complaints of hypersexuality and gambling are more easily elicited than hyperphagia and impulsive spending.

Mo-163

Creativity induced by dopamine agonists in Parkinson's disease

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Objective: 1/ to describe creativity as part of a spectrum of behavioural changes induced by dopamine replacement therapy (DRT) in PD and 2/ to show that it is preferentially modulated by dopamine agonists.

Background: PD is characterised by loss of cognitive function such as flexibility, conceptualisation and visuospatial abilities. Creativity results precisely from such cognitive skills. Case studies however show emergence or enhancement of creativity in the course of PD.

Methods: By means of a newly developed behavioural scale for PD, we selected 11 creative (CR), compared to 22 control PD patients (CT) who all underwent STN DBS. CR selection was based on a recent (re)emergence of creativity. Artistic creativity started in 6/11 CR while on DRT. Cognition, behaviours and mood fluctuations were assessed before surgery and one year after.

Results: Baseline characteristics and cognitive efficiency did not differ between groups. While there was no difference in total DRT, when only dopamine agonists are taken into account CR had a larger equivalent dopamine agonist dose (mean (SD) = 402 (71) mg/day) than CT before surgery (mean (SD) = 270 (131) mg/day) ($p = 0.01$). CR had higher scores for mania ($p<0.0001$), hobbyism ($p<0.0001$) and "on" euphoria ($p<0.0001$). They did not differ from CT in gambling, shopping, hypersexuality, irritability or addiction to DRT. Postoperative improvement in UPDRS motor score (52%), stimulations parameters and mean DRT reduction (68.6%) were the same in the two groups. Apathy increased in both groups ($p<0.005$). Only 1/11 CR was still creative after surgery.

Conclusions: We showed that creativity in PD is linked to dopamine agonist therapy. Creativity arises with other modifications belonging to a positive hyperdopaminergic spectrum, but not to impulse control disorders. As shown in other hyperdopaminergic behaviours, creativity disappears after STN surgery, when DRT is (too) drastically reduced.

Mo-164

Prevalence and phenomenology of psychosis in Parkinson's disease patients seen at an academic movement disorders clinic

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Objective: To determine the prevalence and phenomenology of psychosis in Parkinson's disease (PD) patients seen at a tertiary referral academic outpatient movement disorders clinic.

Background: Psychosis is a common and feared complication of PD associated with increased risk of institutionalization and mortality. Understanding the prevalence of psychosis in community based cohorts is critical in designing meaningful trials aimed at addressing this complication.

Methods: A systematic chart review of 782 active PD patients seen at the University of Rochester Movement Disorders Clinic was performed. Patients were assessed for presence of PD psychosis using standard criteria.[1] Demographics were collected on thoe with and without psychosis and compared using 2-sample t-tests. Medication use was collected on patients with psychosis.

Results: Psychosis was present in 166 of the 782 patients assessed (14.8%). The mean time between PD diagnosis to psychosis onset

was 9.2 ± 6.3 years. Patients with psychosis were significantly older (74.2 ± 7.8 vs. 69.8 ± 10.9 years, $p<0.0001$) and had a longer duration of disease (11.1 ± 6.3 vs. 7.1 ± 6.1 years, $p<0.0001$) than those without psychosis. No gender differences were seen. The presence of dementia was noted in 20% of patients with psychosis. Visual hallucinations were most common and seen in 102 patients (86.9%) followed by illusions (n = 17), delusions (n = 6), and presence hallucinations (n = 3.5%). One patient suffered from auditory hallucinations. Most patients were treated with levodopa (99%) followed by dopamine agonists (37%), COMT inhibitors (25%), and MAO inhibitors (19%). Twenty-three percent were on combination therapy with levodopa and a dopamine agonist. Only 11% were taking antipsychotics, most commonly quetiapine (79%), and 9% were taking acetylcholinesterase inhibitors.

Conclusions: Psychosis in a community based cohort of PD patients is common and is associated with older age and longer disease duration. Visual hallucinations are the most common manifestation of psychosis in PD. Further study is warranted on the role of medications and other disease and patient factors associated with this complication. It is likely feasible to perform clinical trials of PD psychosis at academic movement disorders outpatient clinics. 1. Ravina et al. Movement Disorders. 2007; 22:1061-1068.

Mo-165

Retinal thickness and smell identification in early Parkinson's disease

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Objective: To determine if measures of retinal thickness and olfactory function are correlated in early Parkinson's disease.

Background: It has become increasingly recognized that Parkinson's disease (PD) can no longer be considered purely a motor disease, as sensory deficits, most notably visual and olfactory ones, are now known to occur at the time, or even before, its initial clinical presentation. Standardized psychophysical olfactory tests reveal olfactory dysfunction in up to 90% of early-stage PD patients. Electrophysiological studies show that the retina is the most distal site of visual dysfunction in PD and retinal thinning is now known to be present in more than two-thirds of PD patients, as measured by Optical Coherence Tomography (OCT).

Methods: Olfactory function was quantified in 12 early stage PD patients (less than 2.5 H-Y) using the University of Pennsylvania Smell Identification Test (UPSIT). Thickness of the perimacular retina was quantified using a Fourier-Domain OCT by Optovue (Fremont, California). The inner and outer retinal thicknesses were separately quantified using an imaging speed of ~25,000 axial scans/second.

Results: A significant negative correlation was present between UPSIT percentiles and the entire outer layers of the retina in both the superior ($r = -0.589$, $p \leq 0.01$) and inferior ($r = -0.579$, $p \leq 0.01$) hemispheres.

Conclusions: Our data confirm previous results: both the inner and outer perimacular retina are thinned in PD. This preliminary study further suggests a correlation between a quantitative measure of olfactory function and outer retinal thickness in early stage PD. The basis for this association is unknown. It is noteworthy that, unlike the olfactory bulb, it is unknown if the retina is a site of alpha synucleinopathy. Our results suggest the need for larger scale studies to better understand the early pathophysiology of PD.

Mo-166

Neuropsychiatric morbidity in a cohort of Parkinson's disease patients assessed for DBS: A prospective study

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Objective: To study the neuropsychiatric morbidity in a prospective cohort of patients receiving DBS for PD.

Background: DBS is an established intervention for the treatment of PD, essential tremor and dystonia. Since its introduction, concerns have been raised regarding the procedure's possible neuropsychiatric and neuropsychological sequelae. It can be difficult to disentangle the effects of surgery from those of drug treatment and of the underlying disease process or other psychosocial risk factors, especially when pre-operative assessments differ across centres. Impulse control disorders, mood disorders, psychosis and rarely, suicide have all been cited as potential risks.

Methods: In our service, patients receive routine neuropsychiatric assessment prior to a decision being made by the multidisciplinary team regarding surgery. This service has run for 4 years. Assessment included use of the BDI and HADS. Further neuropsychiatric assessment was by semi-structured interview, post operatively or at a similar time interval after initial assessment if they were declined surgery.

Results: We report the first 50 preoperative assessments of patients with PD. 27 had a past psychiatric history (predominantly mood and anxiety disorders). 10 had current mental illness, 6 were depressive disorders. Several others had minor subsyndromal psychopathology. 19 were not offered surgery. 30 have now had a DBS procedure: 27 STN, 2 VIM, 1 GPi. Preliminary results of these 30 followed up at variable time points suggest most patients selected for surgery show improvement or resolution of psychopathology. 4 patients without identified preoperative risk factors have significant persistent psychiatric morbidity postoperatively.

Conclusions: Collecting prospective data on neuropsychiatric comorbidity in pre and post surgical patients with PD is important. Comparison of outcome between patients selected for surgery and those deemed inappropriate for surgery may be informative. Preliminary results suggest that in appropriately selected patients, significant post-operative psychiatric morbidity may still affect 10% of patients. Ongoing assessment and management of these problems should be part of the comprehensive aftercare of this population.

Mo-167

Development of a standardised postsurgical assessment of neuropsychiatric comorbidity in DBS patients

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Objective: 1. To design a standard tool for the assessment of neuropsychiatric morbidity in patients offered deep brain stimulation (DBS) for the treatment of Parkinson s disease (PD) and other movement disorders. 2. To pilot this tool for ease of use and acceptability.

Background: Data exists on the incidence and possible risk factors for the development of neuropsychiatric side effects with DBS. However, some patients with these risk factors never develop them while those without them occasionally do. Furthermore, no uniform method of preoperative assessment exists nor is it clear what level of postoperative surveillance is optimal.

Methods: We used the most consistently reported neuropsychiatric side effects and experience from our own clinic to design a semi-structured interview tool. This was trialled in 10 postoperative patients, which informed its further development.

Results: 1) Preoperative Interview: A 15-item semi-structured interview tool was designed. This has been trialled preoperatively in 12 consecutive patients as part of a detailed assessment, including neuropsychology, to assess the ease of use and tolerability of this tool. All patients, carers and the clinician found the interview tool acceptable. 2) Postoperative Interview: An 18-item semi-structured interview was designed. Items denoting satisfaction with surgery and ease of the interview itself were also included. Of 20 consecutive patients, 16 were contactable. All patients, carers and the clinician found the questionnaire acceptable. The interview took 10.9 minutes on average. 3 patients rated items as significant concerns and were offered a prompt clinic appointment for full psychiatric assessment.

One of these had suffered an impulse control disorder preoperatively (pathological gambling).

Conclusions: The tool is acceptable and easy to use. The routine use of such an interview tool could facilitate detection of psychiatric morbidity in surgical patients. Further studies are needed to establish the validity and reliability of the tool in order to standardise the assessment. By using the same tool to guide clinical assessments in both preoperative screening and postoperative surveillance, it is hoped that the natural history of this group of patients can be better understood.

Mo-168

Disturbed behavioral function and enhanced sensitivity for psychoactive drugs in the rat 6-hydroxydopamine Parkinson model

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Objective: We here characterized rats with bilateral 6-hydroxydopamine (6-OHDA) lesions in behavioral paradigms for cognitive function and motivation. Additionally, after injection of apomorphine and dizocilpine (MK801) rats were tested for enhanced sensitivity for drug-induced hyperlocomotion and deficient prepulse inhibition (PPI) of the acoustic startle response, an indicator of sensorimotor gating that is disturbed in certain neuropsychiatric conditions.

Background: In Parkinson's disease (PD), the progressive loss of dopamine (DA) neurons in the substantia nigra leads to disturbed motor function, but cognitive and psychiatric disturbances are increasingly recognized as disabling factors. Rats with 6-OHDA induced lesions show significant motor impairment reminiscent of PD, and recent studies also indicate cognitive impairment in this model.

Methods: Retrograde degeneration of the rat nigrostriatal DA system was induced by bilateral striatal injection of 6-OHDA (11 µg in 3 µl PBS), sham-lesioned rats (controls) received vehicle. Three weeks after injection rats were tested for learning and memory (spatial continuous alternation T-maze task) and for motivation (progressive ratio test, breakpoint of 5 min inactivity in the Skinner box). Thereafter, rats were tested for PPI and locomotor activity after injection of the DA-receptor agonist apomorphine (0, 1, 2 mg/kg) and the NMDA-receptor antagonist dizocilpine (MK801; 0, 0.07, and 0.15 mg/kg).

Results: Rats with 6-OHDA lesions made more errors during continuous alternation, indicating disturbed learning and memory. Additionally, the breakpoint was reduced, indicating disturbed motivation. The apomorphine and MK801 induced PPI-deficit was stronger in lesioned rats compared to controls, indicating enhanced sensitivity for psychoactive drugs, while the drug effect on locomotor activity was similar in both groups.

Conclusions: We conclude that rats with bilateral 6-OHDA lesions may be used to investigate the biological basis of cognitive and psychiatric disturbances in PD, and to develop and test new therapeutic strategies for these symptoms ranging from pharmacological treatment to neurosurgical intervention.

Mo-169

Artistic productivity and Parkinson's disease

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Objective: To assess creative thinking in non-demented PD patients by the Torrance test (TTCT) (Torrance Test of Creative Thinking, 1974).

Background: Increased artistic productivity has been reported in PD. Analogously behaviours involving creativity have been described in the context of fronto-temporal-dementia. Because PD patients produce large amount of artist work in a compulsive matter (R.H. Walker 2006) there may be a relationship with impulsivity or frontal lobe involvement.

Methods: We investigated 38 PD patients (27 men; age 64±9; education 10±4 years; disease duration 10±6; MMSE >24) and 40 healthy controls (16 men; age 64±9; education 12±5 yrs). TTCT evaluates creative factors, namely flexibility, fluidity, originality and elaboration. PD patients were categorized as creative (N=10) or non-creative (N=28) based on patient history. We did not include establish artists. All PD patients were on stable therapy with levodopa and dopamine agonist for at least four weeks.

Results: There were differences between creative and non-creative PD in the Torrance component for fluidity (30,8 vs 19,2; p 0.001) and elaboration activity (71,8 vs 33,5; p 0.001) but not for flexibility and originality. Non-creative PD results lower compared to control subjects but no differences in creative<-PD and control. Impulsivity (BIS), frontal lobe function (FAB), Raven and Token test, total levodopa equivalents dose did not differ.

Conclusions: Increased artistic drive in PD is underlined by excessive production without relevant frontal lobe defects, possibly linked to dopaminergic medication exposure.

Mo-170

Deep brain stimulation and eating disordrers

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Objective: To evaluate effects of deep brain stimulation on eating disorders in patients with Parkinson's disease.

Background: In recent years, several authors have highlighted the possible impact of deep brain stimulation (DBS) in parkinsonian patients on hypersexuality, pathological gambling or drug addiction, sometimes in a context of thymic variations. Very little data exist regarding eating disorders occurring after this surgery.

Methods: We observed a cohort of 150 patients followed prospectively before and after DBS surgery.

Results: We report the case of 6 parkinsonian patients, having atypical eating disorders associated with weight gain, 3 women and 3 men (57 years old +/- 1.9) with an Parkinson's disease duration for 10 years. Each oh the patient has psychiatric antecedents (anxio-depressive syndromes, bipolar disorder, assessed with DSM IV criteria). In four patients, eating disorders occur only in the post-operative period, in two patients an aggravation was assessed. At 3 months after surgery BMI increases of 2.9 kg/m2 (+- 0.5). Craving for sweet was found in 3 patients, two of them having night awakenings. In all cases the scores at BITE remains unchanged at three months. Atypical eating disorder occur most often in a context of euthymic state except for a patient.

Conclusions: These changes in eating behaviour after DBS, ask for the role of stimulation in their occurrence and their relationship with mood disorders.

Mo-171

Memory decline in Parkinson's disease and correlation with cerebral atrophy and metabolism

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Objective: To study the pattern of memory dysfunction and its anatomic and functional substrate in PD.

Background: In addition to the executive functions, memory is frequently impaired in PD patients with dementia. There is a lack of knowledge about the adequate test to asses this deficit.

Methods: PD patients with at least 10 years of disease and 60 years old were studied using MRI, FDG-PET scan and a neuropsychological battery of tests. Memory was assessed by the Buschke test that evaluates learning process, free recall and recognition. Patients were classified in PD cognitively normal-PDCN, PD with mild cognitive impairment-PDMCI based on Peterson's criteria, and PD wirh dementia-PDD. A voxel based analysis using multiple regression was

performed for both MRI and PET data, using cognitive group and age as covariates. Correlation between the Busche scores and the

Results: 44 PD patients (17 PDCN, 13 PDMCI and 14 PDD) were studied. The mean age was 70,95 y.o. and the PD duration 13,4 years. Total Buschke scores were: PDCN: 47,6 (SD: 0,8) PDMCI: 44,7 (SD: 3,8) PDD:29,6 (14,9). Busche free recall scores were: PDCN: 28,5 (SD: 4,3) PDMCI: 19,2 (SD: 4,6) PDD: 10,5 (8,4). Busche scores after clues were: PDCN: 19,1 (SD: 4,1) PDMCI: 25,5 (SD: 3,4) PDD: 19,1 (9,1). There was a correlation between the free recall Buschke score impairment, a bilateral hyppocampal atrophy and hypometabolism and a right parieto-temporal hypometabolism. The total Buschke score impairment correlated in a similar way with the hyppocampal atrophy and hypometabolism. but less extensively.

Conclusions: Patients with PDMCI have a selective impairment in free recall with normal scores in the global function as assessed by the Buschke test, because of the compensation with clues. In PDD the decline affects both the free and total scores. Free recall and total memory scores correlates with hypocampal atrophy and hypometabolism.

Mo-172

Freezing of gait in Parkinson's disease is sensitive to doorway width

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Objective: To measure the effects of doorway width on the freezing behaviour and gait of PD patients who freeze, and to assess the effects of medication and deep brain stimulation (DBS) on the affected gait parameters.

Background: Freezing of gait (FoG) is a locomotor phenomenon exhibited in a subgroup of patients with Parkinson's disease. In FoG a patient comes to an involuntary halt while walking, or cannot start walking despite a desire to do so. FoG commonly occurs in certain environmental conditions, including walking through doorways. However, the basis of these effects is poorly understood.

Methods: PD patients, who had DBS surgery several years prior to the experiments, walked in the laboratory in four conditions. In the first condition there was no doorway present. In the other three conditions a doorway was present in the walking path and its width was scaled to the shoulder width of the walker (100%, 125% and 150% shoulder width). The order of presentation of the three door width conditions was randomised between participants. Kinematic records of movement were taken. We also assessed the impact of (i) dopaminergic medications and (ii) deep-brain stimulation on these effects.

Results: The freezing phenomenon was sensitive to the presence of a doorway and to its width. More freezes occurred with a doorway present than without. The total time spent frozen was inversely proportional to door width (narrower doors caused more freezing) ($p = .035$). The proportion of trials on which a patient froze also decreased with door width ($p = .015$), medication and DBS. Using a motion capture system we showed that the presence of a doorway affected gait parameters even on trials where no overt freezes occurred. There were decreases in heel lift, step time and step length in the approach to the doorway.

Conclusions: The results show that the freezing phenomenon is highly sensitive to the surrounding environment and suggests an atypical coupling between perceptual input and motor output in patients who freeze. Consistent with recent work, our data imply that freezing results from gradual changes in gait patterns and further reveal the sensitivity of these changes to subtle environmental manipulations such as door width. In some patients medication and DBS are effective treatments for these problems.

Mo-173

Depression in Parkinson's disease

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Objective: The objective of present study was to determine the frequency of depression in patients with Parkinson's disease (PD).

Background: PD is the second most common neurodegenerative disease and affects 1-2% of the population over 65 years of age. Depression is the most frequent psychiatric complication in patients with PD which affects approximately 50% of all patients with PD. Diagnosis of depression in patients with PD may be difficult because of overlapping symptoms of the two disorders. Comorbid depression increases disability and impairs subjective and objective quality of life independent of motor deficits.

Methods: This study enrolled 103 patients diagnosed with PD according to the international criteria of PD (presence of at least two of the following signs or symptoms: bradykinesia, tremor, muscular rigidity and postural instability). Normal CT investigation with good response to L-dopa treatment. We used the Unified Parkinson Disease Rating Scale (UPDRS) the Hoehn-Yahr Scale (HY), Mini Mental State Examination(MMSE) and Hamilton Depression Rating. Patients with dementia associated with PD were excluded.

Results: Our patients (67 female and 36 male), the mean age of patients was 62.5 years. Depression was diagnosed in 42,7% of the patients. Depressive patients had higher HY score.

Conclusions: Depression are the most common non-motor symptoms in PD and was correlated with severity of motor disability. Early diagnosis and appropriate clinical management is essential to improving quality of life and preservation of daily function.

Mo-174

The changing profile of Parkinson's disease-associated psychosis: A prospective study using the new NINDS-NIMH criteria

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Objective: To specify the full spectrum of psychotic symptoms in a population of consecutive outpatients with Parkinson's disease (PD), and to assess the prevalence of PD-associated psychosis (PDAP) by using two different set of criteria.

Background: In the criteria for PDAP recently forwarded by a NINDS-NIMH workgroup (Ravina et al, Mov Disord 2007), psychotic symptoms include hallucinations, delusions, sense of presence and visual illusions. In most previous studies, only hallucinations (mainly visual) and delusions were assessed.

Methods: Population consisted in a clinic-based sample of 116 consecutive outpatients fulfilling UK Brain Bank criteria for PD (age: 67.0 y $\pm$9.9; M/F: 75/41; duration of PD: 9.1y $\pm$5.8). Severely demented patients were excluded. Forty-six (40%) patients used psychoactive drugs, clozapine in 4 cases. Patients were applied a 10-items structured questionnaire on all psychotic symptoms included in the NINDS-NIMH criteria, which had occurred in the preceding month. The same questionnaire was applied to 30 healthy controls (spouses of patients).

Results: Hallucinations were present in 42% of the patients, including visual in 16% and non-visual in 35% (auditory: 18%, tactile: 12%, somatic:1%, olfactory: 11%, gustatory: 3%), delusions in 4%, and minor symptoms (sense of presence, visual illusions or passage hallucinations) in 45%. The prevalence of PDAP was 43% using the usual definition (hallucinations and/or delusions) and 60% using the NINDS-NIHM criteria. Psychotic symptoms were occasionally present but significantly rarer in controls: 20% reported hallucinations (non-visual), 17% minor phenomena, and none delusions. PDAP according to both criteria correlated with the duration of PD and the use of psychoactive drugs. PDAP according to usual definition also correlated with age, while PDAP according to NINDS-NIMH criteria correlated with the daily levodopa-equivalent dose.

Conclusions: Minor symptoms and non-visual hallucinations are an important part of the PDAP spectrum which has been commonly restricted to visual hallucinations and delusions. Both frequencies and correlations with demographic and clinical characteristics vary according to the definition of PDAP. The prevalence and associated factors of PDAP should be re-evaluated by using the new criteria.

Mo-175

Quetiapine improves visual hallucinations in PD but not through normalization of sleep architecture: Results from a double-blind polysomnography study

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Objective: To confirm quetiapine's efficacy in PD for improving visual hallucinations (VH) in a double-blind trial and to determine whether alteration of REM sleep architecture is a significant contributor to its efficacy.

Background: Polysomnograhy conducted on PD patients with VH, showed higher percentages of stage 1- REM compared to non-hallucinators. VH and percentages of stage 1 REM decreased when PD patients were given a sedating agent, clonazepam. Quetiapine is a sedating atypical antipsychotic, regarded as first line treatment for VH in PD but efficacy has yet to be proven in placebo-controlled trials.

Methods: We performed a double-blind, placebo-controlled, parallel-group, forced-titration study on quetiapine for PD patients with VH.8 patients were randomized to quetiapine and 8 patients to placebo. Quetiapine was initiated at 25 mg at bedtime and increased by 25 mg until 150 mg nightly of quetiapine was reached or alternatively a complete resolution of VH was experienced. Patients underwent pre- and post-treatment polysomnography as well as Clinical Global Impression Scale (CGIS), Brief Psychiatric Rating Scale (BPRS) and UPDRS motor subscale at 3 months.

Results: Our cohort had a mean age of 68 years, 50% males, with an average UPDRS on motor score of 44.6 (SD 10.58). There were no differences in baseline characteristics between the treatment arms except that the placebo group had a longer stage REM at baseline. Eleven out of 16 patients completed the study. Data were imputed for all patients who prematurely discontinued (4 quetiapine and 1 placebo) in an intention-to-treat analysis. The average quetiapine dose was 58.3 mg/day. While there was no significant difference in the change in stage REM architecture pre- vs. post-treatment, patients randomized to quetiapine improved on the CGIS ($p=0.03$) and the hallucination item of the BPRS ($p=0.02$). No difference was noted in the UPDRS motor scores.

Conclusions: Despite the small sample, this is the first double-blind trial to show quetiapine's efficacy over placebo in controlling VH in the PD population. However, normalization of sleep architecture is not supported as the mechanism.

Mo-176

Spouse behavior changes in follow up of Parkinson's disease

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Objective: To study the changes of involvement of the spouses during the follow up of patients with Parkinsons disease, and their influence on symptoms evaluation, follow-up and treatment changes during the consultations, and to assess the spouse complaints and their influence on follow up and medical attitude.

Background: Parkinson's disease, as a chronic disease, has great effects on the family life and especially on the spouse, who is often the caregiver. Inversely, the spouse could change their behavior, according to the patient motor or mental changes, and the success of previous treatment modifications.

Methods: 12 couples were recorded twice, during the current follow up of their disease. All the couples included a patient with an idiopathic Parkinson' s disease. Patient and their spouse gave written informed consent to both study and videotape. They were aged from 63 to 75 years. They were all non demented patients (MMS 28 to 30). The evaluation during consultation consisted in: a screening of biographical details of their common life were recorded, the spontaneous partners complaints or reports, the UPDRS III scale, an evaluation of the apathy. all the consultations were videotaped, and studied in a second time for evaluation of the speech time (patient and the spouse), the ask for treatment change by the patient or by the spouse, the treatment untake, the success of the treatment change at the second consultation, and the improvement of UPDRS III.

Results: In 7/12 patients, the prescription has been changed after the first videotaped consultation. During the second videotape, there was an improvement in UPDRS of 5/12 patients. 3/12 spouses told the treatment changes were positive the changes of treatment. There was no change in spouse behavior during the consultation (speech timing, speech cut, treatment knowledge and asks) for the 7/12 patients who did not improved their UPDRS scale. The patients who had a better UPDRS scale had an increase of their speech time, and less agressivity for two of them. The couples who did not change their behavior were those whom parkinsonian patient had a greatest apathy.

Conclusions: Motor improvement seems to be link with a possible behavioral adaptation inside the couple. By contrast, apathy leads to a more fixed behavior from consultation to another, whatever the treatment changes and spouse self evaluation of the situation.

Mo-415

Decision-making in impulsivity vs apathy associated with Parkinson's disease

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Objective: To compare the performance on behavioural tasks measuring aspects of impulsivity in three behaviourally distinct Parkinson's disease (PD) groups in different medication states.

Background: Decision-making differences such as risk taking and self-control, which are key components of impulsivity, have been described in non-PD conditions associated with impulsivity, such as substance abuse and pathological gambling. In PD, impulse control disorders (ICD) may be driven in part by differences in these factors. Experimental studies on impulsive decision-making are needed in order to help elucidate why some PD sufferers develop ICD.

Methods: Three groups of PD participants (ICD; apathy; and controls) were compared using a delayed discounting task (DDT), which is a measure of degree of self-control derived from the ability to tolerate delay in order to maximize gain, as well as a probability discounting task (PDT), which measures the propensity to take risks when presented with a smaller, more immediate reward vs a larger, delayed reward. Each participant completed the tasks twice: "on" and "off" dopaminergic medication. Results on the DDT and PDT were compared using the indifference points which were used to plot a linear regression and calculate parameter values that define group levels of self-control and risk taking.

Results: The three groups were well matched on key demographic and clinical factors, except the apathy group had an older age of onset and a greater proportion of the ICD group were on dopamine agonists. Scores on the self-rated Barratt Impulsiveness Scale (BIS-11), demographic and clinical characteristics in relation to performance on the behavioural tasks will be reported.

Conclusions: Behavioural tasks such as the DDT and PDT can contribute to our understanding of the neuropsychological basis to impulsive behaviour and changes in decision-making in PD.

Tu-160

High incidence of impulse control disorders (ICD) in Parkinson's disease (PD) patients with sudden onset of sleep (SOOS) at the wheel

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Objective: To evaluate predictive episodes of SOOS at the wheel.

Background: A motor vehicle accident due to SOOS is an important issue in PD. Higher age, longer disease duration, male sex, the report of sleep disturbances, and treatment with non-ergot dopamine

agonists have been pointed out for predictors of SOOS. However elder patients with advanced PD have few chance of driving. In order to prevent motor vehicle accidents with SOOS, detailed situation of the accident and the predictors of SOOS at the wheel should be studied.

Methods: In our routine movement disorders practice (2003-2008), we encountered 9 PD patients who caused motor vehicle accidents due to SOOS. We assessed detailed situation of the accident, the relationship to their medical therapy, and co-existing feature of their behavior from detailed interview of the patient and family member.

Results: Nine (5 males and 4 females) out of 308 PD patients in our movement disorder clinic experienced 11 motor vehicle accidents due to SOOS within 5 years. The mean age was 59.2 (SD 6.2) years and the mean disease duration was 7.6 (SD 4.6) years. All accidents happened between afternoon and early-night in easy driving situation with few traffic signals. Most of the accident happened between 20 and 30 min after starting driving. Eight patients were using both L-dopa/DCI and pramipexole and the rest of one was on pramipexole-monotherapy. Six out of them experienced ICD including punding (4), pathological gambling (2), pathological shopping (1), and hypersexuality (1).

Conclusions: For the prevention of motor vehicle accidents due to SOOS, PD patients using pramipexole should not drive easy road for more than 20 min in the afternoon. At the same time, ICD was a predictor of motor vehicle accidents due to SOOS. There may be the special population easily affected by pramipexole in sleep and impulses.

Tu-161

Impulse control disorders in PD patients and their relationship to the dopamine dysregulation syndrome

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Objective: To elucidate the relationship between ICDs and DDS, PD patients with ICDs are evaluated.

Background: Impulse control disorders (ICDs) such as hypersexuality, pathological (problem) gambling, and punding have been reported in PD patients. ICDs have also been described in dopamine dysregulation syndrome (DDS), which is defined as compulsive use of dopamine replacement therapy. However, the relationship between ICDs and DDS is not clear.

Methods: Semi-structured interviews and neuropsychological tests were conducted on 169 outpatients with PD (male 93 and female 76) who agreed to receive the survey. The mean age of the patients were 66.85 years (±8.99, range 42-86 years) and the mean age of PD onset was 58.31 years (±11.26, range 29-83 years). The neuropsychological tests used were Mini-Mental State Examination (MMSE), Beck Depression Inventory and Frontal assessment battery (FAB). Dopamine replacement therapy was reviewed and total levodopa equivalent daily dose (LEDD), was calculated based on previous reports.

Results: ICDs ware identified in 8 patients: hypersexuality in 7 patients, pathological gambling in 2 patients, and punding was seen in 2 patients. 3 patients showed two ICDs. DDS was not found in our series. The mean dose of levodopa with carbidopa or benserazide in patients with ICDs was 481.25 mg (±244.86, range 0-750 mg). LEDD was not significantly different between PD with ICDs and without ICDs. There was also no significant differences in the age, the age of PD onset, and the neuropsychological test results between two groups.

Conclusions: The occurnce of ICDs in PD are not correlated with DDS. In contrast to ICDs, DDS appears to be a rare event. The apomorphine injection that is assumed to be the trigger of DDS is not available in Japan, and this may be one of the reasons that no patients with DDS was found in our series.

Tu-162

Depressive and anxiety symptoms in idiopathic rapid eye movement sleep behavior disorder (RBD)

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Objective: To evaluate the severity of depressive and anxiety symptoms in idiopathic rapid eye movement (REM) sleep behavior disorder (RBD).

Background: Idiopathic RBD is characterized by a loss of muscular atonia during REM sleep, resulting in motor activity associated with dream content. Studies have reported that idiopathic RBD is a risk factor for developing neurodegenerative disorders, particularly Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Psychiatric symptoms such as depression and anxiety frequently occur in the early stages of PD and DLB.

Methods: Sixty patients with idiopathic RBD (45 men; age, 66.73 ± 10.60) without neurological disease or dementia and 69 healthy controls (35 men; age, 65.80 ± 9.54) were studied. All participants were administered the Beck Depression Inventory, Second Edition (BDI-II) and the Beck Anxiety Inventory (BAI). Mann-Whitney U tests were performed to compare between-group differences on the BDI-II and BAI. The χ^2 test was used to compare the proportion of participants in each group with a score over nine on the BDI-II, which was considered the cut-off for significant depressive symptoms. Results are expressed as means ± standard deviation.

Results: No between-group differences were found for age. Idiopathic RBD patients scored higher than control subjects on both the BDI-II (9.70 ± 6.84 vs. 5.96 ± 5.74; $p = 0.001$) and BAI (8.70 ± 7.90 vs. 5.30 ± 5.47; $p = 0.01$). Significant depressive symptoms were found in 42% (25/60) of idiopathic RBD patients and 19% (13/69) of controls. The proportion of participants having significant depressive symptoms was higher in idiopathic RBD patients than in controls (χ^2 test = 6.99; df = 1; $p < 0.01$).

Conclusions: This study shows that idiopathic RBD patients are at risk for depressive and anxiety symptoms. Prospective studies will allow us to determine whether idiopathic RBD patients with significant depressive symptoms are at higher risk for developing PD or DLB.

Tu-163

Depressive and anxiety symptoms in Parkinson's disease with rapid eye movement sleep behavior disorder (RBD)

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Objective: To determinate the effect of the presence of rapid eye movement sleep behavior disorder (RBD) on the severity of depressive and anxiety symptoms in Parkinson's disease (PD).

Background: Depressive and anxiety symptoms as well as RBD are frequent non-motor features of PD. Few studies have examined the association between RBD and depressive or anxiety symptoms in PD, and these studies have methodological limitations, such as the absence of polysomnographic (PSG) confirmation for RBD, the use of insufficiently sensitive or specific depression scales, or the absence of a control group for comparison.

Methods: Ninety-three participants were studied, including 21 PD patients with PSG-confirmed RBD (18 men; age, 65.14 ± 7.91), 15 PD patients without RBD (7 men; age, 63.00 ± 10.18), and 57 healthy controls (30 men; age, 64.61 ± 8.14). All participants completed the Beck Depression Inventory, Second Edition (BDI-II) and the Beck Anxiety Inventory (BAI). Individuals with dementia or who were taking antidepressant, hypnotic, or anxiolytic drugs were excluded.

Results: The three groups did not differ with age. PD patients with and without RBD did not differ in disease duration, overall disease severity, or dopaminergic medication dosage. Between-group differences were found on the BDI-II (H[2] = 11.72; $p = 0.003$).

PD patients with concomitant RBD scored higher on the BDI-II than controls (11.29 ± 7.71 vs. 6.04 ± 6.00; $p < 0.001$). Differences between PD patients with and without RBD (7.40 ± 5.08) and between PD patients without RBD and controls were not statistically significant. Between-group differences were also found on the BAI (H[2] = 16.04; $p < 0.001$). PD patients with concomitant RBD (13.62 ± 11.36) scored higher on the BAI than PD patients without RBD (6.93 ± 7.91; $p = 0.02$) and controls (4.64 ± 4.48; $p < 0.001$). No statistical difference was observed between PD patients without RBD and controls.

Conclusions: Our results suggest that the presence of RBD in PD is associated with more severe depressive and anxiety symptoms. There were more males in the PD-RBD subgroup, which may have reduced between-group differences for BDI and BAI, because both depression and anxiety symptoms are more prevalent among females than males.

Tu-164

Motor impairment in rat model of Parkinson's disease (PD) exhibited at 20 weeks post lesion: Evidence from behavioral assessment

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Objective: To determine the degree of lesion in the rat model of PD after 20 weeks of 6-OHDA injection

Background: Animal models of PD are essential to gain insights into the possible pathological mechanism of the disease. 6-hydroxydopamine (6-OHDA) is one of the most frequently used toxins for producing rodent models of PD. Previous studies have shown that intracerebellar injection of 6-OHDA initiate degeneration of the exposed neurons (dopaminergic) within 3-4 days and the maximal damage is caused by the end of 3 weeks. Our study with 6-OHDA lesioned and control group of rats found a significant difference in a behavioral parameter performed 20 weeks after lesion to assess the motor disturbance using rotarod.

Methods: Adult male Wistar rats were anaesthetized with sodium pentobarbital (50mg/kg) i.p., pretreated with desipramine (20mg/kg) i.p., 30 min prior to 6-OHDA injection and placed in a stereotaxic frame. 6-OHDA (10μg) in 4μl of ascorbic acid saline (0.02%) was injected through a burr hole in the skull into the substantia nigra pars compacta (SNc) {coordinates: AP=-5.3mm, L= 2.0mm, DV=7.7mm (Paxinos)}. The injection was given at a rate of 1μl per min. The rats were transferred back to its cage for recovery. The test was done 20 weeks after surgery for 2 weeks. A total of five rats received 6-OHDA injection in a similar manner and control rats (n=4) did not received any kind of surgical injections. The animal was kept on the rod (speed set at 10 rpm) and the fall time was recorded (cut off time= 300s). The same was repeated 3 times per day for 3 consecutive days. The mean of the time of both the groups were analyzed using One-way ANOVA and compared.

Results: Data from the behavioral assessment showed that in 6-OHDA model PD could maintain their balance on rotarod for less than 50s whereas the control animals could easily maintain themselves for more than 180s.

Conclusions: The current data from the rotarod experiment indicates abnormality in the motor coordination of the rats even after 20 weeks of 6-OHDA injection. Whereas the control animals showed no delay in learning to stay on the rod, the lack of motor coordination in the lesioned group is an indication of disrupted neuronal control of movement.

Tu-165

Caregiver strain in Parkinson's disease is related to frontal behavioural impairment

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Objective: Caregiver burden may be severe in persons caring for patients with Parkinson's disease (PD). The aim of the study is to find out whether frontal cognitive and behavioural impairment contribute to caregiver burden in PD.

Background: Caregiver strain increases with disease duration, severity of motor impairment, dementia, hallucinosis and incontinence.

Methods: Included are consecutively hospitalized PD patients without or with mild to moderate dementia with negative history of impulse control disorder or major behavioural and psychiatric symptoms (hallucinosis, paranoia). The following tests have been performed: UPDRS-III (practical off), cranial CT or MRI, Minimental State Examination (MMSE), the Frontal Behavioural Inventory (FBI; 0 no -72 max. impairment; Kertesz 1998), Frontal Assessment Battery at Bedside (FAB; 18 no–0 max. impairment; Dubois 2000), Caregiver Strain assessment (CGS; 0 no-12 max. strain; Robinson 1983). Moreover, the majority of the PD patients have undergone testing with the CERAD-plus, the Wisconsin Card Sorting (WCST) and the Stroop Word Colour test (SWCT). PD patients are compared to patients with frontotemporal dementia (FTD; Neary 1998)- behavioural variant.

Results: 41 PD patients (21 male, 20 female) and 20 patients with the clinical diagnosis of FTD (4 male, 16 female) have been included. Age is 74.8±9 (PD) and 71.1±8.1 (FTD; mean±SD), MMSE scores (z-scores related to normal controls of comparable age, education and gender) tend to be lower in FTD than PD (-2.8±2.2 and -1.2±2.4). The CGS score is 3.4±2.6 in the PD and 5.2±4.4 in the FTD group ($p<0.05$), the FAB score 15.3±3.5 and 13.1±4.0 ($p>0.05$), the FBI score 14.0±12.1 in PD and 25.9±13.1 in FTD ($p<0.01$). UPDRS III during practical off is 40.9±16 in the PD group. CGS correlates with FAB and FBI scores in FTD ($p<0.01$) and with the FBI score ($p<0.05$), but not age, MMSE, UPDRS-III, and FAB scores in the PD group. The results of CERAD-plus, WCST and SWCT will be reported.

Conclusions: Frontal behavioural impairment is variable and frequent in PD, but less severe than in FTD. Nevertheless, it may significantly contribute to caregive strain in PD, even in patients without severe dementia or evidence for behavioural symptoms, psychotic episodes and impulse control disorder.

Tu-166

Clock drawing test in Parkinson's disease: association with different clinical features

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Objective: We investigated cognitive problems reflected by clock drawing test (CDT) in Parkinson's disease (PD) patients and their relation to clinical features.

Background: Prevalance of various cognitive problems among nondemented PD patients range between 17 to 53%. CDT traditionally reflects visuo-spatial abilities and parietal lobe functions but may also be useful to detect cognitive decline among nondemented PD patients.

Methods: Consecutive 32 PD patients (age range: 37-78 years, mean 59.9 years; 75% M) who were at Hoehn-Yahr stage II were prospectively enrolled into study. Patients with dementia, depression and psychosis were excluded according to DSM IV criteria and standardized mini mental test. CDT was performed by a psychologist according to 2 different methods, patients were asked: 1- to draw a circle or to use a predrawn circle in 8 cm diameter (when micrography existed), 2- to place the numbers, 3- to show the time as ten past eleven. Results were assessed quantitatively (4 points) and qualitatively (planning, memory and visuo-spatial abilities), and their relation to clinical features including sex, and age, symptom and side at PD onset were analysed.

Results: Mean score of CDT was 3.1±1.4 in whole group. In 32% of patients, test score was below the normal range. Most commonly encountered problems were in planning and visuo-spatial abilities. Abnormal CDT findings were more frequently seen in women, and patients with dominant side involvement and older than 60 years

at PD onset. However, these were statistically insignificant. Memory problems were more frequent among males than females (27.3% and 12.5%). Frequently encountered findings were forgetting numbers, perseveration, false placement of the arms of clock, placing additional numbers.

Conclusions: Although our findings suggest a cognitive involvement even in early stages of PD and visuo-spatial abilities as leading cognitive problem in nondemented PD patients, there is still requirement for further evaluations in larger patient groups. CDT may be useful for quick screening cognitive involvement in early stages of PD.

Tu-167

Severity of cognitive deficit among patients with Parkinson's disease/Parkinson syndrome

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Objective: To investigate the severity of cognitive deficit dementia among patients with Parkinson's disease/ Parkinson Syndrome (PD/PS).

Background: The problem of PD/PS is exacerbated in Armenia because of low rates of early diagnostics and treatment start, but higher number of patients who started treatment in late stages of disease, with prominent capability or disability.

Methods: 24 patients with PD/PS were selected for this study, 15 men and 9 women, mean age 69 9 years. Mean length of disease course was 12 6 years. All patients underwent cognitive testing in MMSE and modified Wechsler test to reveal severity of cognitive deficit. To compare our results with control two groups of healthy respondents were selected 10 men and women, matching age groups, who underwent similar testing.

Results: Moderate or severe dementia was found in 19 patients with PD/PS, mild cognitive impairment (MCI) in 5. Only six out of 20 healthy controls collected scores for MCI and two for moderate dementia. The severity of dementia in healthy controls coincidences with progression of age.

Conclusions: Patients with PD/PS shows significantly worse scores on both scales compare to healthy control. The severity of cognitive dysfuntion does not correlate with the age of patients, but with the disease progression. Thus proves also necessity of early diagnostics and start of treatment of PD/PS.

Tu-168

Unimpaired reward learning but elevated temporal discounting in Parkinson's disease patients with impulse control disorders

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Objective: To determine the cognitive underpinnings of impulse control disorders (ICDs) in Parkinson's disease (PD).

Background: It has been suggested that ICDs in PD reflect overvaluation of rewards. An alternative hypothesis holds that ICDs reflect excessive discounting of future rewards. To test these hypotheses we investigated whether medicated PD patients with and without ICDs showed aberrant learning of stimulus-reinforcement associations or elevated delay discounting.

Methods: Sixteen medicated PD patients without an ICD (PDn), 11 medicated PD patients with an ICD (PDi) and 20 matched controls were tested on a reward learning game, the salience attribution test (SAT), and the Kirby delay discounting questionnaire (KDDQ). On the SAT, participants made a speeded response in order to win money; the probability of reward was indicated by a different cues. The KDDQ yields measures of delay discounting at small, medium and large reward levels.

Results: On the SAT, participants rated reinforcement significantly more likely on high-probability relative to low-probability reinforced trials, representing adaptive motivational salience. However, PDn patients exhibited significantly reduced learning about high-probability reinforcement stimuli relative to controls and to PDi patients, who did not differ from each other. By contrast PDi patients exhibited highly elevated delay discounting at all three reward levels on the KDDQ relative to PDn patients and to controls, who did not differ from each other.

Conclusions: We identified a striking double dissociation between reward learning and delay discounting in PD patients with and without ICDs. While PDn patients were impaired at learning high-probability stimulus-reward associations, PDi patients were able to learn such associations as well as controls. We also demonstrated for the first time that PDi patients show highly elevated delay discounting (an index of impulsivity) while PDn patients do not differ from controls on this measure. Therefore, we propose that dopaminergic medication induces excessive devaluation of future rewards in PD patients with ICDs, driving maladaptive behaviour in these patients, rather then over-valuation of rewards per se.

Tu-169

Effects of bupropion on depression of Parkinson's disease: Open-label 12-week trial in Korea

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Objective: To evaluate efficacy and tolerability of bupropion in treatment of depression in patients with Parkinson's disease (PD).

Background: Depression is one of the most common non-motor symptoms of PD and reduces quality of life independent of motor deficits. Recent studies suggest that dopaminergic and noradrenergic mechanisms may play important roles in pathophysiology of depression in PD. The American Psychiatric Association practice guidelines recommends bupropion, a dopamine reuptake inhibitor, as a first-choice treatment of depression in PD. Bupropion seems to be a reasonable choice from a theoretical poin of view, but there is no randomized, placebo-controlled study on its efficacy and safety.

Methods: We used the DSM-IV criteria for the diagnosis of depression. We performed an open-label 12-week trial. Treatment with bupropion was initiated with 150mg/day, and increased up to 300mg/day the next week. This was followed by a 10-week fixed-dose maintenance phase, during which all the patients were maintained on bupropion at 300mg/day. The primary efficacy variable was change in mean Hamilton Depression Rating Scale (HAM-D) score from baseline to the last week of the study.

Results: We enrolled 15 patients (7 male, 8 female) with PD with depression prospectively. Mean age of patients was 57.2 ± 6.5yrs. Mean duration of disease was 7.9 ± 4.5yrs and mean UPDRS scores recorded at best 'on' phase was 37.5 ± 5.5. The mean HAM-D score was significantly reduced after the 12-week trial (11.12 ± 6.51) compared with the baseline (23.11 ± 5.05, $p<0.05$). There was no significant change in UPDRS score after the trial (35.7 ± 6.03). All the enrolled patients were completed the trial without significant adverse effects including hallucinations and any other confusional symptoms. The most common adverse events were dizziness and nausea.

Conclusions: Our data suggest that bupropion have effects on depression in patients with PD without significant adverse effects. To confirm these results, large, double-blind, placebo-controlled, randomized trials may be required.

Tu-170

A 5HT2A polymorphism is associated with pathological gambling in Parkinson's disease

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Objective: To determine if pathologic personality traits, or dopamine receptors (DR) and serotoninergic genes polymorphisms predispose to pathological gambling (PG) in Parkinson's disease (PD).

Background: It is admitted that dopamine agonists are responsible for PG, but the reason why only a minority of patients receiving a dopamine agonist develop PG remains unclear. To study serotonin and dopamine pathways is interesting since they contribute to regulate the reward mechanisms.

Methods: Ten PD patients with PG according to DSM-IV criteria underwent a psychiatric examination including a personality scale (SCID II), a depression scale (MADRS), and a general psychopathology scale (BPRS). Seven polymorphisms were studied: DRD2 (TaqI; allele C); DRD3 (Ser9Gly); DRD4 (exon III); serotonin transporter 5HTT promoter (ins/del 44bp); and serotonin receptor 5HT2A (T102C; His452Tyr).

Results: Five patients were or had been depressed but no pathologic personality trait was observed. The His452Tyr T/T genotype (5HT2A) was observed in three patients when the prevalence in control patients is only 0.7%; (Fischer exact test: p=0.0001). All the T/T patients had a history of major depression. Two other results have shown a tendency which did not reach significance. The prevalence of the Taq minor A1 allele (DRD2) was slightly higher than expected: A1/A1 in one patient (3.5% in controls), A1/A2 in three patients (22.4% in controls). The prevalence of the L/L genotype (5HTTPR) was higher than expected: 50% versus 29.1% in controls. The patients did not display other polymorphisms which may prompt susceptibility to PG.

Conclusions: This study indicates an association between the His452Tyr polymorphism of the 5HT2A gene and PG. The L/L genotype was observed in three patients, all of them being depressed. It has been hypothesized that 5HT2A polymorphisms could be associated with various mood disorders, but no link was clearly demonstrated. To test more patients could help to determine if PG alone is associated with this polymorphism or if it has to be accompanied by depression. A larger study could also precise the interest of other polymorphisms. A better understanding of the risk factors could help to manage PG in PD.

Tu-171

Variants of DRD3 and GRIN2B and impulse control and related disorders in Parkinson's disease

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Objective: To assess whether allelic variants of dopamine receptor, glutamate receptor, and serotonin transporter genes are associated with impulse control and related disorders (ICRD) in Parkinson's disease (PD) with dopamine replacement therapy(DRT).

Background: ICRD has been recently recognized as behavioral complications of DRT in PD. The pathophysiology of ICRD is not fully known, but it is suggested that alterations in the mesocorticolimbic dopaminergic system due to the disease process or to the DRT, may play an important role. The glutamate and serotonin neurotransmitter systems may be also involved in the addiction process and impulse control. We hypothesized that there may be a genetic predisposition to the occurrence of ICRD in PD in any of these three neurotransmitter systems.

Methods: We surveyed ICRD in consecutive Korean patients with PD who were treated with stable DRT using modified Minnesota Impulsive Disorders Interview over a period of 4 months. In the 404 patients who completed the interview and the 559 Korean healthy normal controls, genotyping was performed for variants of the dopamine receptor D3 (S9G in *DRD3*), dopamine receptor D2 (*Taq1A* in *DRD2*), glutamate *N*-methyl-$_D$-aspartate receptor 2B (C366G, C2664T and T-200G in *GRIN2B*) genes and the promoter region of the serotonin transporter gene (5-HTTLPR).

Results: Fifty-eight (14.4%) of the 404 patients had behavioral abnormalities suggestive of ICRD. Variants of *DRD2 Taq1A* and 5-HTTLPR were not associated with the risk of developing ICRD. However, the AA genotype of *DRD3* S9G and the CC genotype of *GRIN2B* C366G were more frequent in patients with ICRD than in non-affected patients (68.4 vs 49.3%, $p=0.0085$; and 46.6 vs 28.6, $p=0.0071$, respectively). After controlling for clinical variables in the multivariate analysis, carriage of either AA genotype of *DRD3* or CC genotype of *GRIN2B* was identified as an independent risk factor for ICRD (adjusted odds ratio: 2.57, 95% confidence interval: 1.27-5.20; p=0.0086).

Conclusions: Variants of *DRD3* S9G and *GRIN2B* C366G may be associated with the appearance of ICRD in PD with DRT.

Tu-172

Emotional dysfunction in Parkinson's disease: Depression or apathy?

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Objective: Investigating depression and apathy in Parkinson's disease.

Background: Depression and anxiety are core non-motor symptoms in Parkinson's disease. But it is still unclear to what extent depressive signs and depressive symptoms are related to neurodegeneration, psychological adaptation processes, or disease-specific apathy. Therefore, the characteristics depression, depressive states, disease-specific anxiety, and apathy were investigated in Parkinson's disease patients undergoing conventional drug therapy.

Methods: Eighty-four non-demented patients (Hoehn & Yahr stages I – III) were studied with respect to the clinical manifestations of depression, anxiety, subjective symptom intensity, coping habits, quality of life, and the disease (UPDRS, neurological and neuropsychological assessments). Depression and anxiety were assessed using a structured clinical interview (SKID). In addition, psychological variables were obtained from standardized questionnaires (e.g., BDI, MADR, HAKEMP-HOM; EQ-5d; Apathy-Scale AES-D etc.). Both dementia and severe cognitive impairment were excluded by means of an extensive neuropsychological examination.

Results: According to BDI scores, more than 40% of the patients showed signs of depression but less than ten percent displayed clinical manifestations of either major depression or dysthymia, respectively. Only half of these patients received anti-depressive treatment, whereas 15% of the non-depressive patients received anti-depressive medication. All of the latter showed elevated scores of apathy. Apathy and depression (BDI) were mutually unrelated. With the exception of selected patients with a positive history of depression, none of the depressive parkinsonian patients displayed disease-specific cognitive alterations of depression (e.g., "cognitive triad", specific attributional styles, etc.). Neither duration of the disease nor symptom intensity were related to depression or depressive sates, respectively.

Conclusions: Results show that signs of depression in Parkinson's disease are frequently better understood with respect to apathy. Psychological short-term interventions may help to activate parkinsonian patients and may therefore help to improve medical treatment.

Tu-173

Reward and decision-making in impulsivity in Parkinson's disease: An fMRI study

I. Leroi, M. Andrews, S. McKie, R. Elliot (Blackburn, Lancashire, United Kingdom)

Objective: Impaired decision-making and differential responses to reward may play a role in the etiology of the impulse control disorders (ICDs) in Parkinson's disease (PD). Dopamine-replacement therapy (DRT) may affect such processes further.

Background: To explore neural correlates in PD sufferers with a active ICD compared to those without ICD ("PD control") using decision-making and reward-loss tasks and differential medication (DRT) states in functional magnetic resonance imaging (fMRI).

Methods: Each participant was scanned twice during performance two tasks: "off" DRT (12-hours after the last dose) and "on"

DRT. The tasks included a risk-based decision-making (probability discounting) and a reward-loss task. Associations between blood oxygen level dependent (BOLD) response, presence of ICD and medication state were sought. The statistical model, with inferences corrected for volume analyzed, was based on trial-by-trial rewards and penalties. The analysis was an event-related characterization of the neural response to these.

Results: Participants had a mean age of 55.6 (SD10.5) years with a mean duration of motor symptoms of 101.4 (SD72.0) months. Groups were well matched on key demographic, disease & medication variables (eg. LEDD). During the probability discounting task, the BOLD response was most prominent in subcortical areas when participants were "off" as compared to the "on" medication. This was also seen in the PD control group as compared to the ICD group. A differential neural response was also seen in the ICD vs control groups in the following areas bilaterally: cerebellum, inferior parietal lobule, and inferior temporal gyrus, and bilateral hippocampus. Results from the reward-loss task will also be reported.

Conclusions: Both DRT and the presence of ICD appears to modulate neural responses during risky decision-making and reward-loss tasks. Compared to ICDs, PD controls appear to utilize cortical areas more during risky decision-making tasks, whereas ICDs seem to react "emotionally". fMRI of brain activity during these tasks may further our understanding of the neural correlates of ICDs in PD.

Tu-174

Predictors of the impulsive and apathetic behavioural phenotypes in Parkinson's disease

I. Leroi, M. Andrews, J. Byrne, A. Burns (Blackburn, Lancashire, United Kingdom)

Objective: To compare the demographic and clinical correlates of 3 groups of Parkinson's disease (PD) sufferers: those with impulse control disorders, those with apathy and those with neither.

Background: Behavioural phenotypes defined by level of motivation and reward processing in PD include the "impulse controls disorders" (ICDs) and the apathy syndrome. ICDs in PD include pathological gambling, hypersexuality, binge eating, compulsive shopping and dopamine dysregulation. Apathy in PD is characterised by diminished drive and loss of motivation in various spheres of functioning. The risk factors and clinical and behavioural correlates of these disorders are not well understood.

Methods: This is a preliminary analysis of an ongoing, single phase cross-sectional descriptive study of 3 groups of non-demented PD participants. The "apathy" group was defined by having a score of ≥14 on the modified Apathy Scale (AS). The "impulsivity" group met criteria for dopamine dysregulation syndrome in PD (Giovannoni et al, 2000) or had clinical diagnoses of other forms of ICDs. A gold-standard semi-structured interview (SCID-NP), cross-sectional psychiatric ratings scales, measures of impulsiveness and motivation and a cognitive screening battery was administered to all participants.

Results: 90 participants, divided into three groups (ICD, apathy and control) were included. Disease severity (UPDRS total score), disability (Schwab and England score) and cognitive impairment were significantly greater in the apathy group compared to the impulsivity and control groups, although there was no difference in duration of disease, or total levodopa equivalence dose (LEDD). The PD control group had significantly less psychiatric morbidity than the other two comparison groups. Multiple regression analysis with degree of motivation as the independent variable revealed age of onset of motor symptoms as a key association.

Conclusions: This is the first reported direct comparison of ICD and apathy in PD. Distinct behavioural phenotypes in PD, according to degree of motivation may be predicted according to associated risk factors.

Tu-175

Premorbid personality in Parkinson's disease with impulsivity and apathy

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Objective: To explore associations of premorbid personality traits in PD sufferers with different behavioural syndromes: impulse control disorders (ICD), apathy, and neither.

Background: Behavioural manifestations in Parkinson's disease (PD), such as impulsivity or apathy, are most likely driven by differing patterns of predisposing risk factors. Among these are premorbid personality traits, including levels of novelty seeking, risk taking and harm avoidance, which may in part be dopamine-dependent.

Methods: 90 PD sufferers were divided into three different groups according to associated behavioural syndrome (ICD, apathy and control) and compared on detailed clinical and demographic factors, including premorbid personality as measured by the NEO-FFI questionnaire. The NEO-FFI was rated by both the PD sufferer as well as a knowledgeable carer. The relationship between factors on the NEO-FFI and the presence of a behavioural syndrome and degree of motivation, based on the scores on the Apathy Evaluation Scale (AES-C), was explored.

Results: Premorbid neuroticism was significantly associated with both the ICD and apathy groups compared to controls. Increased levels of premorbid extraversion and decreased levels of agreeableness were associated with the ICD group compared to the control and apathy groups. In a linear regression model of demographic and clinical risk factors with level of apathy as the independent variable, premorbid neuroticism was highly predictive of higher levels of apathy.

Conclusions: This is the first direct comparison of premorbid personality traits in different behavioural syndromes in PD. Premorbid personality traits have a role in predicting behavioural outcome in PD.

We-163

Is retinal nerve fiber layer correlated with presence of hallucinations in patients with Parkinson's disease?

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Objective: Our objective was to study if presence of visual hallucinations could be correlated with retinal nerve fiber layer (RNFL) in patients with Parkinson's disease (PD).

Background: Visual hallucinations are frequent in PD. Several risk factors (age, treatment, cognitive decline) have been proposed. RNFL has been found significantly thinner in patients with PD than in controls.

Methods: 18 patients with PD were prospectively selected. UPDRS III, Folstein mini mental test and BREF were performed in every patients as well as research of visual hallucinations. RNFL was studied with Stratus OCT Tm (Carl Zeiss Meditec).

Results: RNFL was found within normal limits in all patients. Futhermore despites a trend to a thinner RNFL in patients with visual hallucinations (89.4 +/- 14.5 μ) than in patients without hallucinations (101.4+/6 9.5 μ), difference did not reach significativity ($p>0.05$).

Conclusions: These preliminary results do not bring arguments for visual impairement (RNFL) as a risk factor for visual hallucinations occurence in patients with PD.

We-164

Blunted early emotional processing in patients with Parkinson's disease and isolated apathy

M. Martinez-Corral, S. Martinez-Horta, G. Llebaria, A. Gironell, J. Kulisevsky (Barcelona, Spain)

Objective: To explore the early processing of emotional stimulus in patients with Parkinson's disease (PD) and apathy without cognitive impairment nor depression.

Background: Apathy is a frequent feature associated with PD. Some PD patients may exhibit apathy without depression. Although apathy seems to be especially related to executive dysfunction, the putative role of limbic dysfunction in its development in patients exhibiting apathy without cognitive impairment has not been formally studied. To define a limbic component of apathy in PD could identify subgroups of apathetic PD patients with a different therapeutic approach.

Methods: Prospective, controlled study of 19 PD patients with (n=9) and without (n=11) apathy as assessed by the Apathy Evaluation Scale. Early emotional processing was assessed by event related brain potentials (ERPs). A passive view task of emotional pictures (International Affective Picture System) was used to elicit two well known ERPs linked to emotional processing: The Early Posterior Negativity (EPN), reflecting rapid affective amygdala processing, and the Late Posterior Positivity (LPP), reflecting enhanced encoding for arousing stimuli by limbic structures. (EPN: Negative deflection <300ms after stimulus onset. LPP: Positive deflection <600ms after stimulus onset). Patients with cognitive impairment (CDR ≥0,5), probable depression (HADS-depression ≥11) or visuospatial impairment assessed by the Cortical Vision Screening Test were not included. ANOVA analysis were performed between groups.

Results: ERPs (EPN and LPP) elicited by emotional pictures shown significantly lower amplitudes in PD patients with apathy (EPN (Cz) Positive stimuli p=0,013; Negative stimuli p=0,029)(LPP (Cz) Positive stimuli p= 0,019; Negative stimuli p=0,004). No differences were found for ERPs elicited by neutral stimulus.

Conclusions: Blunted early emotional processing in PD patients with apathy compared to non-apathetic PD patients points towards an involvement of the limbic system in the development of apathy in PD.

We-165

Contribution of cognitive control and response inhibition in the apathetic symptoms of Parkinson's disease

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Objective: To assess the implications of executive dysfunctions in apathetic Parkinson's disease (PD) patients without cognitive impairment.

Background: Apathy has been frequently linked with PD and can appear without dementia/depression. The evidence of executive dysfunctions in PD has been reported in numerous studies but the role of these dysfunctions in the development of apathy and which structures should be involved in it stills unclear. Cognitive control of action, thoughts and emotions became a crucial process to carry out an adaptive behavior in a constantly changing environment. As the structures involved in cognitive control participate in the organization of these processes, their functional study will be performed in order to asses if they are related with the development of apathy in PD.

Methods: Prospective, controlled study of 19 PD patients with (n=9) and without (n=11) apathy was assessed by the Apathy Evaluation Scale. Cognitive control and response inhibition was assessed by event-related brain potentials (ERPs). A Go/Nogo task was used to elicit two well known ERPs components linked with response inhibition: The N2-Nogo (negative deflection around 200ms), and the P3-Nogo (positive deflection around 400ms), both linked with ACC activity and found in frontal sites for correct inhibited trials. Patients with cognitive impairment (CDR 0,5), probable depression (HADS-D>11) or visuospatial impairment assessed by the Cortical Vision Screening Test were not included. ANOVA was performed in order to evidence differences of latency, amplitude and behavioral performance between groups.

Results: N2 and P3 Nogo elicited by the go/nogo task shown significantly lower amplitudes (N2-Nogo (Fz) p=0.0195 (Cz) p=0.050 P3-Nogo (Fz) p=0.041 (Cz) p=0.0155) and larger latencies (N2-Nogo (Fz) p=0.001 P3-Nogo (Fz) p=0.0001 for the apathetic group. We do not find significantly differences between groups for RT's and error rate.

Conclusions: The differences of the ERPs amplitudes and latencies suggest the participation of similar neural networks underlying the functional integrity of cognitive control on the development of apathy in PD.

We-166

Impairment of fine leg movements induced by STN DBS

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Objective: To investigate the coexistence of impairment of voluntary movement and improvement of parkinsonian motor signs, both resulting from STN DBS.

Background: STN DBS improves parkinsonian motor signs often including skilled motor tasks such as handwriting. Recently two patients presented with difficulties performing fine and/or skilled movements as a result of STN DBS despite marked improvement in UPDRS motor scores. It is noteworthy that in both cases these skilled movements were not impaired prior to surgery.

Methods: Concentric circles (0.5m and 0.2m dia.), which were drawn on either a horizontal or vertical surface, were presented to the two patients whilst standing or seated respectively and upper body supported. With the leg unsupported and foot in the air they performed two tasks: 1) trace the circles slowly and repetitively with the big toe; 2) hold the toe stationary over the circles' centre. Movements of leg segments were recorded in 3-D (Coda). DBS stimulation voltage and electrode contact were varied. The positions of electrode contacts were determined using postoperative stereotactic MRI. One patient was studied on and off dopaminergic medication.

Results: STN DBS produced clinical improvement in both patients (table).

Table (We-166). Patients' clinical motor scores

	Months post-surgery	UPDRS III off stim*	UPDRS III on stim*	% improvement
Patient 1	18	40	6	85
Patient 2	12	57	21	63

*Scores obtained off medication.

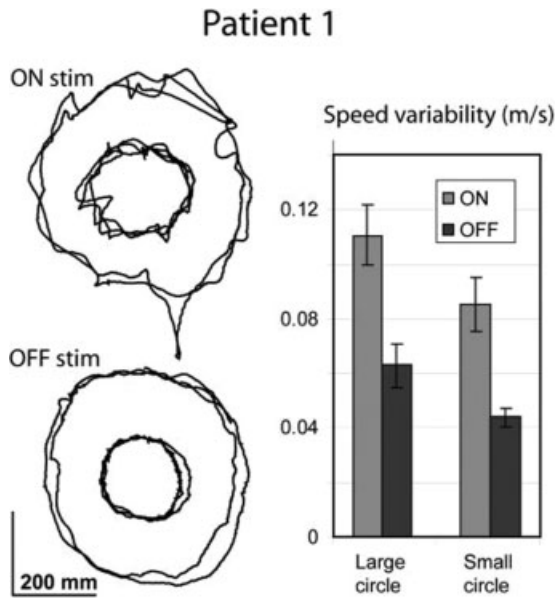

FIG. 1 (We-166).

However, both were impaired in similar ways in their ability to trace circles with the toe. When DBS was turned on using therapeutic stimulation levels the movements became jerky resulting in increased trajectory and speed variability (figure). The ability to hold the leg stationary was also affected. These impairments of fine motor control were dependent on site of stimulation (dorsal tip of STN most disruptive) and became worse with increasing stimulation amplitude and dopaminergic medication.

Conclusions: In some patients STN DBS can impair the execution of fine leg movements while alleviating parkinsonian signs. This impairment may be due either to a disruption of the motor control process or intrusion of involuntary movements.

We-167

Opposite effects of levodopa on conditioned behaviors

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Objective: To study the conditioning of inhibitory and executive actions in patients with Parkinson's disease (PD) on versus off Levodopa therapy.

Background: The basal ganglia (BG) have been implicated in the conditioning of behavior. Accordingly, it could be expected that in dopamine deficient parkinsonian patients an impairment of this function will be restored by Levodopa treatment.

Methods: Sixteen PD patients with Levodopa monotherapy and fourteen controls took part in the study. They engaged in a modified Go/NoGo task, the PD patients being tested twice in an on and off Levodopa state. In this, four equiprobable stimuli were repeatedly presented in pseudorandomised order. One of the stimuli was defined as target to which a button press had to be performed (Go task) or withheld (NoGo task). Both tasks comprised two conditions, one in which the target stimulus was always preceded by the same non-target stimulus (Conditioning), and another one in which the 'non-target to target sequence' was at random (Unconditioning). Go and NoGo task consisted of 800 stimuli in which conditioning and unconditioning were alternated within 4 blocks, avoiding a vigilance effect in one of the conditions.

Results: In the NoGo task, controls and PD patients off Levodopa had a significant increase of errors from the coupled to the uncoupled condition (pushing the button although they had to withhold this response). In contrast, PD patients on Levodopa did not perform differently between conditions. In the Go task, controls and PD patients off Levodopa did not perform differently between coupled and uncoupled condition. However, PD patients on Levodopa showed a significant increase of errors from the coupled to the uncoupled condition (omitting the button press although they had to execute this response).

Conclusions: Levodopa has opposite effects on the conditioning of executive and inhibitory behaviors: it hampers the conditioning of NoGo-stimuli as opposed to the deconditioning of Go-stimuli. This appears to indicate enhanced Levodopa-induced event coupling specifically under executive demands. As unmedicated PD patients followed the conditioning-deconditioning pattern of controls, this probably reflects a generic dopaminergic effect which might relate to complex dysfunctional behaviors in thus treated patients, as e. g. gambling and punding.

We-168

Accuracy demands differentially modulate impaired anticipatory control of object tilt and force sharing patterns during multi-digit grasping in Parkinson's disease

T.L. McIsaac (New York, New York)

Objective: To examine the effect of increased task accuracy demands on the coordination of multi-digit grasping forces during object grasping and lifting.

Background: Anticipatory control of multi-digit grasping forces has been shown to be impaired in patients with Parkinson's disease (PD). Focused attention on the accuracy of a task improves performance measures in healthy adults. We hypothesized that constraining the accuracy of a multi-digit grasping task would mediate the impaired anticipatory grasping control seen in PD.

Methods: Ten subjects with Parkinson's disease (PD; OFF and ON medication) and ten healthy age-matched control subjects lifted a manipulandum that measured grasping forces at each digit and object position. The accuracy of maintaining the object upright was either constrained (high demand) or unconstrained (low demand) and the object's center of mass (CM) was changed from trial to trial in either a predictable (blocked) or unpredictable (random) order.

Results: All subjects modulated individual fingertip forces to counterbalance forces exerted by the thumb and minimize object tilt after lift-off. Subjects with PD OFF medication exhibited an impaired ability to use anticipatory mechanisms resulting in less differentiated scaling of individual finger forces to the object CM location. These between-group differences in force modulation were similar regardless of the accuracy demands. Conversely, subjects with PD OFF medication minimized erroneous tilt of the object to a greater degree than healthy controls when accuracy demands were low and normalized their control of object tilt during high accuracy demands. These tilt corrections occurred as quickly with PD OFF subjects as healthy controls.

Conclusions: These findings in subjects with PD indicate that: (a) inaccurate scaling of fingertip force amplitude and sharing patterns before object lift is unaltered by increased demands of task accuracy; (b) however, control of object tilt is normalized when the accuracy demands are constrained and (c) the temporal recovery of erroneous object tilt is unimpaired in PD.

We-169

Deep brain stimulation of subthalamic nuclei modulates recognition of emotional facial expressions at different spatial frequencies

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Objective: To evaluate the effect of deep brain stimulation on impairments of emotional facial expressions at different spatial frequencies.

Background: Deep brain stimulation of subthalamic nuclei (STN) is an efficient technique to remediate motor symptoms in Parkinson's disease (Benabid, Pollak, Gervason, Hoffmann, Gao, Hommel, Perret, & de Rougemont, 1991). However, different studies have shown that DBS may, in some cases, induces emotional, cognitive or addictive disorders (Dujardin, Blairy, Defebvre, Duhem, Noël, Hess, & Destée, 2004; Doshi, Chhaya, & Bhatt, 2002; Houeto, Mesnage, Mallet, Pillon, Gargiulo, du Moncel, Bonnet, Pidoux, Dormont, Cornu, & Agid, 2002; Ulla, Thobois, Lemaire, Schmitt, Derost, Broussolle, Llorca, & Durif, 2006).

Methods: We conducted an emotional facial recognition task, at different spatial frequencies, under suboptimal (200 ms) presentation of the stimuli.

Results: Deep brain stimulation differentially modulates emotional facial expression recognition at different spatial frequencies for two specific facial expressions that are assumed to be related to basal ganglia. More precisely, deep brain stimulation improves recognition of fearful and disgusted faces at low spatial frequencies but with a concomitant impairment of recognition of these two emotional facial expressions at high spatial frequencies.

Conclusions: Results are discussed with regards to the Ledoux's model and embodiment theory.

We-170

Are parkinsonian gait characteristics present in patients with SWEDDs?

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Objective: To compare the gait of patients with SWEDDs (Scans without evidence of dopaminergic deficit) with the gait of Parkinson's disease (PD) patients and healthy individuals in order to help further understanding of the pathophysiology of SWEDDs, particularly its distinction from PD.

Background: About 10-15 percent of patients thought to have PD turn out to have normal dopaminergic function based on imaging. The diagnosis in these patients remains unclear and they have been referred to as SWEDDs.

Methods: 6 SWEDDs patients (mean age = 74), 7 PD patients (mean age = 71), and 8 healthy control participants (HC; mean age = 72) walked up and down a laboratory walkway at a self-selected, comfortable speed several times whilst whole body movements were tracked using a 3D motion capture system. Walking was performed A. unconstrained and B. with medio-lateral foot placements constrained to a central line (line-walking). Patients had been off medication for at least 12 hours. Results are in the form mean ± SD.

Results: Walking speed tended to be slower in the patient groups although differences were not statistically significant (HC 1.00 ± 0.20, PD 0.92 ± 0.16, SWEDDs 0.82 ± 0.33). An increase in average anterior trunk tilt and elbow flexion were present in the PD group ($p < .05$, relative to HC) but not present in the SWEDDs group. Normalized arm swing, summarized as shoulder flexion/extension motion divided by hip flexion/extension motion, was lower in both PD (0.29 ± 0.11) and SWEDDs (0.32 ± 0.11) than in HC (0.48 ± 0.15) on the side of smallest arm swing ($p <. 05$). All participants were able to perform line-walking unaided. The variability in foot-relative-to-pelvis trajectory during line-walking was not significantly different between groups.

Conclusions: Our preliminary results indicate SWEDDs patients tend to exhibit arm swing dysfunction but not the flexed posture of parkinsonian gait.

We-171

Anxiety disorders in Chinese patients with Parkinson's disease

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Objective: This study aimed to assess the frequency of Anxiety disorders and their correlates in Chinese PD patients.

Background: Anxiety disorders commonly occur in patients with Parkinson's disease (PD) but their socio-demographic and clinical correlates have not yet been unequivocally determined.

Methods: A total of 133 patients of PD with detailed demographic and clinical data were recruited from three neurology outpatient clinics. Participants' neurological, cognitive and psychiatric status was assessed using standardized rating instruments. Anxiety disorders were diagnosed by a qualified psychiatrist using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders–4th Edition (SCID-DSM IV).

Results: Thirty-six patients (27.1%) were diagnosed with some type of Anxiety disorder. Generalized Anxiety disorder, Agoraphobia and Social Phobia were the commonest subtypes of Anxiety disorders in PD (n=11, 8.3%, in each subtype). In multivariate analysis, younger age of onset of PD (OR=2.545, p=0.032), Geriatric Depression Scale score (OR=1.177, p=0.004) and musculoskeletal pain (OR=2.440, p=0.042) were independent risk factors of Anxiety disorders.

Conclusions: Anxiety disorders are common in Chinese PD patients. Younger age of onset of PD, severity of depressive symptoms and musculoskeletal pain are independent risk factors of the diagnosis of an Anxiety disorder, which suggests that anxiety in PD has multifactorial origin.

We-172

Symmetric Parkinson's disease and atypical degenerative parkinsonism: Common and differential aspects

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Objective: To study patients with symmetrical parkinsonism that does not fulfill essential criteria for diagnosis other than Parkinson's disease, looking for similarities with atypical parkinsonism (AP) patients.

Background: Parkinson's disease (PD) is typically asymmetric with unilateral onset. Traditionally, the finding of symmetry is a clue to AP. However, a minority of parkinsonism cases presents with symmetrical features and do not fulfill formal criteria of AP syndromes. Previous studies described that SPD patients have carry a more severe phenotype than classical PD, with increased frequency of dementia, psychosis, postural instability, sharing several features of AP.

Methods: We selected 70 patients with SPD and 110 AP, including 40 cases of PSP, 37 of MSA and 33 of LBD. All individuals were evaluated following a standardized protocol including demographic data, motor and non-motor features. Established criteria for symmetry, dementia, REM sleep behavior disorder (RSBD), psychosis and restless legs syndrome (RLS) were used. Postural instability and gait disorder (PIGD) score was formed using the sum of 5 UPDRS items.

Results: Mean age of onset difference was not significant among SPD and AP cases (67,0 ± 10,5 vs. 65,5 ± 8,7). We found significant differences in regards to age at the time of assessment (73,9 ± 9,6 vs. 69,9 ± 8,7; p:0,005) and disease duration (6,8 ± 4,3 vs. 4,3 ± 1,8; p<0,0001). AP patients presented worst H&Y staging (p<0,001), PIGD score (p<0,0001), higher frequency of dementia, RLS and rigid-akinetic parkinsonism (p<0.0001). Occurrence of psychosis (p=0,7) and RSBD (p=0,4) were similarly frequent.

Conclusions: SPD patients carry more features of typical asymmetric PD than AP. On the other hand, we demonstrated that SPD and AP share features such as psychosis and RSBD, typical finding of LBD and MSA, respectively. SPD patients do not share additional features with AP cases using the parameters used here, including current, disease duration and staging, postural instability and gait disorders score, and frequency of dementia, RLS and rigid-akinetic parkinsonism. We hypothesize that SPD may be halfway in a spectrum that includes in one end the typical asymmetric, levodopa responsive phenotype of PD and in the opposite end the more aggressive neurodegenerative disorders known as AP.

We-173

Laterality of motor onset in patients with Parkinson's disease and impulse control disorders

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Objective: To compare laterality of Parkinson's disease (PD) onset in patients with and without impulse control behavior (ICB) during dopamine agonist therapy.

Background: Patients with PD have an increased risk to undergo characteristic behavioural changes during dopamine agonist therapy, by developing features known as ICB. Experimental studies revealed an association between asymmetry in dopamine receptor availability and positive incentive motivation.

Methods: Retrospective study of 182 patients with PD who received dopamine agonist (DA) therapy in a single movement disorder clinic. Fourteen patients receiving subthalamic deep brain stimulation (DBS) were excluded from the analysis, due to possible behavioral effects of DBS. Chi-square test and student's t-test were used to analyze demographic and clinical data.

Results: Twelve patients developed ICB while being treated with DA agonist (7.1%). Laterality of PD motor onset was not equally distributed. Patients without ICB had a predominant right onset of motor symptoms in (86 vs. 70, 55.1%). On the other hand, patients developing ICB when treated with DA agonists showed a tendency to have left-onset motor symptoms, (7 vs. 5, 58.3%). This difference was not statistically significant.

Conclusions: Our data suggest an overall higher vulnerability of the left brain hemisphere's dopaminergic system, associated with more frequent right onset of PD motor symptoms. Left-onset PD motor symptoms, while less common in our population, might act as an independent risk factor for developing ICB while treated with DA therapy. This trend did not reach statistical significance, possibly due to a small sample bias, but it is intriguing in light of the known association between asymmetry in dopamine receptor availability and positive incentive motivation. Larger population analysis is needed to confirm this findings.

We-175

Reckless generosity in Parkinson's disease

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(London, United Kingdom)

Objective: To describe a new non-motor feature associated with the use of dopamine agonists in Parkinson's disease.

Background: There is an increasing awareness of impulse control disorders (ICDs) associated with patients treated for Parkinson's disease (PD). Pathological gambling and hypersexuality have been the most widely reported phenomenena, but compulsive shopping and binge eating are also well recognised. Excessive generosity not related to hypomania has not been previously described in the context of PD and its treatment.

Methods: We describe an impulsive behaviour associated with the use of dopamine agonists in three patients with PD, characterised by excessive and inappropriate philanthropy. We discuss potential mechanisms for the development of this behaviour, involving aberrant reward pathways.

Conclusions: In all cases, the generosity combined with other ICDs caused significant financial strains. We suggest that excessive generosity is a not uncommon phenomenon in PD. The possibility of this adverse effect should be mentioned to patients considering or taking dopamine agonists, and to their carers, and should be actively enquired about by treating physicians.

We-176

Increased dopamine neurotransmission in Parkinson's patients with Impulse control disorders in response to rewarding visual stimuli: A pilot study

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Objective: To evaluate changes in dopamine neurotransmission in Parkinson's disease (PD) patients with impulse control disorders (ICDs) compared to PD control patients in response to rewarding visual stimuli using 11C-Raclopride Positron Emission Tomography (PET).

Background: A group of patients with PD suffer from ICDs related to dopaminergic medication use. This could be related to dopamine neurotransmission fluxes in the ventral striatum (VS) and the related circuitry, as these neural networks are known to mediate aspects of 'natural' rewards such as food. A recent study using PET with 11C-raclopride, a marker for postsynaptic dopamine D2/D3 receptors, shown that compulsive drug use in PD is linked to sensitisation of the VS circuitry (Evans et al 2006). Currently, the changes in dopamine neurotransmission amongst PD patients with ICDs in response to "reward-related" visual stimuli remains unclear.

Methods: Four non-demented PD control patients, and 7 non-demented PD patients with ICDs (the 'PD +ICD group'), matched for age, disease duration and L-dopa equivalent dose (LED), underwent two randomized 11C-Raclopride PET scans after a levodopa challenge (Madopar dispersible 250mg); in one scan they were shown "rewarding" images related to appetizing food, gambling, money and sex, and in the second scan they were shown images of neutral objects. Region-of-interest (ROI) approach was employed and RAC ROI binding potentials (BPs) were calculated using the simplified reference tissue model (SRTM) with cerebellum as a reference tissue.

Results: In the PD + ICD group, there was a maximum reduction of 37% (mean 13.4%+/-0.05%) in VS RAC-BP from the scan with neutral images to the scan with rewarding images. This corresponds to a maximum reduction of 21% (mean 6.6%+/-0.09) in VS RAC-BP of PD control group, indicating a greater release of dopamine in the PD + ICD group.

Conclusions: Using 11C Raclopride PET, we demonstrated a greater reduction in VS RAC-BP of PD patients with ICDs in response to reward-related visual stimuli compared to PD controls. This study further supports the role of dopaminergic pathways in mediating the non-drug addictive tendencies, namely ICDs, associated with antiparkinsonian dopaminergic medications.

We-177

Nitric oxide synhase inhibitors effects on acute and chronic L-dopa-induced dyskinesias in the 6-OHDA rat model of Parkinson's disease

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Objective: In the present study we further investigate the nitric oxide synthase inhibitors effect on dyskinesias induced by acute and chronic administration of L-DOPA in rats with unilateral 6-hydroxydopamine lesion.

Background: Rats with 6-hydroxydopamine lesion of dopaminergic neurons chronically treated with L-3, 4-dihydroxyphenylalanine (L-DOPA) develop a rodent analog of human dyskinesia characterized by severe axial, limb, orofacial and locomotor abnormal involuntary movements. While the mechanisms by which these effects occur are not clear, they may involve the nitric oxide system.

Methods: Single dose of L-DOPA (100mg/kg or 30mg/kg; oral-gavage) and chronic L-DOPA treatment (high fixed dose, 100mg/kg/day; low escalating dose, 10-30mg/kg/day; oral-gavage) induced diverse amount of dyskinesia changes. Nitric oxide synthase inhibitors, NG-nitro-L-arginine (50 mg/kg i.p.; L-NOARG neuronal and endothelial nitric oxide synthase inhibitor) or 7-Nitroindazole (1-30 mg/kg i.p.; 7-NI, selective neuronal nitric oxide synthase inhibitor) was given 30 min before L-DOPA.

Results: L-NOARG reduced dyskinesias after L-DOPA 100mg/kg chronic ($p<0.05$) but not acute administration ($p>0.05$); in contrast, L-NOARG prejudices stepping test performance after acute but not after chronic L-DOPA treatment. 7-Nitroindazole attenuates dyskinesia on acute or chronic L-DOPA administration ($p<0.05$) improving motor performance in the rota-rod test ($p<0.05$).

Conclusions: These results suggest the possibility that nitric oxide synthase inhibitors may be valuable to L-DOPA-induced dyskinesia treatment.

We-178

Patients and duodopa treatment. Psychiatric problems in patients before and after the stabilization of motor symptoms with duodopa

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Objective: The objective of this study was to describe the emergence of psychiatric problems in Duodopa treated PD patients after alleviation of motor fluctuations.

Background: Patients with advanced drug resistant Parkinson's disease and severe fluctuations can be treated successfully with an

intraduodenal infusion of a gel containing fluent anti-parkinson medication, Duodopa. The motor disturbances as well as some of the non motor disturbancescan be alleviated to at large degree when treating with Duodopa. Psychiatric problems is common in PD ollong wiht other non motor symptoms. These problems may cause a problem to peroral medication.

Methods: In a descriptive study we examined 15 doparesponsive PD patients. 6 men and 9 women, mean age 65 years, range 53-77 years. Disease duration over 8 years. All were on standard peroral medication with multiple drugs.

Results: Five patients had psychiatric problems prior to the Duodopa infusion. (2 depression, 4 anxiety, 1 delusion), and eight patients experienced problems in the period after introduction of Duodopa, (4 depression, 7 anxiety, 4 delusions). Patients without psychiatric symptoms prior to Duodopa treatment could experience symptoms. The symptoms were successfully treated with benzodiazepines and anti-depressants and the symptoms were alleviated over time. Psychiatric problems can be more prominent in the period 2 to 6 month after stabilisation of the motor symptoms.

Conclusions: It is important to recognize the symptoms of depression, anxiety and delusions/ hallucinations in patients and actively engage in treatment of symptoms in the period after adjusting medication with Duodopa. This require at setup where doctors and nurses are available on a short notice and with high degree of accessibility. These symptoms are not considered to be a side effect of Duodopa treatment in itself, or an organic psykosyndrome after surgery, but a result of an effective treatment of motor symptoms. The transition from being very sick vith PD to less affected influenced the patients psychiatric state. The alliveance of motor complications gave the patients time over to tell their doctors how they felt and to focus on other things than talking about regulation of medication. The prognosis is good and the symptoms could effectively be treated with consultations and standard psychiatric medication.

We-179

Dimensional approach to depression in Parkinson's disease

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Objective: To evaluate the heuristic value of a dimensional dissection of the Beck Depression Inventory (BDI) in different pharmacological interventions in Parkinson's disease depression.

Background: Depression is common in Idiopathic Parkinson's disease, difficult to recognize, under managed, and has been identified as a major determinant of health-related quality of life. Current categorization of diagnosis in psychiatry poorly applies to the protean manifestations of mood disorders presented by parkinsonian patients.

Methods: The 21 items of the BDI were classified in two new factors: hyperkinetic (items expressing dishinhibition of reflexive behaviours) and hypokinetic (items expressing loss of self-generated and reflexive behaviours). These factors have been analyzed in three different studies.

Results: The three sets of analyses using the hypo/hyperkinetic factor dichotomy favour a neurobiological dissociation of the two factors in response to different pharmacological interventions: the hyperkinetic group is responsive to serotonergic drugs while the hypokinetic group is not and may even be deteriorated by SSRI's. The hypokinetic group, on the other hand, is responsive to dopaminergic drugs and may even be deteriorated by serotonergic drugs. Furthermore, the two groups seem to transiently dissociate on placebo intervention aiming at correcting either mood or motor status.

Conclusions: The dimensional approach to depression symptomatology may be of heuristic value in probing aminergic modulation in clinic and imagery of distinct aspects of behaviours neglected up until now in the core symptomatology of IPD. It may also help in establishing new correlations between cognitive, affective, and motor subtype of behaviours presently concealed by the use of traditional categorical approaches.

Th-161

A study of cognitive fatigue in Parkinson's disease

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Objective: To establish a correlation between subjective and objective measures of cognitive fatigue in PD and healthy subjects.

Background: A significant portion of Parkinson's disease (PD) patients complain of severe fatigue. However, the objective basis of this complaint is unknown. Prior research demonstrated objective motor fatigue in PD patients but did not find a correlation between this objective fatigue and subjective complaints. No study to date has used an objective test of mental fatigue to understand subjective complaints in PD. As PD patients are known to have frontal lobe dysfunction, we hypothesize that they will also have mental fatigue on prolonged tasks demanding executive control.

Methods: We recruited 7 healthy subjects and 5 PD patients. Subjects completed three hours of a continuous performance Stroop task. Their reaction times and accuracy were recorded on a trial by trial basis. Overall performance was quantified using reaction times, with a doubling of reaction time for error trials. Fatigue was quantified as the percent change in performance after a training block of the first 390 trials to the last 390 trials.

Results: While PD subjects were slower than controls at baseline, this effect was not significant and there were not significant task specific differences. There was a significant decrement in performance over time for both groups of subjects ($p<0.01$). The percentage change in performance for the Normal subjects was 9.1%, 9.3%, 20.8%, and 14.5% for congruent color, congruent word, incongruent color, and incongruent word respectively. The overall percentage change was 11.9%. The percentage change in performance for the PD subjects was 56.5%, 45.3%, 25.1%, and 58.7% for congruent color, congruent word, incongruent color, and incongruent word respectively. The overall percentage change was 45.3%. PD subjects demonstrated a significantly greater decrement in task performance for all tasks (mean difference = 33.4%, $p < 0.05$) except for incongruent color (mean difference = 4.3%, $p=0.14$). No statistically significant correlation was found between any measures of subjective fatigue and objective performance.

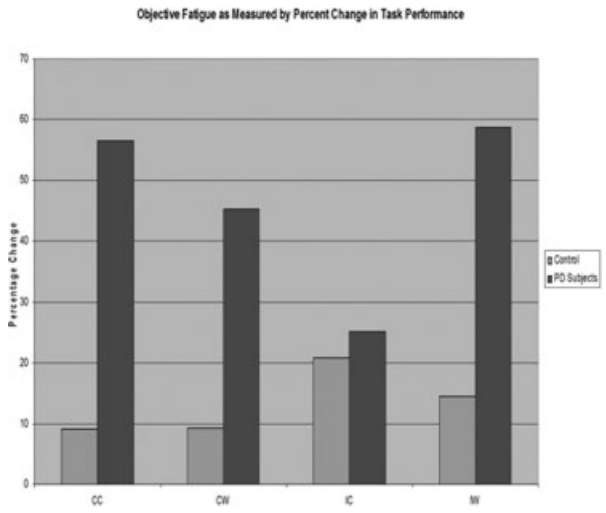

FIG. 1 (Th-161).

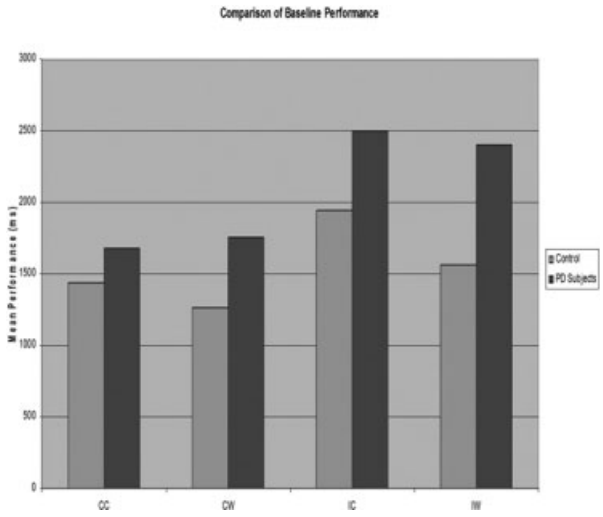

FIG. 2 (Th-161).

Conclusions: PD subjects showed greater cognitive fatigue than healthy controls. This objective cognitive fatigue does not appear to correlate with subjective fatigue complaints.

Th-162

Differences in gait characteristics of Parkinsons disease patients related to depression

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Objective: Aim of this study was to compare gait pattern characteristics in depressed and non-depressed PD patients.

Background: Gait performance and motor activity alterations are clinically observable phenomena of depressed patients. Using various methodologies to monitor gait pattern, several studies found that in depressed patients walking is correlated to affective and cognitive status. Depression in PD patients is one of the major non-motor symptoms of the disease, and has been associated with alterations in locomotion and increased fall risk. However, impact of depression status on gait characteristics is not well described. It has been found that improvement of depressive symptoms with medication improve gait characteristics, however differences and possible effects are not elucidated.

Methods: Patients were divided into two groups according to DSM IV criteria for depression. Also, evaluation included Hamilton Depression Rating Scale, total UPDRS to assess motor status and MMSE test, in order to exclude demented patients. Subjects performed a simple walking task, a dual-motor task, a dual-cognitive task, and a combined motor and cognitive task. Measurement of spatiotemporal gait characteristics was performed on the GAITRite walkway. Calculated parameters were gait velocity, cadence, step and stride length, single and double limb support, swing time, gait cycle and variability of those parameters (CV).

Results: We analyzed 48 PD patients, with mean age of 63.28±8.63 years (34 men, 14 women). 26 patients were with depression and 22 without depression. There was significant difference in stride time variability, double support time variability as well as swing time variability. Results show that performance on dual tasking while walking in PD patients was affected by the presence of depression. Patients walked in shorter steps, stride time and double support time were longer and variability of these parameters increased with more demanding parallel tasks, being significantly bigger in depressed PD patients in comparison to non-depressed PD patients.

Conclusions: Therefore, it is concluded that depressive symptoms in PD are associated with gait impairment during demanding dual tasking, stressing contribution of clinical symptoms to disturbance of gait.

Th-163

The course of depressive symptoms in early Parkinson's disease

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Objective: To measure the course of depressive symptoms in early PD.

Background: Little is known about the course of depressive symptoms in Parkinson's disease (PD).

Methods: We studied the course of clinically significant depressive symptoms using data from two clinical trials that followed 413 early, untreated PD subjects for 12-18 months. We measured depressive symptoms with the 15-item Geriatric Depression Scale (GDS-15); a score of ≥5 indicates clinically significant depressive symptoms. We used a time-dependent Cox model to examine the association between demographic variables, PD severity, and medication use on the time to resolution of depressive symptoms.

Results: 114 of 413 (27.6%) subjects screened positive for depression during the study, with a median GDS-15 score of 6, indicating mild symptoms. Within 6 months, 47% of subjects experienced remission of clinically significant depressive symptoms. Subjects with mild depressive symptoms were more likely to develop moderate to severe depressive symptoms (GDS≥10) than those without prior symptoms (relative risk = 6.16). Increasing severity of depressive symptoms, older age, and longer PD duration predicted a lower likelihood of symptom resolution (hazard ratios 0.83 to 0.92).

Conclusions: Mild depressive symptoms have a variable course, with remission and development of more sustained and severe symptoms occurring over time. More severe depressive symptoms may herald a protracted course.

Th-164

Nitric oxide production is decreased in the striatum of rats with L-dopa-induced dyskinesia

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Objective: Considering that NO oxidizes to the stable metabolites nitrite and nitrate measurement of these metabolites has been regarded as one of the most suitable and practical method to assess NO synthesis *in vivo*.

Background: Previous results from our group demonstrated that nitric oxide synthase inhibition decrease dyskinesias induced by chronic administration of L-DOPA in rats with unilateral 6-hydroxydopamine lesion.

Methods: In this study groups of parkinsonian and dyskinetic *Wistar* rats had their brain removed to measure tissue levels of nitric oxide metabolites NO(x)(-) (nitrite plus nitrate) in the striatum using the Griess reaction. Chronic L-DOPA treatment (30mg/kgX gavagen X 21 days) induced dyskinesia changes.

Results: 7-Nitroindazole (10 mg/kg; 7-NI) a selective to neuronal nitric oxide synthase inhibitor given 30 min before L-DOPA attenuated dyskinesia (*t-test*, $p<0,05$). NOx levels increased in the striatum ipsi and contralateral to lesion ($p<0,05$). 7-nitroindazole pretreatment reduced NOx in the striatum ipsilateral to lesion *(ANOVA,* $F_{1,18}=4,58$; $p<0,05$). L-DOPA chronic treatment *per se* reduced the levels of NOx in the striatum ipsilateral to lesion (*ANOVA,* $F_{1,28}=4,41$; $p<0,05$). 7-nitroindazole pretreatment to dyskinetic rats induced no further NOx reduction *(t-test,* $p>0,05$).

Conclusions: NO(x)(-) levels in the brain largely reflects the metabolites of neuronally, endothelially and inducibly derived

NO. The finding that exposure to 7-NI did not significantly lowered the levels of NO(x)(-) in the contralateral to lesion striatum was contrary to what was anticipated. Why this effect occurred is not immediately clear but experiments are in progress with increased 7-nitroindazole concentration.

Th-165

Cognitive dysfunctions and pathological gambling in patients with Parkinson's disease

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Objective: To investigate the neuropsychological correlates of pathological gambling (PG) in Parkinson's disease (PD).

Background: The relationship between PG and cognitive dysfunctions has been poorly explored in PD. In a previous study no difference in frontal lobe functions, evaluated with the Frontal Assessment Battery (FAB) between PD patients with PG (PD+PG) and PD patients without PG (PD–PG) was found despite more impaired planning in the former group. Thus far, no study has assessed such specific cognitive processes as cognitive flexibility or abstract reasoning that might underlie the development and persistence of PG in PD patients.

Methods: Fifteen PD patients affected by PG (identified based on DSM-IV criteria; PD+PG) without clinically evident dementia were compared with 15 non-demented PD patients not affected by PG (PD–PG). Two groups of PD patients were matched for age, length of education and gender. Clinical and neuropsychiatric features were assessed; several cognitive domains, mainly related to executive functions, were explored by means of standardized neuropsychological tasks.

Results: PD+PG and PD-PG did not differ on clinical and neuropsychiatric aspects. PD+PG patients performed significantly worse than PD–PG patients on cognitive tasks that evaluated visuo-spatial long-term memory and several frontal lobe functions. After Bonferroni correction, differences remained significant on the Frontal Assessment Battery (FAB) ($p=0.001$), on phonological fluency task ($p=0.003$) and on the Trail Making Test, part B minus part A ($p=0.002$). Logistic regression analysis demonstrated that low scores on the FAB were the only independent predictor of PG (odds ratio, 27.9; 95% CI: 2.82-277.95, $p= 0.004$).

Conclusions: The results indicate an association between PG and frontal lobe dysfunctions in non-demented PD patients. Low scores on the FAB indicate PD patients at high risk for PG.

Th-166

Bilateral and partial lesions of the VTA dopaminergic neurons in rat: A model of parkinsonian apathy in rat?

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Objective: To develop and characterize the hypo-dopaminergic behaviors induced by a selective and partial destruction of the Ventral Tegmental Area (VTA) dopaminergic (DA) neurons.

Background: In PD patients with motor symptoms well-controlled by STN-DBS, DA treatment can be greatly reduced. However, some stimulated patients complained of lack of motivation after drug withdrawal. In this case, STN-DBS could be not effective enough to fully replace the action of DA drugs on non-motor symptoms probably resulting from VTA DA denervation. This post-operative apathy might also be a direct consequence of STN-DBS. Therefore, whether this apathetic state is unmasked by drug withdrawal or directly results from the STN-DBS is a critical question.

Methods: Bilateral partial (50-60%) lesions of the VTA were performed by in situ injection of 6-hydroxydopamine (6-OHDA). Lesioned rats were tested with different behavioral tests: 1) Accelerating rotarod: to evaluate the sensorimotor coordination; 2) Runway paradigm for food: food-restricted rats were required to traverse a straight alley (100 cm long) in order to obtain food. Control and lesioned rats were placed in a starting box with a sliding door separating the box from the runway. The latency for each rat to reach and eat the food placed at the far end of the runway was recorded. By this mean, the motivation of the animals to obtain food reinforcement was evaluated; 3) Novelty seeking test: Rats have been placed in an open field that contains a novel and unfamiliar, inanimate object. The latency to start and the time spent at exploring the novel object was measured.

Results: Absence of locomotor deficit was observed in lesioned rats and was a good criterion for the selectivity of the VTA lesion. Data showed that VTA lesion induced a loss of motivation for food seeking in the runway paradigm and a significant increase of the latency to start and of the time spent at exploring the novel object.

Conclusions: DA lesion of the VTA seems to be the best candidate for underlying apathetic-like behaviors. Effects of levodopa and selective DA agonists as well as those of STN-DBS are actually evaluated. Neurochemical, electrophysiological and cellular approaches will be used to clalrify the anatomical-functional substrate involved in the apathetic-like behaviors observed.

Th-167

Dopaminergic addiction to increase artistic creativity

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Objective: We want to draw attention to patients with Parkinson's disease (PD) who are engaged in a creative and artistic profession who may have a higher susceptibility to develop compulsive abuse of dopaminergic drugs in order to maintain or enhance their creativity.

Background: A small group of PD patients develops a pattern of compulsive medication use leading to disabling motor and socially destructive behavioural features. Management of patients who have developed such a dopamine dysregulation syndrome (DDS) can be very difficult. Hence, to early identify and carefully monitor at-risk individuals is crucial.

Methods: We describe four illustrative cases of PD patients (3 male, 1 female) who were all professional artists and developed compulsive abuse of dopaminergic drugs.

Results: All patients had onset of PD at a relative young age (range 28 to 48 years) with a fairly benign disease course from a motor point of view, even after a mean disease duration of 13.5 years. Despite their objectively well controlled physical symptoms, they shared a constant need for increased doses of dopaminergic drugs. This led to development of a DDS with abnormal behaviours such as pathological gambling (case 1), hypersexuality (case 1), paranoia and delusions (cases 1, 3, 4), punding (case 4), and placed considerable strain on personal relationships (cases 1-4), caused legal difficulties (cases 1, 4), and severe dyskinesias (case 4). All 4 patients admitted to need increased doses of dopaminergic drugs to enhance their creative impulses. In case 1 withdrawal of the dopamine agonist together with introduction of clozapine and cognitive behavioural therapy resolved the abnormal behaviours, in case 2 self-administration of higher doses could so far be prevented by patient education, in case 3 paranoid delusions and morbid jealousy improved with switching from cabergoline to levodopa, while in case 4 all attempts to treat her DDS remained unsuccessful due to lack of compliance.

Conclusions: PD patients engaged in an artistic profession may–besides the well known risk factors such as young age at onset, male gender, heavy alcohol consumption, illegal drug use, history of affective disorder–be at risk to develop a DDS. Balancing the drug requirement for treating motor symptoms of PD on the one hand and improving creativity on the other hand have to be evaluated with caution.

Th-168

Effects of DBS on and off on voice quality and fluency of speech

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Objective: To examine the effects of deep brain stimulation of the subthalamic nucleus (STN-DBS) treatment for Parkinson's disease (PD) on voice quality and articulatory fluency as influenced by speech task.

Background: The use of STN-DBS in PD improves tremor and rigidity, but has variable effects on motor speech. The interactions between speech characteristics, speech task and STN-DBS effects are not known. To study the effects of DBS on cerebral control of speech, this project focused on voice quality and fluency, using acoustic measures obtained in two motor speech tasks.

Methods: Six persons diagnosed with PD, who were treated with STN-DBS, provided speech samples in the ON and OFF-DBS states, separated by at least a week and without morning medication. From a sample of conversational speech, 30 phrases were excerpted for a repetition task. This enabled within-subject measures of syllables and vowels for similar phrases spoken as conversation and repetition in ON and OFF DBS states. To examine voice quality, harmonic-to-noise ratios (HNR), a measure of resonance, were obtained for vowels using PRAAT speech analysis software. As a fluency measure, syllables were delineated in the wave form and proportions of dysfluent syllables were calculated.

Results: An analysis of the HNR of vowels extracted from conversational speech and from repeated phrases taken from the conversations revealed significant effects of speaking task (conversation versus repetition) [$F(1,5) = 13.821$; $p = 0.014$] and an interaction between speaking task and DBS [$F(1,5) = 10.399$; $p = 0.023$]. HNR was higher for repetition in the OFF state compared to DBS ON, when HNR did not differ with task. An analysis of the speech fluency during the two tasks also revealed significant effects of DBS [$F(1,5) = 9.094$; $p = 0.03$] and task [$F(1,5) = 7.421$; $p = 0.042$]. The percentage of syllables produced was closer to the number of target syllables (more fluent) in the DBS OFF condition and during repetition.

Conclusions: STN-DBS affected voice quality and speech fluency differently, improving voice quality while decreasing fluency. These effects varied with speech task. Voice quality and articulatory fluency measures showed greater impairment in conversation than repetition, especially on the OFF state [Supported by R01 DC007658].

Th-169

Frequency of compulsive traits in 90 newly diagnosed patients with Parkinson's disease

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Objective: To assess behavioural and cognitive features in newly diagnosed PD patients before the initiation of dopamine replacement therapy.

Background: A range of compulsive behaviours has been reported in treated PD but whether this is linked to medications or rather to predisposing personality traits is debated.

Methods: We evaluated 90 consecutive newly diagnosed PD patients (mean age: 59.97±9.16yy; mean duration: 15±14 mm; mean UPDRSIII: 16.9±9; M/F=61/29), who had never been treated with dopaminergic therapy. General cognitive assessment was performed using MMSE and FAB; compulsive sexual behaviour, compulsive buying, intermittent explosive disorders, were assessed by the Minnesota Impulsive Disorders Interview (MIDI). We also evaluated collecting behaviour, pathological gambling (South Oaks Gambling Screen, SOGS) and impulsivity (Barratt Impulsiveness Scale, BIS11), obsessive-compulsive symptoms (Maudsley Obsessional-Compulsive inventory, MOCQ), and depression (Geriatric Depression Scale, GDS).

Results: Overall 34% PD patients (31/90) reported at least one compulsive behavioural (CB) trait at MIDI. However, none of them satisfied DSM-IV criteria for impulse control disorders. Compulsive buying, collecting behaviour and compulsive sexual behaviour were the most common (12%). Mean BIS 11 score was 63.4±9.713; MOCI mean total score was 4.8±3.5. Intermittent explosive disorder was more frequent in males (8/52 vs. 0/29). We found that patients with at least one CB had longer PD duration (19.38±16.7 months) than patients without CBs (12.61±13.5 months) and differed in education years (13.23±4.7 yrs vs. 10.76±4.2). However, they did not differ in MMSE and FAB scores.

Conclusions: Our data show that CB traits are frequent in PD and their identification requires specific scales. Prospective assessment will determine whether pathological behaviours will emerge in these patients during chronic dopaminergic therapy. Nonetheless, we think these results support a key role for predisposing personality in behavioural disorders.

Th-170

Development of Synuclere: A novel small molecule that effectively reduces brain alpha-synuclein aggregation and improves motor dysfunction

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Objective: To identify and develop novel small molecule compounds that specifically target alpha-synuclein aggregation in Parkinson's disease.

Background: Synuclere represents the development of a novel small molecule that specifically targets alpha-synuclein aggregation in Parkinson's disease. From a unique small molecule library developed at ProteoTech, lead compounds were identified that caused a marked reduction in alpha-synuclein aggregation in vitro and in cell-based assays, and showed good "drugability" characteristics and non-toxic/safety profiles.

Methods: Thioflavin T fluorometry, Congo red binding, and CD spectroscopy demonstrated effects of Synuclere lead compounds on inhibition of alpha-synuclein aggregation in vitro. For cell culture studies, neuronal cells that overexpressed A53T alpha-synuclein and accumulate Thioflavin-S positive intraneuronal aggregates following rotenone treatment were used. Lead compounds were administered i.p. (50mg/kg/day) for 6 months to 12-month old alpha-synuclein transgenic mice. Synuclein levels in brain were determined by western blotting and quantitation. Motor function was determined by the beam traversal test, rotorod test, pole test and/or olfactory test.

Results: Three major lead compounds were identified that demonstrated a marked inhibition of alpha-synuclein aggregation in vitro and in cell culture. These compounds demonstrated good "drugability" characteristics including a) non-binding to brain receptors, transporters, and/or channels, b) no significant CyP450 enzyme inhibition, c) good levels of free drug in plasma (i.e. plasma protein binding), and d) moderate to high stability in human and mouse microsomes. Compounds administered to 12-month-old human alpha-synuclein transgenic mice (for 6 months) demonstrated a significant marked reduction of brain alpha-synuclein levels (by 40-70%). These compounds also demonstrated a significant marked improvement (by 30-40%) in motor dysfunction primarily as shown by the beam traversal test.

Conclusions: ProteoTech has identified a novel small molecule that is believed to represent a new disease-modifying drug for the treatment of alpha-synuclein aggregation and accumulation (in Lewy bodies) in Parkinson's disease and related disorders.

Th-171

Suicide and suicidal ideation in Parkinson's disease

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Objective: To evaluate suicide-specific mortality in a cohort of PD patients, and suicidal and death ideation in PD, and their relationship to clinical and demographic data.

Background: Little is known about the prevalence and correlates of suicidal behavior in Parkinson's disease (PD).

Methods: In the first part of our study, we conducted an 8-year follow-up of a cohort of 102 consecutive PD patients, recruited in our out-patient clinic from January to April, 2000. In the second part, we tested 128 PD patients for death and suicidal ideation and administered an extensive neurological, neuropsychological and psychiatric battery.

Results: Suicide-specific mortality in our patients group was 5.3 (95% CI 2.1-12.7) times higher than expected. Current death and/or suicidal ideation was registered in 22.7%. On univariante logistic regression analysis, psychiatric symptoms (depression, but also anxiety and hopelessness), but not the PD-related variables, were associated with such ideation. On multivariate logistic regression analysis this association held for major depression (odds ratio=4.6; 95% CI 2.2-9.4; p<0.001), psychosis (odds ratio=19.2; 95% CI 1.4-27.3; p=0.026), and increasing score of the Beck Hopelessness Scale (odds ratio=1.2; 95% CI 1.0-1.4; p=0.008).

Conclusions: The suicide risk in PD is maybe not as high as it may be expected, but is certainly not trivial. According to our data almost a quarter of PD patients had death and/or suicidal ideation, that may significantly influence their quality of life.

Th-172

Increased striatal dopamine release in parkinsonian patients with pathological gambling: A 11C raclopride PET study

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Objective: We describe results of a [11C] raclopride PET study comparing dopaminergic function during gambling in PD patients with and without PG following dopamine agonists.

Background: Pathological gambling (PG) is an Impulse Control Disorder (ICD) reported in association with dopamine agonists used to treat Parkinson's disease (PD). Functional imaging studies have consistently demonstrated abnormalities of dopaminergic function in patients with drug addictions, but to date no study has specifically evaluated dopaminergic function in PD patients with ICDs.

Methods: Seven PD patients with PG and seven PD patients without history of gambling participated in the study. All patients with PG developed pathological gambling on exposure to dopamine agonists (pramipexole n= 5 or ropinirole n= 2) independent of the timing of initiation of levodopa therapy. Subjects were studied after overnight withdrawal of their anti-parkinsonian medications with [11C] raclopride PET to measure changes in striatal dopamine D2/D3 receptor binding during gambling. Each subject underwent two [11C] raclopride PET sessions, one during performance of a gambling task and one during a control task.

Results: Patients with PG demonstrated greater decreases in binding potential in the ventral striatum during gambling (13.9 %) than control patients (8.1 %), likely reflecting greater dopaminergic release. Ventral striatal bindings at baseline during control task were also lower in patients with PG.

Conclusions: Although prior imaging studies suggest that abnormality in dopaminergic binding and dopamine release may be markers of vulnerability to addiction, this study presents the first evidence of these phenomena in PG. The emergence of PG in a number of PD patients may provide a model into the pathophysiology of this disorder.

Th-173

Prevalence and clinical correlates of apathy and depression in Parkinson's disease

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Objective: To investigate prevalence and clinical correlates of apathy and depression in Parkinson's disease (PD) and to clarify whether apathy is a distinct syndrome or only a symptom of depression.

Background: Although PD is mainly a movement disorder, non-motor symptoms including psychiatric and behavioral problems are frequently observed. Apathy and depression are the most prominent symptoms among them. Depressed patients often have symptoms of apathy. However, it has been suggested that apathy can occur in the absence of depression.

Methods: One hundred and fifty patients with PD (mean age, 69.7 years) having a mean disease duration of 6.3 years were asked to complete the Beck depression inventory (BDI) to assess depression and the Japanese version of the Starkstein's apathy scale(AS) to assess apathy and QOL battery comprising of the EQ-5D and PDQ-39 to assess QOL. A complete neurological examination including the Hoehn and Yahr (Yahr) stage, the Unified Parkinson's Disease Rating Scale (UPDRS), and the Mini- Mental State Examination (MMSE) was performed on the same day.

Results: Apathy (AS>16) was diagnosed in 60 % of the patients and depression (BDI> 13) in 56%. In 43% of the total sample, apathy coexisted with depression, whereas 13% had depression without apathy, and 17% apathy without depression. Twenty-seven percent of the PD patients had neither apathy nor depression. There were significant correlations between AS and BDI scores (P<0.001). However, AS scores were significantly associated with low MMSE scores (P<0.001), higher UPDRS scores (P<0.001), higher Yahr stages (P<0.01) and higher age (P<0.01), whereas a significant correlation was found only between BDI and UPDRS scores for such variables. Both AS and BDI scores were significantly correlated with the scores of both ED-5D (P<0.001 and P<0.001, respectively) and PDQ-39 (P<0.001 and P<0.001, respectively). However, multiple regression analysis revealed that depression in PD was strongly correlated with emotional well-being (P<0.001) and communication (P<0.001), whereas apathy was mainly determined by cognition (P<0.01).

Conclusions: The present study suggests that apathy and depression may be separable in PD, although both of them are common in the PD patients and are associated with QOL.

Th-174

Do affective symptoms depend on motor disability and activities of daily living in Armenian patients with Parkinson's disease?

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Objective: To determine relations between affective symptoms and motor disability and activities of daily living in patients with Parkinson's disease (PD) in Armenia.

Background: Depression and anxiety are among most commonly seen behavioral abnormalities in PD being possible preclinical risk factors. Relations between affective symptoms and disease itself are not clear. Biological rather than reactive basis for mood disorders is suggested for PD.

Methods: Fifty-nine non-demented PD patients aged 43-80 (Mean age=66.4 years, F=47.5%) were enrolled in the study. PD was diagnosed according to UK PDS Brain Bank criteria. Patients passed evaluation through all UPDRS domains, Hoehn&Yahr (H&Y) staging and Schwab and England Activities of Daily Living (ADL) Scale. Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) were used for assessment of depression and anxiety. Severity of depression was assessed according to HAMD score: mild depression (10-16), moderate (17-27), severe (>27). Severity of anxiety was assessed according to HAMA score: mild anxiety (18-24), moderate (25-29), severe (>29). Proportional analysis and Spearman's correlation test were used for statistics.

Results: Enrolled patients had H&Y stages 1-4 and ADL scores 40-100%. Thirty patients (51%) had clinically significant depression (14%–severe, 37%–moderate) and 8 patients (13.6%) had marked anxiety (3.4%–severe, 10.2%–moderate). Results by HAMD scale positively and significantly correlated with HAMA scores (r=0.663, p<0.01). We found also significant positive correlations between

UPDRS domain 1 and both HAMD and HAMA: r=0.673 and 0.545 respectively ($p<0.01$) but no correlation with UPDRS domains 2, 3 and total score. Results show no relation between HAMD and HAMA scores and H&Y and ADL values.

Conclusions: We found that affective symptoms are prevalent in Armenian PD patients. UPDRS domain 1 (mentation, behavior and mood) could be suggestive for mood disorders and their further evaluation. Severity of depression and anxiety did not correlate with motor disability, stage of disease and ADL. Our results are suggestive of endogenous origin of affective symptoms in PD.

Th-175

Impairment of visuomotor control in Parkinson's disease

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Objective: To investigate whether Parkinson's disease (PD) patients become impaired in tasks requiring them to release the button on perception of a visual target captured by making a saccade.

Background: PD patients are not only impaired in initiation of motor actions but also in visual perception. However, how the visual impairment relates to motor behavior is unclear. In daily activities, we plan and control our motor actions based on visuospatial information collected by proactive gaze shifts and fixation.

Methods: 74 PD patients and 66 age-matched controls. Subjects performed visually guided saccade (VGS), gap saccade (GAP) and memory guided saccade (MGS), each started by pressing a button. In VGS and GAP, a central spot of light came on after the button press, requiring them to fixate. After a random period, the spot went away and a target appeared at random locations to the left or right, which the subjects had to foveate. Shortly thereafter, the target point dimmed, upon which they had to release the button. In MGS, while the subjects fixated the central spot, a peripheral stimulus ("cue") appeared briefly. They were required to maintain fixation until the spot disappeared, when they had to make a saccade based on their memory to where the cue had appeared. The target spot turned on again 600ms after the offset of the fixation point and dimmed, and the subjects were required to release the button. The time from target presentation to dimming (target duration) was randomly varied across trials. In each task, latency, amplitude and velocity of the first saccade were measured. The reaction time (RT) of button release was also measured from the time of target dimming.

Results: In both normal subjects and PD patients, RT gradually decreased with increasing target duration, reaching a plateau at durations of above 1500ms. RT in PD patients was consistently slower, but decreased more rapidly with duration. In addition, it reached a plateau at longer target durations.

Conclusions: The longer RT in PD is not only due to the slowed movement but also due to delayed visuomotor control. This suggests that PD patients are slow in performing motor actions not only because of bradykinesia or impaired visual perception, but also because they are slower in preparing actions based on visuospatial information collected by saccades.

Th-176

Predictors of depressive symptoms in patients with Parkinson's disease

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Objective: To determine the predictors of the depressive symptoms valued by the administration of the Modified Beck Depression Inventory (BDI) in PD patients.

Background: It is estimated that about 30–90% of patients with Parkinson's disease(PD) are suffering from depression. Factors including stage of PD, progression of motor decline and cognitive impairment can be related to the development of depression in PD patients.

Methods: 74 patients with diagnosis of PD in according to clinical criteria of the UKBBPD have been enrolled. The patients were assessed using Hoehn and Yahr stage (HY), Unified Parkinson's Disease Rating Scale (UPDRS), Modified Beck Depression Inventory (BDI), de Boer's Parkinson's disease quality of life questionnaire, and Mini-Mental State Examination (MMSE). Patients with mild, moderate, or severe depression were classified using cut-off BDI scores of 10, 19, and 30 or more, respectively. Stepwise regression analyses were conducted to identify determinants of depression in PD patients.

Results: 26 male and 48 female patients were included. The mean age was 61.2 yrs (range 36-80), the mean HY stage was 2.7 (1.0-5.0) and the mean disease duration was 6.1 yrs (1-16). The patients mean score of BDI was 18.17 (SD 8.13; range 0-33) with the following distribution for categories: absence of depression in 15.8% of patients; mild 31.7%; moderate 42.5%; severe depression 10.0%, respectively. Patients with depression had longer duration of disease ($p<0.005$), more advanced HY stage ($p<0.01$), greater akinesia subscore on UPDRS ($p<0.005$), and lower quality of life score on Boer ($p<0.001$) than non depressed patients. In contrast, there were no significant differences in patient age, age of onset, sex, and tremor subscore on UPDRS. When the predictors were entered into a stepwise regression analysis, rigidity ($p<0.001$), akinesia ($p<0.001$), motor score on UPDRS III ($p< 0.007$), and reduced quality of life ($p<0.001$) on Boer were the most significant predictors (44.6% of the variables) of development of depression in PD patients. This association was not seen between BDI score and cognitive function on the MMSE.

Conclusions: Results replicate that higher levels of self-reported depressive symptom in patients with PD are associated with greater impairment of motor function and reduced quality of life but not cognitive decline. These findings suggest that depression in PD may occur independently of cognitive decline.

Th-177

Is upper limb freezing related to freezing of gait in patients with Parkinson's disease?

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Objective: (1) To evaluate the relationship between the occurrence of freezing episodes in the upper limbs (FO-UL), freezing of the feet, freezing of gait (FOG) and clinical outcomes in PD patients with and without FOG.

Background: Previous study suggests a correlation between FO-UL and FOG (Rs=0.64[1]). The general nature of freezing problems in PD is not fully understood at present.

Methods: A group of freezers and non-freezers as defined by the FOG-Questionnaire and matched for disease severity completed 2 bimanual coordination tasks in the off-phase of the medication cycle: flexion/ extension of the index finger (task 1) and pronation/ supination movements of the forearm (task 2). A Micro 1401 acquisition unit recorded angular displacements of fingers and hands at a sampling frequency of 2000Hz by means of analogue encoders. 2 coordination modes (in-phase and anti-phase) were effectuated. The number and duration of FO-UL episodes defined as '*a period of involuntary stop or of clear absence of effective cyclic movements lasting longer than 75% of normal cycle duration*' were determined. In addition, the number of freezing episodes during three trials of alternating foot movements and patients' scores on UPDRS III were recorded clinically.

Results: Preliminary analysis of 5 freezers and 5 non-freezers demonstrated that FO-UL episodes were present in all freezers in the fingers (task1) and highly correlated with FOG-Q scores (Rs=0.93) and the presence of freezing episodes during foot movements (Rs=.79) which occurred in 4 of 5 freezers. Only 2 freezers showed freezing in the forearm (task2). Freezing episodes in finger, forearm and foot movement were absent in non-freezers. Both presence and

duration of FO-UL (in task1) were correlated with scores on UPDRS items 23-25 for finger and hand coordination (Rs=.72 and Rs=.74). Freezing episodes were more often present in anti-phase than in-phase mode ($p<.05$).

Conclusions: These data suggest that FOG is related to a general motor deficit that affects different types of bilateral coordination. Freezing episodes appeared easier to provoke when coordination is less stable, such as movement of distal joints (fingers, feet) vs. proximal joints (forearm), particularly in anti-phase mode. [1] Nieuwboer A. et al. *EJN, in press.*

Th-178

Association between dopamine and serotonin transporter availability, psychiatric symptoms, and cognitive abilities in Parkinson's disease

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Objective: To determine the association between dopamine and serotonin transporter (DAT and SERT) availability and non-motor symptoms in Parkinson's disease (PD).

Background: In PD there is a loss of substantia nigra dopaminergic neurons with secondary nigrostriatal impairments in dopaminergic function. In addition, PD pathological changes occur relatively early in the serotonin-producing dorsal raphe nuclei. It has been suggested that impairments in both neurotransmitter systems may contribute to the high prevalence of non-motor symptoms in PD, but there has been little neuroimaging research specifically examining this. The integrity of the dopaminergic and serotonergic systems can be specifically assessed with SPECT functional imaging using the ligands [99mTc]TRODAT-1 and 123I ADAM, which binds to the DAT and SERT, respectively.

Methods: 11 PD patients underwent TRODAT scanning, and an additional 9 underwent ADAM scanning. Patients were assessed with a comprehensive psychiatric and neuropsychological battery. Partial correlations (controlling for age and disease severity) and t-tests were used to examine the associations between DAT availability, SERT availability, and non-motor variables.

Results: Characteristics of the TRODAT group were: sex =72.7% male, mean (SD) age =59.2 (10.4) years, PD duration =5.1 (3.4) years, and current depression diagnosis =54.5%. Increasing severity of depression as measured by the GDS-15 ($r= -.76$, $p=.02$), with a suggestion for the IDS ($r= -.61$, $p=.08$), was associated with decreased left caudate:left anterior putamen DAT availability. Increasing severity of anxiety symptoms was also associated with a diminished left caudate:left anterior putamen DAT availability ($r= -.69$, $p=.04$). Analyses for the 9 ADAM patients are underway and will be completed in time to present at the MDS meeting.

Conclusions: These pilot results suggest that depressive and anxiety symptoms are associated with changes in the dopaminergic system in PD. Specifically, the association between increasing severity of affective symptoms and relatively greater denervation of the left caudate nucleus suggest that denervation of specific nigrostriatal pathways may contribute to psychiatric symptoms in PD.

PARKINSON'S DISEASE: CLINICAL TRIALS

Mo-177

Observer bias in biological/surgical trials of novel Parkinson's disease therapies

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Objective: To assess the relative importance of placebo effect and observer bias in clinical evaluations of surgical therapies for Parkinson's disease.

Background: Six times in the last 10 years a surgically administered biological therapy for Parkinson's disease (PD) that appeared to yield significant clinical effect in open-label feasibility studies, failed to generate similar improvements when tested in a prospective, double-blind fashion. While much has been made of the fact that the actively treated patients failed to improve more than the sham-surgery controls, little has been written about the importance of observer bias in the initial open-label trials.

Methods: Meta-analysis of the clinical response data reported from both the open-label feasibility trials and the subsequent double-blind, sham surgery-controlled trials of these six biological/surgical therapies.

Results: For the three fetal cell transplantation therapies (two human; one porcine) a direct comparison of the clinical responses observed in the initial open-label trials and the subsequent double-blind trials could not be made because different outcome measures were employed for each study. Nevertheless, the reported responses in the double-blind trials were far less dramatic than those reported in the open-label trials. For the three most recently tested therapies, a striking and measurable trend is noted. In four open-label trials of these three therapies (intraputaminal infusion of glial-derived neurotrophic factor, transplantation of retinal pigmented epithelial cells (ie SpheramineTM), and Adeno-associated virus-Neurturin gene therapy) an average 43% (range: 36-57%) improvement in motor function is reported as measured in the off state with the Unified Parkinson's Disease Rating Scale Motor Sub-score (UPDRSM). In the subsequent double-blind trials, however, the off state UPDRSM improvement averaged just 11%.

Conclusions: Observer bias appears to be just as important as placebo effect in explaining why six promising biological/surgical therapies for PD have ultimately proven ineffective when tested in a double-blind fashion. These data call into question the value of open-label feasibility trials of novel PD therapies. Instead, blinded, videotaped evaluations by qualified independent investigators should be conducted before progressing to the risk and expense of a sham surgery-controlled trial.

Mo-178

Intraputaminal AADC gene therapy for Parkinson's disease: Results of a phase 1 study

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Objective: To evaluate the safety and tolerability of gene therapy with human aromatic L-amino acid decarboxylase (*AADC)* in an open-label study of patients with moderately severe Parkinson's disease (PD).

Background: Levodopa therapy seems to become less effective over time in patients with PD. This has been attributed to progressive loss of AADC, which converts levodopa into dopamine, as a result of degeneration of nigrostrial neurons. In a nonhuman primate model of PD, infusion intrastriatally of the *AADC* gene using an adeno-associated viral (AAV) vector is associated with a good therapeutic response to low-dose levodopa with minimal side effects, in contrast to the complications associated with higher doses of levodopa.

Methods: Ten patients with moderate to advanced PD received bilateral convection-enhanced infusion of AAV-AADC vector into two sites in each putamen. The first 5 patients received 9×10^{10} vector genomes (vg) and the next 5 patients received 3×10^{11}vg. We used standardized clinical rating scales (UPDRS and motor diaries), and performed PET scans using the AADC tracer, fluoro *meta*-tyrosine, at baseline and 6 months after infusion as an in-vivo measure of gene expression. (ClinicalTrials.gov registry, number NCT00229736.)

Results: The treatment was well tolerated although there were three intracranial hemorrhages, one symptomatic (with near-complete recovery) and two asymptomatic (revealed by postoperative MRIs). There were improvements in the total and motor UPDRS rating

scales in both groups of patients. Motor diaries also showed increased on-time and reduced off-time without an increase in on-time with dyskinesia. At 6 months after gene transfer, the PET studies showed an increase of uptake (K_i^c) in the putamen of 30% in the low-dose cohort and 75% in the high-dose cohort.

Conclusions: The AAV-AADC gene therapy was thus well tolerated and provided dose-dependent gene expression as judged by the PET scan data. The data suggest some efficacy of this treatment. A phase 2, double-blind, study involving sham therapy now seems warranted to determine more clearly the therapeutic role of AAV-AADC gene therapy and exclude placebo effects.

Mo-179

Intrajejunal levodopa infusion in Parkinson's disease: A pilot multicentre study of effects on non-motor symptoms using the PD non motor scale

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Objective: Report from a prospective observational international multi-centre open label study where the effects of intrajejunal infusion of levodopa/carbidopa gel on non motor symptoms (NMS) of advanced PD and on the relationship with motor changes and health related quality of life (HrQoL) were explored.

Background: Advanced PD is complicated by NMS and some can respond to dopaminergic therapy. A holistic quantification of NMS of PD is possible using the internationally validated PD NMS Scale (NMSS).

Methods: Percutaneous endoscopic gastrostomy (PEG) was performed by the gastroenterologist under local anaesthesia and sedation with a benzodiazepine. Levodopa/carbidopa gel infusion via the PEG was started and the dose titrated to the patient's need in the next 7-18 days of hospitalization. Infusion period varied between 12 -24 hrs, in 6 cases nighttime rotigotine patch was used to counteract rebound nocturnal akinesia where 24hr infusion was not possible. The primary outcome measure was the NMSS domains and total (NMSST) score over a 6 month follow up period.

Results: 22 cases with advanced idiopathic PD (as per the PDS-UK Brain Bank criteria) from centres in the UK (6 cases), Germany (9 cases) and Italy (7 cases) initiated on the gel infusion in 2007 and 2008 and followed-up prospectively. Patients were 72.7% males, age 58.6±9.1 yrs and disease duration 15.3±5.9 yrs (median:14; IR: 12–17 yrs). A statistically significant beneficial effect was shown in 6 out of the 9 NMSS domains: Cardiovascular, Sleep/Fatigue, Attention/Memory, Gastrointestinal, Urinary and Miscellaneous and for the NMSST alongside significant improvement of motor symptoms (UPDRS part 3 and 4 in "best on" state) and dyskinesias/motor fluctuations, the Parkinson's disease sleep scale (PDSS) and the PDQ-8 (QoL measure). The PDQ-8 scores highly significantly improves with the changes in NMSST while a moderately strong correlation observed with UPDRS changes. The highest proportion of improvement was related to the Sleep/Fatigue domain of NMSS (86.4%).

Conclusions: This first report of the levodopa infusion effect NMSS in advanced PD shows a striking improvement on several NMSS domains mainly sleep, hence highlighting the dopaminergic basis of some NMS of PD. Improvements in NMS also have a robust correlation with HrQoL.

Mo-180

Glycopyrroniumbromide for the treatment of sialorrhea in Parkinson's disease

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Objective: To determine the efficacy and safety of glycopyrroniumbromide 1 mg t.i.d. in the treatment of sialorrhea in patients with PD.

Background: Sialorrhea affects approximately 75% of patients with Parkinson's disease (PD). Sialorrhea is often treated with anticholinergics, but central side effects such as drowsiness, confusion or memory impairment limit their usefulness. Glycopyrroniumbromide is an anticholinergic with a quaternary ammonium structure that does not cross the blood-brain barrier in great amounts. Glycopyrroniumbromide exhibits minimal central side-effects, which may be an advantage in patients with PD of whom a significant portion already has cognitive deficits.

Methods: We conducted a 4-week randomized, placebo-controlled, double blind, cross-over study with glycopyrroniumbromide 1 mg t.i.d. in 25 patients with idiopathic PD. The severity of the sialorrhea was scored on a daily basis by the patients or a caregiver with a sialorrhea scoring scale ranging from 1 (no sialorrhea) to 9 (profuse sialorrhea).

Results: Two patients were excluded prior to randomisation because they met the exclusion criteria. Patients included had a mean (SD) age of 70.0 (±7.8) years and a mean (SD) disease duration of 10.2 (±8.6) years. One patient was excluded from the efficacy analysis due to a protocol violation. The mean sialorrhea score (SD) significantly improved from 4.7 (±1.7) with placebo to 3.9 (±1.6) with glycopyrroniumbromide ($p=0.048$). Nine patients (40.9%) had a clinically relevant improvement of at least 30% with glycopyrroniumbromide versus one patient (4.5%) with placebo ($p=0.021$). Sixteen patients (72.7%) had at least some improvement with glycopyrroniumbromide, compared to five (22.7%) with placebo. There were no significant differences in adverse events between glycopyrroniumbromide and placebo treatment. We did see a trend in dry mouth being reported more frequently with glycopyrroniumbromide. This adverse event is directly linked to the therapeutic effect of glycopyrroniumbromide.

Conclusions: Glycopyrroniumbromide 1 mg t.i.d. is an effective and safe treatment option for sialorrhea in patients with PD.

Mo-181

Which Parkinson's disease (PD) patients function well without levo-dopa (LDopa) treatment for more than 5 years?

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Objective: To study the clinical characteristics of PD patients who stay well without Ldopa for more than 5 years after diagnosis.

Background: Dopamine agonists (DA) is the preferred initial therapy in patients with de-novo PD with age less than 70. But most of them eventually require Ldopa. Studies showed that only around 16% of such patients can stay on DA alone without Ldopa 5 years after diagnosis. The clinical characteristics of those PD patients who enjoy good functional status without Ldopa are not well described.

Methods: All PD patients who have been followed up in our PD clinic are enrolled into our PD data bank The diagnosis was made on UK Brain Bank Criteria. At the time of analysis, patients with PD diagnosed for more than 5 years were identified from our PD data bank and included in this study. Those not taking LDopa after 5 years of diagnosis were studied and compared with the rest of the cohort.

Results: 170 patients in our data bank had diagnosis of PD for more than 5 years. 18 of them died and 20 lost follow-up. In the remaining 134 patients, 21 were classified as tremor predominant. 11 (8.2%) of the 134 patients were doing well without Ldopa therapy at 5 years after diagnosis. The mean age at diagnosis of these 11 patients was 55, similar to 56 in the rest of the cohort, The mean period of no LDopa treatment after diagnosis in these 11 patients was 8.2 years, whereas the mean of the rest of the cohort was 2 years. During their last assessment in year 2008, 9 of these 11 patients had good motor function with Hoehn & Yahr stage <3, which was significantly more than the rest of the cohort (37/123); $p<0.001$ Tremor predominant type was significantly more common in the group not requiring Ldopa 5 years after diagnosis (64% Vs 11%,$P<0.001$).

Conclusions: Only 8% PD patients can stay well without Ldopa treatment 5 years after diagnosis. They are mostly tremor predominant patients with similar age of disease onset as other PD patients.

Mo-182

Physical therapy (PT) in Parkinson's disease (PD): A systematic review of randomized controlled clinical trials

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Objective: To review and to reevaluate systematically the literature on PT in PD.

Background: PT is widely used in PD and supposed to be useful with respect to dopamine responsive as well as to nonresponsive symptoms. Rehabilitation programs are well accepted and appreciated by patients and caregivers and contribute markedly to the total costs of healthcare in PD. In contrast to this wide use in PD the literature is poor. Most studies are small, use different techniques or are not blinded.

Methods: Only randomized studies, identified by a PubMed-search and published as full papers (1980-09/2008) with a minimum of 20 patients, a blind rater and stable medication during the study were included for further evaluation.

Results: 21/46 studies were found eligible for evaluation. The studies were very heterogeneous designed. Among the studies comparing PT with no intervention, most studies focused on dopamine-nonresponsive symptoms. The duration of the interventions varied from 3 weeks to 4 months. Follow-ups were done in only 3 studies. Some benefit has been reported in all studies but significancy was often failed. Most of the benefit was only transient and redeterioration was found 6 months after the interventions. In studies in which 2 rehabilitation techniques were compared, especially the cueing of movements might result in some benefit for the patients. In many studies, complex rating scales such as UPDRS have been used as primary outcome parameters. Thus partial benefit in any special motor function might have been missed.

Conclusions: In contrast to the long clinical experience and many empiric recommendations there is still a considerable lack of objective data and only limited evidence from randomized studies for the usefulness of PT in PD. Many studies do not fulfill the minimal criteria on a qualified study. The partial benefit which was seen in most of the small studies was less pronounced in the 3 largest studies and lost during follow-up. Almost no reliable data are available on the superiority or inferiority of different methods. Thus, despite numerous clues from various studies, with respect to the clinical and economical significance of PT in movement disorders, more carefully planned randomized studies, as well as an intensification of systematic clinical research, are urgently required in this field.

Mo-183

LRRK2 G2019 mutation in Parkinson's disease: A clinical, neuropsychological and psychiatric study in a large Algerian cohort

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Objective: To evaluate motor function and cognitive profiles in a series of 106 patients affected by Parkinson's disease (PD) and to compare the results beween LRRK2 (leucine-rich repeat kinase2) G2019S mutation carriers and non carriers..

Background: A high frequency of the LRRK2 G2019S mutation was recently demonstrated in North-African sporadic and familial PD population.

Methods: A new series of 106 unrelated Pdand 66 healthy Algerian controls were screened for LRRK2 G2019S mutation. Exon 41 of LRRK2 gene was amplified by PCR and sequenced in both directions. All the patients underwent extensive clinical, neuropsychological and psychiatric examinations. Qualitative and quantitative comparisons of demographic and clinical characteristics in patients with and without mutation were made.

Results: The G2019S mutation was identified in 34 patients (32%)(28 sporadic and 6 familial PD). It was heterozygous in familial cases and most sporadic cases (1 homozygous carrier found in a consanguineous family). Clinical characteristics of G2019S mutation carriers were comparable with non carriers but the prevalence of L Dopa–related complications such as dyskinesias were significantly higher in the carriers. Cognitive analyse did not show major differences between the two groups of patients.

Conclusions: LRRK2 G2019S mutation is frequent in Algeria which its research on first intention in PD patients. Our analysis showed that the G2019S mutation might play a role in the development of L Dopa–related motor complications such as dyskinesias.

Mo-184

Transcranial direct current stimulation for the treatment of Parkinson's disease: A randomized, double-blind, sham-controlled study

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Objective: To investigate efficacy and safety of transcranial direct current stimulation (tDCS) in the treatment of Parkinson's disease (PD).

Background: Progression of PD is characterized by motor deficits, which eventually respond less to conventional dopaminergic therapy and, thus, pose a therapeutic challenge. Deep brain stimulation (DBS) has proven its efficacy, but carries risks and is not possible in all patients. Non-invasive brain stimulation has shown promising results and may provide a therapeutic alternative.

Methods: This is the first long-term study to investigate efficacy and safety of tDCS in the treatment of Parkinson's disease using a randomized, double-blind and sham-controlled design. In eight sessions over 3 weeks, anodal stimulation was applied alternately to the motor and the frontal cortex. Assessment over a period until 3 months after the intervention included timed tests of gait and bradykinesia, Unified PD Rating Scale (UPDRS), Serial Reaction Time Task (SRTT), Beck Depression Inventory (BDI), Quality of Life (QoL) questionnaire, and a self-assessment of mobility.

Results: Twenty-five PD patients were investigated including 13 receiving real and 12 sham stimulation. Compared to sham intervention, tDCS improved bradykinesia in on and off condition for longer than 3 months and gait only in the off condition. Changes in UPDRS, SRTT, BDI, QoL or self-assessment did not differ between real and sham tDCS. No adverse events were observed.

Conclusions: TDCS of motor and frontal cortex improves bradykinesia for a longer time period and also gait in moderate PD. An immediate improvement in all measures after sham and real stimulation indicates a substantial placebo-effect which underlines the need for sham-controlled studies. The improvement beyond optimal dopaminergic treatment suggests efficacy also on non-dopaminergic deficits and its potential usefulness as an adjunctive therapeutic tool in PD. Better stimulation parameters need to be established in future therapeutic studies.

Mo-185

Training dual tasking during gait in Parkinson's disease

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Objective: To determine if dual task training of one type of added task during gait leads to improvements in dual tasking with other types of tasks.

Background: Despite studies showing the serious effects of dual task interference on gait parameters in Parkinson's disease (PD), to date there have been few studies to guide training of dual tasking. As motor learning literature emphasises the importance of task speci-

ficity, the importance of specificity of training dual tasking when walking was studied.

Methods: Gait performance under single and six dual task conditions was tested at baseline and immediately after one twenty-minute dual task training session in 14 people with ideopathic Parkinson's disease. Stride length and gait speed were measured using a GAITrite® gait mat system when walking at a comfortable speed (gait only) and when walking and simultaneously performing one of six added tasks, including cognitive and motor tasks. One twenty-minute session of training was performed focussing on improving stride length while concurrently performing cognitive tasks (word generation and counting) with verbal responses.

Results: Stride length demonstrated a significant time ($p=0.005$), task ($p=0.022$) and time x task ($p=0.011$) interaction. There was a significant increase in stride length when walking and performing all six tasks after training. Gait speed showed no time effect ($p=0.107$), but a task ($p=0.006$) and a time x task interaction ($p=0.015$). Gait speed increased when walking and performing the same type of cognitive tasks as were trained. There was no improvement in gait speed when performing added tasks that were not trained. There was no change in correct response rate from pre to post for any task.

Conclusions: Training to improve stride length whilst concurrently performing a cognitive task led to transfer of improvement in that modality (stride length) when performing all types of added tasks. It appears that people with PD were able to concentrate on and improve stride length without compromising added task performance. While training gait speed was emphasised less, it led to task-specific improvements where only the cognitive tasks trained showed improvements. These findings highlight the importance of gait training specificity and indicate that the strategy of dual task training may be more important than the tasks trained in people with PD.

Mo-186

Task switching during dual task gait training is difficult for people with Parkinson's disease

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Objective: To determine the effect of directing attention during dual task walking training on gait in people with PD.

Background: Gait is frequently impaired in people with Parkinson's disease (PD), particularly when doing another task simultaneously, but recent reports suggests this may be improved with dual task training. Dual task training studies report that greater improvements occur in older adults when trained in a variable priority manner (switching attention between tasks), than fixed priority (attending equally to both tasks).

Methods: Forty people diagnosed with PD attended a 20 minute dual task walking training session. Half were instructed to attend equally to gait and a variety of added cognitive tasks (50-50%, fixed priority). The other half were instructed to switch attention between tasks with every trial (eg. 80% attention on cognitive task trial 1, 20% trial 2, variable priority). Spatio-temporal gait performance under dual task conditions and correct response rate of the added tasks were measured pre and post training and compared between the two groups. Attendance to each task during training was evaluated via self reported visual analogue scales (VAS), and measurement of gait speed and added task performance during training.

Results: After training, both groups showed an increase in step length and velocity when dual tasking ($p<0.001$). There was no difference in dual task step length ($p>0.511$) or gait speed improvement between the groups ($p>0.686$). Both groups increased their correct response rate of the added task post training ($p<0.007$). When the self-reported VAS scores were investigated, it appeared that the variable priority group did not switch attention between tasks as instructed (mean inaccuracy 36% +/- 18%), whereas the fixed priority group reported maintaining attention closer to their goal (mean inaccuracy 10% +/- 12%).

Conclusions: Whilst varying the priority of attention between tasks is suggested to maximise dual tasking gains with training, this cohort of people with PD found switching of attention between a gait and cognitive task from trial to trial (variable priority training) difficult. This strategy may be more useful as a progression in this population rather than an initial approach.

Mo-187

Positron emission tomography (PET) study of preladenant in healthy male subjects

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Objective: To determine with PET, preladenant plasma concentration and dose needed to inhibit ^{11}C- SCH442816 binding to human brain adenosine A_{2A} receptor.

Background: Preladenant is a novel, nonmethylxanthine, highly selective A_{2A} receptor antagonist being investigated for the management of movement disorders, including idiopathic Parkinson's disease.

Methods: This was an open-label, single-center, single-dose pharmacokinetic/pharmacodynamic study performed in 18 healthy males. All subjects received an intravenous injection of the radiotracer ^{11}C-SCH442816, showing a 20,000-fold selectivity for A_{2A} receptor over A_1, A_{2b}, and A_3 receptors. A subset also received preladenant 10, 50, or 200 mg orally at various times prior to radiotracer. Extent, location, and inhibition of radiotracer binding were evaluated with PET; images were coregistered with patient MRIs. Compartmental modeling was applied to time activity curves generated by interrogating the dynamic time series with regions of interest to generate specific ^{11}C-SCH442816 binding potentials. Preladenant plasma levels were also determined.

Results: Putamen A_{2A} receptor occupancy by preladenant increased rapidly with dose and was maximal at a plasma concentration of ~50 ng/mL. The relationship between preladenant plasma concentrations and receptor occupancy was described by an Emax model. The model-predicted Emax was 85% and preladenant plasma concentrations corresponding to 50, 80, and 90% receptor occupancy were predicted to be 6, 25, and 50 ng/mL, respectively. Combined with pharmacokinetic data from 4 phase 1 studies, it was estimated that preladenant doses of 5 and 50 mg BID given 8 hours apart would provide ≥50% receptor occupancy for 12 hours/day and ≥80% receptor occupancy for 18 hours/day, respectively, in 75% of the population.

Conclusions: These results show that A_{2A} receptor occupancy is maximal at low preladenant plasma concentrations (50 ng/mL) and that occupancy duration increases with increased dosing of preladenant in healthy male subjects. Preladenant doses as low as 5 mg BID given 8 hours apart are projected to result in ≥50% receptor occupancy for the majority of waking hours in the majority of subjects.

Mo-188

Group therapy improves no motor aspects in patients with Parkinson's disease (PD)

T. Capato, M.E. Piemonte (Sao Paulo, Brazil)

Objective: The aim of this study was to assess the efficiency of a group motor training on no motors aspects like quality of life (QL), depression and fatigue.

Background: Besides motor alterations attributed to PD, now it is known that non motor aspects like fatigue and depression also interfere in the functional independence and motor performance of PD patients. Depression may be associated to diversification of size step, mainly during direction changings, predisposing to falls. Recent studies show that training in teams with general physiotherapeutic exercises, using music, gets significant results and functional improvement in PD. Evidences show that a early and regular physiotherapeutic interference, at the beginning of initial stages of PD, provides

improvement in the quality of life and in the functional skills of PD patients.

Methods: A blinded examiner carried out an assessment in the gait of 36 PD patients, average age of 65.91 years (DV=6,51), at stages 2 to 3 of Hoehn and Yarn Classification, matched by age and sex, before and after 10 training sessions (5 weeks with 45 minutes long). Patients were assessed in individual sessions using session II of UPDRS to assess independence to daily life activities AVDS and session III to assess motor performance . Through interviews, QL was assessed using Parkinson's Disease Quality of Life (PDQL), at the same way were the scales for fatigue (FSS) and Beck Depression form (BECK). Patients were elucidated and had to sign a permission term. After an initial assessment, patients performed a general motor program (MT). At the same period, the control group remained without physical activities, has only received general orientations.

Results: It was found a significant improvement after training to every non motor assessed aspects: QL ($p<0,01$), BECK ($p<0,01$), FSS ($p<0,01$). There was a significant improvement at the score of sessions II of UPDRS ($p<0,01$) and sessions III of UPDRS ($p<0,01$).

Conclusions: Such significant improvement of global motor performance through motor training in groups provided improvements in the levels of depression and fatigue in PD patients. The improvement in the QL reinforces that Physiotherapy is fundamental to minimize functional harm in PD. The improvement on fatigue may have brought functional benefits as PD patients burned less energy to do activities resulting in the improvement of QL.

Mo-189

Rythmical auditory cues improve balance control in PD patients

T. Capato, M.E. Piemonte (Sao Paulo, Brazil)

Objective: The objective of this study is to assess the efficiency of a global motor training, connected to rythmical auditory cues not associated to specific movements, on balance performance.

Background: Progressive balance disturbs restrict patients PD functional independence and life quality. There are evidences that sensorial integration deficiency causes difficulties to perform balance reactions in a right time, spreading to the difficulty of a posture maintenance. Few studies investigate trainings to improve balance and little is known in relation to the use of external auditory to the training itself.

Methods: A blinded examiner carried out an assessment in the balance of 20 PD patients, average mean age of 65.91 years (DV=6,51), at stages 2 to 3 of Hoehn and Yahr Classification, matched by age and sex before and after 10 training sessions(5 weeks with 45 minutes duration). Balance perform was assessed through BERG test (BT) e Postural Stress Test (PST). Patients also carried out an assessment of independence to the AVDs and motor performance through UPDRS. After a previous assessment, patients were divided in two groups, for order of arrival, according inclusion rules. One of the groups (GEP), carried out a motor program to balance, associated to rythmical auditory cues, the other group carried out the same program without cues (GESP).

Results: Results show that, after a motor training connected to the use of rythmical auditory cues (GEP), there was a significant improvement of balance in relation to the control training group (GESP) in an average BERG score ($p<0,01$), PSTQ ($p<0,01$) PSTO ($p<0,01$), so significant improvement in the score of session II of UPDRS ($p<0,01$) and session III of UPDRS ($p<0,01$).

Conclusions: Rythmical auditory cues provide significant improvement in PD patients balance. This improvement was obtained not only with motor training, but the exigency from the presence of the cues, established such a rythm to the motor responses which was fundamental to the improvement to the antecipatory and compensatory balance responses.

Mo-190

Rythmical cues has no influence in the improvement of gait performance in PD patients

T. Capato, M.E. Piemonte (Sao Paulo, Brazil)

Objective: The aim of this study was to evaluate a global motor training efficiency connected to auditory cues not related to walking on gait performance.

Background: Studies have investigated new treatment possibilities to shorten gait changes in PD. It is known that functional treatment improves motor difficulties in patients at the beginning of the disease. Trainings proposed in previous studies explored the use of auditory and visual cues presented in a rhythm way, connected to steps, to improve cadence, velocity and steps size. Nevertheless the very action mechanism of rhythmical cues to the improvement of the gait, has remained without explanation up to now.

Methods: A blinded examiner carried out an assessment in the gait of 24 PD patients, average age of 65.91 years (DV=6,51), at stages 2 to 3 of Hoehn and Yarn Classification, matched by age and sex, before and after 10 training sessions (5 weeks with 45 minutes long). Gait performance was assessed in short and long distance through agility test (AG), time test UP and Go(TUG) and the gait velocity in 21 an anterior displace (DA). Patients were also assessed for independence to daily life activities and motor performance using session II and III of UPDRS. Patients were elucidated and had to sign a permission term. After an initial assessment patients were divided in two groups for order of arrival, according to inclusion rules. One group (EMT) performed a global exercises program associated to the use of auditory cues and the other group performed the same program without cues (MT).

Results: After training there was a significant improvement for both groups in every applied gait test: AG($p<0,01$), DA($p<0,01$), TUG($p<0,01$), like significant improvement in the score of session II of UPDRS ($p<0,01$) and session III of UPDRS ($p<0,01$) not related to the use or not of rhythmical cues.

Conclusions: Motor training not associated with the presence or not of rythmical auditory cues, was efficient to the improvement of gait velocity to short and to long distances, besides improvement of daily life activities. Probably, the improvement of the gait occurred through general aspects of the training like: improvement of muscular vigour, flexibility, agility and *endurance*, so, rythmical cues that are not straight associated to the training of gait, has no influence in the improvement of the gait in PD patients.

Mo-191

Effects of robot-assisted gait training on freezing of gait in patients with Parkinson's disease

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Objective: Proof-of-concept pilot study to evaluate benefits of robot-assisted gait training on freezing in patients with Parkinson's disease.

Background: Freezing of gait (FOG) can be defined as an episodic inability to generate effective stepping in absence of any cause other than parkinsonism or higher level gait disorders. Its pathophysiology remains enigmatic and it is difficult to treat. We hypothesize that robot-assisted gait training can decrease frequency of freezing in Parkinson's disease (PD).

Methods: Inclusion: 1) Diagnosis of idiopathic PD by UK Brain Bank criteria. 2) Men and women ages 18 to 85. 3) FOG by self-report, verified by MD. 4) Ability to walk unassisted. Exclusion: 1) Cognitively unable to understand instructions required by the study. 2) Weight > 100kg. 3) Presence of medical or other neurological infirmity that might contribute to significant gait dysfunction or injury. 4) Significant/poorly controlled cardiovascular issues (recent MI, HTN, diabetes). 5) Inability to participate and complete training. 6) deep brain stimulation. Baseline and endpoint visits included

UPDRS, gait analysis (GaitRite instrumented walkway), freezing analysis (videotaped gait), subjective assessment of freezing (FOG-Q), and quality of life (PDQ-39). Videotaped assessments of gait and freezing were done at each training session. The patients underwent 10 sessions of robot-assisted gait training each lasting 30 minutes over 5-10 weeks. Patients kept a freezing/falling diary and video assessments were blindly rated for degree of freezing. Follow-up assessments occurred at 1 and 3 months after the end of the training sessions.

Results: Current data show improvement in the FOG-Q, PDQ-39, and visual blinded assessments of freezing during walking. Overall UPDRS did not show change, but improvement occurred with 13-15 and 29-30 of the UPDRS which relate to posture, gait, falls, and freezing. Gait analysis showed improvement in velocity, stride length, and cadence. Over the total training period, a lower rate of freezes were reported per day.

Conclusions: Our study suggests that freezing of gait in Parkinson's patients is improved with robot-assisted gait training. Possible mechanisms of action include separately or the combination of peripheral tactile stimulation, audio and visual cues, and physical exercise.

Mo-192

Ropinirole prolonged release improves nocturnal symptoms in patients with advanced Parkinson's disease with sleep disturbances

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Objective: To assess the effect of ropinirole prolonged release on nocturnal symptoms in patients with advanced Parkinson's disease (PD) not optimally controlled with L-dopa.

Background: The efficacy and safety of adjunctive ropinirole prolonged release was compared with placebo or ropinirole immediate release (IR) in two Phase III, double-blind, parallel-group, 24-week studies (EASE-PD Adjunct [101468/169], PREPARED [ROP105323]).

Methods: Patients were randomized to once-daily ropinirole prolonged release (2–24 mg/day) or placebo (EASE-PD), or three-times-daily ropinirole IR (0.75–24 mg/day; PREPARED). Nocturnal symptoms were assessed retrospectively by mean change from baseline in Parkinson's Disease Sleep Scale (PDSS) total score (range: 0–150, $\leq$100=significant sleep dysfunction).

Results: At baseline, 94/200 (47%) and 76/173 (44%) patients receiving ropinirole prolonged release had a PDSS total score $\leq$100 (EASE-PD and PREPARED studies, respectively), *vs* 90/190 (47%) for placebo and 67/164 (41%) for ropinirole IR. Mean PDSS total score in the $\leq$100 group was $\sim$77 at baseline across treatment groups. A treatment benefit of ropinirole prolonged release over placebo was seen for patients with PDSS total score $\leq$100 at baseline. In EASE-PD, mean (SD) change from baseline in PDSS total score for ropinirole prolonged release *vs* placebo at Week 12 observed case (OC) was: 14.2 (22.8.0) *vs* 2.8 (17.60); at Week 24 OC: 11.3 (25.58) *vs* 4.0 (20.62); and at Week 24 last observation carried forward (LOCF): 10.3 (24.44) *vs* 2.5 (20.96). In PREPARED, mean (SD) change from baseline in PDSS total score was greater with ropinirole prolonged release than ropinirole IR at Week 12 OC (17.4 [24.27] *vs* 11.7 [18.80]); similar at Week 24 OC (18.6 [23.03] *vs* 18.9 [21.27]); and greater at Week 24 LOCF (15.4 [23.41] *vs* 12.6 [21.35]). No clinically meaningful change from baseline to Week 12 or Week 24 OC/LOCF was seen for patients with a PDSS total score $>$100 at baseline in any treatment group.

Conclusions: Clinically relevant improvements in nocturnal symptoms are achieved with both ropinirole prolonged release and ropinirole IR in patients with advanced PD displaying sleep disturbance. These improvements are evident when utilizing the PDSS total score, which includes non-dopaminergic sleep-related symptoms.

Mo-193

Cholinergic augmentation in frequently falling subjects with Parkinson's disease

K.A. Chung, B.M. Lobb, J.G. Nutt, F. Horak (Portland, Oregon)

Objective: To determine if donepezil will reduce the frequency of falls in Parkinson's disease (PD).

Background: Falling due to postural instability is a significant problem in advancing PD, and is minimally impacted by dopaminergic therapy. Anticholinergic medications increase the frequency of falls in the elderly. Further, CNS cholinergic neuron loss occurs in PD. We hypothesized that acetylcholine augmentation in PD subjects who frequently fall may reduce the incidence of falling events.

Methods: We conducted a randomized, double-blinded crossover clinical trial of donepezil and matched placebo. The primary outcome was daily fall frequency using subject-completed postcards on which the number of falls each day was recorded. Secondary outcomes were near-fall recordings on postcards, Activities of Balance Confidence (ABC) scale scores, UPDRS part III, Hoehn & Yahr, and both the investigator and subject rated global impression of change at the end of each phase. Each study medication phase lasted 6 weeks with a 3 week washout between phases.

Results: 23 subjects consented to participate, 4 dropped out before 2nd phase data was collected (2 on donepezil, 1 on placebo, 1 during washout), thus were excluded from analysis. Of the remaining 19 (15 male, 4 female) the mean age was 68 y, and duration of disease was 9.6 y+/- 5.6 (SD). The fall frequency per day on placebo was 0.25 +/-0.08 (SEM) compared with 0.13 +/- 0.03 on donepezil ($p<0.05$). No carry-over effect occurred. The frequency of near-falls was not significantly different between phases. The ABC scale and UPDRS scores did not differ between phases.

Conclusions: PD subjects fell approximately half as often during the 6 week period on donepezil than on placebo. The near-falls rate was not significantly different, and may be partly due to the subjective nature of evaluating a "near-fall" event. The reason for reduced falls on donepezil is not explained by our study, but could involve improved attention, planning or other cognitive function. It also could suggest that cholinergic mechanisms are involved in other ways, as normal maintenance of balance is not well understood. Reducing falls in PD patients is important in lessening injury and improving quality of life. This is the first pharmacologic therapy shown to lessen the frequency of falling in PD. Further larger trials of cholinergic augmentation are warranted.

Mo-194

Effects of age and gender on preladenant pharmacokinetics in healthy subjects

D.L. Cutler, A. Tendolkar, J. Hunter (Kenilworth, New Jersey)

Objective: To determine the effects of age and gender on the single-dose pharmacokinetics of preladenant in healthy subjects.

Background: Preladenant is a novel, nonmethylxanthine, and highly selective A_{2A} receptor antagonist being developed for the management of movement disorders, including idiopathic Parkinson's disease.

Methods: This was a phase I, open-label, single-center, parallel-group study performed in healthy males and females (N=48). Subjects were divided into 2 age groups (aged 18–45 years and $\geq$65 years); each age group consisted of 12 males and 12 females. All subjects received 1 oral dose of preladenant 25 mg after an overnight fast. Plasma samples were analyzed for preladenant and its 2 major metabolites using a validated LC-MS/MS assay with a lower limit of quantitation of 2 ng/mL. Pharmacokinetic parameters were evaluated using model-independent methods. Log-transformed AUC and C_{max} were statistically analyzed using ANOVA to evaluate age, gender, and age*gender effects.

Results: No statistically significant age*gender interaction was observed for AUC and C_{max}. Mean T_{max} ranged from 0.927 to 1.22

hours. Intersubject variability in AUC and C_{max} was high, with %CV ranges of 46% to 56% and 51% to 73%, respectively. The LS mean ratio (90% CI) of $AUC_{(tf)}$ values comparing female with male subjects was 1.38 (1.02–1.87), with elderly females experiencing the highest exposure compared with younger females and either male subgroup. The gender-related differences in preladenant exposure could not be explained on the basis of the 2 major metabolite exposures. Adverse event (AE) incidence was highest among young females (75%; 9/12) compared with elderly females (17%; 2/12) and young (0%) and elderly (33%; 4/12) men. There were no serious AEs or discontinuations due to AEs.

Conclusions: Preladenant exposure was 38% higher in females than males; however, no significant differences in exposure were observed solely on the basis of age. Preladenant was rapidly absorbed and plasma concentration showed high intersubject variability. Elderly females, who experienced the highest preladenant exposure, reported only 2 AEs, suggesting that increased exposure following a single dose did not affect preladenant's safety profile.

Mo-195

Treatment disparities in Parkinson's disease

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Objective: To compare treatment for Parkinson's disease (PD) in the 6 months following initial diagnosis between Medicaid-enrolled white and African American patients.

Background: The association between race and initial treatment for PD has not been previously studied. The racial disparities in treatment seen for other health conditions may exist for PD as well. Differences in age, sex or geography may lead to under-treatment among traditionally underserved minorities.

Methods: We used Pennsylvania state Medicaid claims from 1998 to 2003 to identify incident cases of PD. An incident case was defined as a billing claim for PD (ICD-9 332.0) for an individual with no PD claim in the preceding 12 months and no history of treatment for PD. Subjects with a prior history or stoke, bipolar disorder or schizophrenia were excluded. We then identified claims for levodopa, dopamine agonist, monoamine oxidase inhibitor, amantadine, trihexyphenidyl and physical therapy in the 6 months following the initial PD claim. Chi-squared tests were used to examine differences between African Americans and whites. Logistic regression was used to determine predictors of treatment.

Results: 307 incident cases of PD were identified; 264 (86%) were white and 43 (14%) were African American. There was no difference by race/ethnicity in mean age at diagnosis or sex. African Americans were more likely to live in a large metropolitan area ($p<0.001$). In unadjusted analysis, African Americans were significantly less likely to receive dopaminergic therapy (9% vs. 22%, p-value 0.05), any medication therapy (12% vs. 33%, p-value 0.005) and any medication or physical therapy (12% vs. 38%, p-value <0.001). After controlling for age, sex and location of care, African Americans were still four times less likely than whites to receive any PD treatment [OR 0.24, 95% CI 0.09-0.64, $p = 0.005$].

Conclusions: Despite equal healthcare insurance and pharmacy coverage, African Americans with newly diagnosed PD were less likely to receive standard PD treatment than whites. Investigating the source of these disparities such as physician/patient preferences or biases, differences in clinical presentation or specialty referral is warranted. Physician and community awareness of these racial differences in PD treatment is the first step in addressing healthcare disparities.

Mo-196

Addictive behaviors and Parkinson's disease

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Objective: This study has evaluated the prevalence of main aspects of addiction (alcohol, tobacco, gambling, sex, medication) in PD patients on dopamine replacement therapy (DRT) comparing with general population.

Background: Recently, compulsive behaviour such as extreme reliance on medication, addiction to gambling and others have been described to affect people with Parkinson's disease (PD). At the same time, relationship between dopamine, PD and addictive behaviours has been already illustrated and growing evidences show that the same processes lie behind all addictions, behavioural or chemical.

Methods: A cross-sectional, self questionnaire-based study was undertaken. The self-report explored quantitative and qualitative addictions (AUDIT, Fagerström, TDAS, SOGS...) with substance (alcohol, tobacco...) or without (gambling, sex) in PD patients and healthy controls. HAD scale was used to assess the contribution of mood disorder.

Results: 138 non-demented patients with PD and 115 age and sex matched control subjects were studied. There are no significant differences between the two groups concerning prevalence of smokers, means alcohol drinking scores, means gambling scores. In contrast, we found that PD patients had significantly higher scores than controls for sex addiction, anxiety and depression but there are significantly higher hazardous or alcohol dependant drinkers in control group. In PD group, there are three times more "probable pathological gamblers" (3.1%); three times more "probable presence of depression disorders (11.4%); more than twice "probable presence of anxiety disorders" (28.9%); 2 cases of "probable sex addict" (1.8%) *vs.* none in control group. In the total group of PD patients, 13.3% could be diagnosed with Hedonistic Homeostatic Dysregulation (HHD).

Conclusions: This study seems to confirm that PD patients are not affected by all forms of addictions, but preferentially by gambling, sex and dopamine replacement therapy addictions. Further analyses will conduct us to study coaddictions; relation with mood disorders and links between HHD and DRT.

Mo-197

Can a smell identification test predict the results of a DaT-Scan in patients with suspected Parkinson's disease: Interim analysis?

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Objective: To assess whether reduction of the sense of smell, measured with the University of Pennsylvania smell identification test (UPSIT), can accurately predict DaT-Scan results in patients with suspected Parkinson's disease.

Background: Dopamine transporter protein scan (DaT-Scan) is a highly sensitive test indicating reduced uptake even in pre-clinical stages of Parkinson's disease[1]. Reduced sense of smell is widely recognised as an early feature in Parkinson's disease[2].

Methods: In this prospective study of patients with suspected Parkinson's disease referred for DaT-Scan, Mini-mental state examination (MMSE), Non-motor symptom questionnaire (NMS), Unified Parkinson's disease Rating score (UPDRS) and UPSIT score are performed immediately prior to the scan by researchers blind to why a scan was requested. The accuracy of the UPSIT score as a predictor of the DaT-Scan result will be assessed with sensitivity, specificity, positive and negative predictive values. Results from the first 18 patients are presented here.

Results: The UPSIT scores of 18 patients were assessed between March 2007 and Dec 2008. UPSIT scores were significantly higher (Mann Whitney U-test, $P=0.000$) in the 8 patients with a normal scan (median 29.5, range 23-33) than in the 9 with an abnormal scan

(median 16, range 8-23). One patient had an inconclusive DaT-Scan. Using the optimal cut-point for the UPSIT score of $\leq$23 as indicative of parkinsonism, estimates of sensitivity and specificity of 100% (95% confidence interval: 66% to 100%) and 88% (95% confidence interval: 47% to 100%) respectively were obtained, with positive and negative predictive values of 90% and 100%.

Conclusions: Early experience is promising but we hope to recruit larger numbers in the trial, to substantiate these results and establish a reliable cut-point for the UPSIT score. 1. Seibly JP, Marek KL, Quinlan D, et al. Decreased single photon emission computed tomography (123 I)B-CIT striatal uptake correlates with symptom severity in Parkinson's disease. Ann Neurol 1995; **38**:589-98. 2. Double KL, Rowe DB, Hayes M, et al. Identifying the pattern of olfactory deficits in Parkinson's disease using the brief smell identification test. Arch Neurol. 2003; **60**:545-9.

Mo-198

Pilot randomized controlled trial of telemedicine for individuals with Parkinson's disease

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Objective: Establish the feasibility of providing telemedicine care to individuals with Parkinson's disease (PD).

Background: Telemedicine may improve access to specialized medical care for PD patients by eliminating burdensome travel requirements.

Methods: Fourteen patients (4 from a nursing home and 10 in the community) living 150 miles from our institution participated in this study. Community participants were randomized to telemedicine care (n=6) or standard care (n=4). All four nursing home patients were assigned to receive telemedicine. Three telemedicine visits took place over the course of the six months. Feasibility was determined by the ability of telemedicine participants to complete telemedicine visits. Secondary analyses were the change from baseline to six months between those randomized to telemedicine and to standard care on measures of quality of life (PDQ-39), mood (GDS-15), satisfaction with care (GHAA), cognition (MoCA) and motor function (motor UPDRS) using Wilcoxon Signed Rank Tests. Nursing home residents receiving telemedicine were evaluated separately.

Results: Participants randomized to telemedicine and standard care had similar baseline characteristics. Those randomized to telemedicine completed 100% (18/18) of their telemedicine visits. Telemedicine participants showed significant improvements compared with those receiving standard care in quality of life (6.3 improvement vs. 17.2 point worsening; p=0.03) and the motor UPDRS (0.33 improvement vs. 6.5 point worsening; p=0.03). Relative improvements were also seen in satisfaction with care (6.2 vs. 0.75 point improvement; p=0.34). The four nursing home telemedicine participants completed 94% (15/16) of their telemedicine visits as scheduled. Relative to baseline, nursing home participants experienced trends toward improvement in satisfaction with care (15.5; p=0.13), quality of life (-18.3; p=0.25), depression (-2.3; p=0.25), and cognition (3.0; p=0.25). Nine of the ten participants assigned to telemedicine opted to continue receiving their care via telemedicine.

Conclusions: Telemedicine is a feasible means for providing care to patients with PD living far from sub-specialists and may provide clinical benefits.

Mo-199

Alpha-2 adrenergic antagonist effects in Parkinson's disease

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Objective: To evaluate the safety and efficacy of acute adrenergic alpha-2 blockade on Parkinson's disease (PD) severity and the motor response complications associated with chronic levodopa therapy, fipamezole was assessed (1) as monotherapy and (2) in combination with a steady state levodopa infusion.

Background: Adrenergic alpha-2 receptors regulate dopamine release and modulate function of the direct and indirect pathways within the basal ganglia. These receptors also regulate the baroreflex pathways in the CNS and the periphery. Fipamezole, a selective alpha-2 antagonist, reduces dyskinesias and prolongs levodopa's antiparkinsonian activity in MPTP-lesioned monkeys. Patients with advanced PD may also experience orthostatic hypotension, which tends to worsen with most antiparkinsonian medications.

Methods: We conducted a double-blind, placebo-controlled, proof-of-concept study in patients with moderate to advanced PD. Fipamezole was administered as a buccal spray in single ascending doses of 15, 30, 60 and 90mg. Efficacy was assessed using UPDRS part III and modified AIMS. Vital signs and adverse events, reported spontaneously or observed by the investigators, were recorded.

Results: Final data analysis. We enrolled 21 patients, age 57$\pm$11, H&Y score >2.5 in 62% of patients, and symptom duration 17$\pm$7.5 years. Fipamezole was generally safe and well tolerated, and adverse events were mostly mild to moderate and included pallor, hypoaesthesia, nausea, dizziness, sweating, and transient buccal mucosa discoloration. There were no serious adverse events. Fipamezole reduced the severity of dyskinesias by 23% at 60 mg ($p<0.05$) and by 31% at 90 mg ($p<0.05$), without diminishing the antiparkinsonian response to levodopa. Fipamezole prolonged the duration of the antiparkinsonian effect of levodopa by 41 min. at 90 mg ($p<0.05$). Fipamezole had no antiparkinsonian activity as monotherapy. There was an additional 13$\pm$4.2 mm Hg (p= 0.053) drop in orthostatic SPB during levodopa infusion after placebo and 0.0$\pm$4.8 mm Hg after fipamezole 90 mg.

Conclusions: The findings suggest that adrenergic alpha-2 blockade with fipamezole in levodopa-treated parkinsonian patients can improve motor dysfunctions and could prove useful as an adjunct treatment, especially in those suffering from orthostatic hypotension.

Mo-200

Dopamine transporter imaging in very long-standing Parkinson's disease

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Objective: To evaluate [^{123}I]FP-CIT SPECT uptake in very long-standing Parkinson's disease (PD).

Background: Dopamine transporter imaging is a sensitive marker for loss of presynaptic dopamine transporters in early PD. SPECT studies have demonstrated a rapid decrease of dopamine transporter ligand uptake in early PD followed by a slowing of the degenerative process in advanced disease. The estimated annual decline of striatal binding is 6-10% within the first years from disease onset. There is only scarce data concerning [^{123}I]FP-CIT uptake in very long-standing disease.

Methods: [^{123}I]FP-CIT SPECT was performed in 15 patients with very long-standing PD, (mean age 67$\pm$7 years, mean disease duration 18.7$\pm$3.0 years) and compared to 14 patients with early stage (mean age 54$\pm$10 years, mean disease duration 2.2$\pm$0.9 years) and to 9 patients with advanced disease (mean age 68$\pm$7 years, mean disease duration 10$\pm$2 years). [^{123}I]FP-CIT was correlated with UPDRS, MMSE, and depression score.

Results: [^{123}I]FP-CIT was still detected in patients with long-standing disease, with a more significant decline contralateral to the more affected side in the putamen and caudate. There were significant differences in uptake between this group and patients with early PD, but not with patients with advanced disease in all parts of the striatum. No correlation was found between clinical scales and [^{123}I]FP-CIT uptake in patients with very long-standing disease.

Conclusions: Loss of dopamine transporters in PD is not complete and reaches a plateau within approximately 15 years from disease

onset. This might implicate that even patients with long standing disease might benefit from future novel therapeutic strategies in PD.

Mo-201

The effects of balance exercises in Parkinson's disease patients with a home based program

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Objective: To investigate the effects of home based exercises on the balance and functional capacity in patients with Parkinson's disease.

Background: The cardinal symptoms of Parkinson's disease are rigidity, bradykinesia, tremor and postural instability. These symptoms are affecting the functional status of patients and causing impairments on gait, rising chair, rolling in bed. Postural instability develops in the late stage of the disease and is related with impairments of balance. The positive effects of physiotherapeutic techniques on mobility have been previously reported.

Methods: This prospective study consisted of 27 Parkinson's patients (9 female, 18 male). The onset of the disease, the fall history in last 6 months, the disease severity with Hoehn-Yahr stage, balance capacity according to the Berg Balance Scale (BBS), performance capacity (sit to stand test, timed up&go test, functional reach test) were recorded before and after the home program. The home program was designed individually related to the severity of the disease and consisted of balance and coordination exercises.

Results: The mean age of patients was 68.96 ± 8.69 and the mean disease duration was 4.92 ± 4.11 years. The disease severity according to Hoehn-Yahr scoring system was mild to moderate. After the exercise program on 3rd month, the BBS scores and timed performance tests (sit to stand test, timed up&go test, functional reach test) were significantly improved ($p<0.05$).

Conclusions: The static and dynamic balance capacity of patients without imbalance complaints are improved after the home exercise program, which consisted of specific balance and coordination exercises. Our study suggests the benefits of specifically designed exercises.

Mo-202

Sniffin sticks in Swahili: Smell testing in Tanzanian Parkinson's disease patients – A pilot feasibility study

C.L. Dotchin, A. Jusabani, R.W. Walker (North Shields, Tyne and Wear, United Kingdom)

Objective: The aim of this pilot study was to determine whether or not the Sniffin Sticks test could be adapted for use in Tanzania, and whether the adapted version was useful in discriminating between those with PD and those without.

Background: Olfactory function is frequently impaired in patients with Parkinson's disease (PD), affecting 70-90% of patients, and can occur before the onset of motor symptoms. Olfactory loss is said to be independent of anti-parkinsonian medication and occurs early in the disease [i], and possibly could be used as a marker for PD before motor symptoms develop. We believe this is the first time olfactory function testing for PD has been reported in rural Africa. [[i]] Tissingh G, Berendse H, Bergmans P, DeWaard R, Drukarch B, Stoof J et al. Loss of olfaction in de novo and treated Parkinson's disease. Movement Disorders 2001; 16(1): 41-6.

Methods: We carried out a community-based prevalence study of PD in rural Tanzania, using the UK PD Society Brain Bank Criteria to confirm diagnosis [i]. Additionally we used Sniffin Sticks to assess olfactory function in 20 patients and 25 community-based controls (spouses of patients, relatives or neighbours). Subjects were asked to smell the "Sniffin sticks" pens with both nostrils and to select the odour from a selection of 4 possible choices. To ensure that the choices were odours that were familiar to the Tanzanian population, the PD nurse specialist and local assistant medical officers reviewed all odours. If familiar, a Swahili translation was made. If not recognisable (e.g. blackberry), an alternative local smell was chosen. [i] Dotchin CL, Msuya O, Kissima J, Massawe J, Mhina A, Moshi A, Aris E, Whiting D, Masuki G, Walker RW "The prevalence of Parkinson's disease in rural Tanzania" Movement Disorders 2008; 23(11): 1567-72.

Table (Mo-202). Sniffin sticks scores

	Patients	Controls
Mean total score (range)	5.5	8.2
Most frequently identified odour	Coffee	Coffee and Peppermint
Least frequently identified odour	Leather	Leather
Number normosmic (>10/12)	2 (10%)	5 (20%)
Number hyposmic (6-10/12)	8 (40%)	18 (72%)
Number anosmic (<6/12)	10 (50%)	2 (8%)

Results: 20 patients (13 male) and 25 controls (6 male) were tested. Mean age of patients was 82.5 years, compared to 46.5 years of controls. Scores are shown in table 1.

Conclusions: PD patients were more likely to have olfactory dysfunction than controls. The test was acceptable and easy to use in this setting, though some of the answer stems had to be adapted to what was known locally. The patients were significantly older than the controls, so age may partly account for the decrease in olfactory function.

Mo-416

Transdermal rotigotine results in suitable pharmacokinetic properties for various patient subpopulations

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Objective: To characterize the pharmacokinetic (PK) properties of the dopamine agonist rotigotine applied as transdermal patch.

Background: Once-daily rotigotine transdermal patch provides continuous 24-hour drug delivery. The patch was developed for early- and advanced-stage Parkinson's disease (PD) as well as moderate to severe restless legs syndrome (RLS).

Methods: The PK properties of transdermal rotigotine have been investigated in several clinical studies in healthy subjects and target patient populations.

Results: The PK of rotigotine after transdermal administration is similar in healthy subjects and in the target patient populations. Age and gender do not influence the PK and there are no differences between ethnic groups (Caucasian, Black African and Japanese subjects). Mean rotigotine plasma concentrations increase dose proportionally over the whole therapeutic dose range, even up to supratherapeutic doses. The drug is metabolized by various metabolic routes (sulfation, glucuronidation, various CYP450 isoenzymes). Less than 1.0% of rotigotine is eliminated into urine as unchanged compound. The drug shows no liability for drug-drug interactions with respect to drug metabolism or plasma protein binding. Interaction studies showed no evidence for PK interactions with commonly used concomitant medication (levodopa/carbidopa, domperidone). PK and pharmacodynamic effects of oral contraceptives are not affected by rotigotine. No dose adjustment of rotigotine is necessary in patients with different stages of chronic renal insufficiency (incl. patients on hemodialysis) and in patients with moderate impairment of hepatic function.

Conclusions: These characteristics demonstrate that transdermal delivery of the dopamine agonist rotigotine provides relevant advantages for chronic treatment of patients with early and advanced stages of PD, and for patients with RLS. Moreover, continuous transdermal delivery of drugs is neither affected by food nor by impaired gastrointestinal motility, which affects many PD patients. In addition, a transdermal system may be considered an ideal route of administration under conditions such as perioperative settings and intensive care.

Tu-178

Aplindore, a partial dopamine agonist, improves motor aspects of Parkinson's disease in a 14-day escalating dose paradigm

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Objective: The primary objective was to evaluate safety and tolerability of aplindore in patients with early stage Parkinson's disease (PD) given BID over 2 weeks using varying titration schedules and across different dose ranges. The secondary objective was to generate pilot data using the UPDRS and the Non-Motor Symptoms Questionnaire (NMSQ).

Background: Aplindore is an orally available, small molecule partial agonist of the D_2 dopamine receptor. Aplindore was efficacious in two widely used animal models of PD, the Ungerstedt rodent model and the MPTP primate model. Aplindore has also been evaluated in approximately 250 subjects enrolled in 7 Phase 1 clinical studies designed to assess safety, tolerability, pharmacokinetics, and receptor occupancy.

Methods: This study enrolled 39 patients, ages 37 to 77 years with early-stage PD. Aplindore was administered BID over two weeks to patients assigned to 1 of 5 cohorts, each with a different titration schedule and maximum dose achieved (i.e. 2mg, 3mg, 5mg, 9mg and 15mg, BID) during 2 weeks of treatment. In each cohort, up to 6 patients received aplindore and 2 received placebo. The UPDRS was assessed before, during and after treatment.

Results: Compared with placebo, clinically meaningful and statistically significant improvement was observed in the Motor Score (Part III) of the UPDRS in aplindore-treated patients titrated up to 2 mg BID, 3 mg BID and 5 mg BID. See Table.

Table (Tu-178). UPDRS (part III) 2 Hours Post-Dose Compared to Baseline

	Maximum achieved dose of aplindore (2 weeks of dose escalating treatment)					
	pooled placebo (n=10)	2 mg BID (n=5)	3 mg BID (n=6)	5 mg BID (n=6)	9 mg BID (n=6)	15 mg BID (n=6)
Baseline	19.3	22.0	20.2	20.2	14.2	17.7
Mean change from baseline	−3.3	−10.8	−12.3	−10.2	−4.8	−5.3
p-value		0.0243	0.0026	0.0107	ns	ns

ns = not statistically significant.

Improvements in UPDRS at higher doses (9mg and 15mg BID) did not reach statistical significance. Differences from placebo on the non-motor UPDRS subscales and NMSQ were not statistically significant. Aplindore was generally well tolerated in the cohorts starting at a lower initial dose and slower titration schedule. In the 2mg cohort the incidence of adverse events was similar to placebo. There were no withdrawals due to adverse events and no serious adverse events reported in the study.

Conclusions: Despite the brief exposure to aplindore in a relatively small number of patients, this study provides evidence that aplindore may be adjusted to effective dosages in as short as two weeks, with good tolerability and significant improvement in motor signs and symptoms of PD.

Tu-179

Effects of NMDA receptor antagonist on levodopa induced dyskinesia – Meta analysis of controlled clinical trials

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Objective: To compare the efficacy of NMDA receptor antagonists such as dextrometorphan and amantadine versus placebo in reducing levodopa induced dyskinesias in Parkinson's disease.

Background: Dyskinesias are disabling side effects of levodopa therapy. N-methyl-D-aspartic acid (NMDA)-receptor antagonists may reduce dyskinesias in patients with Parkinson's disease without worsening parkinsonian symptoms and may even produce motor improvement.

Methods: Randomized controlled trials of the effects of NMDA receptor antagonists on levodopa induced dyskinesias were identified through search of Pubmed (1990–2008), medline (1966-2008) and EMBASE (1974-2008). The reference lists of the identified studies were checked for additional references. Cochran Q and I square inconsistency tests were used to examine heterogeneity and the effect size for the included studies were calculated using fixed and random effect model.

Results: Eleven studies met the inclusion criteria. The pooled data consist of 153 patients in the treatment group with the mean age of 61.5 years and 124 patients in control group. NMDA receptor antagonists significantly reduced the severity of dyskinesia measured with clinical dyskinesia rating scale, Abnormal Involuntary Movements Scale and modified Goetz scale for dyskinesia with the large effect size of d= -0.9 (p =0.013). No significant effect of NMDA antagonists on motor function in Parkinson's disease was detected.

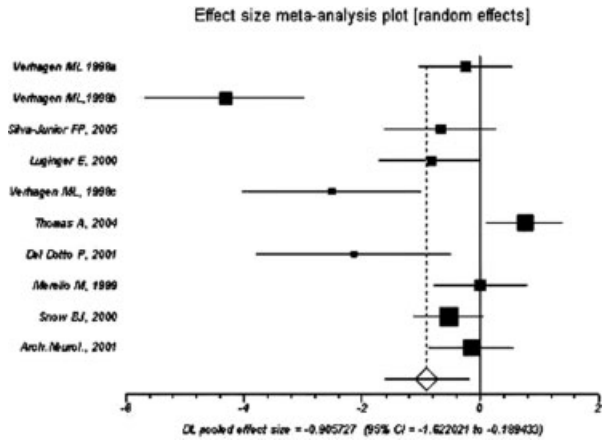

FIG. 1 (Tu-179).

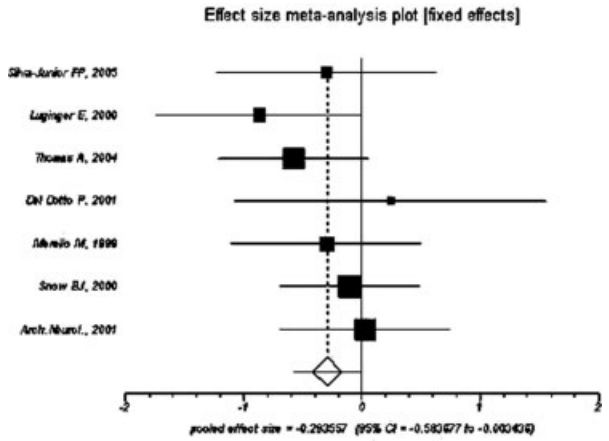

FIG. 2 (Tu-179).

Conclusions: This meta-analysis supports the beneficial effects of NMDA receptor antagonists on levodopa induced dyskinesias in Parkinson's disease.

Tu-180

Exploratory study of yoga as a therapeutic modality for Parkinson's disease

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Objective: This pilot study was designed to evaluate the feasibility and efficacy of yoga as a therapeutic modality in people with Parkinson's disease (PD).

Background: Yoga practice is a popular form of exercise where the body is moved through a series of highly structured poses. Yoga has been effective in improving range of motion, strength, and stride length in older and young adults. It is reasonable to believe these positive changes will also occur in persons with PD. However, few well organized and controlled studies are available for this cohort.

Methods: Two women (69.5 ± 4.9 yrs) with early stage PD (H/Y = 2) participated in an 8-week yoga intervention program. Poses were modified for each person's ability and comfort level, yet became progressively demanding through the course of the intervention and as the participant's skill increased. Chairs, blocks, and straps were used as necessary for safety and to facilitate performance of the poses. Prior to and upon completion of the 8-week intervention, UPDRS, lower extremity strength, walking speed and stride length were measured. Walking speed was measured while the participant walked at their comfortable pace on a 10m walkway, unassisted. Stride length was measured during this task via a motion capture system (VICON 612, Oxford, UK). Lower extremity strength was measured by one repetition maximum effort (1RM) on a leg press machine (Keiser, Fresno, CA).

Results: UPDRS scores decreased post intervention (Table 1). Lower extremity strength, walking speed and stride length also increased post intervention (10-14.5%).

Conclusions: Results from this feasibility study encourage further investigation of yoga as a beneficial therapeutic modality for PD. Improvements in walking speed, stride length and strength are likely to manifest as improvements in activities of daily living and functional capacity, thereby improving quality of life in this population. Using the data obtained from this small feasibility study, we plan to expand these investigations in the future.

Table (Tu-180). Measured variables pre and post yoga intervention with standard deviations (SD).

	Phase			
Measure	Pre	SD	Post	SD
UPDRS	18.5	10.6	13.0	5.7
Mentation	0.0	0.0	0.5	0.25
ADL	3.5	0.33	3.0	0.33
Motor	15.0	0.54	9.5	0.43
Walking Speed (m/s)	1.42	0.08	1.58	0.4
Stride Length (m)	1.38	0.19	1.54	0.05
Leg Press (N)	983.0	412.9	1080.5	508.4

Tu-181

Continuous levodopa/carbidopa gel therapy improves dyskinesias in Parkinson's disease

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Objective: An analysis of the effect of continuous dopaminergic stimulation (CDS) with Levodopa/Carbidopa duodenal infusion on dyskinesias in patients with advanced Parkinson's disease.

Background: Fluctuations occur in a large proportion of the patients with peroral L-dopa therapy. The likely reason for this phenonema is the unstable plasma and striatal concentration of Levodopa/dopamine. This problem has not been solved by improvements of the oral therapy, including the introduction of MAO-B and COMT- inhibitors. L-Dopa/Carbidopa gel infusion is a possibility to establish this and is now since 4 years on the market in several countries. In the present investigation we perform a detailed quantitative analysis of the effect of Levodpa/Carbidopa gel infusions on dyskinesias.

Methods: Nine patients with advanced idiopathic Parkinson's disease including motor fluctuations and dyskinesias were included in a prospective non-controlled study on the effect of L-dopa/Carbidopa duodenal infusion on motor symptomatology. The patients were followed for a minimum of 6 months, with evaluations before start of therapy and after 6 months. The following scales were used: *(A)* UPDRS I-VI and AIMS & Goetz scores were performed in defined off and defined on in frames of a L-dopa challenge test with fixed dose of 200mg L-Dopa. *(B)* Visual Analogue Scale (VAS) for dyskinesias (performed by patient, every 60 minutes of awake day) and patient diaries (performed by patient, every 60 minutes of awake day) over three days.

Results: There was an improvement in all motor symptom parameters. *A* AIMS score in "defined on" (in L-dopa test) was reduced from 9.3 to 2.8); Goetz score was improved from 1.6 to 0.4. *B R*eduction in mean dyskinesia intensity was 89.6% according to the VAS scale and reduction of awake time with dyskinesias 46.6% according to patient diaries. The health-related quality of life measured with PDQ-8 improved from 15.6 to 7.1 (54.5%).

Conclusions: CDS with L-Dopa/Carbidopa gel improved the severity and duration of dyskinesias. Further the degree of dyskinesias after a fixed dose of Levodopa was less pronounced after six month of pump treatment.

Tu-182

A clinical pharmacology study to determine the selective and non-selective doses of the monoamine oxidase type B (MAO-B) inhibitor, rasagiline

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Objective: To assess tyramine sensitivity when administered with rasagiline and to determine the selectivity of rasagiline for MAO-B.

Background: Rasagiline inhibits MAO-B and is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease (PD). Even for "selective" MAO-B inhibitors, the selectivity for inhibiting MAO-B diminishes and is ultimately lost as the dose is increased. The dose at which rasagiline retains selectivity for MAO-B has not been fully characterized.

Methods: Double-blind, single center, clinical pharmacology study incorporating placebo, positive and comparator controls, conducted in healthy male and female subjects aged 40 to 70 years. There were 6 treatment groups in which subjects were to be randomly assigned to receive a MAO inhibitor (MAO-I, n=16) or placebo (n=8) for 14 days. MAO inhibitors tested are shown below; rasagiline 2 mg/d was also given for 30 days. A 7th treatment group was unblinded and all subjects in this group received phenelzine (n=16). In this 3-period study, subjects received one dose of tyramine HCl (TYR, 5 to 800 mg) daily in Periods 1 and 3, and MAO-I in Periods 2 and 3. TYR dose was increased daily until systolic blood pressure increased by 30 mmHg for 3 consecutive measurements over 10 min (TYR30). Primary outcome measure was the ratio of TYR30 in Period 1 (no MAO-I) to the TYR30 in Period 3 (in the presence of steady-state MAO-I). Blood pressure, pulse and ECG were monitored closely in the post-TYR interval. Blood was sampled for rasagiline, tyramine and dihydroxyphenylglycol (an index of MAO-A inhibition).

Results: The TYR30 ratio for each MAO-I appears below (geometric mean): Phenelzine, 15 mg TID, 14d (17.32) Selegiline, 5 mg BID, 14d (2.47) Rasagiline, 1 mg/d, 14d (2.03) Rasagiline, 2 mg/d, 14d (3.33) Rasagiline, 2 mg/d, 30d (2.45) Rasagiline, 4 mg/d, 14d (4.50) Rasagiline, 6 mg/d, 14d (5.10) Pooled Placebo, 14d (1.50).

Conclusions: The results indicate selective MAO-B inhibition by rasagiline at the maximum recommended dose for the treatment of PD, 1 mg/d.

Tu-183

External cueing and gait in Parkinson's disease: A controlled evaluation

H.J. Griffin, R. Greenlaw, P. Limousin, K. Bhatia, N.P. Quinn, M. Jahanshahi (London, United Kingdom)

Objective: To assess the impact of visual cues presented via virtual reality glasses (VRG) and real-world cues on gait in mid-stage Parkinson's disease (PwPD). We simulated real-world challenges and freezing triggers in a laboratory walking task, using appropriate placebo conditions.

Background: PwPD have a slow, shuffling gait, and sporadic freezing of gait (FoG), but may climb stairs well. PET has shown that cueing eliminates deficits in fronto-striatal activation in PwPD, present during self-initiated movement. Cueing devices have improved gait and reduced FoG. However, no single type of cue benefited all PwPD and assessments are often on treadmills or in home settings with limited controls.

Methods: We assessed 26 PwPD, on and off medication, on a walking task incorporating FoG triggers. Cueing interventions were: visual flow (VF), rhythmic and static placebo cues presented via VRG; transverse lines (TL) on the walkway; and two no-cueing control conditions. Objective measures of gait (task completion time; velocity, cadence and stride length; FoG frequency) self-ratings of fear of falling (FoF) and confidence were recorded.

Results: 19 PwPD completed the task (age 64.1±6.73; H&Y 2.34±0.37). Cueing intervention affected completion time only off-medication ($p<.0005$): Comparisons to the initial no-cueing condition revealed that PwPD completed the task faster with TL ($p<.05$) and with VF ($p<.07$). TL reduced cadence ($p<.06$), increased stride length ($p<.0005$) and reduced FoG ($p<.03$). Rhythmic cueing increased task completion time ($p<.04$), and reduced velocity ($p<.02$) and confidence ($p<.02$). In the final no-intervention condition PwPD completed the task quicker ($p<.0005$), walked faster ($p<.01$) with longer strides ($p<.01$) and froze less ($p<.07$).

Conclusions: TL cues improved gait speed and quality, VRG VF cues improved gait speed but not quality. Rhythmic cueing impeded gait. Static placebo VRG cues did not affect performance. The improvement in the final no-cueing condition suggests that practice and motivational factors influence gait in PD, which has implications for future study design. Although the VRG produced modest improvements, their flexibility are an advantage. These results endorse the use of TL and justify further testing and customisation of VRG cues for individual PwPD.

Tu-184

Environmental and occupational factors in Bulgarian patients with Parkinson's disease

D.R. Hristova, I.S. Grozdev, Z.I. Zahariev (Plovdiv, Bulgaria)

Objective: We carried out a case-control study to investigate the environmental and occupational factors associated with Parkinson's disease.

Background: Examples of specific toxins that can cause dopaminergic cell death and parkinsonism(P) include manganese, carbon monoxide, carbon disulfide and cyanide, however the role of these toxins in Parkinson's disease (PD) is not known. In recent epidemiological studies of PD environmental and occupational exposures to metals, pesticides and solvents have received most attention as risk factors.

Methods: We recruited all males who were diagnosed by UK PDS Brain Bank criteria in Parkinson Center of Neurology clinic of UMHAT "St. George" Plovdiv. Age and sex matched controls with no PD,P and history of neurological illness, were selected from the community around the patients. A standardized questionnaire was administered to both cases and controls, to record demographic and epidemiological data.

Results: All together 110 subjects affected by PD(110 male) were enrolled in the study. The mean age for cases was 65.91 ± 0.78(range 40-80) years, but the mean duration of PD was 2.20 ± 0,12 years. The selected controls were 110 with mean age 64.49 ± 0.91(range 40-80) years. Of the factors instrumental occupationally those that increase the risk of developing PD are: working with heavy metals like manganese, mercury, lead and cadmium(OR 3.55); working with paints and lacquers (OR 1.82); working with acetone(OR 1.53). Of the environment contamination factors in residential areas those that increase the risk of falling ill with PD are living in the neighbourhood of: factories that produce and store pesticides (OR 8.0); plants for the production and storage of agricultural fertilizers (OR 2.33); plants for the production of heavy and nonferrous metals (OR 1.44).

Conclusions: Our study suggest the potential role of heavy metals, paints, lacquers, acetone, pesticides, agricultural fertilizers as factors that increase the risk of developing PD and necessity of more detailed information regarding the aspects of exposure (duration, peak values etc.).

Tu-185

Efficacy of preladenant, a novel A_{2A} antagonist, as an adjunct to levodopa for the treatment of Parkinson's disease

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Objective: To assess the efficacy of a range of preladenant doses in patients with moderate to severe Parkinson's disease who were on a stable dose regimen of L-dopa and other adjunctive treatments and experiencing both motor fluctuations and dyskinesias.

Background: Preladenant is a novel, potent, and highly selective A_{2A} receptor antagonist being investigated for the management of idiopathic Parkinson's disease and other movement disorders.

Methods: This was a phase 2, 12-week, randomized, double-blind, placebo-controlled study (N=253). Patients were equally allocated to 5 treatment groups: preladenant 1 mg, 2 mg, 5 mg, or 10 mg BID or placebo BID. The primary efficacy end point was the change from baseline to end point in average hours per day spent in the OFF state. Additional end points included the change from baseline in average hours per day spent in the ON state, the change from baseline in average absolute ON time with dyskinesia, and the change from baseline to end point in UPDRS scores.

Results: Preladenant 5-mg and 10-mg treatment groups experienced statistically significant reductions in awake time spent in the OFF state (–1.6 h [$P=.049$] and –1.7 h/day [$P=.019$], respectively) compared with the placebo group (–0.5 h/day). Preladenant 5-mg and 10-mg treatment groups also experienced statistically significant increases in awake time spent in the ON state (1.4 h [$P=.024$] and 1.3 h/day [$P=.049$], respectively) compared with the placebo group (0.2 h/day), without overall worsening of dyskinesias.

Conclusions: Preladenant, at doses of 5 mg and 10 mg BID, provided significant reductions in OFF time and increases in ON time compared with placebo in patients with moderate to severe Parkinson's disease. These changes were not accompanied by an overall worsening of dyskinesia.

Tu-186

Pharmacokinetic profiling of pramipexole extended-release in Parkinson's disease (PD): Implications for dosing in PD patients with renal insufficiency

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Objective: To model the pharmacokinetics of pramipexole extended-release (ER) taken qd by nonparkinsonian subjects and patients with early Parkinson's disease (PD), to develop dosing recommendations in PD patients with renal insufficiency.

Background: Pramipexole is cleared renally. In PD, pramipexole immediate-release (IR) is typically administered tid. An ER formulation would increase patient convenience and might improve compliance.

Methods: Nonlinear mixed-effects pharmacokinetic modeling was applied to pramipexole data from nonparkinsonian subjects, normal or renally insufficient (creatinine clearance [CRCL] >30 mL/min) receiving a single dose of IR 0.25 mg, and then to PD patients in an 18-week ER trial (0.375-4.5 mg qd). Using the final model, pharmacokinetic profiles were predicted for ER after single and multiple doses in PD patients with CRCL from 7.5 to ≥80 mL/min. The total 24 h exposure ($AUC_{0\text{-}24}$) and the peak exposure (C_{max}) after adaptation of dosing and/or dosing frequency were simulated for patients with a mild, moderate, and severe renal impairment.

Results: After the initial 0.375 mg dose of pramipexole ER, the simulated C_{max} was similar for patients with normal renal function or mild and moderate renal impairment. No adaptation is needed for CRCL of 50-79 (mild renal impairment). Patients with CRCL of 30-49 (moderate impairment) should receive ER 0.375 mg every 2 days for the first 7 days. Further dose titration (in ≥ weekly intervals) can be made by 0.375 mg/d increments up to a dose of ER 2.25 mg/d, which would resemble total and peak exposure of a dose of ER 4.5 mg/d given to a patient with CRCL of ≥80 mL/min.

Conclusions: Although impaired renal function can be expected to increase pramipexole exposure, initiation of ER in PD patients at 0.375 mg, the standard lowest dosage, may be suggested in renal impairment (at any CRCL ≥7.5 mL/min). No specific dosing recommendation is proposed for patients with CRCL <30 mL/min. In moderate renal impairment, adjustment of dosage or dosing frequency is predicted to provide exposure similar to that in patients with mild or no renal impairment.

Tu-187

Impact of A_{2A} receptor antagonist preladenant on dyskinesia in moderate to severe Parkinson's disease: Post hoc analysis of dose-finding study

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Objective: To analyze the effect of multiple doses of preladenant on the proportion of ON time with dyskinesia in patients with moderate to severe Parkinson's disease treated with levodopa and other adjunctive therapy.

Background: Preladenant is a novel, potent, and highly selective A_{2A} receptor antagonist being investigated for the management of idiopathic Parkinson's disease and other movement disorders. Studies in animal models suggest that preladenant improves motor function without increasing dyskinesia.

Methods: A total of 253 patients experiencing motor fluctuations and dyskinesia were randomized in a phase 2, 12-week, double-blind, placebo-controlled study, in which they received twice-daily treatment with placebo or preladenant (1 mg, 2 mg, 5 mg, or 10 mg). The primary efficacy end point was the mean change from baseline to end point in awake hours per day spent in the OFF state. Safety assessments were performed during active treatment and for 6 weeks after last dose. A post hoc analysis was performed to assess changes in the proportion of ON time with dyskinesias in the preladenant and placebo groups. Dyskinesias were defined as troublesome or nontroublesome in patient diaries.

Results: Reductions in OFF time compared with baseline were greater than placebo at the preladenant 2-mg, 5-mg, and 10-mg doses; statistically significant reductions were observed at the 5-mg and 10-mg doses. At baseline, the percentage of ON time with dyskinesias (LS mean) was 36% to 47% across treatment groups; the percentage of ON time with troublesome dyskinesias (LS mean) was 10% to 12% across treatment groups. Changes from baseline to end point in these parameters were small (0%–5%), similar in the placebo and preladenant treatment groups, and no evidence of preladenant dose dependency was noted.

Conclusions: Subtherapeutic and therapeutic doses of preladenant did not increase the proportion of ON time with dyskinesia or dyskinesia severity over 12 weeks of treatment in patients with moderate to severe Parkinson's disease. These clinical findings were consistent with animal models.

Tu-188

The PARS study: Enriching a population at-risk for Parkinson's disease

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Objective: The PARS study is designed to develop and test a strategy to identify a large-scale cohort 'at risk' for Parkinson's disease (PD) using combined olfactory testing and dopamine transporter (DAT) imaging.

Background: There is a lengthy pre-motor phase of PD during which nigral and extra-nigral neurodegeneration precedes the onset of motor symptoms. Pathological changes in the anterior olfactory region may be the earliest site for neurodegeneration in PD. Olfactory deficits are documented in early PD and olfactory loss in asymptomatic relatives of PD has been associated with a 20% risk of DAT deficit and a 10% risk of developing clinical PD within 2 years (Ponsen, et al 2004).

Methods: The ongoing PARS study will enroll 5,000 first-degree relatives of PD patients and individuals from the general population. Eligible subjects are >50 yrs old or within 10 yrs of PD onset of in their affected relative. A 40-item University of Pennsylvania Smell Identification Test (UPSIT) is completed and returned by mail. Participants with decreased olfactory identification and a subset with normal olfaction will undergo longitudinal clinical visits, [123I]β-CIT/SPECT imaging and biological samples collection.

Results: In the first 12 months, 5,033 were recruited through 15 US movement disorders centers and 2,402 participants (51%) completed testing. Demographics of those returning UPSIT's: mean age 58.5 yrs, 38.6% male and 61.4% female. 493/2,402 (20.5%) are hyposmic (UPSIT ≤20th percentile for age and gender). Thus far, 82 subjects have completed clinical and imaging evaluations and a decrease in putamenal dopamine transporter uptake is present in approximately 20% of hyposmic subjects.

Conclusions: The PARS study is a multi-center study employing a two-step screening approach for the identification of individuals at-risk for Parkinson's disease. Review of the data at this stage demonstrates that this design is a feasible and effective approach to recruit this at-risk cohort. Preliminary imaging data suggests that hyposmic individuals are at increased risk for a dopamine transporter deficit. The PARS cohort will provide a unique opportunity to study clinical, imaging and biochemical markers of the immediate pre-clinical stage of PD.

Tu-189

Smell tests, transcranial sonography, and 123I-MIBG cardiac scintigraphy for early diagnosis of Parkinson's disease

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Objective: The purpose of this study is to evaluate the usefulness of diagnostic tools for Parkinson's disease (PD): the odor stick identification test for Japanese (OSIT-J), transcranial sonography (TCS) of substantia nigra (SN), and 123I-MIBG cardiac scintigraphy in Japanese PD patients.

Background: Reduction of olfactory function, SN hyperechogenicity, and reduction of myocardial MIBG uptake are known to be present in PD patients. However, the diagnostic potentials of these tests have not yet been fully determined.

Methods: The subjects were forty-nine patients who were clinically diagnosed as having PD and assessed by OSIT-J, TCS and MIBG cardiac scintigraphy. Eleven patients with atypical parkinson

syndrome (APS), progressive nuclear palsy (PSP, N=5), multiple system atrophy (MSA, N=3), and essential tremor (ET, N=3) were also studied.

Results: Forty (82%) of all 49 PD patients showed a significantly impaired olfactory function. Twenty-two (71%) of 31 PD patients in whom the midbrain was clearly identified by TCS showed SN hyperechogenicity. And twenty-nine (59%) of all PD patients showed reduction of myocardial MIBG uptake. On the other hand, four (36%) of 11 APS patients showed impairment of olfactory function. Two (29%) of 7 APS patients in whom the midbrain was clearly identified by TCS showed SN hyperechogenicity. And two (17%) of 11 APS patients showed reduction of myocardial MIBG uptake.

Conclusions: Our data suggest that these tests used in combination could contribute to a better differential diagnosis of PD.

Tu-190

Clinical signs associated with levodopa-induced dyskinesia in Parkinson's disease

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Objective: We investigated symptoms associated with L-dopa-induced dyskinesias (LID), in particular whether tremor, bradykinesia or rigidity are differentially linked with the severity of LID.

Background: L-dopa therapy for Parkinson's disease (PD) often causes LID. It has been suggested that both the degeneration of dopaminergic neurons and the non-physiological, pulsatile stimulation of striatal dopamine receptors by L-dopa play a role in the development of LID. Several clinical factors are associated with the occurrence of LID such as disease duration or age at PD onset. However, it is unclear whether the type of the predominant motor symptoms also influences the development of LID.

Methods: In a retrospective analysis of 97 consecutive treated PD patients, we performed non-parametric Spearman correlations between the severity of LID, as assessed by 1) the Unified Parkinson's Disease Rating Scale IV (UPDRS IV) and 2) the Abnormal Involuntary Movement Scale (AIMS), and the following variables: duration of L-dopa treatment, stage of disease (Hoehn & Yahr: H&Y), age at PD onset, PD duration, motor performance (UPDRS III) and actual L-dopa dose (calculated L-dopa equivalent dose). Furthermore we analyzed whether the type of initial symptoms influences the severity of dyskinesia (in UPDRS IV, t-test).

Results: The severity of LID (UPDRS IV, AIMS) was significantly associated with a higher actual L-dopa dose, a longer duration of PD, a higher stage of disease and younger age at PD onset. A higher AIMS was also associated with a lower severity of resting tremor both as initial symptom and at the time of investigation, but was not associated with the degree of rigidity or bradykinesia. The mean UPDRS IV in patients with tremor as initial symptom was 4.4 compared to 8.6 in the non-tremor group (t-test, $p<0.01$) in spite of similar UPDRS III in both groups.

Conclusions: Not only the stage of the disease but also the type of the predominant symptoms might influence the development and expression of LID. In particular, resting tremor as initial symptom is negatively associated with the severity of LID. Furthermore our data confirm other known risk factors for LID like a higher actual L-dopa dose and younger age at PD onset.

Tu-191

Long-term effects of amantadine for levodopa-induced dyskinesias and motor impairment in Parkinson's disease: Retrospective report

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Objective: To evaluate long-term effects of amantadine for levodopa-induced dyskinesias (LID) and motor impairment by investigation retrospectively of patient's with Parkinson's disease (PD).

Background: LID are difficult to treat. Amantadine, an anti-glutamatergic agent, has been shown to improve motor abnormalities and a current available drug with an evidence-based recommendation on efficacy for LID. Although, short-term effects of amantadine for LID are established, long-term effects are still unknown.

Methods: We investigated 281 records of patient's with PD during one year from Oct. 1st 2007 to Sep. 30th 2008.

Results: Nineteen patients (male/female;3/16) was treated with amantadine for LID. Mean age was 64.3(SD 6.3) years old. The mean age of disease onset was 47.8 (SD 10.9) years old. Mean disease duration was 16.2 (SD 10.7) years. Mean levodopa treated duration was 13.9 (SD 10.8) years. Mean age of onset of LID was 60.9 (SD 8.1) years old. Mean dose of amantadine was 300(SD 0) mg for men and 222(SD 79) mg for women. Duration of administration of amantadine was that 11 patients were over 1 year (max 5 years) and that remaining 8 patients was less than 1 year. Seventeen patients were evaluated to be effective for LID and motor impairment by Goetz dyskinesia score and UPDRS respectively. Seven patients were reduced amantadine from 300 mg/day to 150mg/day by adverse effects such as slight visual hallucination or constipation.

Conclusions: Our data suggest sustained effects of amantadine on LID and motor impairment of patients with PD. Long-term, double-blind, placebo-controlled study of amantadine for LID in PD is required.

Tu-192

Research and epidemiologic disease registries: The Washington State Parkinson's disease registry experience

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Objective: To compare the design of the Washington State Parkinson Disease Registry (WPDR) with other Parkinson's disease (PD) registries and to present WPDR as an integral resource for Parkinson's researchers and community.

Background: Disease specific registries are effective tools in advancing the knowledge of diseases such as PD. However, registries can also be utilized as resources to connect patients and researchers.

Methods: In collaboration with advocacy groups and the Washington State Department of Health, WPDR began operations in the summer of 2007 to recruit patients with a high likelihood of PD and who are willing to be contacted about research participation. A validated screening questionnaire is administered in person or by phone to exclude cases with a low likelihood of PD. Detailed personal and medical information are then collected and updated on a yearly basis and securely stored in databases accessible only to registry coordinators. Applications to use WPDR are reviewed by WPDR executive board and accepted based upon scientific merits.

Results: As of January 2009, a total of 559 subjects have been screened, and of these, 471 actually fully enrolled. 67% of registrants are male, 12.5% report a family history of PD, and 95% reside in the State of Washington. The average age at onset is 60.7 +/− 11 years. All registrants have a prior diagnosis of PD. 53% percent of registrants were diagnosed by general neurologists, whereas 37% were diagnosed by movement disorder specialists. To date, four research projects have applied to utilize the WPDR.

Conclusions: Surprisingly, the WPDR registrants approximate the demographics of community PD. However, unlike epidemiologically oriented PD registries, WPDR provides ready access to a well-characterized sample of PD subjects who are highly motivated to participate in research. We believe the WPDR fulfills a previously unmet need for researchers and PD patients.

Tu-193

Fear of falling can independently predict future falls in people with Parkinson's disease

M.K.Y. Mak, M.Y.C. Pang (Hong Kong, China)

Objective: To examine whether fear of falling could independently predict recurrent falls in people with Parkinson's disease (PD).

Background: Recurrent falls is common in PD patients and can lead to devastating problems such as fractures and/or head injuries, functional incapacity and higher incidence of institutionalization and mortality rate. Therefore, early identification of potential fallers is needed. Although previous studies have reported that history of fall is a significant fall predictor, it is not a modifiable factor. Identification of modifiable risk factors is essential so that early interventions can be implemented to the needy patients.

Methods: Seventy patients with PD subjects completed the study. Thirty-two patients had at least one fall in the previous 12 months. Most of patients with PD had moderate disease severity (Hoehn and Yahr stage III). Fear of falling was assessed by the activities-specific balance confidence (ABC) scale. PD-specific motor and balance impairment was determined by Unified PD rating scale (UPDRS). Functional mobility was measured by timed-up-and-go (TUG) test. All patients were followed for 12 months by phone interview to register monthly fall incidence.

Results: Fifteen patients reported more than one fall within one year (i.e. recurrent fallers). PD recurrent fallers had significantly higher HY staging score ($p=0.031$), higher UPDRS motor score ($p=0.003$), and lower ABC score ($p<0.001$) than non-recurrent fallers. Results of stepwise discriminant analysis showed that after adjusting for the fall history ($F=32.57$, $P<0.001$) and UPDRS motor score ($F=25.23$, $P<0.001$), ABC score ($F=18.84$, $P<0.001$) remained as a significant predictor of recurrent falls. We further established a cut-off ABC score of 69 (i.e. 0-100, 0 indicates no confidence and 100 indicates full confidence) had the best sensitivity (93%) in predicting future falls in PD patients.

Conclusions: The results indicate that those with an ABC score <69 at baseline had significantly higher risk of sustaining recurrent falls in the next 12 months. Findings of the present study highlight the importance of considering fear of falling during fall risk assessment in patients with PD.

Tu-194

Lumbar spine bone mineral density in patients with Parkinson's disease: Association with trunk muscle strength

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Objective: This purpose of this study was to determine the association of trunk muscle strength with lumbar spine bone mineral density (BMD) in patients with PD.

Background: Patients with Parkinson's disease (PD) have a higher rate of vertebral fractures than the reference population, and low bone mass is one of the major risk factors. Muscle loading provides important mechanical strain to the bone tissue, and may thus have a protective effect on bone.

Methods: Forty-three PD patients and 29 controls participated in this study. Dual-energy X-ray absorptiometry was used to measure lumbar spine BMD of PD patients. Additionally, all subjects were evaluated for trunk rigidity and trunk muscle strength by using an isokinetic dynamometer. Independent t-tests were used to compare the trunk muscle parameters between patients with PD and healthy controls. Multiple regression analysis was performed to identify the significant determinants of lumbar spine BMD in PD patients.

Results: Approximately 21% and 37% of our PD patients had osteoporosis and osteopenia, respectively. PD patients had significantly lower trunk muscle strength, but more trunk rigidity than controls by 46.6% and 162.8%, respectively ($P<0.001$). In bivariate correlation analysis, lumbar spine BMD was significantly related to trunk muscle strength ($r=0.475$, $P=0.001$), but not trunk rigidity ($r=0.271$, $P=0.079$). In multiple regression analysis, trunk muscle strength remained a significant determinant of lumbar spine BMD, accounting for 9.8% of the variance ($R^2=0.344$, $F_{7,35}=3.838$, $P=0.027$), after adjusting for other relevant factors such as age, gender, height, Unified Parkinson's Disease Rating Scale (UPDRS) score, physical activity and trunk rigidity.

Conclusions: Trunk muscle strength is independently associated with lumbar spine BMD in PD patients. Strengthening of muscles specific to the lumbar spine region might be important in enhancing lumbar spine BMD but will require further study.

Tu-195

Home-based rehabilitation to reduce falls and disability in Parkinson's disease: Protocol for a randomised controlled trial

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Objective: To provide the rationale and methodological justification for a unique randomised controlled trial comparing the effects of a home-based physical rehabilitation program and a life-skills program to reduce falls and disability in people with idiopathic Parkinson's disease (PD).

Background: Falls and movement disorders are common and disabling features of PD. There is emerging evidence that physical rehabilitation programs, including strength and movement-strategy training, may be effective in improving mobility and health-related quality of life (HQoL) in people with PD; however, previous trials have investigated rehabilitation services delivered in hospitals or outpatient settings. Given that people with PD are mostly elderly and community-dwelling, home-based therapy may provide an affordable and effective model of service provision, targeting falls where they most often occur.

Methods: 180 community-dwelling people with PD will be randomised to receive either (i) a physical rehabilitation program, comprising strength and movement-strategy training and falls prevention education; or (ii) a lifeskills program including topics such as medications, managing stress, driving and other daily activities. All therapy will be delivered within participants' homes, once per week, for six weeks. Falls frequency and injuries will be recorded over a 14 month period using a patient calendar and telephone contact. Disability and HQoL will be quantified using the UPDRS, PDQ39 and EuroQOL. Health care costs will also be evaluated as part of a concurrent economic evaluation.

Results: A comparison of the effects of home-based physical rehabilitation versus home-based lifeskills training will be conducted. It is hypothesised that the physical rehabilitation group will demonstrate a reduction in falls and disability, with improved HQoL compared to the lifeskills control group. An economic analysis will investigate the feasibility of home-based service delivery for people with PD.

Conclusions: This is the first large scale randomised controlled trial to investigate the clinical efficacy and economic viability of home-based rehabilitation for people with PD. The results of this study may influence the future of non-pharmacological management of people with PD.

Tu-196

An open-label extension study to determine the safety of pimavanserin in patients with Parkinson's disease and psychosis

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Objective: A multi-center, open-label, extension study is being conducted to determine the safety of pimavanserin during long-term administration in subjects with Parkinson's disease and Psychosis who, in the opinion of the Investigator, may benefit from continued treatment of pimavanserin.

Background: Previous short-term clinical studies have shown that pimavanserin is safe and well-tolerated in subjects with PDP through four weeks of treatment.

Methods: This interim analysis was performed to assess safety data through 18 months of treatment. Clinical evaluations occurred two weeks, one month, 2 months, and 3 months after starting treatment, and every three months thereafter, adverse event and concomi-

tant medication assessment, administration of clinical rating scales, physical exam, 12-lead ECG, clinical laboratory tests, and plasma pimavanserin level determination were performed. The starting dose of pimavanserin was 20 mg/day, which may have been increased by 20 mg/day, to a maximum of 60 mg/day, after at least two weeks of treatment at the prior dose level. A total of 39 subjects were enrolled, 21 and 18 respectively had received pimavanserin and placebo in a previous clinical study.

Results: Eleven (28.2%) and 22 (55.4%) subjects had received a dose escalation to 40 mg and 60 mg, respectively. Six (15.4%) subjects received a dose reduction after increase. Thirty-four (87%) subjects experienced at least one treatment-emergent AE. 14 (36%) subjects experienced at least one treatment-related AE. Thirteen (33.3%) subjects experienced a total of 23 SAEs, of which 1 was considered to be treatment related. The majority of AEs were mild to moderate in severity. Constipation (20.5%) and Urinary tract infection (18%) were the most common treatment-emergent AEs.

Conclusions: Long-term administration of pimavanserin up to 60 mg daily appears to be safe and well-tolerated in subjects with PDP.

Tu-197

Automated auditory biofeedback training to enhance postural control and mobility in patients with Parkinson's disease: Preliminary results from SENSACTION-AAL

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Objective: To test whether 4 weeks of training with auditory biofeedback (ABF) enhances postural control, mobility and health-related quality of life (QOL) in patients with Parkinson's disease (PD).

Background: Diminished postural control and mobility are common among patients with PD. Traditional therapeutic approaches are often not effective at treating these motor deficits. Previous work has demonstrated that ABF may be used to enhance postural control in patients with vestibular dysfunction. We speculated that ABF could be applied to augment treatment of the motor deficits in PD.

Methods: A 3-D accelerometer (McRoberts) worn on the lower back was used to estimate sway and target position. ABF at target positions (correct postures or stepping) was provided via headphones or speakers. Subjects participated in 4 weeks of training, 3 times a week, for approximately 30 minutes each session. Tasks trained included postural control (sitting and standing), transfers (sit-to-stand), stepping and reaching. Pre-post testing included the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS), the Timed Up and Go (TUG), Berg Balance Scale (BBS), postural control (sway during quiet standing and with eyes closed) and the PDQ-39, a measure of health-related QOL.

Results: These preliminary results include data from 3 PD patients (H&Y stage II-III; mean age:72 years (71-73), mean disease duration 5 years (4-6), and disease severity (UPDRS motor score) of 32.7±15.0. Improvements were found in the TUG, with an average change of 1.2±1.6 sec (8.2%) from pre test. All subjects had a change of 2 points in the BBS with improvements in tandem standing, one leg stance and stepping. Two subjects improved in postural control (UPDRS pull test), demonstrating a change of 2-5 points on this test. The mobility domain in the PDQ-39 improved by an average of 3.5 points, and all subjects reported less missteps or near falls during the month of training.

Conclusions: To our knowledge, this is the first time that ABF has been applied as part of a training program. Initial experience using this paradigm suggests that this mode of therapy is efficacious for patients with PD and worthy of further study.

Tu-198

Clinical efficacy of istradefylline (KW-6002) in the treatment of Parkinson's disease: A randomized placebo-controlled study

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Objective: To evaluate the efficacy and safety of istradefylline in Parkinson's disease (PD) patients with motor complications on levodopa therapy.

Background: Istradefylline, a non-dopaminergic, first-in-class selective adenosine A_{2A} receptor antagonist, has shown antiparkinsonian activity in animal models of PD as well as in fluctuating patients with PD to reduce the length of the OFF period.

Methods: Clinical subjects consisted of 363 patients on levodopa with motor fluctuations; they were randomly allocated to one of the three groups, i.e., istradefylline 20 mg once daily, 40 mg once daily, or placebo. The treatment period was 12 weeks. The primary endpoint was the change in the total hours of OFF period during awake time per day. The safety was assessed based on treatment emergent adverse events (TEAEs).

Results: The total hours of OFF period during awake time per day reduced from baseline by 1.31 hours for 20 mg/day istradefylline, 1.58 hours for 40 mg/day istradefylline, and 0.66 hours for placebo, showing that 20 mg/day ($p=0.013$) and 40 mg/day ($p<0.001$) istradefylline statistically significantly reduced OFF time compared with placebo. UPDRS Part III score (ON state) reduced from baseline by 5.7 for 20 mg/day, 5.7 for 40 mg/day, and 3.7 for placebo, showing that 20 mg/day ($p=0.006$) and 40 mg/day ($p=0.006$) istradefylline statistically significantly reduced UPDRS Part III score compared with placebo. Istradefylline at 20 mg/day and 40 mg/day was well tolerated, with no marked differences from placebo in terms of the incidence or severity of TEAEs or drug-related TEAEs. One of the most frequently reported TEAEs was dyskinesia, which occurred in 8.5% (10/118) of subjects receiving 20 mg/day istradefylline, 6.4% (8/125) of subjects receiving 40 mg/day istradefylline, and 2.5% (3/119) of subjects receiving placebo.

Conclusions: Istradefylline at 20 mg and 40 mg is effective in reducing the length of the OFF period and in improving motor symptoms during the ON period without significant TEAEs in PD patients with wearing off.

Tu-199

Gait analysis is more sensitive than finger tapping or UPDRS motor scores in assessment of the motor response to levodopa in Parkinson's disease

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Objective: To compare the sensitivity of gait analysis, finger tapping and UPDRS motor scores in assessment of the motor response to orally dissolving (OD) carbidopa/levodopa (C/L) and conventional oral (C/L) in patients with Parkinson's disease (PD).

Background: Finger tapping and UPDRS motor (part III) scores are typically used in the assessment of motor response to medication in PD. Our recent studies have demonstrated the efficacy of ambulatory gait analysis in assessment of locomotor response to C/L.

Methods: PD patients (20) participated in a single dose, double-blind, double-dummy, placebo-controlled, cross-over trial of OD and oral C/L over two days. On the 1st day subjects received either OD C/L and an oral C/L placebo or OD C/L placebo and oral C/L, which was reversed on the 2nd day. After medication administration, subjects performed finger tapping and walking trials every 5 min for 60 min. Stride length was measured using an ankle mounted gait monitor (SAGE-M, IM Systems, Baltimore MD) developed by the investigators.

Results: Tapping and UPDRS III scores did not show any significant differences between OD and oral C/L. Gait analysis (N=10) showed that stride length increased to 50% of the difference between baseline and final values in 31.3(SD 12.0) minutes with OD C/L vs.

37.6(SD 19.1) minutes with oral C/L, NS. Stride length data was grouped into 3 bins, each spanning four data collection points; 5-20 min, 25-40 min, and 45-60 min post medication administration. The mean increase in stride length from baseline was significantly greater (ANOVA) with OD C/L for all bins; 5-20 min, OD C/L 7.3 cm (SD 13.6) vs 2.1 cm (SD 6.2) oral C/L (p=0.044); 25-40 min, OD C/L 27.7 cm (SD 25.1) vs 13.5 cm (SD 13.2) oral C/L (p=0.044); and 45-60 min, OD C/L 38.1 cm (SD 19.9) vs 23.8 cm (SD 18.1) oral C/L (p=0.0029). The more pronounced increase in stride length with OD C/L vs tapping was consistent with patient preference: 12 preferred OD C/L, 6 preferred oral C/L, and 2 felt they were identical.

Conclusions: The results of this pilot study suggest that stride length analysis is more sensitive to the motor response to C/L in PD than finger tapping or UPDRS part III. Ambulatory monitoring of gait may prove effective in objective assessment of the efficacy of pharmacological interventions in PD.

Tu-200

A pilot study of the benefit of occupational therapy in Parkinson's disease

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Objective: The purpose of the study was to scientifically evaluate if individualized occupational therapy (OT) interventions for patients with Parkinson's disease (PD) are indeed beneficial.

Background: PD results in impairment of activities of daily living (ADLs) as a result of motor and non-motor dysfunction. Although, patients are often referred for OT to improve their abilities to participate in ADLs, etc. there is little evidence examining its efficacy.

Methods: In this randomized, controlled, single-blind pilot study, 30 patients with PD (Hoehn & Yahr stage 2) were randomized 1:1 to receive individualized OT or to a control group that did not receive OT for 8 weeks. The primary outcome measures were timed tests consisting of four common ADLs (brushing teeth, putting on a buttoned shirt, putting on shoes and socks, writing a short passage), the Purdue Pegboard Test (PPT), and a timed tapping task. Secondary outcome measures included the UPDRS, PDQ-39 scale and therapist administered measures. Pre- and post-intervention comparisons in each subject as well as between the OT group vs. control group were made to evaluate the beneficial effects of OT. Statistical analysis was done using Mann-Whitney-Wilcoxon (MWW) Test, Fisher's Exact Test (FE), and Wilcoxon Signed Rank Test (WSR).

Results: There were no significant changes in the primary outcome measures of the timed ADLs, PPT and timed tapping tasks between the control vs. OT group. There was a significant improvement in the OT group on the Part II subscale of the UPDRS as compared to the controls. Similar improvement on Part III UPDRS scores was also noted but it was not statistically significant due to a large amount of variability. The Timed Get-up and Go, Tinetti Gait and Balance Test, and 9-Hole Peg Test used on selected participants, showed positive changes from pre-testing to post-testing in the OT group.

Conclusions: Although primary outcome measures showed no significant change, the improvement in Parts II & III of the UPDRS and other gait and balance tests in a small trial of 8 weeks, eludes to a potential benefit of OT in PD patients. A larger trial with better tools to assess performance may be necessary to conclusively show benefit.

Tu-201

Carry-over effects of movement strategy training in Parkinson's disease

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Objective: To investigate the extent to which any improvements in movement speed and disability are retained three months after movement strategy training delivered as part of an inpatient rehabilitation program.

Background: Studies of the effectiveness of movement strategy training for people with PD have to date focused on services delivered in an outpatient or community setting. Although these studies have reported some short term benefits of movement strategy training, little is currently known about the carry-over effects of such interventions.

Methods: In this single-blind controlled trial, 28 people with idiopathic PD were randomised to a group receiving either movement strategy training or generic musculoskeletal exercises delivered in addition to usual multidisciplinary care as part of a 2-week inpatient rehabilitation program. Outcome measures including the Unified PD Rating Scale (UPDRS), gait speed and endurance, balance and quality of life (QoL) measures were taken in the "on" phase of the PD medication cycle at baseline, 2 weeks and 3 months.

Results: At the end of the inpatient rehabilitation period the movement strategy group demonstrated a reduction in disability as measured on the UPDRS ($p=.003$), and a significant improvement in gait speed ($p=.003$), walking endurance ($p=.000$) and standing balance ($p=.002$). In contrast, there was no significant change in disability, gait speed, endurance or balance for the generic exercise group. Both groups reported significant improvement in QoL from admission to discharge ($p<.002$). At 3 months, the increased gait speed recorded by the movement strategy group at discharge was retained, despite regression of the UPDRS scores toward baseline values. There was no significant change in QoL measures from discharge to 3 month follow-up in either group.

Conclusions: Our data suggest that movement strategy training for people with PD may be effective in reducing disability, improving walking performance, balance and QoL when delivered as part of an inpatient rehabilitation program. Carry-over benefits of movement strategy training were shown in this sample with 3 month follow up data. Further research investigating the optimal intensity and frequency of movement strategy training to maximize walking performance in people with PD, despite disease progression, is warranted.

Tu-202

Evaluation of a computerized telephone system to monitor falls

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Objective: To evaluate a computerized telephone system enabling long-term monitoring of fall incidents, to be tested initially in patients with Parkinson's disease (PD), but with a possible use for patients with other movement disorders as well.

Background: Decreasing the frequency of falls is an important aim in the therapeutic approach of PD. To evaluate the effect of fall prevention strategies, it is necessary to have a reliable and patient-friendly tool to record fall events during a prolonged time.

Methods: We developed a computerized telephone system (the Falls Telephone) to monitor falls. The Falls Telephone automatically calls patients weekly and asks them to record their number of new fall incidents in the preceding week. We evaluated the reliability of this Falls Telephone in 124 non-demented PD patients who participated in a prospective falls prevention trial. A cross-sectional sample of 90 patients (mean age 68 years, range 44-81) evaluated the system on patient satisfaction.

Results: In total, 2476 automated telephone calls were made. In 2343 occasions the patient had not fallen. In a random sample (n=173) of these telephone calls without falls, we used a telephone interview to evaluate whether the Falls Telephone was correct. All interviews were confirmed as non-falls. In 133 telephone calls, patients had indicated one or more fall incidents, 126 of which were verified by a telephone interview. 83.2% of the automated telephone call answers were confirmed to be actual fall incidents. The majority of the patients reported positively on several aspects of the Falls Telephone. The mean overall rating on a 10-point scale (1 bad–10 excel-

lent) was 8.3 (range 6-10). Almost all patients regarded the telephone system as an attractive and feasible system.

Conclusions: The Falls Telephone can reliably ascertain subjects who do not fall, and is also reasonably reliable for detecting new fall events in the home situation. The system also scores high on patient satisfaction. The Falls Telephone is a feasible and efficient tool in falls research, because only patients who indicate having fallen in the preceding week need to be called by the researcher to obtain a good measure of their frequency of falls during a prolonged time.

Tu-203

Long-term efficacy and safety of zonisamide on Parkinson's disease: Up to 9 years

M. Murata, I. Kanazawa (Tokyo, Japan)

Objective: To evaluate the long-term efficacy and safety of zonisamide on Parkinson's disease (PD).

Background: Zonisamide has been used to treat epilepsy in Japan for more than 10 years; is currently used in all over the world. In 2001, we found zonisamide has beneficial effects on PD. Then we conducted some randomized clinical trials of zonisamide for advanced PD patients and reported that zonisamide (25-100mg/day) improves motor function in PD. Finally zonisamide has approved as the antiparkinsonian drug for marketing in Japan at January 2009. Here we report the long-term efficacy and safety of ZNS on PD up to 9 years.

Methods: Eight patients with PD were observed before ZNS administration until 9 years after ZNS adding. Mean onset age was 49.5(43-57) y/o, mean zonisamide start age was 57.9 (47-65) y/o, mean duration of PD until now was 13.5 (9-17) years, and mean duration of zonisamide was 7.5 (5.5-9) years. Patients were given 50-150 mg of zonisamide once daily in addition to their anti-parkinsonian drugs.

Results: 1) Efficacy. Zonisamide improves cardinal parkinsonian symptoms especially wearing-off and intractable tremor, and it was maintained to at least 3 years. Though after 3 years antiparkinsonian drugs were increased in some patients, total score of UPDRS III (on) and Yahr staging (on) at the final assessment are equal or less than before zonisamide for 5 of 8 patients. When one patient was stopped zonisamide at 4 years, wearing-off was appeared so he started again within 1 month. 2) Safety; In the observed period two patients developed hallucination when their dopamine agonist was changed. One patients died by heat stroke but he did not have oligohydrosis. There is no patient with disabling dyskinesia in this observation period.

Conclusions: Zonisamide showed excellent long-term efficacy even in advanced PD. Although long-duration of PD there is no patient with disabling dyskinesia. There is no adverse event relevant to zonisamide administration. Zonisamide is the new effective and safety drug for PD.

Tu-414

Piribedil: First results of an observational study (PIR-001/K) investigating tolerability, effectiveness and prescribing practice of piribedil in Germany

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Objective: This prospective, open-label study was performed to explore tolerability and effectiveness outcomes of Piribedil treatment and to collect data under daily practice. Special attention was directed to the effects of Piribedil on day-time-sleepiness.

Background: Piribedil, a non-ergot D2/D3 dopamine agonist (DA) with α2-noradrenergic antagonistic properties, was firstly introduced in Germany in 2007 for the treatment of Parkinson's disease.

Methods: Prospective, open-label, multicentre, online documentation (eCRF). Patients received Piribedil in monotherapy (=without L-Dopa, other antiparkinsonian medication allowed) or in combination with L-Dopa. Patients with DA-pretreatment were switched overnight or in an overlapping manner to Piribedil. Treatment was observed over a 3 months period with 3 visits.

Results: 202 patients included. Demographic data: male 59,9% female 40,1%; mean age: 67,7 years; mean duration of the disease: 6,1 years. Treatment: 41,6% (n=84) received Piribedil in monotherapy; 58,4% (n=118) in combination with L-Dopa. Mean daily dosage in monotherapy and in combination with L-Dopa was comparable (177mg/d and 175mg/d respectively). In combination with L-Dopa Piribedil was administered >150 up to 250mg/d in 46% and well tolerated. After mean treatment duration of 80 days mean reduction of UPDRSIII of – 8,2 was documented. Overall assessment of efficacy: 22,6% very good, 62,4% good; 11,8% moderate, 3,2% poor. Overall assessment of tolerability: 48,7% very good; 41,3% good; 5,3 % moderate; 4,8% poor. Patients who were impaired by day-time-sleepiness (n=81) under pre-study medication could benefit (very much improved: 18,5%; improved: 48,1%). High initial values in Epworth Sleepiness Scale (≥10) could be reduced.

Conclusions: These present data of first experience with Piribedil in Germany documented general improvement of motor symptoms and good tolerability. Day-time-sleepiness under pre-study conditions improved under Piribedil, controlled studies should be performed to confirm these findings. Due to it's unique receptor profile providing positive effects on vigilance and cognition and against the background of prescribing restrictions of ergot-DA (risk of cardiac fibrosis) the non-ergot-DA Piribedil represents a useful therapeutic option in the treatment of Parkinson's disease in Germany.

We-180

Is there a difference in the pharmacokinetics between entacapone and levodopa?

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Objective: To aim of this study is to clarify whether there is a difference in the pharmacokinetics between entacapone and levodopa or not.

Background: Entacapone is a peripherally Catechol-O-methyltransferase (COMT) inhibitor used in patients with Parkinson's disease (PD), as an adjunctive therapy to levodopa in order to prolong its bioavailability. The effect is reversible and competitive inhibition. Therefore, entacapone and levodopa must be synchronized in terms of pharmacokinetics for entacapone to work effectively. It has been presented that approximately 30% of PD patients were non-responder to entacapone. However the reason has not been fully elucidated.

Methods: Three healthy volunteers were administrated levodopa/benserazide (100/25mg) co-administrated with entacapone (100mg) in the morning fasting. Venous blood was taken before and after the drugs administration. Plasma concentrations of levodopa and entacapone were determined using a HPLC.

Results: Tmax of levodopa in three cases was 30min, 90min, and 150min, respectively. Tmax of entacapone, which was 90min, 90min, and 180min, corresponded to that of levodopa individually. Thus the cases who showed delayed absorption of levodoa also presented delayed absorption of entacapone.

Conclusions: Pharmacokinetics of entacapone is synchronized with that of levodopa.

We-181

Rasagiline as add on therapy in levodopa-treated patients with Parkinson's disease and motor fluctuations: A randomized placebo-controlled study

N. Oztekin, F. Oztekin, H. Okkan, F. Ak, S. Bilen (Ankara, Turkey)

Objective: To determine the safety, tolerability, and efficacy of rasagiline in levodopa-treated patients with PD and motor fluctuations.

Background: Rasagiline mesylate, an irreversible monoamine oxidase type B inhibitor, improves symptoms of early Parkinson's dis-

ease (PD). Several recent studies suggest that this compound may also be effiective in levodopa-treated patients with PD and motor fluctuations.

Methods: This is a randomized, placebo-controlled study in Parkinson's disease patients (N = 40) with at least 10.5 hours of daily "off" time, despite optimized treatment with other anti-PD medications (Levodopa and other agonists) and randomized either to receive rasagiline, 1.0 or 0.5 mg/d, or placebo. Main outcome measures were change from baseline in total daily off time measured by patients' home diaries during 26 weeks of treatment period, percentage of patients completing 26 weeks of treatment, and adverse event frequency. Secondary end points, were the mean change in scores on an investigator-rated clinical global impression scale (CGIS)and the Unified Parkinson's Disease Rating Scale $^{(UPDRS)}$(activities of daily living in the off state and motor performance in the "on" state).

Results: During the treatment period, the mean adjusted total daily off time decreased from baseline by 1.45 hours (32%) in patients treated with 1.0 mg/d of rasagiline, 1.32 hours (18%) with 0.5 mg/d rasagiline, and 0.71 hour (11%) with placebo. Patients treated with 1.0 mg/d rasagiline had 0.88 hour less off time per day, and patients treated with 0.5 mg/d rasagiline had 0.42 hour less off time per day compare to placeo treated patients. Secondary end points, including scores on an investigator-rated CGIS and the UPDRS (activities of daily living in the off state and motor performance in the "on" state). also improved during rasagiline treatment compared to placeo. Rasagiline was well tolerated without prominant side effects.

Conclusions: The results of this study supported the findings of previous studies emphasizing that rasagiline improves motor fluctuations and PD symptoms in levodopa-treated PD patients. and is a promising new treatment for PD.

We-182

Amantadine given as adjuvant to levodopa in the treatment of levodopa induced dyskinesias and motor fluctuations in Parkinson's disease

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Objective: To determine the effects of the N-methyl-D-aspartate (NMDA) antagonist amantadine on levodopa-associated dyskinesias and motor fluctuations in Parkinson's disease (PD).

Background: Amantadine, an antiviral drug with dopaminergic properties and a NMDA receptor antagonist, has been demonstrated to ameliorate L-DOPA induced yskinesias in primates and to provide symptomatic improvement and dyskinesia benefit in some patients with PD. Amantadine has shown a beneficial effect on L-Dopa induced dyskinesias in advanced Parkinson's disease patient's in serveral clinical studies.

Methods: 32 patients with advanced PD enrolled in a placebo-controlled study. Patients were randomised in a ratio 1:1 (16 patients in each group) followed by a 3 week treatment period. All patients received identically appearing capsules containing amantadine (100 mg) or placebo for 3 weeks. Amantaine dose was titrated up to 400 mg/d. Motor fluctuations and dyskinesias were assessed at baseline and end visit with the UPDRS IV, item 32 and 33. In addition a self-scoring 24 hour On-Off diary had to be filled out 53days prior to the the visits. The primary outcomes measures were the Clinical Dyskinesia Rating Scale (CDRS) and the Unified Parkinson's Disease Rating Scale (UPDRS) part IV score changes. The secondary outcomes were the UPDRS II and III score changes.

Results: All the patients completed the 3 week trial period. Amantadine reduced dyskinesia severity by 60% ($p = 0.001$), decreased the duration of dyskinesia and its influence on daily activities ($p=0.04$) and the UPDRS II score ($p=0.01$) compared to placebo, without altering the antiparkinsonian effect of levodopa. Motor fluctuations occurring with patients' regular oral levodopa regimen also improved according to UPDRS and patient-kept diaries. Amantadine also changed the CDRS score for hyperkinesia or dystonia, but the results were not statistically signficant.

Conclusions: These findings suggest that amantadine given as adjuvant to levodopa can markedly improve motor response complications and support the view that hyperfunction of NMDA receptors contributes to the pathogenesis of levodopa-associated motor complications.

We-183

Safety of recombinant human erythropoietin (rhEPO) in Parkinson's disease (PD): A three month report

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Objective: To evaluate (1) the safety and tolerability of rhEPO and (2) the effects of rhEPO on motor, cognitive and emotional functions after three months of rhEPO therapy in patients with PD using the Unified PD Rating Scale (UPDRS), Dementia Rating Scale (DRS) and Hamilton's Depression test.

Background: rhEPO is an haematopoietic factor. It has shown to improve motor and cognitive functions in animal models of PD. rhEPO has been previously reported in other neurological and psychiatric diseases with good tolerability, but there is only one report with two PD patients.

Methods: We conducted an open label phase I study for administration of rhEPO (60IU/kg once a week for five weeks of treatment) to ten patients with PD. Changes of motor performance and cognitive impairment were evaluated one week and three months after treatment according to UPDRS, DRS (Mattis), Hamilton's Depression scales. Laboratory tests (hematology) were repeated at the same time by a team of the Clinic of Movement Disorders at CIREN. All adverse experiences were reported spontaneously on general questioning or observed directly by the investigator's records. The non parametric sign test for two dependent samples was used to test the significant difference between initial and three month tests, using a p value <0.05.

Results: The mean age was 53.3 (SD 2.3) years, mean disease duration was 5.8 (SD 3.37) years and I-III stages of Hohen Yahr scale. rhEPO was well tolerated and seemed safe. One patient had arterial hypertension but it was medicated and remained in the study. Hemoglobin had higher scores after treatment but under normal limits. Clinical improvement of the motor function was reflected by the reduction of the basal UPDRS at the OFF condition ($z=2.21$, $p=0.026$). The qualifications of DRS ($z=2.47$, $p=0.013$) and Hamilton's ($z=2.21$, $p=0.026$) decreased too at significant level.

Conclusions: Our data suggest that rhEPO is safe and has a positive secondary effect over the motor and cognitive conditions in PD patients.

We-184

Rasagiline 1 mg/day provides benefits in the progression of non-motor symptoms in patients with early Parkinson's disease: Assessment with the revised MDS-UPDRS

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Objective: To assess the impact of treatment with rasagiline on non-motor symptoms in patients with very early Parkinson's disease (PD).

Background: It is increasingly recognized that non-motor symptoms (i.e. altered mood, apathy, cognitive impairment, sleepiness, pain, fatigue and urinary problems) are an integral part of the PD symptom complex and can emerge before motor signs. A revised version of the Unified Parkinson's Disease Rating Scale (UPDRS), called the MDS-UPDRS recently completed phase II validation (Goetz et al, Mov Disord 2008; 23, 2129). It was designed to be more comprehensive than the original UPDRS, and includes a specific section on Non-Motor Aspects of Experiences of Daily Living (nM-EDL); a draft version of this was employed in the placebo-controlled phase of the ADAGIO study.

Methods: 1176 untreated early PD patients were randomized to receive rasagiline 1 or 2 mg/day or placebo for 36 weeks. The nM-EDL scale was assessed at baseline and at the week 36 or early withdrawal visit. Adjusted means of change from baseline to last observed visit for each rasagiline group were compared to placebo using an ANCOVA model that included treatment group, center and baseline nM-EDL scores as covariates.

Results: A total of 1150 subjects were included in the efficacy analysis. Patients in the placebo group showed a larger deterioration (0.34 units) from baseline in nM-EDL scores compared to both the 1 mg/day (0.01 units) and 2 mg/day rasagiline groups (0.09 units). The difference versus placebo was significant for the 1 mg rasagiline group (treatment difference -0.33 units; $p<0.05$).

Conclusions: This is the first report of the use of any component of the MDS-UPDRS in a clinical trial and the first evidence that this new tool can effectively assess change in non-motor features in early PD. In such patients, rasagiline 1 mg/day showed significant benefits versus placebo in the nM-EDL section of the recently validated MDS-UPDRS scale. In addition to its established efficacy in treating motor symptoms, rasagiline monotherapy can also provide benefits in the treatment of non-motor symptoms of PD.

We-185

Pramipexole extended-release is effective in early Parkinson's disease

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Objective: To investigate the efficacy and safety of pramipexole extended-release (ER) as once daily treatment for early Parkinson's disease (PD).

Background: Pramipexole immediate-release (IR), administered tid, has well-established efficacy in PD. Pramipexole ER may provide similar therapeutic benefit, with more convenience and potentially better compliance.

Methods: Patients with early PD were randomized (2:2:1) to double-blind pramipexole ER (0.375-4.5 mg qd), IR (0.125-1.5 mg tid), or placebo. Drug was flexibly titrated over 7 weeks, then maintained for an additional 26 weeks. Interim analyses at Week 18 were planned to evaluate pramipexole ER vs placebo on UPDRS II+III score (primary endpoint), and CGI-I and PGI responder rates (key secondary endpoints; responder defined as much/very much improved/better), on a subset of ~250 patients. A final analysis of the full population at Week 33, using non-inferiority testing of ER vs IR, was also planned (pre-defined non-inferiority margin was -3 points for the primary endpoint).

Results: At Week 18, 253 (ER: 102, IR: 101, placebo: 50) of the 259 randomized patients were eligible for the interim analyses. Superiority of pramipexole ER over placebo was confirmed for primary and key secondary endpoints. In the final analysis at Week 33, non-inferiority was demonstrated between the 2 pramipexole formulations (Table 1), with an adjusted mean change in UPDRS II+III score of -8.6 points for ER (n = 213) and -8.8 points for IR (n = 207), between-group difference = -0.2 and 97.5% CI = [-2.2; ∞).

Table 1 (We-185). Non-Inferiority of Pramipexole ER Compared With Pramipexole IR in UPDRS Part II + III Change From Baseline at Week 33

		Pramipexole ER	Pramipexole IR	Difference (ER-IR)
FAS	N	213	207	
	Mean	−8.6	−8.8	−0.2
	97.5% CI	[−9.9, −7.2]	[−10.2, −7.4]	[−2.2, 1.7]
	97.5% CI (one-sided)			3 ∉[−2.2; ∞)*
PPS	N	158	163	
	Mean	−9.8	−10.0	−0.2
	95% CI	[−11.1, −8.4]	[−11.4, −8.6]	[−2.0, 1.7]
	97.5% CI (one-sided)			−3 ∉[−2.0; ∞)*

*Pramipexole ER is non-inferior to pramipexole IR (α-level = 0.05; predefined non-inferiority margin = -3). FAS = Full analysis set; PPS = Per protocol set.

Table 2 (We-185). Clinical Global Impressions-Global Improvement (CGI-I) and Patient Global Impression (PGI) Responder Rates at Week 33 (FAS)

	Placebo (%) N = 102	Pramipexole ER (%) N = 210	Pramipexole IR (%) N = 206
CGI-I responder rate 95% CI	29.4 [20.8, 39.3]	43.3 [36.5, 50.3]	46.1 [39.2, 53.2]
PGI responder rate 95% CI	21.4 [13.9, 30.5]	34.4 [28.1, 41.2]	33.3 [27.0, 40.2]

Response was defined as "much" or "very much" improved/better. FAS = Full analysis set.

Table 2 displays CGI-I and PGI responder rates at Week 33. Comparable efficacy was observed for both pramipexole formulations, at similar mean total daily doses and dose distributions.

Adverse event rates were also similar for pramipexole ER and IR, and were only marginally higher than for placebo.

Conclusions: Superiority of pramipexole ER over placebo was demonstrated at Week 18. Non-inferiority between ER and IR formulations was demonstrated in the final statistical analysis at Week 33. Pramipexole ER and IR were well tolerated and showed a comparable safety profile.

We-186

A non-randomised blinded comparison of entacapone (E) and conventional release (CR) with E and slow release (SR) levodopa (L) in Parkinson's disease (PD)

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Objective: To compare the duration of action of a single dose of CRL and SRL when combined with E for the treatment of end of dose effects in PD.

Background: Entacapone is first line treatment for end of dose in PD, however the benefits in extension of the duration of action of a single dose of L can be variable, short lived and is of low utility for the patient. Alternatives include the use of tolcapone, selegeline or high dose dopamine agonists, all with associated side effects. This study reports on the combined use of CRL, SRL and E to determine efficacy in control of end of dose.

Methods: Experienced nurses, blinded to the investigation, monitored subjects with PD on an hourly basis as inpatients over a 2-3 week period. Measures included a timed get up & go (GUGT) and a five points scale for tremor and dyskinesia for 3 different conditions utilising CRL, CRL&E and CRL&SRL&E combinations after adjusting the L dose to optimise mobility with minimal side effects. The SR dose was up adjusted to match the CR dose because of reduced bioavailability. Medication was only administered when an objective measure of end of dose occurred. Measures were averaged for 2 days for each condition prior to a change in condition or prior to discharge. Comparisons were performed with paired T tests.

Results: Patients (29) were recruited over 12 months. The group was predominantly male (17) with a mean age of 67.3 years and disease duration of 9.6 years. The UPDRS III scores were 14.3 (ON) and 26.2 (OFF) and UPDRS II scores were 11 (ON) and 22.1 (OFF) respectively. Mean ON time was significantly ($P< 0.044$) improved with E &CRL by 0.45 (sd = 0.8) hours above CRL. The CRL&SRL&E however significantly ($P< 0.018$) increased ON time by 2.25 (sd=1.3) hours per dose compared to E &CRL. Significant improvement ($P<0.000$) occurred in the GUGT (13.3 cf 11.2 sec) and the tremor score (0.95 cf 0.81) ($P<0.001$) but with an increase in dyskinesia (0.9 cf 1.4) ($P<0.000$).

Conclusions: The combination of CRL&SRL&E produced prolonged, consistent and clinically useful control of end of dose effects compared to E&CRL. It is suggested that a randomised cross over

study be considered to establish this approach in routine practice because of the enormous potential benefit to this patient group.

We-187

Safety and tolerability profile of preladenant as an adjunct to L-dopa in patients with Parkinson's disease

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Objective: To assess the safety and tolerability of a range of preladenant doses in patients with moderate to severe Parkinson's disease experiencing motor fluctuations and dyskinesias on a stable dose regimen of L-dopa and other adjunctive treatments.

Background: Preladenant is a novel, potent, and highly selective A_{2A} receptor antagonist being investigated for the management of Parkinson's disease and other movement disorders.

Methods: This was a phase 2, 12-week, double-blind, placebo-controlled study in 253 randomized patients. Patients received preladenant (1, 2, 5, or 10 mg BID) or placebo BID. Safety parameters were assessed at predetermined times during treatment and all patients who either completed or discontinued returned for safety follow-up visits 2, 4, and 6 weeks after the last day study drug was taken. Safety assessments included all reported adverse events (AEs), serious AEs, vital signs, and laboratory and ECG parameters.

Results: Treatment was discontinued in 51 (25%) preladenant- and 8 (16%) placebo-treated patients. AE-related treatment discontinuations occurred in 29 (14%) preladenant- (24%, 4%, 10%, and 18% in the 1-, 2-, 5-, and 10-mg groups, respectively) and 7 (14%) placebo-treated patients; the 5- and 10-mg preladenant groups experienced significantly reduced OFF time compared to placebo. Parkinsonism, somnolence, and dyskinesia were the most frequently reported AEs and occurred at approximately the same frequency in the preladenant and placebo groups. There was no clinically significant drug effect on vital signs, labs, or ECG parameters.

Conclusions: Preladenant was safe and generally well tolerated at all 4 doses. Overall AE incidence and the incidence of the most frequently reported AEs were similar in the 4 preladenant and placebo groups. AE-related discontinuations occurred at similar rates regardless of whether the patients were administered therapeutic doses of preladenant or placebo.

We-188

Following GDNF: Four year follow-up after bilateral intraputamenal infusion

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Objective: To document the long term clinical course in a patient with Parkinson's disease following participation in a clinical trial of bilateral intraputamenal (IPu) delivery of glial cell-line derived neurotrophic factor (GDNF).

Background: GDNF has been shown to exhibit neuroprotective and neurorestorative effects on dopaminergic neurons in animal models. Following the positive results of an open-label study in Parkinson's patients, a phase II randomized double blind clinical trial failed to produce significant overall improvement in the primary endpoint. However, a patient we treated, who received active drug for 9 months, showed sustained improvement over 24 months following the cessation of GDNF delivery. He then slowly declined over the following 18 months but remained improved over baseline.

Methods: Unified Parkinson's Disease Rating Scale (UPDRS), Perdue Peg Board and Timed Walk Testing scores were evaluated at 2 and 4 years post GDNF infusion. These scores were compared with this patient's study related scores. Pre and post study PET scan data is included.

Results: The UPDRS motor "on" score improved by 90% and practically defined motor "off" score improved 80% over baseline after 9 months of GDNF therapy. Remarkably, motor "on/off" scores remained improved by 90% "on", and 60% "off" for two years without further drug infusion. By four years, motor scores declined but remained improved by 78% "on" and 28% "off" over baseline. Perdue Peg Board scoring in "off" medication state was 3 pre-trial, escalated to 12 at drug termination, and remained level at 13 four years out. Timed walk score was 17 prior to GDNF therapy and 12 at four year follow-up in the off state. Baseline F-dopa uptake was 0.0027 in bilateral posterior putamen. After six months of GDNF infusion, F-dopa uptake increased to 0.0042.

Conclusions: Bilateral IPu infusion of GDNF has been a successful treatment for this Parkinson's patient. Motor scores demonstrate consistent improvement over two years post-infusion and a sustained, though diminished, improvement after four years following therapy. Interestingly, the UPDRS scores at four years would have been too low to meet original study inclusion criteria. Although, the phase II randomized, double-blind trial failed to produce significant results in the study cohort, at least one patient received enduring objective benefit as a result.

We-189

Effects of antiparkinsonian medications on forward and backward gait patterns in persons with Parkinson's disease (PD)

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Objective: To investigate the effects of antiparkinsonian medications on forward and backward gait patterns in individuals with Parkinsons disease (PD).

Background: Backward walking is often used to perform many activities in daily living, such as when backing away from closets, kitchen sink. Stepping back is rather used than turning around in some tight and dangerous situations e.g. avoiding incoming objects (approaching vehicles). This task may be particularly difficult for persons with PD. Information on the effect of anti-parkinsonian medications on forward and backward gait in persons with PD is not yet available. Therefore, we aimed to investigate the effects of medications on forward and backward gait patterns in individuals with PD.

Methods: Seventeen subjects with PD were recruited. Their mean age was 71.47 $\pm$ 9.15 yr. The mean of the Unified Parkinson Disease Rating Scale (UPDRS) motor score was 34.00 $\pm$ 7.72 while off anti-parkinsonian medication, and 23.59 $\pm$ 5.92 while on medication. Average Hoehn and Yahr stage was 2.79 $\pm$ 0.25. The average time since diagnosis was 9.41 $\pm$ 6.12 years. Forward and backward walk patterns were recorded during on and off anti-parkinsonian medications on the same day. Subjects were instructed to walk forward and backward at their self-selected speed on the GaitRite. Each walk was repeated twice and the average of the two trials was used in data analysis.

Results: Gait speed of the forward and backward walks increased from 77.36 $\pm$ 25.94 cm/s to 88.21 $\pm$ 20.19 cm/s ($p=.014$) and from 37.05 $\pm$ 15.73 cm/s to 49.10 $\pm$ 19.66 cm/s ($p=.005$) by anti-parkinsonian medications, respectively. Stride length was increased by medications from 76.92 $\pm$ 21.45 cm to 95.20 $\pm$ 17.05 cm ($p= .000$) for forward walk, and from 39.40 $\pm$ 18.45 cm to 49.84 $\pm$ 18.24 cm ($p= .018$) for backward walk. Cadence of both forward and backward walks were not changed by the medications (from 126.55 $\pm$ 39.36 steps/min to 115.07 $\pm$ 25.52 steps/min, $p = .087$ for forward walk, and from 120.32 $\pm$ .22 steps/min to 120.25 $\pm$ 23.02 steps/min, $p=.994$ for backward walk).

Conclusions: Anti-parkinsonian medications improved gait speed and stride length during forward and backward walks. No medication effect was found on the cadence of both walks.

We-190

Review of clinical trials and controversy of first drug of choice in Parkinson's disease

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Objective: To review different clinical trials for Parkinson's disease to discuss controversy of drug of choice for initiation of treatment in PD and develop a simplified protocol for first drug of choice for Parkinson's disease.

Background: There has always been discussion among neurologists about the drug of choice for initiation of treatment of PD. There has been a knee jerk response of starting levodopa among general practitioners for any patient of Parkinson's disease irrespective of individual variation from patient to patient. Neurologists and in particular movement disorder neurologists may have to deal with long term complications of less optimal treatment in these patients.

Methods: We reviewed different drug trials for treatments of Parkinson's disease including DATATOP, ROPINAROLE study, SINEMET-CR study, CALM-PD, STRIDE-PD, ELLDOPA, PRESTO, LARGO, ADAGIO, TEMPO study and other trials.

Results: We tried to formulate a simplified protocol in this regard.

Conclusions: Individual variations such as age, stage of disease, comorbidity, nature of symptoms, functional status and risk of side effects should be considered from patient to patient when deciding initial drug of choice in PD patients. Developmenting simplified protocol and enhancing eduaction among physicians including neurologist is necessary in this regard.

We-191

The effect of rasagiline in early Parkinson's disease (PD): The ADAGIO delayed start trial

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Objective: To describe results of a large prospective double-blind trial using the delayed-start design to assess the effect of rasagiline on PD progression.

Background: Previous laboratory studies and clinical trials suggest rasagiline might have disease modifying effects in PD.

Methods: 1176 untreated early PD patients were randomized to receive rasagiline 1 or 2 mg/day for 72 weeks (early start) or placebo for 36 weeks followed by rasagiline 1 or 2 mg/day for 36 weeks (delayed start). The primary analysis included three hierarchal endpoints based on Total-UPDRS scores: a) superiority of slopes between weeks 12-36; b) superiority in change from baseline to week 72; c) non-inferiority of slopes (0.15 margin) during weeks 48-72. The secondary endpoint was change in Total-UPDRS from baseline to last observed value in the placebo-controlled (PC) phase. An additional endpoint was the need for anti-PD therapy in the PC phase, analyzed by logistic regression and the time to need for anti-PD therapy analyzed by Cox proportional hazards regression.

Results: Early treatment with rasagiline 1 mg/day met all 3 endpoints of the primary analysis compared to delayed start: a) superiority of slope in weeks 12-36 (-0.05; $p=0.013$, 95%CI $-0.08,-0.01$); b) change from baseline to week 72 (-1.7 units; $p=0.025$, 95%CI: -3.15,-0.21); c)non-inferiority of slope in weeks 48-72 (0.0; 90% CI -0.04,0.04). The 2 mg/day dose did not meet the second primary endpoint. Rasagiline 1mg/day also significantly improved Total-UPDRS scores vs placebo at week 36, with an adjusted effect size of -3.0 (95%CI: -3.9,-2.2, $p<0.0001$). The need for additional anti-PD treatment in the PC phase was ~60% less in the 1 mg/day group compared to placebo (odds ratio = 0.41, 95%CI: 0.25-0.65, $p=0.0002$; hazard ratio = 0.39, 95%CI: 0.25-0.60, $p<0.0001$).

Conclusions: Early treatment with rasagiline 1 mg/day significantly diminished the progression of parkinsonian symptoms versus later initiation of the drug. This suggests that disease-modifying effects occurred with the 1 mg/day dose. While no disease modifying effect could be demonstrated at the 2 mg/day dose, both doses provided superior symptomatic benefit and delayed the need for additional anti-PD therapy versus placebo.

We-192

A longitudinal program for biomarker development in Parkinson's disease

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Objective: To determine the feasibility of a program for biomarker development and long-term follow-up of PD cohorts.

Background: Long-term follow up is necessary to understand the natural history of Parkinson's disease (PD), but may be difficult to accomplish. The Longitudinal and Biomarker Studies in PD (LABS-PD) is a systematic program to evaluate PD cohorts with the goals of measuring the evolution of motor and non-motor features of PD from early- to late-stage illness. Further, LABS-PD aims to connect these clinical data to biomarkers that assess risk for PD and progression. The organization of LABS-PD is based on the premises that research subjects who conclude their participation in randomized clinical trials can continue to be followed in observational studies and that data from the antecedent trial can be linked. To test the feasibility of this strategy, we examined enrollment and biomarker sampling in the initial cohorts in LABS-PD.

Methods: The first LABS-PD cohort (PostCEPT) derives from the de novo PD clinical trial of a mixed lineage kinase inhibitor CEP-1347 (PRECEPT), which used standardized clinical endpoints and dopamine transporter imaging to measure progression. We assessed recruitment from PRECEPT to PostCEPT, the ability to link data from the two studies, and the feasibility of using this platform to sample a variety of biomarkers.

Results: 537 of 709 eligible PRECEPT subjects (76%) enrolled in PostCEPT, and 511 of the 537 (95%) subjects had repeat dopamine transporter SPECT imaging. The PostCEPT clinical and imaging data were linked to PRECEPT data to provide 3–4 year follow up. A biomarker sub-study enrolled PD cases from PostCEPT and healthy and disease controls to measure olfaction and peripheral blood markers of gene expression, alpha synuclein, and proteomic profiles. We were successful in linking clinical and biomarker data to DNA samples that have been collected and inventoried in the publicly accessible Coriell repository. Clinical data have been made publicly available through the PD Data and Organizing Center (www.pd-doc.org).

Conclusions: The PostCEPT cohort and associated studies support the feasibility of the LABS-PD approach of retaining and repurposing clinical trial cohorts to collect and distribute longitudinal clinical and biomarker data.

We-193

Efficacy and safety of botulinum toxin type B for the treatment of sialorrhea in Parkinson's disease (PD)

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Objective: This Phase 2 study was designed to determine the efficacy, safety and tolerability of ascending doses of Botulinum Toxin Type B or (BoNT-B) versus placebo for the treatment of sialorrhea in PD.

Background: Sialorrhea, defined as excessive salivation or pooling of saliva, can cause morbidity and diminished quality of life. There are no FDA approved treatments for sialorrhea. BoNT-B blocks acetylcholine parasympathetic transmission, and may be useful for treating sialorrhea.

Methods: This was a multicenter, double-blind, placebo-controlled, sequential dose escalation study comparing 3 active doses (1500, 2500, 3500 U) of BoNT-B to placebo. Patients were randomized 3:1 (drug to placebo) with divided doses injected intra-glandularly into both parotids and submandibular glands. Patients with PD and troublesome sialorrhea (18-85 y.o.) were eligible for treatment and follow-up over 20 weeks. The study was conducted under GCP with IRB approval and informed consent.

Results: 54 patients were enrolled, making this the largest controlled study conducted in sialorrhea. The primary endpoint, the Drooling Frequency and Severity Scale demonstrated statistically significant reduction in drooling 4 wks post-treatment for all 3 dose groups: 31%, 47% and 50%, $p=0.019$, $p<0.0001$, $p<0.0001$, respectively. Unstimulated salivary flow rate, a quantitative secondary endpoint, demonstrated statistically significant reduction in drooling 1 week post-treatment for 2 doses: 1500 and 2500 U, $p=0.0015$ and $p=0.0144$, respectively; and for all doses 2 weeks post-treatment:

p<0.0001, p<0.0001 and p=0.0033, respectively. Efficacy remained statistically significant at 12 weeks. There were no treatment-related SAEs or deaths reported. Two AEs of special interest, choking and dysphagia, occurred with placebo.

Conclusions: The use of BoNT-B to treat troublesome sialorrhea in PD patients is highly efficacious, with effects lasting between 12 and 16 weeks. The overall safety profile demonstrated that injections of BoNT-B were well tolerated in the population studied. These data suggest that BoNT-B injections may be efficacious for treating other secretory or glandular disorders.

We-194

Rehabilitation in Parkinson's disease: The effect of cueing therapy on gait in a drug naïve population in the Hai district of northern Tanzania?

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Objective: To explore the feasibility of delivering rehabilitation in northern Tanzania and to evaluate the effect of cueing therapy on gait in non-medicated PD.

Background: The main approach to symptom management in Parkinson's disease (PD) is with medication, however as the disease progresses there is a ceiling effect on gait which becomes increasingly difficult to control. Complementary methods aimed at improving gait are therefore required.

Methods: 21 people with PD who were identified as part of a PD prevalence study took part. They received 9 x 30min sessions of cueing therapy for gait problems delivered over 3 weeks from a trained therapist delivered in their home and community environment. Cueing therapy consisted of walking in time to a metronome beat to correct step length and cadence and practising cued gait tasks as part of a range of functional activities. Gait was measured and recorded on video immediately before and after therapy. The UPDRS sections 11 and 111 were also carried out at the same time by a trained PD Nurse. Patients were assessed in their nearest clinic. The videos were analysed in the UK by an assessor not involved in the study. Data were analysed in Minitab and a *P* value of 0.05 was considered significant.

Results: Cueing therapy resulted in a significant improvement in walking speed (.17m/s) step length (.07m) ($P<.0001$), and a reduction in step frequency (7.8steps/min) ($P<.046$). There was also a significant improvement in motor impairment (UPDRS 111) ($P<.004$) and Activities of Daily Living (UPDRS 11) ($P<.011$).

Conclusions: Significant improvements in walking in non-medicated PD provide promising evidence for the potential role of rehabilitation in the management of PD to delay medication onset or reduce medication intake. In addition, this study supports the feasibility of rehabilitation in PD to manage symptoms and improve mobility in community environments in sub-Saharan Africa.

We-195

A maintained reduction in "off" time is achieved with ropinirole prolonged release in patients with advanced Parkinson's disease not optimally controlled with L-dopa

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Objective: To retrospectively evaluate the proportion of patients with advanced Parkinson's disease (PD) not optimally controlled with L-dopa who maintained a meaningful reduction in "off" time with ropinirole prolonged release.

Background: The once-daily dosing and simple dose titration of ropinirole prolonged release offers patients stable plasma levels and continuous delivery of ropinirole over a 24-hour period. The efficacy and safety of ropinirole prolonged release has been evaluated in the Phase III, 24-week EASE-PD Adjunct study (101468/169).

Methods: Patients were randomized to adjunctive ropinirole prolonged release (2–24 mg/day) or matched placebo. Primary endpoint: mean change from baseline in daily awake time spent "off" at Week 24 last observation carried forward (LOCF). Retrospective analyses were performed to assess the proportion of patients with a ≥20% reduction from baseline in "off" time maintained to study endpoint and present for ≥2 consecutive visits.

Results: At baseline, mean awake time spent "off" was 7.0 hours in each treatment group. At Week 24 LOCF, ropinirole prolonged release significantly reduced daily awake time spent "off" from baseline compared with placebo (adjusted mean treatment difference: –1.7 hours; 95% CI: –2.3, –1.1; $p<0.0001$). At Week 24 LOCF, significantly more patients achieved a ≥20% maintained reduction from baseline in "off" time in the ropinirole prolonged-release group than in the placebo group (104/201 [52%] *vs* 45/190 [24%]; adjusted odds ratio: 3.52; 95% CI: 2.27, 5.47; $p<0.001$). This treatment benefit was seen in some patients as early as Week 2 observed case, when the proportion of patients with a ≥20% maintained reduction from baseline in "off" time was 35/197 (18%) *vs* 13/189 (7%). Mean (SD) dose of ropinirole prolonged release at Week 24 LOCF was 18.8 (6.3) mg/day. Mean (SD) daily L-dopa dose had reduced by 278 (193) *vs* 164 (164) mg/day with ropinirole prolonged release and placebo, respectively.

Conclusions: After 2 weeks of treatment, a ≥20% maintained reduction in "off" time was attained by more patients on adjunctive ropinirole prolonged release than placebo. By Week 24, over 50% of patients receiving ropinirole prolonged release achieved a maintained reduction in "off" time.

We-196

A Canadian approach to exercise rehabilitation: A systematic evaluation of strategies to reduce the symptoms of Parkinson's disease

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Objective: The current study compared three common exercise interventions, a non-exercising control group and a novel sensory-attention focused intervention (PD $SAFE_x$).

Background: While animal models have demonstrated the potential to slow and even reverse the progression of Parkinson's disease (PD) through exercise, there is much debate about whether exercise can result in similar benefits in humans. Variable lengths of intervention, differences in outcomes measured, omission of control groups, and lack of a washout period, have made it difficult for adequate comparisons to be made between exercise interventions.

Methods: All interventions lasted twelve weeks and all participants were assessed by the same blinded evaluator, using the Unified Parkinson's Disease Rating Scale motor section (UPDRS III). Eighty-nine participants received either aquatic exercise (n=12; age=63.1 ±9.2); aerobic training (n=17; age=65.8 ±9.9); strength training (n=18; age=68.7 ±8.3); sensory attention focused exercise (PD $SAFE_x$) (n=24; age=68.0 ±11.0); or, were enrolled as part of a non-exercise control group (n=18; age=68.6 ±8.1). Participants were evaluated *pre* and *post* intervention, as well as following a minimum six week non-exercise period (*washout*).

Results: UPDRS scores revealed that only the PD $SAFE_x$ and strength training groups significantly improved PD symptoms at post-test compared to pre-test ($F(4,84)=4.60$, $p<.002$). Additionally, % change in UPDRS score was calculated to allow comparison between groups regardless of pre-test symptom severity. Percent change scores revealed that the PD $SAFE_x$ (24.2%) and strength (18.6%) groups significantly improved symptom severity relative to the control group (-5.1%) ($F(4,84)=6.36$, $p<.001$). Washout scores suggested that the PD $SAFE_x$, strength training and aerobic interventions had some maintenance of post-test PD symptom severity.

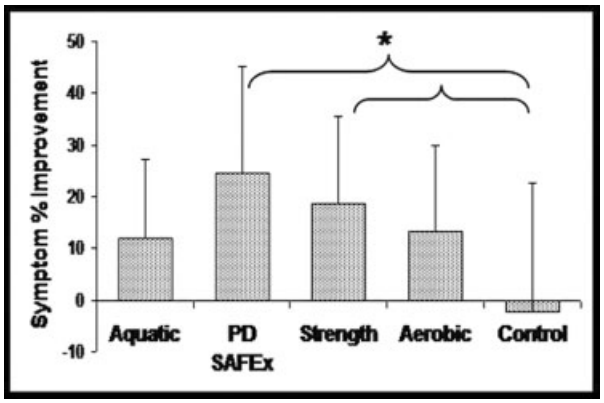

FIG. 1 (We-196).

Conclusions: Overall, the results suggest that PD $SAFE_x$ and strength training have the greatest impact on PD motor symptoms. Further, secondary quantitative outcome measures including timed-up-and-go, grooved pegboard and spatiotemporal aspects of self-paced gait revealed similar improvement trends as symptom assessment. Thus, continued exploration into the use (individually or combined) of PD $SAFE_x$ and strength training as adjunct therapies in the management of PD is warranted.

We-197

Pilot study of the efficacy and safety of piclozotan in Parkinson's disease patients with L-dopa induced motor complications

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Objective: To evaluate the efficacy and safety of piclozotan in improving L-dopa associated motor complications in PD without aggravating parkinsonism.

Background: 5-HT neurons may be a key source of unregulated striatal dopamine (DA) leading to motor complications in PD. Inhibition of 5-HT neuronal activity with $5\text{-}HT_{1A}$ agonists may improve dyskinesia and motor fluctuations associated with L-dopa. Previous investigational $5\text{-}HT_{1A}$ agonists had DA antagonistic activity which limited clinical applicability. Piclozotan, a $5\text{-}HT_{1A}$ agonist devoid of DA antagonist activity, decreased dyskinesia and prolonged L-dopa antiparkinsonian activity without worsening parkinsonism in animal models and would be expected to decrease dyskinesia and increase ON time without worsening UPDRS scores.

Methods: 25 PD patients with dyskinesia on stable dosages of L-dopa were randomized 3:1 to receive an adjunctive IV piclozotan (n=18), or saline (n=7) infusion for two 12-hour periods over 2 days in an in-patient setting. AIMS scores, UPDRS scores, and % time ON without dyskinesia/ON with dyskinesia /OFF were assessed by trained raters.

Results: By Day 2, mean ON time without dyskinesia on piclozotan had doubled (18.8% to 41.0%) and mean OFF time had halved (20.8% to 9.7%). ON time without dyskinesia with placebo did not change, while OFF time worsened (8.9% to 23.2%). Considered together, these results were statistically significant (p=.022). Responders (dyskinesia improved and no increase in OFF time) favored the piclozotan group (56% to 0%) by Day 2 (p=.02). UPDRS Motor scores did not worsen. Nausea/vomiting were high on Day 1 with piclozotan (66%/31%) vs placebo (29%/0%), but by Day 2 had lowered to near placebo (22%/6% piclozotan vs 20%/0% placebo). Residual piclozotan concentrations from Day 1 allowed for a smaller loading dose on Day 2, which may account for these findings. Overall safety was consistent with known effects of $5\text{-}HT_{1A}$ agonists.

Conclusions: By Day 2, piclozotan appeared to be both safe and effective in improving ON time without dyskinesia and reducing OFF time in this pilot study. Tolerability is expected to improve with slower dose escalation.

We-198

A multicenter randomized control trial of amantadine for dyskinesia in Parkinson's disease

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Objective: To determine the efficacy and safety of amantadine in patients with PD who have dyskinesias.

Background: Dyskinesias are one of motor complications often seen in Parkinson's disease (PD).

Methods: A multi-center, cross-over, double-blind, randomized placebo-controlled trial conducted from August 2007 to August 2008. **Setting** Referral movement disorder clinics at 13 sites in Japan. **Patients and methods** Patients with PD presenting dyskinesias were enrolled between August 2007 and August 2008 in Japan. They were randomly assigned to two arms, amantadine (200mg – 300mg /day) or placebo treatment for 27 days. After 15 days of washout, the treatments were crossed over. **Main measure**: Change from baseline in UPDRS and Goetz dyskinesia scores.

Results: Thirty-nine participants gave consent. Excluding 3 patients because of low creatinine clearance 36 were randomized assigned to the arms. Six withdrew and 30 completed the study. The mean reduction in UPDRS-4 and Goetz dyskinesia scores from baseline was significantly higher in amantadine than placebo (–1.83 vs -0.03 in UPDRS-4 and -1.00 vs 0.03 in Goetz dyskinesia score). There was no statistically significant difference in mean changes of UPDRS-1, 2 and 3 between amantadine and placebo treatments. Dyskinesias were improved in 20 patients. There were no significant difference in plasma amantadine concentrations between the responders and non responders. Adverse effects were observed in 8 (5 in amantadine, 1 in placebo, and 1 in washout period) and most common adverse effect was visual hallucination.

Conclusions: Amantadine was almost safe and improved dyskinesias in Parkinson's disease.

We-199

Efficacy and safety of pramipexole extended-release for advanced Parkinson's disease

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Objective: To evaluate pramipexole extended-release (ER) for advanced Parkinson's disease (PD).

Background: Pramipexole immediate-release (IR), administered tid, has well-established efficacy as adjunctive therapy in advanced PD. Pramipexole ER may provide similar therapeutic benefits while requiring only once-daily dosing.

Methods: Advanced PD patients taking levodopa plus a dopa decarboxylase inhibitor were randomized (1:1:1) to pramipexole ER (0.375-4.5 mg qd), or IR (0.125-1.5 mg tid), or placebo. Study drug was flexibly titrated to an optimal dose over 7 weeks and then maintained for an additional 26-week period. Confirmatory analyses (ANCOVA with covariate baseline) were conducted at Week 18 on the primary efficacy outcome (change from baseline in Unified PD Rating Scale [UPDRS] parts II + III score) and the key secondary outcome (change from baseline in percentage off-time during waking hours). Maintenance of efficacy was analyzed at Week 33 on completer patients.

Results: Of 517 treated patients (164 ER, 175 IR, 178 placebo), 507 were eligible for the efficacy analyses. The mean age was 61.5

years overall and the mean daily maintenance dose was 2.8 mg for ER and 2.7 mg for IR. The adjusted mean change in UPDRS II + III at Week 18 was -11.0 points for ER, -12.6 points for IR, and -6.3 points for placebo ($P = 0.0002$ and $P < 0.0001$ for ER and IR vs placebo, respectively). At Week 18, the adjusted mean change in percentage off-time was -13.3 for ER, -15.7 for IR, and -9.0 for placebo ($P = 0.0174$ and $P = 0.0001$ for ER and IR vs placebo, respectively), corresponding to an absolute placebo-corrected improvement of –0.5 hour for pramipexole ER and –1.0 hour for pramipexole IR. Maintenance of efficacy was descriptively demonstrated at Week 33. Adverse event rates were lower for pramipexole ER (54.9%) compared to placebo (55.6%) and pramipexole IR (64.0%).

Conclusions: Pramipexole ER qd was effective and well tolerated in advanced PD. Comparable efficacy was observed for pramipexole ER qd and IR tid, at similar mean total daily doses and similar dose distribution in the 2 groups. Support: Boehringer Ingelheim International GmbH.

We-200

Progression of subtle motor signs in asymptomatic heterozygous PINK1 mutation carriers: A clinical follow-up investigation

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Objective: To test whether previously detected subtle Parkinson's disease (PD) motor signs are a constant and likely progressive feature and to determine the role of non-motor signs in heterozygous *PINK1* mutation carriers.

Background: While homozygous mutations in the *PINK1* gene cause recessively inherited early-onset PD, heterozygous mutations have been suggested a susceptibility factor. In keeping with this notion, six of 11 asymptomatic carriers of a single heterozygous *PINK1* mutation from a large German family (Family W) were identified with signs of probable (n=2) or possible (n=4) PD. Here we present a three-year follow-up examination of 10 of the 11 heterozygous family members.

Methods: All 10 heterozygous family members underwent a detailed videotaped neurological examination using the UPDRSIII protocol. Subsequently, two movement disorder specialists evaluated the videos blinded to the previously obtained scores and a consensus diagnosis was established. In addition, all individuals were tested for hyposmia and a deficit in color discrimination using the *University of Pennsylvania Smell Identification* and the *Farnsworth-Munsell 100 Hue* test.

Results: Both heterozygous family members with signs of probable PD in 2005 demonstrated mild progression of their parkinsonian signs corresponding to higher scores on the UPDRSIII scale and one of them had become symptomatic. One of the four previously possibly affected individuals also demonstrated a progression, now meeting criteria of probable PD. Of the five previously unaffected subjects, three had newly developed possible PD signs. Seven of the now eight clinically affected individuals demonstrated PD signs (mostly bradykinesia/rigidity) on their dominant right-hand side only. Nine of the 10 subjects displayed hyposmia (n=7) or a poor performance on color discrimination testing (n=4).

Conclusions: An increasing number of the 10 heterozygous *PINK1* mutation carriers displayed partially progressive PD signs during the follow-up period. Our results strengthen the hypothesis that heterozygous *PINK1* mutations may act as a susceptibility factor to develop at least subtle PD motor and non-motor signs.

We-201

Questionnaire for Parkinson's disease as a screening instrument for Thais

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Objective: To (1) validate a screening questionnaire for the determination of PD and (2) simplify this questionnaire.

Background: Parkinson's disease (PD) is the second most common neurodegenerative disease in the elderly. However, under-diagnosis and under-treatment are frequently found in clinical practice. Questionnaire commonly used as screening tool may help the medical personals in identifying patients at risk for PD.

Methods: The Thai version of the screening questionnaire for PD was developed with the permission of the author. Reliability of the questionnaire was tested on 20 patients. To validate the questionnaire, 40 patients with PD as well as 93 controls were asked to complete the questionnaire. Multiple logistic regression analysis was used to determine the questions independently associated with PD and a risk score was calculated according to β coefficients. The predictive performance of the sum of risk score was evaluated via the area under the curve (AUC) of a receiver operating characteristics (ROC) curve. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Results: The Thai version of the screening questionnaire for PD showed a test-retest reliability of 0.73, the total content validity was 0.86 (range 0.6–1.0). Of the 11 questions, 4 were independently associated with PD and used to calculate the risk score. The score of these questions was 2(clumsy) + 4(tremor) + 2(masked face) + 2(imbalance while turning). The AUC of a ROC curve for the sum of risk score was 0.95. With a cutoff score of 5 or higher, the sensitivity, specificity, PPV, and NPV were 0.88, 0.95, 0.88, and 0.95, respectively.

Conclusions: The Thai-screening questionnaire for PD is a reliable, valid, sensitive and specific instrument for differentiating patients with PD. The predictive performance of the simplified questionnaire is as good as the original one.

We-202

Trails of multivitamins/antioxidant and nutritional supplements in Parkinson's disease patients

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Objective: To study the nutritional status of PD patients and the effect of multivitamin/ antioxidant supplement.

Background: Parkinson's disease (PD) patients frequently lose weight and are susceptible to malnutrition. The most postulated cause involved in weight loss among PD patients is considered to be the reduced energy intake and /or increases energy expenditure.

Methods: Ninety PD patients (age 59.07±9.07years) satisfying UK PD Brain Bank Clinical Diagnostic Criteria were recruited for the study after obtaining informed consent and approval of the institutes ethics committee. Group A (experimental) consisted of 50 patients age (58.3±4.28.2 years) who were given multi/antioxidant vitamins along the anti-parkinsonian drugs and Group B (control) consisted of 40 patients age (59.9±9.9 years) who were given only anti- parkinsonian drugs. 10 ml of peripheral blood was drawn from all the patients at baseline and after six months for biochemical investigations which included iron, total iron binding capacity (TIBC), total protein, albumin and ascorbic acid estimations. Follow up was possible in 40 patients in group A and 30 in in group B.

Results: In Group A there was a significant increase in the weight of PD patients at the time of follow up (63.25±13.10kgs) as compared to the baseline level (58.37±8.34kgs). In Group B there was significant reduction in the weight of the PD patients at the time of follow up (58.53±9.6kgs) as compared to the baseline (59.70±10.11kgs). There was significant improvement in all biochemical parameters in group A whereas in group B there was no improvement.

Conclusions: The nutritional status of PD patients is poor and can be improved by multivitamin/ antioxidant supplementation.

We-203

Isradipine plasma concentrations in patients with early Parkinson's disease taking isradipine CR, a dihydropyridine Ca channel antagonist

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Objective: To determine plasma isradipine concentrations achieved with various doses of an isradipine controlled release (CR) preparation in patients with early PD.

Background: Recent data suggest that israpadine, a dihydropyridine calcium channel blocker, is neuroprotective in vitro/in vivo models of PD. In mouse models, the neuroprotective effect was achieved with subcutaneous drug administration at a dose that achieved plasma isradipine concentrations of ~2 ng/ml. Isradipine CR is FDA approved in the 5-20 mg dose range for treatment of hypertension. There are limited published data on the pharmacokinetic profile of the drug. In order to proceed with PD human clinical neuroprotective trials, it is essential to demonstrate that the "neuroprotective" plasma concentrations can be achieved with oral administration of the drug within the FDA approved dosing range.

Methods: Plasma isradipine concentration measurements are part of the on-going open label dose escalation tolerability study of isradipine in patients with early PD. Subjects received isradipine CR daily, for 14 weeks. The initial 5 mg dose was escalated by 5 mg every 2 weeks up to 20 mg as tolerated. Blood samples for plasma isradipine concentration measurement by LC-MS/MS (C min) were collected at baseline and every 2 weeks in the morning before administration of the daily dose of isradipine.

Results: We report data on the first five subjects who have completed the protocol. The maximum dose exposure was 20 mg for 3 subjects, 15 mg for 1 subject and 10 mg for one subject. Mean (± SD) plasma concentrations of isradipine CR, in ng/ml, were: 5 mg dose, 0.78 (0.32); 10 mg dose, 1.73 (0.84); 15 mg dose, 2.63 (1.72); 20mg dose, 2.07 (1.01).

Conclusions: Oral isradipine CR administration at the daily dose ≥ 10 mg achieves plasma concentrations within the range demonstrated to be neuroprotective in preclinical models. Despite the small sample size in the present report, there is a good linear relationship between dose and plasma concentration over the 5–15 mg dose range. These data support the feasibility of achieving "neuroprotective" concentrations at doses within the FDA approved dosing range. Additional data are being collected on the larger cohort of the subjects.

We-204

Is there the association between high-sensitivity C-reactive protein level and idiopathic Parkinson's disease?

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(Seoul, Republic of Korea)

Objective: In this prospective study, we conducted to investigate the clinical value of hs-CRP level in patients with de novo PD.

Background: High sensitivity C-reactive protein (hs-CRP) is a sensitive systemic marker of inflammation, infection and tissue damage and increased level of hs-CRP is strongly associated with inflammatory reactions. Idiopathic Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder associated predominantly with the degenerative of the melanized dopaminergic neurons. Microglia-mediated neuroinflammation has been hypothesized to play an important role in the pathogenesis of PD, primarily based on findings from postmortem studies and animal experiments. However, the clinical value of hs-CRP in patients with PD is poorly defined yet.

Methods: We examined a total of 212 patients with de novo PD, 253 patients with acute ischemic cerebrovascular disease (iCVD) served as disease control group and 119 normal control subjects and investigated differences of hs-CRP among there 3 groups. We classified all patients group with PD into 4 subgroups on the base of H & Y stage to evaluate changes of hs-CRP level by motor severity.

Results: In comparison among 3 groups, there was no significant difference between PD and iCVD groups for mean hs-CRP values, but these two groups demonstrated higher mean hs-CRP values than normal controls group, significantly. In regard to risk factors for ischemic stroke, there were significant differences between PD and iCVD groups for DM, cigarette smoking and hypercholesterolemia but no significant difference for hypertension. The post hoc analysis among 4 subgroups of patients with PD demonstrated no significant differences of hs-CRP values. And this study demonstrated that odds ratio of PD patients for hs-CRP was 2.037 (95% CI= 1.180-3.517, $P = 0.011$).

Conclusions: The pathogenesis of PD is currently unknown, but at the cellular level, significant microglial inflammation is observed in the region of dopaminergic degeneration and some protection against its development occurs when long-term anti-inflammatory medications are taken. The result of our study could support the hypothesis that microglia-mediated neuroinflammation contributed to pathogenesis of PD. Therefore we also suggest that high concentration of hs-CRP maybe have clinical value in patients with PD.

We-205

Detecting freezing of gait in Parkinson's disease with an ambulatory monitor

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Objective: The objective of this study was to detect freezing of gait (FOG) episodes during turns in patients with Parkinson's disease (PD), using an ambulatory gait monitor (Dynaport Minimod (DM)).

Background: FOG is a common and disabling feature, that usually occurs in advanced PD. Clinical assessment of FOG is difficult, and there is currently no method to measure FOG in the patient's own environment. The DM can examine gait by measuring linear trunk acceleration in three directions. We hypothesized that FOG during turns can be detected with the DM.

Methods: Twenty-one patients (table 1) each completed 8 turn tasks in an "off" state, while being videotaped and wearing the DM. Episodes of FOG were identified from the video records by two clinicians and compared with the DM data. Episodes of FOG with the DM were identified using the freeze index (1), defined as the relation between high and low frequencies during a 3 s window of data, modified to take into account other gait features. The high/low ratio was combined with other gait features to indicate the presence of FOG. The ability to discriminate between episodes with and without FOG was assessed using a ROC-curve.

Results: Eleven subjects experienced a total of 52 FOG events, for a total of 676 3 s windows of FOG (table 2) The DM-based algorithm has a sensitivity of 78,9% with a specificity of 82,5%. The area under of the ROC curve is 0.81 and shows good discriminating ability.

Conclusions: The DM can detect FOG during turns in patients with PD. Further research is needed to be able to detect FOG also during actual everyday activities, preferably in the patient's own home environment. 1) Moore ST, MacDougall HG, Ondo WG, Ambulatory monitoring of freezing of gait in Parkinson's disease. Journal of Neuroscience Methods 167 (2008) 340-348.

Table 1 (We-205). patients characteristics

	All patients (n=21) mean (sd)	Freezers (n=15) mean (sd)	Non-freezers (n=6) mean (sd)
Age	61.1 (7.4)	61.3 (8.1)	60.5 (6.0)
H&Y	2.4 (0.4)	2.5 (0.4)	2.2 (0.3)
UPDRS	38.7 (12.9)	35.5 (9.9)	46.8 (16.8)
FOG-Q II*	11,3 (9.9)	15.8 (8.0)	0

*Freezing of Gait Questionnaire II.

Table 2 (We-205). 3 s window data

Number of PD patients	Number of turns	Episodes (3 s window)	FOG events according to video	FOG events according to DM
21	168	676	161	216

We-405

Changes in early morning motor status following adjunctive treatment of advanced Parkinson's disease with rotigotine transdermal system in two large, placebo-controlled trials (PREFER and CLEOPATRA-PD)

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Objective: To assess the change in early morning akinesia prior to treatment in two trials of rotigotine as adjunctive treatment for advanced Parkinson's disease (PD).

Background: Rotigotine is licensed in Europe and the US to treat the signs and symptoms of PD. As once-daily transdermal administration of rotigotine results in stable plasma levels over 24 hours, rotigotine treatment may lead to sustained therapeutic response with possible improvements in early morning akinesia. A pilot study (SP826) also suggested rotigotine efficacy in controlling early morning motor impairment (*Ann Neurol* 2007, S41).

Methods: Results of patient diaries from two previously reported randomized, double-blind, placebo-controlled, 6-month studies (PREFER and CLEOPATRA-PD) of rotigotine as adjunctive treatment for advanced PD were evaluated to examine changes in PD state, off or on without troublesome dyskinesia, upon awakening.

Results: A total of 222 and 200 rotigotine-treated patients and 119 and 100 placebo-treated patients in the PREFER and CLEOPATRA-PD trials respectively, were evaluated. In PREFER, treatment with 8 and 12 mg/24h rotigotine reduced the proportion of subjects awakening in an "off" state by 28.8% and 22.6% compared to 9.1% with placebo; "on" without troublesome dyskinesia increased 27.0% and 20.9% versus 8.5% placebo compared to baseline. In CLEOPATRA-PD, the proportion of subjects awakening in an "off" state when treated with $\leq$16 mg/24h rotigotine decreased 22.6% versus 10.7% with placebo, and subjects awakening "on" without troublesome dyskinesia increased 23.3% with rotigotine versus 11.1% with placebo. After 6 months of rotigotine treatment, there was no change in sleep duration in either group.

Conclusions: Adjunctive treatment with rotigotine transdermal system over 6 months in two trials of subjects with advanced PD resulted in improvements in early morning akinesia compared to placebo.

Th-179

Turning behavior in patients with Parkinson's disease with and without freezing of gait

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Objective: To evaluate 1) the difference in turning behavior between freezers (FRs) and non-freezers (n-FRs) and 2) to explore possible predictors of turning behavior.

Background: Turning is the most important trigger for Freezing Of Gait (FOG) in Parkinson's disease (PD) but why this is so, is presently unknown.

Methods: 16 patients with PD (7 FRs and 9 n-FRs) during the off-period of the medication cycle and 10 age-matched controls were asked to walk straight ahead and to make a right 180° turn at an infrared reflective marker placed on the floor. An 8 camera VICON 3D motion analysis system was used to determine the amount of steps, turn duration and frequency of freezing episodes. The FOG questionnaire, UPDRSIII, Timed UP and Go test (with and without dual task) and the SCOPA-test of cognition were administered in the *on*-period.

Results: No significant differences were found between FRs and n-FRs for age, Hoehn &Yahr stage and UPDRSIII scores. Freezing was provoked in 4 out of 7 FRs during turning and only in one FR when walking straight. FRs needed significantly more steps than controls and n-FRs to complete the turn (15.5 vs. 5.6 and 6.1 steps respectively, $p<0.05$) and tended to have a longer turn duration (12.4 vs. 3.2 and 3.7 seconds respectively, $p=0.085$). However, similar results were found for walking straight (average number of steps was 10.1 vs. 5.8 and 6.8 steps respectively, $p<0.05$ and average turn duration 5.1 vs. 2.6 and 3.3 seconds, $p<0.05$). Turn duration was significantly correlated with number of steps and duration to walk 3m in a straight line, and the FOG questionnaire ($R=.96$, .97 and .75 respectively). Similar correlations were found for the amount of steps during turning ($R=$ .96, .93 and .82, respectively). No correlations were found between turning behavior and UPDRS III, SCOPA-COG and differences between the TUG with and without a dual task.

Conclusions: Turning behavior in FRs shows an abnormally high number of steps, FOG episodes and increased duration. However, turning seems highly dependent on patient's performance during straight-line walking and patient's reported freezing severity, but can not be explained by disease severity or mental function. Further research on turning and freezing should control for parameters of normal walking performance.

Th-180

Ropinirole prolonged release offers patients with advanced Parkinson's disease greater opportunity to reduce their daily "off" time than ropinirole immediate release

F. Stocchi, L. Giorgi, B. Hunter, J. Statham, A.H.V. Schapira (Rome, Italy)

Objective: To compare the efficacy of adjunctive ropinirole prolonged release with ropinirole immediate release (IR) in reducing "off" time in patients with advanced Parkinson's disease (PD) not optimally controlled with L-dopa.

Background: Ropinirole prolonged release offers continuous delivery and more stable drug plasma levels of ropinirole than ropinirole IR over 24 hours.

Methods: The Phase III, double-blind, double-dummy, parallel-group, PREPARED study (ROP105323) randomized patients to adjunctive ropinirole prolonged release 2–24 mg/day or ropinirole IR 0.75–24 mg/day for 24 weeks. Primary endpoint: percentage of patients maintaining ≥20% reduction from baseline in "off" time over two consecutive visits at Week 24 last observation carried forward (LOCF). The percentage of patients attaining ≥20%, ≥30% or ≥40% reduction from baseline in "off" time at Week 24 LOCF was analysed *post hoc*. Mean change from baseline in L-dopa dose was also assessed.

Results: Baseline mean (SD) "off" time was 6.6 (1.95) and 6.7 (1.91) hours in the ropinirole prolonged release and IR groups, respectively. Significantly more patients receiving ropinirole prolonged release than ropinirole IR maintained ≥20% reduction from baseline in "off" time at Week 24 LOCF (adjusted proportions 66% *vs* 51%; adjusted odds ratio [AOR]: 1.82; 95% CI: 1.2, 2.9; $p=0.009$). At Week 24 LOCF, ropinirole prolonged release demonstrated a treatment benefit over ropinirole IR in the proportion of patients attaining ≥40% reduction from baseline in "off" time; 87/172 (51%) *vs* 69/168 (41%; AOR: 1.44; 95% CI: 0.91, 2.28; $p=0.067$) and in the percentage of patients achieving ≥20% (122/172 [71%] *vs* 106/168 [63%] respectively) or ≥30% (102/172 [59%] *vs* 89/168 [53%]) reduction from baseline in "off" time. At Week 24 LOCF, mean (SD) dose of ropinirole prolonged release was 18.6 (6.5) mg/day *vs* 10.4 (6.4) mg/day ropinirole IR; mean (SD) reductions from baseline in L-dopa dose were –162 (226) mg and –113 (138) mg, respectively.

Conclusions: Ropinirole prolonged release provides patients with advanced PD greater opportunity for pronounced reduction in their total daily awake time spent "off", compared with ropinirole IR, at the doses administered in this study.

Th-181

Rasagiline provides benefits in the symptoms of fatigue in patients with early Parkinson's disease

F. Stocchi, ADAGIO Investigators (Rome, Italy)

Objective: To assess the impact of treatment with rasagiline (1 and 2 mg/day) on fatigue in patients with very early Parkinson's disease (PD).

Background: Fatigue is now recognized as one of the most common non-motor symptoms in PD, which can emerge early in the disease with significant negative effects on daily activities and quality of life. Symptoms of fatigue have been shown to be associated with the severity of PD. However, to date, its management has been poorly studied.

Methods: 1176 untreated early PD patients were randomized to receive rasagiline 1 (n=270) or 2 mg/day (n=277) or placebo (n=558) for 36 weeks. The 16 item Parkinson Fatigue Scale (PFS) was assessed at baseline and at the week 36 or early withdrawal visit. Adjusted means of change from baseline to last observed visit for each rasagiline group were compared to placebo using an ANCOVA model, which included treatment group, center and baseline PFS scores as covariates.

Results: A total of 1105 subjects were included in this study. At 36 weeks, patients in the placebo group showed a larger deterioration (0.17 units) from baseline in PFS scores compared to both the 1 mg/day (0.03 units) and 2 mg/day rasagiline groups (-0.02 units). The difference versus placebo was significant for both the 1 mg (treatment difference -0.14 units; $p<0.01$) and 2 mg (treatment difference -0.19 units; $p<0.0001$) rasagiline groups.

Conclusions: In patients with early PD, treatment with rasagiline provided significant benefits in the symptoms of fatigue versus placebo.

Th-182

Ropinirole prolonged release is effective in reducing "off" time in patients with advanced Parkinson's disease even at low doses

F. Stocchi, L. Giorgi, N. Earl, R. Pahwa (Rome, Italy)

Objective: Evaluate the relationship between dose and efficacy of once-daily ropinirole prolonged release in patients with advanced Parkinson's disease (PD) not optimally controlled with L-dopa.

Background: Adjunctive ropinirole prolonged release was compared with placebo (EASE-PD Adjunct [101468/169]) or ropinirole immediate release (IR; PREPARED [ROP105323]) in two Phase III, double-blind, parallel-group, 24-week studies.

Methods: Patients were randomized to ropinirole prolonged release (2–24 mg/day), or placebo or three-times-daily ropinirole IR (0.75–24 mg/day). Primary endpoints: mean change from baseline in daily awake time spent "off" at Week 24 LOCF (EASE-PD); percentage of patients maintaining ≥20% reduction from baseline in "off" time at Week 24 LOCF and the preceding timepoint (PREPARED). Both endpoints were also analysed *post hoc* by dose, utilizing the first occasion at which patients received that dosage of study treatment.

Results: In the EASE-PD study, a significantly greater mean change from baseline in awake time spent "off" was achieved with ropinirole prolonged release than placebo at Week 24 LOCF (adjusted mean treatment difference, –1.7; 95% CI, –2.3, –1.1; $p<0.0001$). A clinically relevant treatment benefit of ropinirole prolonged release was seen at 6 mg/day when mean (SD) reduction in "off" time was –1.8 (2.4) hours; patient benefit was observed even at the lowest dose (2 mg/day), –0.5 (2.2) hours. In the PREPARED study, the proportion of patients maintaining ≥20% reduction from baseline in "off" time at Week 24 LOCF was significantly greater for ropinirole prolonged release than for ropinirole IR (adjusted odds ratio, 1.82; 95% CI, 1.2, 2.9; $p=0.009$). Overall, 84/163 (52%) patients achieved ≥20% reduction from baseline in "off" time with 6 mg/day ropinirole prolonged release, increasing to 55/88 (63%) patients taking the highest recommended dose of 24 mg/day ropinirole prolonged release.

Conclusions: Ropinirole prolonged release offers treatment benefits to patients with advanced PD not optimally controlled with L-dopa even at a low dose (6 mg/day); the beneficial treatment response increases with higher doses.

Th-183

Symptom control in patients with advanced Parkinson's disease: Ropinirole prolonged release versus ropinirole immediate release

F. Stocchi, L. Giorgi, B. Hunter, A.H.V. Schapira (Rome, Italy)

Objective: To evaluate the efficacy of adjunctive ropinirole prolonged release *versus* ropinirole immediate release (IR) in improving symptom control in patients with advanced Parkinson's disease (PD) not adequately controlled with L-dopa.

Background: The Phase III, double-blind, double-dummy, parallel-group study (PREPARED; ROP105323) compared the efficacy of two ropinirole formulations. Ropinirole prolonged release offers a more continuous delivery of ropinirole with fewer fluctuations in plasma levels than ropinirole IR.

Methods: Randomized patients received adjunctive ropinirole prolonged release 2–24 mg/day (n=177) or ropinirole IR 0.75–24 mg/day (n=173) for 24 weeks. Primary endpoint: proportion of patients maintaining ≥20% reduction from baseline in "off" time over two consecutive timepoints at Week 24 last observation carried forward (LOCF). Mean change from baseline to Week 24 in Unified Parkinson's Disease Rating Scale (UPDRS) total motor score (TMS), UPDRS activities of daily living (ADL) score (patients analysed in an "on" state) and L-dopa dose were included as secondary endpoints.

Results: Significantly more patients receiving ropinirole prolonged release than ropinirole IR achieved ≥20% maintained reduction from baseline in "off" time at Week 24 LOCF (adjusted proportions 66% *versus* 51%; adjusted odds ratio: 1.82; $p=0.009$). Ropinirole prolonged release significantly improved mean UPDRS TMS from baseline at Week 24 LOCF compared with ropinirole IR (adjusted mean treatment difference [AMTD]: –2.30; $p=0.022$). A numerical treatment benefit of ropinirole prolonged release over ropinirole IR was seen in the mean change from baseline in UPDRS ADL score at Week 24 LOCF (AMTD: –0.69; $p=0.100$). At Week 24 LOCF, the mean (SD) dose of ropinirole prolonged release was 18.6 (6.5) mg/day *versus* 10.4 (6.4) mg/day ropinirole IR; mean (SD) L-dopa doses had decreased from baseline by –162 (226) mg and –113 (138) mg in the ropinirole prolonged release and ropinirole IR groups, respectively. Ropinirole prolonged release was generally well tolerated, with a safety profile similar to ropinirole IR.

Conclusions: Ropinirole prolonged release improved symptom control in patients with advanced PD compared with ropinirole IR at the doses administered in this study.

Th-184

Treadmill-walking with music shows a synergistic improvement in gait and balance in patients with Parkinson's disease: A randomized controlled trial

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Objective: To assess the synergistic effects of music and exercise (treadmill-walking) on motor function and quality of life in patients with Parkinson's disease (PD).

Background: Alternative therapies such as exercise and music cueing have been suggested to improve function in PD. However, there have been no long-term randomized controlled trials (RCT) to objectively evaluate the distinction between the roles of exercise and music.

Methods: 29 patients with moderate PD were randomized into three groups: walking on treadmill with music (Group M+W, N=10), walking on treadmill without music (Group W, N=9), and music-listening alone (Group M, N=10). Music was selected based upon patient input and cadence-matched to the patient's preferred walking speed. Assigned interventions were for 30 minutes, 2 times a week, over 2 months. Patients were evaluated by a blinded rater at baseline and 2-months on the Gait and Balance Scale (GABS), motor UPDRS (III), and PDQ-39. The primary outcome was mean change in GABS between baseline and 2-months. Differences among M+W, W, and M groups were tested for statistical significance using analysis of covariance with adjustment for baseline score and disease stage.

Results: Mean age of participants was 64.4 years, 62% were male, and mean baseline GABS and UPDRS III scores were 5.2 and 18.0 respectively. At 2-months, the M+W group showed improvement on GABS (mean change -1.7). The W group did not improve (mean change -0.5) and the M group worsened (mean change 0.9). P-value comparing the 3 groups = 0.08. A p-value of 0.07 was obtained for the subgroup analysis comparing the mean change in GABS between the M+W (-1.7) and M (0.9) groups. All three groups showed improvement on the UPDRS III after the 2-month intervention period (mean change -2.1, -3.6, -4.2 respectively; p-value = 0.59).

Conclusions: This is the first long-term RCT to analyze the synchronous effects of music and exercise in PD. A benefit on motor UPDRS is seen with all 3 interventions. However, walking with music appears to confer a functional benefit to gait and balance in moderate PD as measured by GABS.

Th-185

Effect of stair-walking exercise in Parkinson patients

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Objective: To study the effects of stair walking exercise on gait ability in Parkinson patients.

Background: It has been suggested that sequential movements in parkinson patients might be improved by the effects of external rhythmic cues, either visual or acoustic. We have hypothesis that stair-walking exercise, very simple exercise that patients can do at their home without any equipment, may stimulate as visual cue. This is the first trial that study the effect of stair-walking exercise in Parkinson patients.

Methods: Prospective controlled trial was done. Sixteen Parkinson patients, with Hoehn and Yahr stage 2 or 3. Subjects were purposive recruited to stair-walking exercise group and ground-walking exercise group. Subjects in the 2 exercise groups completed 12 exercise sessions over 4 weeks (3 sessions per week). Duration of each session are 30 minutes. Freezing of gait, step length, cadence and walking velocity were measured in both groups.

Results: There are statistically significant improvement of freezing of gait, step length, cadence and walking velocity in both groups after walking exercises compare to baseline by Mann-Whitney U test at $p<0.05$. There are statistically significantly better score of freezing of gait, step length, cadence and walking velocity in stair-walking exercise group compare to ground-walking exercise group by Wilcoxon Signed rank test at $p<0.05$.

Conclusions: Stair-walking exercise can improve gait ability in Parkinson patients morethan ground-walking exercise. Stair-walking exercise may stimulate as visual cue.

Th-186

Safety and tolerability of long-term treatment with ropinirole prolonged release in patients with early or advanced Parkinson's disease

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Objective: To summarize the safety and tolerability data from interim analyses of two ongoing, long-term studies of ropinirole prolonged release in patients with early or advanced Parkinson's disease (PD).

Background: Patients with PD were enrolled from one of five pharmacokinetic or efficacy feeder studies from the ropinirole prolonged-release clinical development programme into multicentre, open-label, flexible-dose, extension studies 101468/196 and 101468/248. Patients with advanced PD received ropinirole prolonged release as an adjunct to L-dopa.

Methods: Safety and tolerability of once-daily ropinirole prolonged release (2–24 mg/day; dosage individually titrated to clinical response) were assessed by the incidence of treatment-emergent adverse events (TEAEs), serious TEAEs (TESAEs) and TEAEs leading to withdrawal.

Results: At the interim analysis, by which patients had been followed for up to 4.5 years, 502 patients had received ropinirole prolonged release: 194 as monotherapy, 346 as adjunct therapy. Overall, 396/502 patients (79%) had been exposed for >1 year and 317/502 patients (63%) were still receiving ropinirole prolonged release at the data cut. Patient distribution across the modal dose group ≤8 mg/day, >8–16 mg/day and >16 mg/day was 23%, 37% and 40%, respectively; mean (SD) dose was 15.9 (6.05) mg/day. In total, 370/502 patients (74%) reported a TEAE, whether related to treatment or not. Peripheral oedema was the most commonly reported TEAE (55/502 [11%]). TESAEs occurred in 78/502 patients (16%), with chest pain reported most frequently (8/502 [2%]). Withdrawal as a consequence of a TEAE was cited for 66/502 patients (13%). The only TEAE leading to study discontinuation in ≥2% of patients was hallucination (10/502 [2%]; monotherapy n=1, adjunct therapy n=9). By the interim data cut there had been four deaths; none was considered treatment related.

Conclusions: Long-term therapy with ropinirole prolonged release is well tolerated by patients with early or advanced PD. The TEAEs reported are as expected for non-ergot dopamine agonists.

Th-187

Long term pramipexole monotherapy in patients with tremor-dominant early Parkinson's disease

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Objective: To evaluate the long-term efficacy and tolerability of pramipexole (PPX) monotherapy in Japanese early Parkinson's disease (PD) patients.

Background: Although the use of dopamine agonist is recommended in the initial treatment of early PD, the approved maximum doses in Japan are generally limited low. PPX is the only dopamine agonist of which the approved maximum daily dose in Japan is the same as that of foreign countries, i.e.4.5 mg.

Methods: Twenty-eight patients with tremor-dominant early PD patients, not receiving levodopa or dopamine agonist (age: 63.3±7.4 years, duration of the disease: 1.9±1.4 years, Hoehn and Yahr stage: 1.6±0.7) were enrolled and evaluated every 3 months until 24 months after the initiation of PPX. PPX was started at a dose of 0.125 mg b.i.d and the dose was increased to 0.25 mg b.i.d at week 2. Then the daily dose was up titrated by 0.5 mg/day at weekly interval, to maintenance dose (1.5-4.5 mg /day). All subjects underwent modified Hoehn and Yahr Staging, UPDRS part 1 to 4, clinical rating scale for tremor (CRST) at baseline, and month 3,6,9,12,24.

Results: UPDRS part 3 as well as total UPDRS scores, CRST scores improved significantly throughout the study. Among items in UPDRS partIII, significant a improvement was seen in bradykinesia (sum of items 18, 19, 23, 24, 25, 26 and 31), tremor (sum of items 20 and 21), and rigidity (item 22), but not in axial signs (sum of items 27, 28, 29 and 30). The PPX dose was gradually increased in the maintenance phase to avoid deterioration in the motor control. Side effects were observed in 11/28 patients (39.3%); somnolence in 5, hallucination in 3 and others, but they were of mild degree. Two patients with hallucination (at month 12 and 18) and 1 patient with somnolence (at month 12) dropped out. The two with hallucination were later diagnosed as DLB. Three more patients dropped out after month 20 due to inadequate motor control by PPX alone, and levodopa/anticholinergics were added.

Conclusions: PPX monotherapy was generally sufficient in controlling motor disturbances and was well tolerated in Japanese early PD patients.

Th-188

Shortened T2 relaxation time at 3-T in the substantia nigra pars compacta of patients with Parkinson's disease and multiple system atrophy

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Objective: To determine the T2 values of the substantia nigra (SN) pars compacta (SNc) in patients with Parkinson's disease (PD)

and multiple system atrophy (MSA) and to compare the results with those of controls.

Background: Patients with PD and the parkisonian variant of MSA (MSA-P) reportedly show hyperechogenicity of the SN. Increased tissue concentration of iron has been associated with the hyperechogenicity. Shortening of T2 relaxation time (T2 value) in the SN pars compacta (SNc) may represent iron accumulation.

Methods: Twenty five patients with PD, 11 MSA, and 13 control subjects had MRI with a 3-T magnet. T2 value was calculated for SNc. Control group consisted of patients with acute cerebrovascular attacks (CVA) who previously had no event of CVA or other diseases in the central nervous system.

Results: There was no difference of age among three groups. Mean T2 value±SD for PD group was 65.9±9.0, for MSA group 63.7±7.6, and for controls 74.4 ±6.1. Values were significantly low in patients with PD and MSA ($p<0.05$) when compared with those of controls.

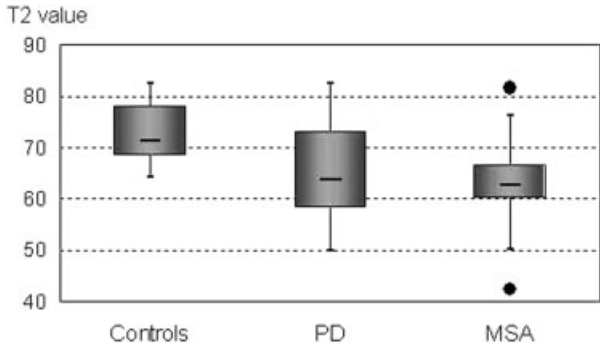

FIG. 1 (Th-188).

Conclusions: High field strength MRI demonstrates shortened T2 relaxation time in the SNc of patients with PD and MSA. T2 values of SNc determined at 3-T may be useful to detect putative iron accumulation in patients with PD and MSA.

Th-189

The effectiveness of a multi-day training program for people with Parkinson's in increasing knowledge about and involvement in clinical research

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Objective: To assess the impact of a multi-day training on increasing the level of knowledge and involvement in clinical research among people with Parkinson's.

Background: Enhancing the role of the public in the clinical research process is a critical variable in building trust in and support for research as well as reducing barriers to moving research forward. Patients have a critical interest in the outcomes of clinical research and a special need for the knowledge and skills to effectively serve as representatives with the clinical research enterprise. The Parkinson's Disease Foundation launched the Clinical Research Learning Institute (CRLI) in 2008 to address this need. The goal of the CRLI is to prepare people with PD to engage in such activities as: educating peers about the importance of clinical research and opportunities for study participation; providing research sponsors and investigators with input on trial design, implementation and evaluation; and working with regulatory entities, such as IRBs and the Food and Drug Administration.

Methods: (1) Following each CRLI presentation, a survey was administered to participants to assess increased content knowledge as well as comfort in sharing information with others. (2) Following the CRLI, a survey was administered to participants to study the type and frequency of their clinical research liaison activities. This survey also assessed the number of persons referred to a study by a CRLI graduate.

Results: (1) In seven of the eleven CRLI presentations, more than 70 percent of participants reported that their knowledge of the content presented increased. In ten of the eleven presentations, more than 50 percent of participants reported that their comfort level in disseminating information increased. (2) Preliminary data received from August through December 2008 indicate that 80 percent of CRLI graduates have served as a clinical research liaison at least once.

Conclusions: The CRLI increased both knowledge and degree of comfort in speaking about clinical research. CRLI graduates have engaged in activities ranging from speaking at a state-wide meeting for support group leaders to applying for a seat on an IRB. These and future findings will influence the curriculum of fall 2009 CRLI and PDF's efforts to maximize the impact of CRLI graduate activities.

Th-190

An open label, parallel-group, repeat-dose study to investigate the effects of end stage renal disease (ESRD) and haemodialysis on the pharmacokinetics (PK) of ropinirole

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Objective: This study investigates the effects of End Stage Renal Disease (ESRD) and haemodialysis (HD) on the pharmacokinetics (PK) of ropinirole and its metabolites.

Background: Ropinirole is cleared predominantly by hepatic metabolism to form two metabolites (SK&F-104557 and SK&F-89124) both of which are renally excreted and do not contribute to the pharmacological activity of ropinirole.

Methods: Ten subjects with ESRD receiving regular dialysis and 10 matched controls were administered 0.5 mg daily and were increased weekly up to 2 mg per day over three weeks. Following up-titration, blood samples for PK analysis were collected over 24 hours, once for healthy subjects and twice, once off-dialysis and once on-dialysis, for HD subjects. Effects of ESRD on ropinirole PK were assessed using steady-state $AUC_{(0\text{-}24)}$ and C_{max} values dose-normalised to a 1 mg dose. Comparisons were made between "off-dialysis" assessments in HD subjects and those obtained in healthy subjects. Simulations were conducted to compare systemic exposure to ropinirole and its metabolites following daily evening dosing of ropinirole IR in subjects with normal renal function (4 mg) with daily evening dosing of ropinirole IR in subjects with ESRD (0.5 mg to 4 mg).

Results: Clearance of ropinirole, SKF-104557 and SKF-89124 was reduced in subjects with ESRD, compared to healthy subjects, by approximately 30%, 80% and 60%, respectively. Ropinirole and its metabolites were not extensively cleared by dialysis.

Conclusions: The daily maximum dose in ESRD should be limited to 3 mg of ropinirole IR for restless legs syndrome (RLS) and 18 mg of ropinirole IR or PR/XL for Parkinson's disease (PD). This provides a similar PK profile and systemic exposure to ropinirole as seen at the top dose of ropinirole in subjects with normal renal function (4 mg/day for RLS and 24 mg/day for PD). Adjustment of the ropinirole dose is not required during the up-titration phase nor are supplemental doses required after dialysis.

Th-191

Aspiration and swallowing in Parkinson's disease and rehabilitation with EMST: The ASPIRE study

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Objective: Test the effects of an expiratory muscle strength training (EMST) vs. a placebo technique (sham) on swallow function in a randomly assigned sample of persons with moderate Parkinson's disease (PD).

Background: Disordered oropharyngeal swallowing can cause aspiration of food and liquids, leading to pneumonia, dehydration, malnutrition, and ultimately death. In those with PD, dysphagia is the main cause of life-threatening morbidity and results in marked

reductions in general health-related quality of life. Changes resulting in penetration/aspiration have been partially attributed to decreased elevation and excursion of the hyolaryngeal complex. EMST's mechanistic underpinning is its ability to generate increased force activation of the submental musculature resulting in improved movement of the hyolaryngeal complex. There have been no clinical trials investigating the effects of restorative dysphagia treatment in persons with PD.

Methods: We completed a blinded, randomized placebo-controlled clinical trial, testing the effects of EMST in a cohort of 60 persons (30 EMST, 30 sham) with PD. Following baseline testing, participants completed four weeks of EMST or sham intervention, depending on their random assignment. Functional, physiological, and swallow-related quality of life measures were completed pre/post intervention. PA scores served as a measure of swallow safety quantifying the presence or absence of penetration/aspiration. Physiological measures quantified the movement of the hyolaryngeal mechanism.

Results: Results revealed significantly lower P-A scores (less penetration/aspiration, safer swallow) in persons who received EMST training as compared to sham ($p=.004$). Additionally, the EMST cohort demonstrated improved hyoid displacements (specifically at laryngeal closure) and hyoid durational measures ($p=.029$), not found in the sham group. Both groups demonstrated improvements in swallow related quality of life.

Conclusions: This study is the first randomized, clinical trial of a restorative dysphagia treatment for PD. Results reveal improvement in functional and physiological measures of swallow function for the EMST vs. sham groups. These results provide strong support for the efficacy of EMST for the remediation of dysphagia in PD.

Th-192

Motivations and concerns of Parkinson's disease patients to participate in clinical trials

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Objective: Evaluate the motivations and concerns of Parkinson's disease (PD) patients regarding inclusion in a clinical trial; assess patients' understanding of the informed consent and placebo concept.

Background: Few systematic data is available regarding the motivations and concerns of PD patients enrolled in clinical trials. Better knowledge about these factors might improve recruitment and quality of clinical trials' design and conduction.

Methods: We conducted a survey on PD patients enrolled in clinical trials between 2002 and 2007 (PD dementia trials excluded). Two distinct close-ended type questionnaires were developed for placebo-controlled and active-controlled trials, and mailed to patients after a phone contact.

Results: From the 127 questionnaires sent, we received 93 responses (73.2% response rate). 91 questionnaires were minimally completed for analysis. Mean age was 67 years, 59% were females, with average schooling of 6.1 years. Main motivations for entering a clinical trial were helping to advance science (63.7%); accessing to a better treatment option (56%); recommendation from neurologist (52.7%); and participating in research for the benefit of others (50.5%). Major concerns were risk of adverse events (49.5%) and aggressiveness of treatment (34.1%). 79.2% of patients agreed or fully agreed with information provided by informed consent. If another trial was offered, 71% would participate, but only 47% definitively or possibly agreed in participating in a placebo-controlled trial. Of the 80 patients enrolled in placebo-controlled trials, only 52.5% seemed to understand the concept of placebo and 49% believed that they definitively or possibly took the active compound tested. 51.3% of those 80 patients obtained great or moderate benefit from treatment.

Conclusions: Patients self interest and altruism were the main motivations for trial participation, while major concerns were safety. Inform consent seems to satisfy patients' expectations, but there is a need to improve understanding of the placebo concept. In placebo-controlled trials, a similar number of patients believe they took the active compound and reported significant improvement with treatment. Overall, the majority would participate in another trial, although less so in a placebo-controlled trial.

Th-193

Socio-demographic and clinical factors influencing the adherence to treatment in Parkinson's disease

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Objective: The aim of this study was to determine the factors modifying therapy adherence in PD patients.

Background: Control of symptoms in Parkinson's disease (PD) relies in correct therapeutic decisions and adherence to treatment. There are many factors contributing to adherence. The lack of physician awareness of the impact and prevalence of suboptimal adherence can also be important. Associated comorbidities in elderly PD patients may contribute to non-adherence because of an increased amount of medications.

Methods: This survey was performed with 169 neurologists all over Spain. A total of 418 patients with PD on treatment with any anti-parkinsonian medication were included. Patient's adherence was assessed through physicians' subjective perception and the Morisky-Green test (MGT). Several social, demographic and clinical features were correlated through bivariate and multivariate analyses.

Results: Mean disease duration was 5.73 ± 5.49 years. More than 75% of patients presented motor complications. Cognitive impairment was present in 25% of patients; depression in 30%; hallucinations in 10%; and psychotic symptoms in 3%. There were 2.37 ± 1.39 chronic comorbidities requiring daily treatment. The mean daily number of medications was 8.86 ± 4.35. According to physician's opinion 79% of patients were clinically controlled, and 93.67% were adherent to therapy. Patients with good knowledge of PD symptoms were 6.62 times more likely to be classified as adherents; by contrast patients with psychiatric pathology were 2.53 times more likely to be non-adherent according to the physician opinion. Assessment through the MGT disclosed that only 60.4% of patients were adherent to medication. Greater adherence was found in patients with higher levels of knowledge of the disease (62.8%), and good disease control (63.6%); married patients (63%) and patients with higher incomes (66.1%) also presented better adherence. Patients with cognitive deterioration and psychiatric pathology were two-fold more likely to be non-adherent.

Conclusions: Physician's impression overestimate the compliance of patients when compared with an objective evaluation such as the MGT. Cognitive impairment and psychiatric symptoms are the clinical variables associated with lower level of adherence.

Th-194

Rationale and design of the ParkFit study: A randomized controlled trial to increase physical activity in patients with Parkinson's disease

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Objective: To evaluate a PD-specific physical activity promotion program.

Background: Many patients with Parkinson's disease (PD) have a sedentary lifestyle, caused by a combination of physical impairments and cognitive dysfunction. Patients should be stimulated to increase their physical activities, for several reasons. First, physical activity has generic positive effects in preventing complications such as cardiovascular disease, diabetes mellitus and osteoporosis. Second, physical activity may have positive effects on PD-specific symptoms such as depression and sleep disturbances. Finally, animal studies suggest

that physical activity could slow disease progression. Simply informing people about the importance of physical activity seems insufficient to initiate and maintain an adequate activity level. The ParkFit study is designed to evaluate a PD-specific physical activity promotion program that aims to increase the level of daily physical activity over a two year period in sedentary patients with PD.

Methods: Specific elements of the ParkFit program include: a personal activity coach; an ambulatory activity monitor with visual feedback of daily activities; an educational activity workbook; and a personal Health Contract. The merits of this program will be evaluated in a multicentre, randomised controlled trial, scheduled to include 700 sedentary PD patients, randomly assigned to either "usual physiotherapy" or to the ParkFit program. Primary outcome measure is time spent on physical activities per week, measured by 7-day recall. Secondary outcome measures are: (1) physical fitness; (2) quality of life; and (3) level of physical activity in kilocalories per week. We also document the risks of improved physical activity. Assessments take place at baseline, and after 6, 12, 18 and 24 months.

Conclusions: The study will clarify whether a PD-specific physical promotion program will result in a meaningful improvement in physical activity levels over a two year period. Furthermore, we will search for possible disease-specific health benefits and risks of improved physical activity, as well as possible (individual) predictors for successful implementation of the program.

Th-195

Botulinum toxin type A (BTX-A) in the management of levodopa-induced cervical dyskinesias in Parkinson's disease: A double-blind, randomized, placebo-controlled crossover study

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Objective: To determine whether cervical intramuscular BTX-A injections can reduce cervical-predominant levodopa-induced dyskinesias (LID) in Parkinson's disease (PD).

Background: Few pharmacological options are available for the treatment of LID in PD.

Methods: Of 12 consecutively screened PD patients with cervical-predominant LID, 8 were randomized to receive standardized EMG-guided BTX-A (200 U) or normal saline injections into sternocleidomastoid, splenius capitis, and trapezius muscles (4 males; age, 70.3±5.6 years; disease duration, 11.1±2.7 years; levodopa equivalent daily dose, 1375±601 mg). Subjects were assessed 0 (baseline), 1, 3 (crossover), 4, and 6 months after enrollment, with injections administered at 0 and 3 months. Primary outcome was change in the Goetz Dyskinesia Rating Scale (GDRS, 0-4) modified for the cervical region, rated by 3 blinded investigators from randomized videotape sequences. Secondary outcomes included the patient-reported Clinical Global Impression of Change (CGIC) and UPDRS-IV. Friedman test was used to compare BTX-A with baseline and placebo groups.

Results: Only 4 patients completed the 6-month study before it was voluntarily stopped due to safety concerns (excessive neck weakness). For analyses, full 1-month data were available for 6 BTX-A patients. BTX-A was associated with improved GDRS scores (1.8±0.7 vs. 2.1±0.8 baseline and 2.5±0.7 placebo, $P=0.018$). CGIC in the BTX-A group ranged from mild worsening to marked improvement. Dyskinesias rated as moderately and severely disabling ($n=4$; UPDRS-IV, item 33) became either mildly ($n=3$ of 4) or not disabling with BTX-A. BTX-A also converted moderately and severely painful dyskinesias ($n=4$; UPDRS-IV, item 34) into mildly or not painful dyskinesias ($n=3$ of 4). All but one subject declined post-study BTX-A injections for ongoing management of LID.

Conclusions: Although BTX-A reduced cervical dyskinesia severity and pain, the unfavorable risk-benefit ratio discourages its clinical use. Better outcomes may be possible with individualized dosages and stringent patient selection. **ClinicalTrials.gov Identifier:** NCT00477802

Th-196

Does botulinum toxin improve gait in Parkinson's disease?

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Objective: To verify if the treatment with Botulinum Toxin of agonist-antagonist hip muscles can improve the gait.

Background: The impairments of gait are frequent in Parkinson's disease (PD) with reduction of the spatio-temporal and kinematic parametres and a reduction of R.O.M. in the upper limbs and in the lower limbs; it depends on the rigidity due to an increase of muscular tone for basal ganglia dysfunction that determines characteristic muscular hypertone of both agonist and antagonist muscles. In the extensor muscles the great adductor plays an important role with EMG activity during the terminal swing and the initial contact. In the flexor muscles the long adductor shows a prolonged EMG activity in particular from the end of the terminal stance until the mid swing.

Methods: Two groups od PD were included in the study: the first (G1) was composed by 14 PD patients, mean age 70.14 years, staged IV H-Y,U.P.D.R.S. III mean score 39.1 in the medication on-state; the second group (G2) was composed by 14 PD patients, mean age 69.92 years, staged IV H-Y, U.P.D.R.S. 39.8 in the medication on-state. The first group (G1) was treated with botulinum toxin 400 U Dysport in the great adductor and 400 U Dysport in the long adductor in both the legs under EMG guide. The second group (G2) was treated with placebo in the same muscles. The two groups were assessed with gait analysis before treatment with Dysport (T0), after 1 month and after 3 months (T3).

Results: After processing abd analysing data of gait analysis we documented in G1 after botulinum toxin at 1 month and at 3 months an increase of the steplength, stridelength, walkspeed and the R.O.M. of the hip. At the T-test analysis in G1 the comparison between pre (T0) and post toxin (T1) registered a significant difference ($p=.001$) in the steplength, stridelength, walkspeed and the flexion and the extension of the hip. The comparison between T0 and T3 registered a significant difference ($p=.001$). In G2 the comparison between T0 and T1 did not register a significant difference in the steplength, stridelength, walspeed and the flexion and the extension of the hip.

Conclusions: This study demonstrates that the treatment with botulinum toxin on synergic agonist and antagonist hip muscles has a positive average effect on spatio-temporal and kinematic gait parameters increasing the quality of gait.

Th-197

Cerebrospinal fluid markers of neurodegeneration in Parkinson's disease

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Objective: The aim of this study was to assess tau-protein, beta-amyoid$_{(1–42)}$, cystatin C and clusterin CSF levels in PD patients and in the control group (CG) and to compare CSF levels between these two groups and correlate to the PD duration and severity of motor impairment.

Background: Parkinson's disease (PD) manifesting itself clinically after the pathology already has reached an advanced stage. According to the Braak's staging the degree of brain pathology is correlated with the motor impairment. The severity of neurodegeneration should correlate with neurodegenerative markers levels in cerebrospinal fluid (CSF).

Methods: Neurodegenerative markers in CSF were assessed in 35 patients with PD (25 males, 10 females, aged 37-73, mean 59.2 +/− 11.35 years), and CG of 20 patients (11 males, 9 females, aged 35-75, mean 51.2 +/− 10.74 years). Hoehn-Yahr scale was used for the assessment of the severity of motor impairment (H&Y). Student t-test, Mann-Whitney test and Spearman correlation were used when assessing statistical significance of the results.

Results: The following statistically significant differences in the CSF were found: higher tau-protein levels in PD patients versus CG ($p=0.05$), higher tau-protein levels ($p=0.03$), tau-protein/beta-amyoid$_{(1-42)}$ ratio ($p=0.04$) and clusterin levels ($p=0.04$) in PD patients with duration less than 2 years vs. PD with duration more than 2 years. No significant correlation was found between the tau-protein CSF levels and the H&Y of PD. No difference in levels of beta-amyoid$_{(1-42)}$ and cystatin C in CSF was found in the CG and PD patients groups.

Conclusions: Tau-protein and clusterin CSF levels were higher in the group of PD patients with disease duration less than 2 years. It can be assumed that the maximum of neurodegenerative changes in PD is happening in the first two years after the disease onset.

Th-198

Long-term safety of rotigotine transdermal patch in early-stage Parkinson's disease: Results from 4 years

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Objective: To examine the long-term safety and efficacy of rotigotine treatment in an open-label extension study in subjects with early-stage Parkinson's disease (PD).

Background: Once-daily, transdermally-delivered rotigotine is licensed in Europe and the US to treat the signs and symptoms of PD and is also indicated for the symptomatic treatment of restless legs syndrome in the EU. Subjects with early PD completing a double-blind, placebo-controlled trial of rotigotine (up to a target dose of 6mg/24h), were allowed to enter an open-label extension phase to assess long-term safety. Results from 4 years of follow-up are reported.

Methods: Following double-blind treatment, all patients were tapered to their starting dose (2mg/24h rotigotine or matching placebo) and (re)titrated over a 3-week period. Rotigotine was limited to $\leq$6mg/24h the first year, after which doses up to 16mg/24h were allowed as needed. Adverse events (AEs), safety measures, dyskinesia and UPDRS (II+III) scores were assessed.

Results: Two hundred sixteen patients enrolled in the open-label extension (n=79 placebo, n=137 rotigotine). The majority (63% [137/216]) remained in the study over 4 years of open-label maintenance. Overall, discontinuations due to treatment emergent AEs were low (17%), with most withdrawals occurring within the first 12 months. Application site erythema, pruritus, inflammation or reactions had occurrences of 14%, 9%, 7% and 5%, respectively. Frequently ($\geq$25%) reported AEs over 4 years of follow-up were somnolence (49%), peripheral edema (34%), fall (28%), nausea (25%) and dizziness (25%). Thirty-four patients (16%) experienced dyskinesia; in most (28/34), dyskinesia developed following initiation of levodopa. The mean time-to-onset of dyskinesia after levodopa initiation was 619.9 days. Mean UPDRS scores after 4 years of open-label rotigotine maintenance remained within 2 points of subjects' original double-blind baseline scores.

Conclusions: Long-term treatment with rotigotine (up to 4 years) was safe and well tolerated with few AE-related discontinuations and a low incidence of dyskinesia.

Th-199

Atomoxetine for the treatment of depression in Parkinson's disease: A randomized, double-blind, placebo-controlled study

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Objective: To assess the efficacy and tolerability of atomoxetine, a selective norepinephrine reuptake inhibitor (NRI), for the treatment of depression in Parkinson's disease (PD).

Background: Depression in PD is common, and associated with impairments in function, quality of life, and long-term outcomes. Antidepressant use, usually a selective serotonin reuptake inhibitor (SSRI), is common in PD, but there is no evidence for SSRI efficacy in PD. Noradrenergic deficits are prominent in PD, and the primary mechanism of action for some antidepressants is to increase central noradrenergic activity.

Methods: 55 subjects with PD and at least moderate depressive symptoms (i.e., Inventory of Depressive Symptomatology-Clinician [IDS-C] score $\geq$22) were randomized to atomoxetine or placebo for 8 weeks of treatment. Atomoxetine was flexibly dosed, with a target dosage of 80 mg/day. Primary outcome measures were two measures of response (>50% decrease in IDS-C score from baseline and final Clinical Global Impression-Improvement [CGI-I] score of 1 or 2) and remission (final IDS-C score $\leq$13).

Results: Preliminary analyses were for subjects who had at least one post-baseline visit (N=50). Mean (SD) age was 64.5 (10.7) years, PD duration =6.7 (6.2) years, and baseline UPDRS motor score =22.5 (11.9); 66% of subjects were male. IDS-C response rates were 20.0% for atomoxetine and 8.0% for placebo (P=.22); CGI-I response rates were 40.0% for atomoxetine and 28.0% for placebo (P=.37). There was a trend for atomoxetine superiority for remission (12.0% vs. 0%, respectively; P=.07). Overall discontinuation rates were similar for the two groups (21.4% for atomoxetine and 22.2% for placebo). Additional mixed methods analyses and other secondary analyses are being conducted and will be presented at the MDS meeting.

Conclusions: In this pilot study, atomoxetine did not demonstrate efficacy for the treatment of depression in PD. However, response rates on both primary outcome measures were higher for atomoxetine than placebo, with a suggestion for a higher remission rate with atomoxetine treatment, so a larger clinical trial is indicated.

Th-200

Possible Parkinson's disease revealed by a pure head resting tremor

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Objective: To show that the pure resting head tremor might be the first sign of Parkinson's disease (PD).

Background: Head tremor is classically considered as a red flag in the diagnosis of PD. Recently, Roze et al have shown that this symptom may be encountered in PD. Here we describe a patient with pure resting head tremor as the initial manifestation of a possible PD.

Methods: A 74-year-old woman presented a head tremor, following a metoclopramide treatment for nausea (15 mg/day) during ten days. This tremor occurred only in supine position when her head was lying relaxed on a pillow but not when standing or maintaining her head in an upright position without any support. There was no medical past history and no family history of movement disorders. The neurological examination showed a head tremor only when the head laid down on a pillow in supine and completely relaxed position. The tremor disappeared during voluntary cervical rotation. The patient had no dysarthria or orofacial dyskinesia, but a slight hypomimia. There was no rigidity or bradykinesia. Postural stability was normal as well as gait. Brain MRI was normal. The surface EMG showed that the head tremor had a 4.7 Hz frequency. A [^{123}I]FP-CIT SPECT showed a marked reduction of tracer uptake in the right striatum consistent with PD. Finally, a levodopa treatment was given 300 mg per day, leading to a clear improvement of the tremor 3 months later.

Results: The characteristics of the rest tremor, its frequency (4-6 Hz), its significant response to levodopa and the result of [^{123}I]FP-CIT SPECT which confirmed the degeneration of the right nigrostriatal dopaminergic pathway led us to suspect the diagnosis of PD.

Conclusions: This observation shows that PD can be suspected in patients presenting a pure resting head tremor. A careful clinical examination completed by electrophysiological recording and sometimes a [^{123}I]FP-CIT SPECT is mandatory to rule out differential diagnosis. However, the final confirmation of the diagnosis will only

be made by the long-term follow-up of the patient if other signs of the parkinsonian triad occur.

Th-201

Neuroprotection trials in Parkinson's disease

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Objective: To summarize key design features and results of randomized clinical trials in humans testing putative disease-modifying drugs in Parkinson's disease.

Background: Establishing an agent as neuroprotective has proven an elusive goal. No pharmacological agent has yet been shown convincingly to slow the progression of Parkinson's disease. Trials to date have varied in key design features and criteria for clinical neuroprotection.

Methods: Randomized trials testing drugs to slow the progression of Parkinson's disease were identified by computerized search of the OVID/MEDLINE database and the Cochrane Central Register of Controlled Trials. Two co-authors independently reviewed each trial and extracted a standard set of data elements based on the CONSORT statement for reporting randomized trials.

Results: Fifteen completed, published trials involving 4087 participants tested 13 different drugs in 18 double-blind comparisons with placebo. Based on the investigators' conclusions, six trials were interpreted as consistent with a neuroprotective effect, three as negative, and five as either confounded or not meeting criteria for futility. The primary outcome was change in the UPDRS score in eight trials and time to need for dopaminergic therapy in seven. Mean participant age was 62 years, 35% were women, the interval from diagnosis to entry averaged 11 months, and the number of participants averaged 272. In all, treatments were randomized and administered double-blinded, but detailed randomization methods were reported in only 20%, and the effectiveness of blinding was not reported in most (87%) trials. Twelve trial designs excluded patients who required anti-Parkinson's medications at entry; 11 included assessment after wash-out periods of two to eight weeks. Mean total UPDRS scores at entry averaged 25 (range 21 to 31), and estimated average duration of follow-up was less than 16 months in all but two trials.

Conclusions: Neuroprotection trials have involved relatively uniform groups of participants early in the clinical disease course, with outcomes weighted heavily toward motor deterioration. Future trials should include participants with wider range of disease stages, assess broader neurological outcomes, and adhere to the CONSORT statement for reporting randomized controlled trials.

Th-202

The efficacy and safety of switching from dopamine agonists to pramipexole in patients with advanced Parkinson's disease

M. Ye, W.G. Liu (Nanjing, China)

Objective: To determine efficacy and safety of switching from dopamine agonists to pramipexole in patients with advanced Parkinson's disease (PD).

Methods: 65 Patients with advanced PD and motor complications not optimally controlled by levodopa and a stable dose of bromocriptine, pergolide and piribedil were converted to pramipexole. 27 cases were in an overnight schedule, and the other were in concomitant usage schedule. Patients were assessed by using Webster Scale and Activity of Daily Living Scale(ADL). All rating scales were administered just before conversion and after 4 and 8 weeks of treatment, when patients were on an optimal dose of pramipexole. Adverse effects were assessed at every visit following a check list.

Results: 65 patients were included in the trial. No patients reported serious side effects (respiratory arrest, dyskinesias, and face edema and abdominal pain). 27 patients reported 6 adverse events. A significant improvement in assessed parameters was obtained ($P<0.01$). Mean madopar dose was decrement from 1000mg/d to 562.5mg/d in 1/3 PD patients. After 3 weeks, the mean dose of pramipexole was 1.5 mg.

Conclusions: Switching from pergolide, piribedil and bromocriptine to pramipexole in an overnight schedule or concomitant usage is safe. The observed clinical improvement may be related to a direct effect of pramipexole, or to a placebo effect, or to the use of low doses of madopar.

Th-203

A triple-blinded, randomized placebo-controlled, multicenter phase II study of efficacy and safety of VF-08, a Chinese herbal medicine mixture, in treatment of Parkinson's disease

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Objective: To evaluate the efficacy and safety of VF-08 in treatment of Parkinson's disease (PD), including motor fluctuation, levodopa requirement and red cell superoxide dismutase (SOD) activity.

Background: VF-08 is a formulated mixture of Chinese herbal medicine containing Radix Ginseng, Cornu Cervi Pantotrichum, Herba Epimedii, Gekko, Semen Allii Tuberosi, Fructus Cnidii, Fructus Evodiae, Rhizoma Kaempseriae and Semen Cuscutae. A previous 6-months open label trial in PD patients showed promising results.

Methods: The study design is triple-blinded, randomized placebo-controlled, multicenter trial. PD patients fulfilling Queen Square Brain Bank Criteria, age ≥30, Hoehn-and-Yahr stage 1-4, were recruited. Patients were randomized to either VF-08 or placebo with treatment phase of 24 weeks. Assessments were at 0, 6, 12 and 24 weeks, including UPDRS II and III, Mini-Mental State Examination, Schwab and England Activities of Daily Living Scale, PDQ-39, Clinical Global Impression Scale, total daily dose of levodopa, daily number of off-hours, red cell SOD levels. Analyses were by full analysis (ITT), per-protocol (PP) and safety sets.

Results: Totally 177 Chinese patients from 6 hospitals were recruited, age range 59-63 (mean 61), 59 female and 118 male, with 88 randomized to VF-08, 89 to placebo. Eighty-two in VF-08 group and 78 in placebo group completed the study. Regression analysis of primary end-point, i.e. 24-week change in UPDRS II and III total score showed no statistical significant difference between the two groups under t-test comparison ($p=0.292$ for ITT, $p=0.106$ for PP). The baseline effects with improvement were significant in both treatment and placebo groups ($p=0.004$ for ITT, $p=0.028$ for PP). There was no significant difference between the two groups in treatment effect for overall trend ($p=0.998$ for ITT, $p=0.781$ for PP), and secondary efficacy endpoints. There was no mortality. Totally there were 6 serious adverse events but none was life threatening, with no significant difference between the groups.

Conclusions: The efficacy of Chinese herbal mixture VF-08 was not statistically significant as compared with placebo in this triple-blinded randomized trial in PD patients over 24 weeks, though it was safe with good tolerance.

Th-204

Magnetic resonance imaging findings of shoulders in Parkinson's disease

A. Yucel, O. Yilmaz-Kusbeci (Afyon, Turkey)

Objective: To draw attention to the lesions of the shoulders in PD with magnetic resonance imaging (MRI) and answer the question that if there is any difference between the patients with mild and severe PD.

Background: Parkinson's disease (PD) is a chronic progressive disorder which is characterized by rest tremor, bradykinesia and rigidity. Skeletal deformities are common and frequently under-recognized features of PD.

Methods: Fifty-six shoulders of 28 patients with PD were included in the study according to Hoehn & Yahr (H&Y) clinical stage and divided into 2 groups. The first group consisted of 26 (46.4%)

shoulders of patients with mild PD (H&Y stage I-II). The second group consisted of 30 (53.6%) shoulders of patients with severe PD (H&Y stage III-IV). As frozen shoulder has a reported cumulative lifetime risk of at least 2% per year in certain population, age-matched control group was not established. All of the patients with PD underwent shoulder MRI. The long head of the biceps, supraspinatus, infraspinatus and subscapularis tendons and muscles, the acromiohumeral distance (AHD), the subacromial-subdeltoid and subcoracoid bursa, the glenohumeral and acromioclavicular joints were examined. AHD was measured, and abnormal findings as partial or complete tear, tendinosis, effusion, bone and joint changes were recorded. Data were analyzed statistically by the t-test and Chi-square test.

Results: There was no significant difference for all parameters, except two parameters, between the patients with mild and severe PD ($P>0.05$). Unexpectedly, there were significantly higher frequency of tremor ($P=.045$) and subcoracoid effusion ($P=.002$) in the mild PD group than severe ones. Although it was not statistically significant, mild PD patients had higher rate of supraspinatus tear (26.9%) than severe patients (16.7%). When we compared two groups according to having rest tremor, not to H&Y, there was higher frequency of complete tear in supraspinatus tendon in the group of having rest tremor ($P=.053$).

Conclusions: Our data suggest that rest tremor may effect the subscapular muscle and may cause subcoracoid effusion, or it may predispose supraspinatus tear as a serious pathology. In the point of view of these results, as a repetitive microtrauma, rest tremor should be taken into importance for the musculoskeletal pathologies in the shoulders of PD patients.

Th-205

Discrimination between healthy subjects and patients with Parkinson's disease using the PLM test and a levodopa challenge test

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Objective: The aim of this study was to investigate whether the Posturo-Locomotion-Manual (PLM) test, an optoelectronic quantitative and objective tool for assessment of movement performance, is able to discriminate between the performance of healthy persons and persons with Parkinson's disease; and if so, to determine which PLM variable would be the most suitable candidate to differentiate between the two.

Background: Retrospective clinico-pathological studies have shown that as many as 15 percent of patients with Parkinson's disease have been misdiagnosed. For many clinicians, the relatively simple and inexpensive levodopa challenge test is a useful tool. Today, assessment of the levodopa test is usually performed with scoring according to the motor part (part III) of the Unified Parkinson's Disease Rating Scale. The coarseness and the subjective nature of such scales makes them susceptible to inter-rater variability. There is a need for objective methods with quantitative assessment of patients' comprehensive movement abilities and deficits, to minimize the element of bias or error that can enter into the rater-dependent assessment procedures.

Methods: The study included 35 patients diagnosed with probable PD according to British Brain Bank Research Criteria, along with 50 healthy controls. The patients were evaluated with the PLM test before and after administration of levodopa, giving movement times (MT) in seconds for a compound standardized movement measuring postural function (P), gait (L), and goal-directed arm movement (M). The healthy controls performed the same test but without administration of Levodopa. A series of logistic regression analyses were performed to evaluate the ability of several different test variables to discriminate between healthy controls and PD patients.

Results: Of the eighteen variables tested, the best one for distinguishing between healthy controls and PD patients was the relative change of movement time, (MT1-MT2)/MT1, which showed a discriminatory ability of 91% (AUC = 0.91).

Conclusions: The PLM test is able to discriminate between healthy controls and patients diagnosed with PD. The best variable to use is the factor (MT1-MT2)/MT1, which in the PD patients represents $(MT_{OFF}\text{-}MT_{ON})/MT_{OFF}$.

Th-206

Laryngeal electromyography in patients with voice complaints at different stages of Parkinson's disease

A.P. Zarzur, B. Cataldo, E. Fonoff, A. Duprat (Sao Paulo, SP, Brazil)

Objective: To study the laryngeal electromyography pattern (LEMG) in patients with different degrees of Parkinson's disease (PD) and vocal complaints.

Background: Vocal and speech abnormalities are known to affect 70% to 92% of patients with PD, many times their first and main complaint. Few studies access this frequent disability and LEMG is the most accurate tool to check intrinsc laryngeal muscle function.

Methods: Forty seven adults with PD (33 male, 14 female) and vocal alterations, in different stages of general handicap (Hoehn and Yahr scale) underwent LEMG (cricothyroid-CT- and thyreoarytenoid-TA- muscles).

Results: No tremor was found on LEMG of the CT and TA muscles, even in cases of clinical tremor. LEMG hypertonicity during voice rest was the typical feature observed in 89% of the patients despite the handicap degree of the disease. The severity of the disease and the treatment did not correlate with LEMG findings. The exam technique was very well tolerated, not a case of complication was observed.

Conclusions: This is the only study reporting the use of LEMG in a large series of patients with different degrees of Parkinson's disease and voice complaints. Patients with PD presented spontaneous intrinsic laryngeal muscles hypertonicity even in voice rest. The typical patterns in LEMG suggest to be a valuable diagnostic tool in PD.

PARKINSON'S DISEASE: COGNITION

Mo-203

Frequency and profile of mild cognitive impairment in Parkinson's disease: A multicentre meta-analysis of neuropsychological data

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Objective: To determine the frequency and profile of mild cognitive impairment (MCI) in PD using data from six large international cohorts.

Background: Numerous single-centre studies of MCI in PD have been published, but are inconclusive due to differences in methodology (type and number of neuropsychological tests used, and definitions of MCI and dementia) and patient populations.

Methods: PD patients without dementia from six prospectively studied cohorts from five centres in US (n=2) and Europe (n=3) were included. Diagnoses of PD and dementia were made according to standardised protocols. Different neuropsychological tests were performed in each cohort, and each test was assigned to one of five cognitive domains. Z-scores were calculated relative to age-, education- and sex-adjusted control scores, and aggregated to an average z-score for each domain. Subjects with a z-score below -1.5 in at least one cognitive domain were classified as having MCI, and then further delineated into one of four MCI subtypes.

Results: A total of 1118 patients were included, 59.4% male. Mean (SD) age was 67.5 (9.9) years, duration of PD 6.1 (5.0) years,

MMSE score 28.3 (1.9), and UPDRS motor score 21.8 (12.7). The median Hoehn and Yahr stage was 2. Using the definitions of cognitive impairment from the primary publications and including patients from 5 of the 6 cohorts (n=906), the frequency of MCI across the cohorts was 45.7% (95% CI 42.5-49.0), with significant variation between the cohorts (range 18.9%–57.5%; Chi square=94.0, df=4, p<.001). There were significant between-center differences in gender, age, duration, and severity of parkinsonism, but the difference in MCI frequency between centres remained significant after adjusting for these factors. Frequency of MCI and subtypes using the method described above will be presented at the meeting.

Conclusions: MCI is common in PD. Different study methodologies and patient populations are likely to contribute to variations in frequency between the cohorts. Substantial variations in the frequency of MCI across different centres demonstrates that there is a need for diagnostic guidelines and criteria for MCI in PD.

Mo-204

A novel task to probe impulsivity in Parkinson's disease

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Objective: To design a task to detect and monitor impulsive behaviour.

Background: Impulse control disorders, including pathological gambling, are recognized as part of the diverse non-motor (cognitive) phenotype of Parkinson's disease (PD) and cause significant morbidity in addition to the familiar motor symptoms. It is difficult to predict which patients might develop impulsive behaviours and therefore to avoid potential precipitants, such as dopaminergic agonists. Eye movements have proven to be a sensitive index of decision making in non-human primates. Here we use an oculomotor paradigm to probe impulsivity in humans.

Methods: We designed a simple, rewarded eye movement 'traffic light' task in which healthy volunteers–young and old (n=43)–and PD patients (n=8) were asked to hold fixation when a central stimulus was red, or changed to amber. But when the signal turned green they had to make a saccade to a target as swiftly as possible. The faster their response, the greater the reward. Crucially, the distribution of amber durations was randomly drawn from a known distribution such that subjects might learn to anticipate when to saccade for greater reward. A simple model was used to fit the distributions of saccadic reaction times. The parameters of best fit for the model were used to compare performance between individuals and groups. In a proof-of-principle study we also attempted to modulate oculomotor impulsivity in healthy volunteers using levodopa.

Results: There is a marked reduction in oculomotor impulsivity (saccadic anticipation) with increasing age. PD patients without impulse control disorders performed similarly to age matched controls. Ongoing studies are examining the effects in PD patients with impulse control difficulties and the effects of a single dose of levodopa in healthy people.

Conclusions: We have developed a novel, objective task to probe impulsivity in both healthy volunteers and PD patients.

Mo-205

L-dopa plasma levels and executive functions in Parkinson's disease

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Objective: Aim of this study was to correlate the pharmacokinetic features of LD with executive functions in PD patients.

Background: Various studied have demonstrated the positive effect of l-dopa (LD) in modulation of prefrontal function in Parkinson' disease (PD), by evaluating the neuropsychological findings during off and on states. However, it is still unclear the role of the effect of chronic dopaminergic stimulation on executive functions and their relationships with motor response.

Methods: We studied 30 non-demented PD patients, by a neuropsychological bettery including MMSE, Clock test, digit span forward and backward, Corsi Test, Rey test, FAB, verbal fluency, CPM, Raven, Weigl Test, Trail Making Test, Stroop Test. In these patients, we have evaluated the LD plasmatic levels, after intaking of 250 mg of LD after overnight witdrawl therapy.

Results: Even if the LD plasma levels showed a marked intraindividual and interindividual variability in all group of study, we found that patients without dysexecutive dysfunctions and better UPRDS motor scores show significantly low Cmax and AUC values, comparing with others patients, while sex, age, duration of disease, LD years exposure, and presence of motor fluctuations appear to have not influence.

Conclusions: In our group of study, normal executive functions in PD appear to be influenced by a reduced pharmacokinetic LD profile and a good motor response. Indipendently by the time of exposure of LD therapy, individual factors, such as genetic, might influence the pharmacokinetic features leading to an optimized motor and cognitive status with a minimum plasma concentrations.

Mo-206

Neuropsychological consequences of bilateral versus unilateral subthalamic deep brain stimulation in Parkinson's disease

F. Andelman (Tel-Aviv, Israel)

Objective: The objective of this study is to systematically examine the neuropsychological consequences of unilateral versus bilateral STN DBS in patients with Parkinson's disease.

Background: Recent research suggests that bilateral subthalamic (STN) deep brain stimulation (DBS) is associated with increased acute and long-term complications including post-operative confusion, speech difficulties and cognitive dysfunction (Alberts et al 2008; Tabbal et al 2008; Agostino et al 2008). Some evidence suggests that unilateral STN DBS in patients with asymmetric symptoms may result in reduced morbidity and sometimes lead to changes also on the ipsilateral side of the body (Benabid et al 2009).

Methods: Results of presurgical and postsurgical standard neuropsychological tests of 20 patients with unilateral and 20 patients with bilateral STN DBS will be examined and statistically analyzed. Preliminary data of six patients is presented.

Results: Pre- and post-surgical neuropsychological test results of four patients with bilateral and two patients with unilateral STN DBS were compared. Three out of four patients following bilateral DBS suffered from cognitive and behavioral decline compared to their preoperative status, particularly in the area of executive functioning. Neither of the two patients who underwent unilateral DBS experienced changes in their neuropsychological functioning postoperatively.

Conclusions: These observations stress the importance of a cognitively demanding presurgical neuropsychological evaluation for DBS STN candidates in order to identify those patients with mild to moderate neuropsychological deficits who may suffer additional post-surgical decline. Secondly, they support the need for a systematic evaluation of the cognitive effects of unilateral versus bilateral STN DBS.

Mo-207

Magnitude estimation in Parkinson's disease

C. Andersen, B. Kluger, C. Garvan, S. Classen, H. Fernandez, M. Mennemeier, D. McCarthy (Gainesville, Florida)

Objective: To determine if there is a significant difference in magnitude estimations by persons with Parkinson's disease (PD) and healthy controls using perceptual stimuli spanning visual, tactile, and proprioceptive continuum.

Background: Patients with PD have deficits in many cognitive domains. These non-motor deficits have been demonstrated to signifi-

cantly impact quality of life and disability. Magnitude estimation is an experimental scaling technique in which subjects use a numerical scale to rate the intensity of sensory stimuli. It is used as a means of determining how subjects perceive their environment. Although there is evidence of perceptual and visual-spatial abnormalities, to date there have been no published studies regarding magnitude estimation and patients with PD.

Methods: We recruited 5 patients with PD and compared these results to previously published data on 83 healthy controls. All subjects performed 5 magnitude estimation tasks which consisted of rating the following domains: projected line length, area of squares, velocity, proprioception, and tactile pressure. Participants rated each stimulus's magnitude using a numerical scale ranging from 10 to 99. The collected data were log transformed and the r^2, intercept, and slope were determined using linear regression. Values for patients with PD were compared to the 95‰ confidence interval (CI) for the 83 subject control group. For our velocity task, we had no previous data and tested 6 healthy controls to use as comparison.

Results: All 5 patients with PD fell outside the 95‰ CI for at least one element in all the perceptual domains we tested. For proprioception, all patients with PD had values outside the 95‰ CI, whereas for tactile pressure, 3/5 patients with PD had values outside the 95‰ CI. For visual precepts, line length and area, 3/5 subjects fell outside the 95‰ CI on all aspects of the regression. For velocity magnitude estimation, however, patients with PD had similar ratings to control subjects.

Conclusions: Our data suggests that magnitude estimation may be impaired in a significant proportion of patients with PD and suggests that further research in this area is warranted. If confirmed, these results may have significant implications for quality of life and disability in patients with PD, particularly in driving.

Mo-208

Influence of cognitive status and dementia in Parkinson's disease on latency of reflexive eye movements

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Objective: To determine whether reflexive saccadic latency is sensitive to cognitive decline in PD.

Background: The influence of cognitive staus on saccade latency in patients with Parkinson's disease (PD) is uncertain.

Methods: 32 PD patients with varying cognitive impairment measured by the Montreal Cognitive Assessment (MoCA) instrument were compared with 21 controls. Reflexive saccades to targets with amplitudes of 5, 10, 15, and 20 degrees and inter-stimulus-intervals of 750, 1000, and 1400ms were examined in trials with either no temporal gap, a 200ms gap, or 200ms overlap between successive stimuli. Saccade latencies from target onset were classified as either anticipatory (i.e. initiated less than 70ms to target onset), express (fast responses, initiated 70-130ms after target onset) or reactive (>130ms after target onset). Anticipatory saccades were excluded from analysis.

Results: Ten PD patients met criteria for dementia (Dubois et al, 2007) and these exhibited prolonged latencies across all conditions compared to non-dementing PD patients and controls ($F(2, 50)=14.62$, $p<0.001$; the non-dementing PD group showed intermediate latencies. Importantly, for each reflexive task, saccadic latency increased linearly as cognitive status declined in PD patients, as defined by the MoCA (all $r > 0.60$, $p < 0.001$). In the gap paradigm, proportion of express saccades also decreased with increasing cognitive decline ($r = 0.50$ $p< 0.002$) with the PDD group producing a lower proportion of express saccades compared to both PD and control groups ($F(2, 50)= 5.15$, $p<0.01$).

Conclusions: Increasing cognitive impairment in PD is associated with increasing reflexive saccade latency, even prior to dementia, and PD dementia in particular is associated with global prolongation of saccadic latency and reduced proportion of express saccades in the gap task. We conclude that reflexive saccadic latency is sensitive to cognitive status and impairment and may be a useful biomarker of disease status and progression in PD.

Mo-209

Two-year clinical follow-up of a cohort with Parkinson's disease and other parkinsonisms. The PRIAMO study

A. Antonini, PaRkInson and Non Motor SymptOms Study Group (Milan, Italy)

Objective: To describe the clinical two years follow-up of a large sample of Italian patients with Parkinson's disease (PD) and other forms of parkinsonisms from the PRIAMO study.

Background: Clinical follow-up data of large cohorts of patients with parkinsonsims are scarce. Moreover, analysis of features that could contribute to patient institutionalization and death are still lacking.

Methods: PRIAMO is a 2-y ongoing longitudinal observational study aimed at enrolling patients with a diagnosis of parkinsonism in 55 centers widely distributed throughout Italy. Every year patients undergo a standardized clinical examination including motor evaluation by means of UPDRS part III and a battery test of self and hetero-evaluation scales.

Results: A cohort of 789 patients affected by PD and other parkinsonisms was followed-up for two years: they were diagnoses idiopathic PD (PD, 90%), vascular parkinsonism (VP, 4%), multiple system atrophy (MSA, 3%), progressive supranuclear palsy (PSP, 2%) and Lewy body dementia (DLB, 1%). Two-year mortality rate was 4.6%, with DLB having the highest proportion of deaths (18%) and PD the lowest (3%); dead patients were older, more severe according to H&Y scale and UPDRS-III and had more non motor symptoms than patients who completed the study. Motor disability as expressed by UPDRS-III, worsened in two year for PD, MSA and PSP patients (+3.4+/-10.8, +15.8+/-11.5, +23.3+/-13.9, respectively $p<.0001$ each); changes were not significant for VP (+4.4 +/-12; $p<0.05$). At follow-up demented PSP patients according to MMSE were 67% Vs 7% at baseline, while 8% of PD patients were demented at baseline Vs 12% at two years follow up. The proportion of patients with frontal lobe dysfunction according to FAB was more stable: 57% of PSP and 33% of MSA and VP patients had frontal lobe impairment both at baseline and follow up; 20% and 22% of PD patients had frontal dysfunction at baseline and at follow up respectively.

Conclusions: Motor and cognitive features decline more rapidly in patients with parkinsonisms than in PD ones.

Mo-210

The role of the subthalamic nucleus (STN) in cognitive processing in Parkinson's disease: A local field potential study

A. Anzak, L. Gaynor, M. Beigi, P. Limousin, M. Hariz, L. Zrinzo, P. Brown, M. Jahanshahi (London, United Kingdom)

Objective: To investigate the involvement of the STN in cognitive tasks requiring the suppression of habitual or inappropriate responses.

Background: Impairments in Verbal Fluency and fast-paced Random Number Generation (RNG) have been reported after deep brain stimulation (DBS) of the STN. This suggests that the STN may have a role in the processing of these tasks. An electrophysiological correlate of local processing is an increase in local gamma band activity. Accordingly, we sought such a change in the STN local field potential (LFP) during task execution.

Methods: LFPs were recorded from DBS electrodes implanted in the STN of 8 patients (16 sides) with Parkinson's disease, prior to internalization of leads. Patients were "on" medication whilst they undertook [1] phonemic and semantic versions of the Verbal Fluency test, and a control word repetition task to account for the motor output involved in response generation, and [2] a paced RNG and control counting task.

Results: Significant increases in LFP power ($p \leq 0.05$, one sample T-test) were seen across a broad gamma frequency band (30-100Hz) in both Verbal Fluency and RNG tasks, after controlling for motor output. The mean % increase in power relative to baseline across this range was 7.4%. A repeated measures general linear model was performed with main effects task type (3 types) and condition (active and control). There was an effect of condition ($F=11.84$, $p<0.01$) but no effect of task type ($F=1.77$, $p=0.21$), and no task type x condition interaction ($F=1.77$, $p=0.20$), indicating that gamma behaviour was similar across tasks.

Conclusions: The increased power observed across gamma frequencies is consistent with involvement of the STN in processing related to the tasks. Such involvement may explain the deficits seen in these tasks with DBS of the STN. As the motor elements of the tasks were subtracted out by the use of appropriate controls, the results raise the possibility that STN may be involved in inhibition of inappropriate or habitual responses, a critical feature of both Verbal Fluency (requiring suppression of words with high semantic associations with already generated words, but inappropriate to instructions) and RNG (suppression of counting in series.).

Mo-211

Rasagiline and cognitive improvement in Parkinson's disease

L.B. Bahroo, B.S. Kightlinger, R.P. Gandhy, F.L. Pagan (Washington, District of Columbia)

Objective: Rasagiline is a selective, irreversible MAO-B inhibitor that is used either in monotherapy or in combination therapy for Parkinson's disease. This study demonstrated improved cognition in patients on rasagiline.

Background: In animal models, rasagiline demonstrated neuroprotective effects. The N-Propargylamine structure up regulates anti-apoptotic genes and suppresses pro-apoptotic genes. Additionally, it increases the expression of free radical oxidizers such as superoxide dismutase. High concentrations of MAO-B enzyme have been located within the basal ganglia and the hippocampus.

Methods: Patients with idiopathic Parkinson's disease and mild cognitive impairment on Montreal Cognitive Assessment (MoCA) were entered into the study. A baseline MoCA was performed prior to starting rasagiline and at a follow up visit. UPDRS was performed at baseline and at the follow up visit.

Results: The mean age of patients was 70.55 years. The mean initial MoCA score was 25 $\pm$ 3.0. The mean follow up MoCA score was 27.14 $\pm$ 1.35. Motor improvement was noted, the mean initial and follow up UPDRS III score were 22.57 $\pm$ 7.37 and 20.57 $\pm$ 5.09 respectively. The mean follow up interval was 3.14 $\pm$ 1.07 months. The most commonly impaired domains were recall, executive function/visuospatial and fluency. Executive function/visuospatial, fluency followed by recall improved significantly.

Conclusions: The data demonstrated improvement of MoCA scores in cognitively impaired patients. Furthermore, cognitive improvement was noted in the most commonly impaired domains. The MoCA better evaluates cognitive function in PD because it contains frontal function tests absent in the MMSE. The sustainability of cognitive improvement needs to be measured with greater follow up times. Additionally, a larger placebo controlled study needs to be undertaken to fully evaluate the cognitive benefits of rasagiline.

Mo-212

DBS of the STN improves learning of weak cue-outcome associations on the weather prediction task in Parkinson's disease

M. Beigi, L. Wilkinson, D. Lagnado, M. Jahanshahi (London, United Kingdom)

Objective: To investigate the effect of deep brain stimulation (DBS) of the subthalamic nucleus (STN) on non-motor implicit learning on the weather prediction task (WPT).

Background: The basal ganglia are considered to mediate implicit learning. Comparison of learning with DBS on vs off provides a direct methodology for investigating the contribution of basal ganglia output to implicit learning. A previous study has suggested that DBS of the STN improved implicit probabilistic classification learning on the WPT, but impaired performance on explicit measures of task performance (Halbig et al, 2004).

Methods: We used modified versions of the WPT with more (200) trials and introduced four stages of testing explicit knowledge (self-insight and task knowledge), after every block of 50 trials. A group of 11 PD patients with DBS of the STN completed two parallel versions of the WPT with DBS on or off; as did 13 age and IQ matched controls.

Results: DBS of the STN had no effect on overall WPT learning. However, compared to DBS off, turning the stimulators on selectively improved learning of weak (implicit) cue-outcome associations. DBS did not alter learning of strong cue-outcome associations on the WPT, task knowledge, or self- insight.

Conclusions: Our results suggest that modulating the output from the basal ganglia with DBS of the STN on vs off affects implicit learning of weak cue-outcome associations on the WPT.

Mo-213

Automated 3D mapping of hippocampal and caudate atrophy and ventricular enlargement in Parkinson's disease with and without dementia

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Objective: To investigate the associations between hippocampal and caudate atrophy and ventricular enlargement and cognitive impairment in patients with Parkinson's disease.

Background: Cognitive decline is exceedingly common among patients with Parkinson's disease (PD), the most common neurodegenerative movement disorder. Parkinson's disease (PD) has been associated with mild cognitive impairment (PDMCI) and with dementia (PDD).

Methods: We applied the radial distance mapping technique to the manual hippocampal and the automated caudate and lateral ventricle segmentations obtained from 3D T1-weighted MRI scans of 20 cog-

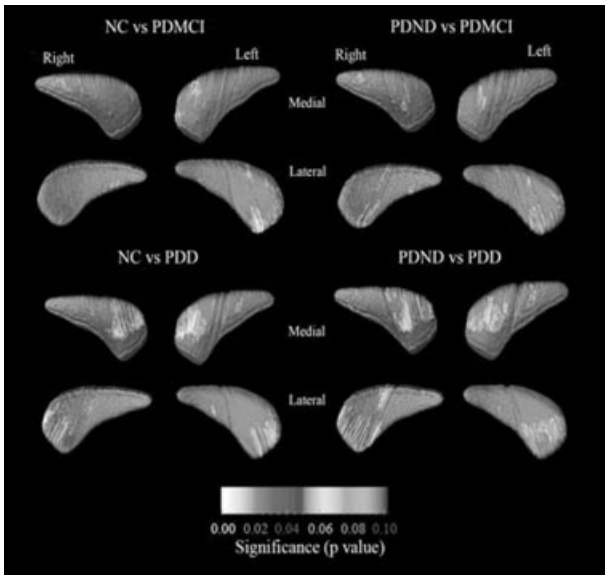

FIG. 1 (Mo-213).

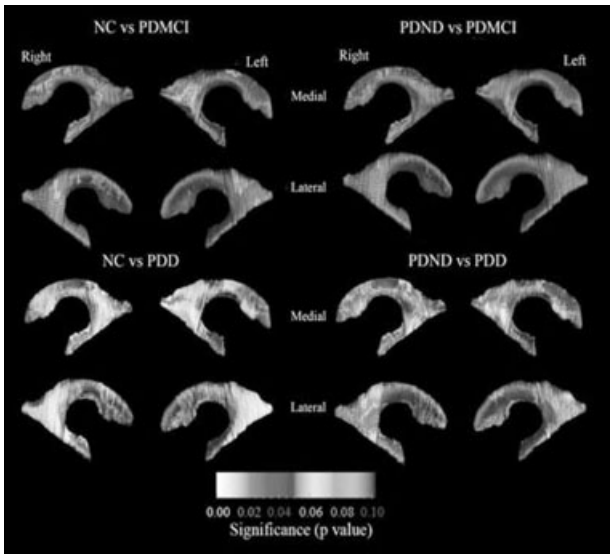

FIG. 2 (Mo-213).

nitively normal elderly (NC), 12 cognitively normal PD (PDND), 8 PDMCI and 15 PDD subjects to examine the 3D structural and volumetric differences between the groups in these regions. We investigated the associations between hippocampal and caudate atrophy and ventricular enlargement and the Unified Parkinson's Disease Rating Scale (UPDRS) and the Mini-Mental State Examination (MMSE).

Results: We did not find hippocampal differences between the groups. 3D caudate statistical maps demonstrated significant left medial and lateral and right medial atrophy in the PDD vs. the NC group, and right medial and lateral caudate atrophy in the PDD vs. the PD group. The PDMCI group showed trend significant left lateral caudate atrophy vs. NC. Both the left and the right ventricles were significantly larger in the PDD relative to the NC and the PD groups. Differences were most pronounced in the posterior portions of the lateral ventricles (body/occipital horn). Statistically significant areas showed 20-30% and 5-20% between-group differences for the caudates and the ventricles respectively. PD severity correlated with ventricular enlargement. Cognitive decline showed significant correlations with expansion of the body, temporal and occipital horns of the lateral ventricles and trend significant correlation with atrophy of the caudate head.

Conclusions: Cognitive decline in PD is associated with anterior caudate atrophy and ventricular enlargement.

Mo-214

Spatial remapping of cortico-striatal connectivity in Parkinson's disease – A resting state fMRI study

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Objective: We test the hypothesis that Parkinson's disease (PD) patients show altered cortico-striatal connectivity, and that this alteration follows the specific spatial pattern of dopamine depletion occurring in this disease.

Background: PD is characterized by focal dopamine depletion in the striatum: while the posterior putamen is heavily affected, the anterior putamen and caudate nucleus are relatively spared. Given that the striatum is one of the most densely connected regions in the brain, these local striatal alterations are likely to change long-range recursive processing (functional connectivity) in cortico-striatal networks. Here we explore this feature of PD, using resting state fMRI to focus on alterations in intrinsic coupling between distant nodes of the cortico-striatal circuit.

Methods: Using a seed-region approach, we compared the connectivity profile of the posterior putamen, the anterior putamen, the caudate nucleus and the posterior cingulate cortex (PCC) between 41 PD patients and 36 matched controls. EMG recordings during scanning enabled us to measure variations in the tremor amplitude and remove this variance from the data.

Results: We found distinct connectivity profiles for each region that were largely shared across groups, such that the posterior putamen was coupled to the motor network, the anterior putamen to a cognitive control network, the caudate nucleus to a prefrontal network and the PCC to the default mode network (Fig 1). Differences between groups were specific to the putamen: while PD patients showed decreased coupling between the posterior putamen and the sensorimotor cortex, we observed enhanced coupling between the anterior putamen and some of these same regions, mainly the parietal operculum (Fig 2).

Conclusions: We conclude that dopamine depletion in PD leads to a remapping of cortico-striatal connectivity: while the posterior putamen becomes isolated from portions of the sensorimotor cortex, the anterior putamen enhances its functional connections to these same cortical regions. This remapping reduces the spatial segregation between two different cortico-striatal loops. We speculate that the alterations in cortico-striatal connectivity we observed may explain PD impairments in dual task performance and sensorimotor integration.

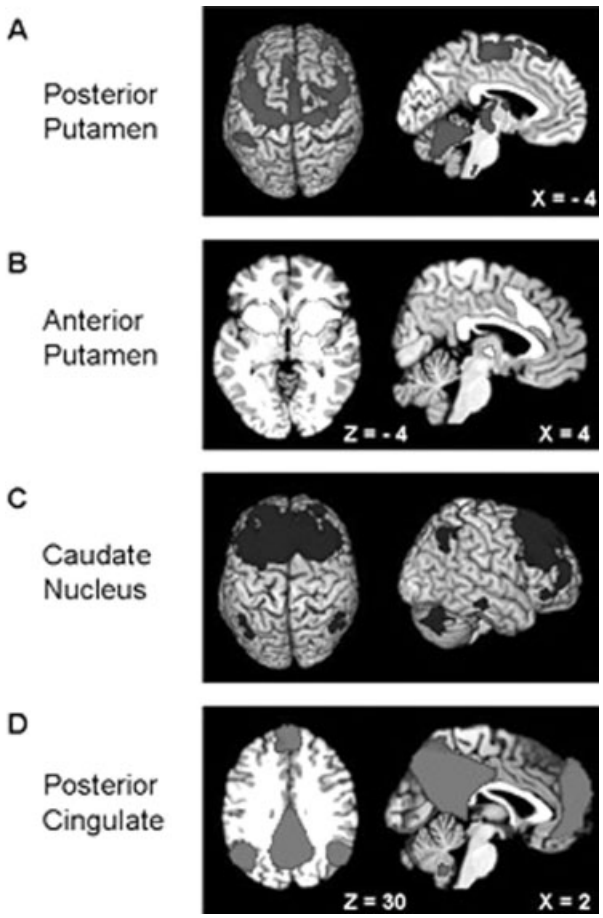

FIG. 1 (Mo-214). Shared spatial patterns of cortico-striatal connectivity across groups. A conjunction analysis of functional connectivity for both patients and controls is shown, separately for each of the four seed regions. T-maps are thresholded at $p<0.01$ FDR-corrected.

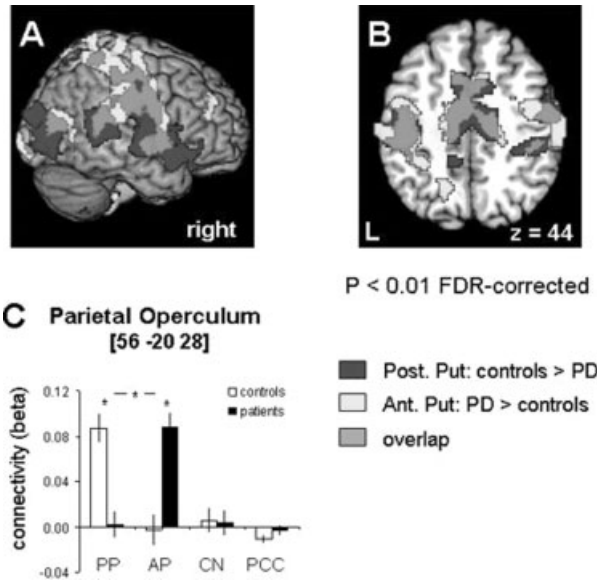

FIG. 2 (Mo-214). Differential spatial patterns of cortico-striatal connectivity across groups. Differential cortico-striatal connectivity is shown. In red, areas that are more strongly coupled to the posterior putamen in controls than in PD patients. In yellow, areas that are more strongly coupled to the anterior putamen in PD patients than in controls. In orange, overlap between the previous two contrasts. T-maps are thresholded at $p < 0.01$ FDR-corrected. PP: posterior putamen; AP: anterior putamen; CN: caudate nucleus; PCC: posterior cingulate cortex.

Mo-215

Brief cognitive assessment in the early stages of Parkinson's disease

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Objective: To assess cognitive function in early stage Parkinson's disease (PD), by using bed-side cognitive tests.

Background: Rapid screening of cognitive dysfunction in early stage PD could help to delineate sub-groups of patients more susceptible to develop dementia and thus amenable to specific therapies.

Methods: 51 early stage PD patients were compared with 46 control subjects on the performance of the Mini Mental Sate Examination (MMSE) and the Frontal Assessment Battery (FAB). Motor function was assessed with the Unified Parkinson Disease Rating Scale part III. Subjects were classified according to cognitive subtype, into frontal (FAB < 12), cortical (pentagon copy <1 and /or word recall test <3) or frontal/cortical groups (both). We tested differences in FAB and MMSE total and partial scores (t-student test) and in the proportion of subjects in each cognitive group (Chi-Square or Fisher tests) and also the relation between cognitive and motor related variables (Pearson). $p < 0.05$ was considered significant, after Bonferronni correction.

Results: PD patients scored significantly lower on FAB total ($p<0.005$) and partial scores ($p<0.05$) (except for environmental autonomy and mental flexibility), and MMSE total ($p<0.05$), visuo-constructive ($p<0.05$) and memory scores ($p<0.005$). There were significantly more patients with frontal dysfunction (20 vs 4, $p<0.005$) and more patients in the frontal/cortical dysfunction (18 vs 3, $p<0.01$) and cortical deficts group (11 vs 0, $p<0.01$). On PD patients group, FAB scores were significantly correlated with MMSE ($r=0.286$, $p=0.042$), memory ($r=0.400$, $p=0.004$) and visuo-constructive ($r=0.425$, $p=0.002$) scores. Visuo-constructive scores correlated significantly with bradykinesia ($r=-0.476$, $p=0.0004$). MMSE was negatively related to dopaminergic treatment ($r=-0.418$, $p=0.003$).

Conclusions: Brief cognitive assessment revealed the presence of frontal, memory and visuconstructive deficits in early stage PD, replicating the findings of other more extensive studies and thus corroborating its usefulness in the early stages of disease. While suggesting that isolated cortical type deficits can be an early finding, it also illustrates the influence of executive and motor dysfunction and dopaminergic treatment on the performance of visuo-constructive and memory tasks, revealing the composite nature of non frontal deficits.

Mo-216

Parkinson's disease and intentionality: Deficits in representation of intention

P. Butler, P. McNamara, R. Durso (Boston, Massachusetts)

Objective: The aim of this study was to explore the impact of PD on intentional memory.

Background: Intentionality is a complex mental phenomenon denoting one's relative commitment to performing an activity. Successful execution of intended goals involves memory of intent to enact and accurate memory of the content of the task to be performed. Evidence suggests representations of intended activities differ in their dynamic properties from other memory contents. Representations of intended compared to nonintended activity persist in a state of increased subthreshold activation. Parkinson's disease (PD) is a neurodegenerative condition marked by deficits in motor, social, and executive function.

Methods: We adapted a task from Goschke et al. 1993. 16 mid-stage PD patients and 24 controls memorized two scripts. Next subjects were randomly assigned to execute (intend) or observe (not intend) one studied script. Before executing or observing the script, subjects completed a memory recognition task that measured response times. We assumed the time required to recall any given probe would be an inverse function of the level of activation to any given memory. Persisting activation of intended activities should theoretically have shorter latencies to retrieval than nonintended activities.

Results: Control subjects displayed faster recognition latencies for intended activities ($\mu=1196.1$ ms, $\sigma=478.6$ ms) versus nonintended activities ($\mu=1307.0$ ms, $\sigma=462.7$ ms), thus confirming the hypothesis that intentional states carry distinct representational properties. PD subjects demonstrated an opposite profile: delayed response time for intended ($\mu=1523.6$ ms, $\sigma=671.2$ ms) versus nonintended activities ($\mu=1293.2$ ms, $\sigma=492.3$ ms). A two-tailed t-test revealed a significant difference between the mean latencies of intended activities in PD subjects versus controls ($t=4.2441$, $p<0.0001$). There was no significant difference between mean responses for nonintended tasks comparing PD participants and controls. This suggests that response time differences were not due to motor slowing in PD participants.

Conclusions: Intended activities are not activated preferentially over nonintended tasks in patients with PD. These delayed activation patterns help to explain passivity and apathy evident in PD patients. Intentional mental states appear to be mediated in part by prefrontal dopaminergic systems.

Mo-217

Parkinson's disease and religiosity: Deficits in the automatic activation of religious concepts

P. Butler, P. McNamara, R. Durso (Boston, Massachusetts)

Objective: The aim of this study was to explore the impact of PD on aspects of religiosity.

Background: Religiosity has to do with sacred beliefs and behaviors. Consciously held beliefs predict intentional and controlled behavior, while subconscious beliefs predict more subtle and sponta-

neous behavior. Individual differences in religiosity are under complex cognitive control. Parkinson's disease (PD) is a neurodegenerative condition marked by deficits in motor, social, and executive function. Previous research suggests PD affects religiosity.

Methods: We adapted an evaluative priming procedure from Wenger et al. 2004 to test 16 mid-stage PD patients and 16 controls. After viewing a prime category term (religious, civic, or neutral), subjects identified whether a given two-word action phrase was possible to perform. Actions were religious, civic, or nonsensical. All possible prime categories and actions were presented randomly resulting in 96 trials. All subjects were administered the Stroop Test.

Results: Control subjects displayed recognition latencies that did not differ statistically across prime category. The mean control response time to nonsensical activities was 859.6 ms (σ=275.0). The mean control response time to civic activities was 781.5 ms (σ=239.7). The mean control response time to religious activities was 789.5 ms (σ=250.6). Subjects with left onset or bilateral PD displayed significant delays in response time to religious activities. Unpaired t-test demonstrated significance in mean response time to religious versus civic activities with a religious prime (t=2.9836, $p<0.0031$). The mean PD response time to nonsensical activities was 1162.8 ms (σ=275.0). The mean PD response time to civic activities was 1141.6 ms (σ= 239.7). The mean PD response time to religious activities was 1263.6 ms (σ=250.6). Right onset PD subjects displayed no significant difference across prime categories. Pearson analysis revealed PD Stroop scores correlated inversely with mean response times to religious activities (r=-0.79877, $p<.001$).

Conclusions: Left onset or bilateral PD subjects exhibited abnormal activation of religious concepts with longest latencies in the religious prime condition. This suggests PD pathology induces a breakdown in cognitive structures supporting religiosity. Religiosity appears to be mediated in part by right prefrontal dopaminergic systems.

Mo-218

Neuropsychological functioning in Parkinson's mild cognitive impairment

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Objective: To examine: (1) utility of psychometric measures in evaluation of cognitive changes associated with early Parkinson's disease (PD) (i.e., without dementia); (2) prevalence of mild cognitive impairment (MCI) subtypes at 2 time points.

Background: Cognitive impairment is common in PD. Simple psychometric measures would facilitate assessment of MCI. The stability of psychometrically defined MCI is not well defined.

Methods: Performances of a group of 51 non-demented older PD patients on standardized psychometric measures were compared to those of a healthy age- and education-matched control group (n = 50), at baseline and 18-months post-baseline assessment using standardized neuropsychological measures.

Results: The Digit Ordering Test (DOT), yet not the traditionally administered Digit Span task, was sensitive to cognitive changes in early PD. Relative to controls, PD patients also performed significantly worse on measures of visual-perceptual judgment and processing speed. Fifty-seven percent of patients met criteria for MCI at baseline. Approximately 70 % of patients and 64 % of controls remained stable in their MCI subtype diagnosis. 20% of patients declined at the 18 month follow-up. Among both PD and controls, the most common subtype of MCI at baseline was SDNA (single domain non-amnestic). This shifted to MDA (multiple domain amnestic) for PD at the 18 month follow up.

Conclusions: DOT was more sensitive to cognitive changes in PD than traditionally administered executive functioning measures. As the DOT is not confounded by visual-perceptual and processing speed reductions, this measure would appear to have utility for evaluation of cognitive deficits associated with early PD. MCI was common at baseline in our sample, and for the majority of our sample, the subtype diagnosis remained stable across an 18-month period.

Mo-219

Mild cognitive impairment and questionable dementia in older Parkinson's disease patients without dementia

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Objective: 1. To determine the prevalence of a mild cognitive impairment based on neuropsychological test performance in older Parkinson's disease (PD) patients. 2. To determine the overlap between MCI and questionable dementia, based on clinical dementia rating scale (CDR) defined cognitive impairment.

Background: Parkinson's disease is commonly associated with cognitive impairment, which progresses to dementia in over eighty percent of PD patients. Features of mild cognitive impairment (MCI) and comparison with other definitions of cognitive impairment short of dementia are under evaluation in PD.

Methods: Performance of a group of 51 non-demented PD patients 65 years of age and older on standardized psychometric measures was compared to that of a healthy age- and education-matched control group (n = 50). Patients were independently assessed via a subject and caregiver interview and patient-centered and informant-centered CDR scores were determined.

Results: Fifty-seven percent of PD patients had MCI at baseline. Single domain, non-amnestic MCI (38%) was most common in our cohort, followed by multi-domain, amnestic MCI (31%), single-domain amnestic (21%) and multi-domain non-amnestic (10%). Among patients, 11/29 (38%) with MCI, had CDR greater than 0 using any CDR rating greater than 0 (based on any score on CDR rating from the caregiver interview or subject assessment) as a cutoff.

Conclusions: Cognitive impairment was common in this older PD cohort. Different methods of defining cognitive impairment overlapped incompletely. The neuropsychological approach was more sensitive than that based on the CDR; however, which approach offers the best prediction dementia will require prospective follow up.

Mo-220

Parkinson's disease dementia mechanisms of cortical neuron dysfunction

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Objective: To test the hypothesis that the small amplitude cortical myoclonus (SACM) in Parkinson's disease (PD) results from abnormal metabolism of α-synuclein in motor cortex neurons.

Background: The common occurrence of dementia in PD and the associated increase in mortality highlights it as a major health problem. A critical prerequisite for developing highly effective treatments of PD-dementia is to determine how PD neurodegeneration causes physiologic dysfunction of cortical areas. The presence of SACM is a well-delineated model for neuronal physiologic dysfunction in the primary motor cortex of PD patients.

Methods: As part of the Sun Health Research Institute brain and body donation program, we do extensive pre-mortem general medical, neuropsychological, behavioral, movement, and electrophysiological assessments. Brain donation occurs in a short post-mortem interval and routine pathological assessment and diagnosis are performed. For this study, motor cortical tissue from autopsied confirmed PD subjects were used to examine for various pools and forms of α-synuclein by ELISA, western blot, and histochemical methods.

Results: Twenty-three cases with clinical and neuropathological PD diagnosis had electrophysiological assessment. Out of the 23 cases, 12 had SACM (PD-SACM group) and 11 no SACM (PD group). Age, UPDRS, and Hoehn and Yahr scores were not significantly different between groups. Dementia was more prevalent in the PD-SACM group. Motor cortex total α-synuclein levels in PD-

SACM were significantly higher than in the PD group by 38% (P=0.028;t-test). Western blot analysis showed that insoluble α-synuclein was prominent in both groups. However, using phophorylated μ-synuclein specific antibody, we detected a higher amount of phosphorylated μ-synuclein in the PD-SACM group than the PD group. Interestingly, the immunoreactive bands corresponding to oligomeric phosphorylated α-synuclein were also more prevalent in the PD-SACM group.

Conclusions: This report confirms the presence of SACM in a subset of pathologically confirmed PD. PD-SACM correlates with abnormally elevated accumulation of α-synuclein in motor cortex. Further study of PD-SACM will provide insight into the neocortical dysfunction in PD and its relationship with PD-dementia.

Mo-221

Activity of daily living to define the dementia in the patient with Parkinson's disease

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Objective: To define the dementia in the patients with Parkinson's disease (PD) by cognitive dysfunction in the activity of daily living (ADL).

Background: Patients with PD already have significant impairment in ADL by their motor symptoms and how can we define ADL impairment by cognition? In spite of some suggestion there has not been comprehensive approach about ADL impairment by cognition to find PD dementia (PDD).

Methods: Thirty-two PD patients participated and were divided into cognitive dysfunction group (PDD, 15 patients, 8 men, age 72.6±6.2) and cognitively intact group (PD, 17 patients, 10 men, age 71.0±7.4) by Korean mini-mental examination score (PDD < below 2 standard deviation from the standard of age-, and education-matched normal controls, PD > above standard of normal controls). Age-, sex-, and education-matched 10 control subjects (5 men, age 68.3±4.2) and 16 patients with Alzheimer's disease (AD, 8 men, age 73.9±8.6) were also recruited. Control subjects and caregivers of the patients were interviewed about ADL comprehensively using modified Barthel index (BI) and Seoul instrumental ADL questionnaire (SIADL).

Results: Total score of BI was significantly decreased in PDD group compared to that of control group but there was no difference between other groups. In instrumental ADL, total scores were significantly differed only between each disease group and control, not between disease groups. When the subjects were asked again about the impairment of each SIADL item was caused by cognitive dysfunction, significant differences could be found between PDD and PD groups, and between PD and AD groups, not between PDD and AD groups. In each item of SIADL, performance of PDD in the item of managing personal belongings, keeping appointments and talking recent events were impaired than those of PD. Items of using telephones, taking medications, managing personal belongings and talking recent events were differed due to cognitive dysfunction between PDD and PD groups, and these differences were reproduced between AD and control groups.

Conclusions: PDD patients showed poor performance in some domains of instrumental ADL compared to those of PD patients due to cognitive dysfunction, such as managing personal belongings and talking recent events. Questions about these activities could be used to diagnose dementia in PD patients.

Mo-222

Tau and phospho-tau cerebrospinal levels correlate with temporal and frontal gray matter reduction in Parkinson's disease and Parkinson' disease with dementia

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Objective: To study the relationship of proposed cerebrospinal fluid (CSF) markers of neuronal loss (tau) and Alzheimer's disease (AD)-type pathology (phospho-tau and beta-amyloid) with gray matter (GM) volume in patients with Parkinson's disease (PD) with no dementia (PDND) and with dementia (PDD).

Background: Clinico-pathological studies support a role for AD pathology in PDD and abnormal levels of CSF tau and beta-amyloid have been found in part of PDD patients. Voxel-based morphometry (VBM) studies in PD have shown GM reductions in medial temporal areas.

Methods: Thirty three PD patients (15 PDD and 18 PDND), and 15 controls underwent lumbar puncture and 3T brain MRI. Standard ELISA techniques and voxel-based morphometry (VBM) were used for CSF and structural studies, respectively. Comparative and regression analysis were carried out for the CSF markers. Correlation analysis between VBM and CSF measures was performed in all PD patients and in PDND and PDD separately with the SPM (Statistical Parametric Mapping) 5 software.

Results: CSF tau and phospho-tau levels were higher in PDD than PDND (p=0.008 and 0.037), without differences between PDND and controls. CSF beta-amyloid ranged from higher levels in controls to lower levels in PDD, with intermediate values in PDND (linear regression, p<0.00001). CSF tau in all PD patients and phospho-tau in the PDD subjects negatively correlated with GM volume in medial temporal and frontal lobe structures (p<0.05; corrected by false discovery rate -FDR- at voxel level). No correlations were found between CSF beta-amyloid levels and GM volume.

Conclusions: The correlation of CSF tau and phospho-tau levels with GM volume in areas previously implicated in PD-related cognitive decline and dementia suggests a relation between neuronal loss in PD and phosphorilated tau aggregates in PDD with atrophy of these cortical regions. Lack of GM volume correlations with CSF beta-amyloid levels and incipient alterations of this CSF marker in PDND subjects suggest that CSF beta-amyloid changes may precede GM volume reduction in PD. Acknowledgement: This work has been funded through "Fundacio La Marato TV3".

Mo-223

A prospective series of neuropsychological outcomes after deep brain stimulation for the treatment of Parkinson's disease

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Objective: To evaluate neuropsychological profiles of 18 PD patients following DBS from a cohort of 46 PD patients referred specifically for consideration of DBS.

Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus internus (GPi) significantly reduce motor symptoms of PD but there remains some question as to operative suitability in the light of pre-existing mild cognitive deficits and whether there are any clinically significant cognitive side-effects in well selected patients. Evidence suggests mild decrements following DBS particularly in executive functions, most consistently in verbal fluency.

Methods: A consecutive series of 18 PD patients underwent comprehensive baseline neuropsychological assessment before DBS and at a mean of 11 months following DBS. Five main cognitive domains were assessed. Pre and post-DBS neuropsychological profiles were compared.

Results: As in our original cohort of 46 PD patients (abstract 290, Mov Dis 2008;23:Suppl 1), this group of 18 PD patients had mild pre-operative intellectual decline relative to their premorbid IQ with co-existing significant impairment on the list-learning verbal recall memory task and on the Brixton and Cognitive Estimates frontal executive tasks. No impairment was found on the verbal-fluency tasks in a subgroup of these PD patients (n=9). Comparisons between pre-DBS and post-DBS evaluations revealed no significant changes in performance on any of the neuropsychological measures following DBS.

Conclusions: Our PD patients had impairments on IQ, list-learning and selected executive tasks (Brixton and Cognitive Estimates) on baseline assessment prior to DBS. Our findings failed to demonstrate decline on any neuropsychological measures including verbal fluency in carefully selected patients at a mean of 11 months following DBS. This may reflect our small numbers. Alternatively, selection programmes for DBS suitability which are based on multidisciplinary input may be effective in advising patients to proceed to DBS. Which components (and their "cut-off" values) of neuropsychometric testing lead to a diagnosis of "dementia" or "mild cognitive impairment" in PD remains to be addressed.

Mo-225

Cognitive impairment in subjects with Parkinson's disease is associated with hippocampal atrophy and ventricular enlargement

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Objective: To determine the association between neuropsychological performance and regional brain volumes in subjects with PD, AD and healthy controls.

Background: There is a growing recognition of the importance of AD pathology and atrophy of the hippocampus in a subset of patients with PD. The University of Pennsylvania Center of Excellence for Research on Neurodegenerative Diseases is conducting a study to develop methods to detect the pathological changes of neurodegenerative dementia in elderly individuals.

Methods: 52 PD patients with and without dementia, 33 AD patients and 42 healthy controls underwent neuropsychological examination with the Mattis Dementia Rating Scale (DRS-2) and structural MRI. Partial correlations were conducted for DRS-2 scores and regional brain volumes and corrected for multiple comparisons by accepting p values of $\leq$.01 as significant. Linear regression models were used to explore differences in regional brain volumes between PD and control groups.

Results: In patients with PD, DRS-2 total scores correlated with hippocampal volume ($p = .003$) and inversely with lateral ventricle size ($p < .001$). In AD and controls, there were no significant correlations. Removing the effect of gender, statistically significant differences emerged between PD and healthy controls in the hippocampus ($p = .01$), parietal white ($p < .001$) and gray ($p = .004$) matter, temporal white ($p = .001$) and gray ($p = .002$) matter, frontal white ($p = .001$) and gray ($p = .010$) matter, and anterior ($p = .005$) and posterior cingulate cortex ($p = .009$) but not in the lateral ventricle, medial temporal lobe or insular cortex. No significant differences existed between groups in left and right hemispheric asymmetry of cortical regions or ventricular size.

Conclusions: Two common features of AD, hippocampal atrophy and ventricular enlargement, are strongly correlated with cognitive performance in this cohort of demented and non-demented PD patients. In addition, PD patients exhibited atrophy in the hippocampus and most cortical regions compared to age matched controls after controlling for gender. Further analysis of additional biomarkers in this cohort will determine if an AD profile may be identified in a subset of patients with PD.

Tu-204

Stimulation of the subthalamic nucleus in Parkinson's disease: A 5 year follow-up of cognition

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Objective: This study evaluated the five year follow-up of cognition in PD patients treated with stimulation of the STN including adjustment for individual differences.

Background: Deep brain stimulation (DBS) is an accepted treatment for advanced Parkinson's disease (PD) refractory to medical therapy. The effects of subthalamic nucleus (STN) stimulation on cognition are however inconsistent and there are only few studies with a long term follow-up. The most consistently reported cognitive changes are reductions in verbal fluency up to three years after surgery. Less common are reports of a decline in memory and attention.

Methods: Eighteen PD patients were assessed before, one year and five years after surgery. The primary outcome measures included standardized tests for memory, executive functioning and attention. Non-parametric testing was applied for comparison between the preoperative assessment and scores at one year after surgery and between both postoperative assessments. The level of significance was 3% after Bonferroni correction. For the significant differences found, reliable change indices (RCI) were calculated which determine if an individual's performance on a measure has changed sufficiently taking into account the measure's reliability and chance error.

Results: The mean age (sd) of the sample at surgery was 55.8 (6.5) years. Compared with preoperative assessment no differences were found at one year after surgery. Comparison of both postoperative assessments showed a decline at five years after surgery on measures of category fluency, selective attention and verbal memory (learning and delayed recall). RCI indicated that 28% of the patients demonstrated clinically significant declines in verbal learning, category fluency and selective attention and 11% in the delayed verbal recall.

Conclusions: From a cognitive point of view, STN DBS seems relatively safe up to one year after surgery. The observed decline at five years after surgery might be due to the progression of the disease and needs further consideration.

Tu-205

Apathy: A predictive factor of dementia in Parkinson's disease

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Objective: The aim of the present study was to examine, through a follow-up study, whether the occurrence of cognitive decline and/or dementia was higher in non depressed non demented PD patients with than without apathy.

Background: Apathy is usually defined as reduced interest and participation in various activities. It may occur as a syndrome in it self or as part of another disorder, notably depression and dementia. It is frequent in Parkinson's disease (PD) where several studies report an association of apathy with more severe cognitive symptoms. However, this association was poorly investigated.

Methods: 40 consecutive patients with PD participated in the study (20 with and 20 without apathy). They were neither demented nor depressed at entry in the study. Their cognitive functions were extensively assessed twice: at entry in the study and after an 18-months follow-up.

Results: At entry in the study, the PD patients with apathy had significantly lower global cognitive status and executive functions. After 18 months follow-up, the rate of conversion to dementia was significantly higher in the group with than without apathy (8/20 vs. 1/20). Even in non demented patients, the decrease in cognitive functions was significantly higher in the group with than without apathy.

Conclusions: The results of this study show that apathy greatly increases the risk to develop dementia in PD.

Tu-206

Neuropsychological deficits associated with the vias mesolímbico-mesocortical and prefrontal-caudate in patients with Parkinson's disease

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Objective: Evidence neuropsychological deficits related with orbitalmedial and prefrontal areas in patients with Parkinson's disease.

Background: Parkinson's disease (PD) is caused by a loss of dopaminergic neurons. The main dopaminergic vias affected in Parkinson's disease are three: 1. Via Putamen-Supplementary Motor Area: linked to the motor symptoms, 2. Via Prefrontal-caudate: from the dorsolateral prefrontal cortex to the caudate nucleus, it has great importance in executive function and working memory, 3. Via Mesolímbico-Mesocortical: from the dopaminergic pathway of Ventral Tegmental Area to limbic areas and dorsolateral prefrontal cortex, important in the non-motor abnormalities such as depression, cognitive and attentional disorders, deficit in processes internally driven and deficit to switch their motor program without foreign keys, poor performance on inhibition and prediction of risk.

Methods: We included 15 patients with PD, with ages from 55 to 75 (mean 61), without depression according to Hamilton scale, no dementia according to Minimental test and UPDRS, stage 2 and 3 of the scale Hoenh and Yarh, under stable treatment with levodopa-carbidopa, neuropsychological evaluation throught the Battery of Executive Function (related with orbitomedial, dorsolateral and prefrontal areas).

Results: Significant difference was found between PD patients and control subjects on inhibitory control tasks, p = 0.009, mean 2.733, SD 1.994; risk detection p = 0.0005, average 40.87, SD 6.093 following rules and p = 0.0463, average 2.07, SD 3.41, Verbal Fluency p = 0.002, mean 4.2; Generating Concepts and Classification p = 0.0485.

Conclusions: The most important significant differences found were in the difficulty to inhibit irrelevant responses (inhibitory control) detection of risk, often characterized by poor self-reflection without proper risk assessment, related to the Via Mesolímbico-mesocortical. The significant differences found in verbal fluency, generation of concepts and classification are related to Via Prefrontal-Caudate. Although we found neuropsychological difficulties on these two vias the most significant are related medial orbitofrontal regions. In contrast, we find no significant differences in the tasks of working memory.

Tu-207

Changes in tau trancription occuring as a function of tau genotype in Parkinson's disease (PD) cortex: A pathogenic substrate for the dementia of PD?

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Objective: To determine if transcription from the tau gene (MAPT) is influenced by common allelic variants at the tau locus in post-mortem PD cortical tissue.

Background: Tau is a microtubule-associated protein which has been implicated in a number of neurodegenerative disorders. Two major haplotypes have been defined spanning the MAPT genomic locus, H1 and H2. In a long-term incident study of PD we have previously shown a significant increase in dementia risk in H1/H1 homozygotes (1). Alternate splicing of transcripts from the tau gene generates transcripts, and ultimately proteins, with either 3 or 4 microtubule binding repeats and it has been suggested that aberrations in this splicing process are important in the pathogenesis of neurodegeneration. (1) Goris A, Williams-Gray CH, Clark GR et al. Tau and alpha-synuclein in susceptibility to, and dementia in, Parkinson's disease. Ann Neurol. 2007 Aug;62(2):145-53

Methods: 61 post-mortem frontal cortex samples (BA 46) from a UK PD brain bank and 15 region and age-matched controls were analysed. DNA and RNA were extracted from cortical tissue samples and cDNA synthesized from RNA. Tau genotype was determined. H1/H2 heterozygotes were identified and allele-specific real-time PCR (RT-PCR) used to assay the relative quantities of 3 repeat (3R) and 4 repeat (4R) containing transcripts originating from both H1 and H2 alleles.

Results: 19 H1/H2 heterozygotes were identified (12 cases, 7 controls). RT-PCR demonstrated a statistically significant increase in the relative quantity of 4R tau transcript originating from H1 versus H2 allele in pathologically confirmed Lewy body disorders ($p=0.02$), with a mean increase of 20%. There was no difference in total tau transcription. This effect was not seen in controls.

Conclusions: In a small sample set we have shown a significant increase in transcription of potentially pathogenic 4R tau originating from the H1 allele in PD cortex, indicating a haplotype-specific effect upon transcript splicing. These changes may in turn contribute to the pathogenesis of dementia in PD, as interactions between tau and alpha-synuclein are increasingly recognised. This work is complimented by our ongoing studies of cortical tau protein levels in PD.

Tu-208

Useful field of view as a reliable screening measure of driving performance in people with Parkinson's disease: Results of a pilot study

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Objective: To determine in people with Parkinson's disease PD (1) correlations of the Useful Field of View (UFOV) with driving performance; (2) how well the UFOV predicts driving performance compared to other clinical tests of vision and cognition; (3) to establish the sensitivity and specificity of the UFOV in predicting failing/passing an on-road test.

Background: PD patients have visuo-perceptual dysfunction and attention deficits during execution of a complex task. The UFOV® is a computer-based test which measures visual search, visual processing and visual attention skills, which are used during driving.

Methods: This approved Institutional Review Board case-control study had 19 randomly selected patients with idiopathic PD, age-matched to 104 controls without PD, who were all referred for a driving evaluation.

Results: Mean age of PD patients = 74.8 (6.1) with 14 (73.7%) men, 18 (94.7%) Caucasians, and 15 (79%) having a degree. The PD duration was 4.86 years (5.47); mean Unified Parkinson's Disease Rating Scale (UPDRS) motor score in the *on* state was 25.6 (6.8) and in the *off* state was 33.8 (9.7). The controls had a mean age of 75.4 (6.4) with 59 (56.7%) men, 96 (92.3%) Caucasians, and 86 (84%) having a degree. From the 19 PD patients 11 passed and 8 (42.1%) failed the road-course vs. 82 controls who passed and 22 (21.2%) who failed the road-course (chi square 8.97, 3 df, $p<.05$). Compared to neuropsychological and clinical tests of vision and cognition, the UFOV showed the strongest correlations ($r \geq .75$, $p<0.05$) with measures of failing a standardized road test and number of driving errors committed. The UFOV Risk Index score of 3 (range 1-5) was established as the cutoff value for passing the on-road test, yielding the most optimal combination of sensitivity (87%) and specificity (82%) with area under the ROC curve, an index of discriminability, of 92%.

Conclusions: The UFOV may be a superior screening measure (compared to measures of disease, cognition and vision) for predicting on-road driving performance in PD patients. Limitations are the small sample and not documenting how many refused study participation. Yet, the small cohort had a wide range of disease severity and duration. But, we need to test the UFOV as an indicator of passing/failing an on-road test in a larger sample.

Tu-209

The Montreal Cognitive Assessment (MoCA): A screening tool for mild cognitive impairment (MCI) in idiopathic rapid eye movement sleep behavior disorder (RBD)

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Objective: To evaluate the sensitivity and specificity of the Mini-Mental State Examination (MMSE) and the Montreal Cognitive

Assessment (MoCA) in detecting mild cognitive impairment (MCI) in idiopathic rapid eye movement sleep behavior disorder (RBD).

Background: MCI is a frequent feature in patients with idiopathic RBD, a sleep disturbance recognized as a preclinical stage of PD and DLB. Although a neuropsychological evaluation using standardized tests is the gold standard for identifying MCI, it is time-consuming, often unavailable, and requires specialized training to administer and interpret. The MoCA and MMSE are two brief, 30-point screening tools that are readily available to health professionals for detecting cognitive impairment.

Methods: Thirty-four idiopathic RBD patients (25 men; age, 67.82 ± 8.50; education, 11.50 ± 3.87) underwent a comprehensive neuropsychological assessment, including the MMSE and MoCA. MCI was defined as 1) objective evidence of cognitive decline, defined as a performance ≥ 1.5 standard deviations below the standardized mean on at least two variables in a cognitive domain; 2) a subjective cognitive complaint on interview; and 3) preserved daily living activities. Receiver operating characteristic curves were created for the MoCA and MMSE to assess their ability to identify MCI in idiopathic RBD patients.

Results: Scores obtained were 24.50 ± 3.57 (range 15–30) for the MoCA and 28.50 ± 1.48 (range 24–30) for the MMSE. MCI was found in 68% (23/34) of idiopathic RBD patients on neuropsychological evaluation. For the MoCA, a cutoff of 26 (≤ 25 indicating impairment) yielded the best balance between sensitivity (74%) and specificity (91%), with 79% correct classifications. Four of the six idiopathic RBD patients with MCI not detected by the MoCA (scores from 26 to 28) had predominant executive dysfunctions. No value for the MMSE was found to have acceptable sensitivity or specificity.

Conclusions: The MoCA is superior to the MMSE in detecting MCI in idiopathic RBD patients, showing moderate sensitivity and excellent specificity. Idiopathic RBD patients with cognitive complaints and a score from 26 to 28 on the MoCA should be considered for further neuropsychological evaluation to identify MCI.

Tu-210

Mild cognitive impairment (MCI) in idiopathic rapid eye movement sleep behavior disorder (RBD)

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Objective: To investigate the frequency and subtypes of mild cognitive impairment (MCI) in idiopathic rapid eye movement sleep behavior disorder (RBD).

Background: Patients with idiopathic RBD often develop neurodegenerative disorders such as PD and DLB. Cognitive impairments, similar to those reported in the early stages of PD and DLB, have been reported in idiopathic RBD. However, no study to date has investigated for the presence of MCI in idiopathic RBD using standard diagnostic criteria for MCI.

Methods: Seventy-two participants, including 32 idiopathic RBD patients (25 men; age, 65.69 ± 8.52; education, 13.44 ± 3.58) and 40 healthy controls (21 men; age, 65.78 ± 8.28; education, 14.54 ± 2.72), underwent a comprehensive neuropsychological assessment. Three cognitive domains were defined: executive functions and attention, verbal learning and memory, and visuoconstructional and visuoperceptual abilities. MCI was defined as 1) a subjective cognitive complaint on interview with the participant and spouse or caregiver; and 2) objective evidence of cognitive decline, defined as a performance ≥1.5 standard deviations below the standardized mean (or, depending on the norms, a scaled score ≤6 or percentile range ≤ 10) on at least two variables in a cognitive domain. To be considered MCI, the cognitive impairment could not result in a significant decline in daily living activities. The χ^2 test was used to compare the proportion of participants with MCI in each group.

Results: No between-group differences were observed for age or education. MCI was found in 50% (16/32) of idiopathic RBD patients (nonamnestic MCI single domain = 9; amnestic MCI multiple domain = 3; nonamnestic MCI multiple domain = 2; amnestic MCI single domain = 2) and 8% (3/40) of control subjects (nonamnestic MCI single domain). MCI was more frequent in idiopathic RBD patients than in healthy controls (χ^2 test = 14.42; df = 1; p = 0.0001). The main MCI subtype observed in idiopathic RBD was nonamnestic MCI single domain with impaired executive functions and attention.

Conclusions: We found that MCI is a frequent feature of idiopathic RBD. Prospective studies will allow us to determine the utility of MCI in predicting neurodegenerative diseases in idiopathic RBD.

Tu-211

The effect of viewing graspable objects in Parkinson's disease (PD)

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Objective: To investigate whether reaction time (RT) in PD is influenced by viewing graspable stimuli.

Background: In healthy individuals, viewing action-relevant graspable objects has a stronger influence on RT than abstract non-graspable stimuli. In contrast, our previous results suggest that while PD patients are affected by external stimuli, they do not show the expected difference between graspable and non-graspable objects. Here we investigated whether it may take longer to emerge.

Methods: Participants (24 PD patients at Hoehn and Yahr stage 3 or less with mean score on the UPDRS motor-subscale of 23.3, and 24 age-matched controls) viewed a door handle (graspable object) or an abstract bar stimulus (baseline) that could be oriented toward their left or right hand. They responded to a stimulus colour change, using their left hand for one colour and their right hand for the other. Stimulus orientation was predicted to produce faster responses from the nearest hand. A third condition in which stimuli were centrally presented allowed us to assess whether the effects of orientation arose from facilitation (faster responses) of the nearest hand or inhibition (slower responses) of the furthest hand. The colour change occurred either 0ms, 500ms or 1000ms after stimulus presentation, allowing evaluation of whether a larger effect for graspable objects may appear in PD if the response is delayed.

Results: The results were consistent with our previous findings. Whilst controls showed the expected stronger effect for the graspable than baseline stimuli, no difference was observed in the PD group, and the effect did not emerge over the longer time-course. For controls, the effect of graspable stimuli was due to facilitation, whilst the effect in the baseline stimuli was due to inhibition. In contrast, for the PD group, both effects were due to facilitation.

Conclusions: The results again suggest that patients do not show a stronger influence from viewing graspable objects. The comparison with the stimuli presented centrally suggests that this may be because they respond to all stimuli as if they were action-relevant. This has implications for understanding the cueing of movement in PD.

Tu-212

Cognitive complaint as a prodromal symptom in Parkinson's disease?

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Objective: To describe the clinical course, neuropsychological testing, and neuropathology of patients presenting with cognitive complaints, without dementia, preceding motor signs of Parkinson's disease (PD).

Background: Cognitive impairment is an increasingly recognized non-motor manifestation of mid- and late-stage PD. Historically, patients with onset of dementia within 1 year of motor parkinsonism are diagnosed with Dementia with Lewy Bodies (DLB). However, some patients who later develop motor PD complain of cognitive decline early in their clinical disease course but do not have sufficient cognitive or functional deficits to fulfill criteria for dementia.

This is a difficult group of patients to classify using current diagnostic criteria.

Methods: From a study sample of normal aging, dementia, and PD, we identified 5 subjects who presented with cognitive complaints prior to the development of PD. We reviewed the clinical and neuropsychological evaluations performed as a part of this longitudinal study. Neuropathologic evaluation was available for two subjects.

Results: Initial MMSE scores were 28 to 30 in all subjects. Clinical Dementia Rating Scale scores were 0.5 in 4 subjects, and 0 in one subject. Initial neurological examination revealed mild parkinsonism in all 5 subjects; 3 of whom had UPDRS motor scores performed, which averaged 6.7. In an average of 7 years, all subjects developed PD, 3 responsive to treatment and two refusing treatment. At the time of PD diagnosis, neuropsychological and clinical evaluations were consistent with mild cognitive impairment in 4 subjects and no cognitive impairment in 1. Two patients ultimately progressed to dementia and later died. Autopsy revealed neuropathology consistent with PD in both and one also had changes consistent with Alzheimer's disease.

Conclusions: All five cases ultimately fulfilled clinical criteria for a diagnosis of PD and the two who later underwent autopsy had pathologically definite PD. However, early cognitive complaints, though without dementia, raise the possibility of DLB. We suggest that cognitive complaints without dementia can be a presenting symptom for PD, and that the criteria for PD and DLB need to be clarified to allow classification of these cases.

Tu-213

Impaired narrative processing in Parkinson's disease

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Objective: To investigate how patients with Parkinson's disease (PD) process the organization of narratives.

Background: While narratives describing familiar activities (e.g., going fishing) unfold sequentially, they may contain a hierarchical internal structure. Executive resources are involved in processing story organization. As PD is associated with executive dysfunction, deficits in planning and organization may interfere with narrative comprehension in these patients.

Methods: We tested 24 PD patients, of whom five had Parkinson's disease dementia or Lewy body dementia (PDD/LBD), and 15 age- and education-matched controls. We presented 22 narratives consisting of six events. Pilot work quantified the degree of association between events, allowing us to group events into hierarchically arranged clusters (figure). Participants judged the order of adjacent/within-cluster, adjacent/different-cluster, and nonadjacent event pairs. Performance was correlated with executive tasks.

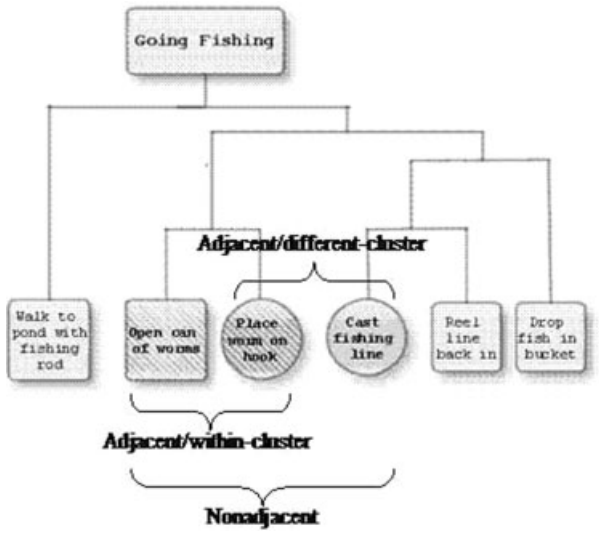

FIG. 1 (Tu-213). Example of hierarchical narrative structure.

Results: PD patients and controls were 93% accurate in order judgments versus 84% among PDD/LBD patients. While PD patients and controls had similar overall response latencies, PDD/LBD patients were half as fast to respond ($p<0.001$). Controls were faster to judge the order of adjacent/within-cluster than adjacent/different-cluster event pairs ($p<0.001$). Patients showed insensitivity to cluster organization, which correlated with difficulty on executive tasks ($p<0.05$). Unlike controls, patients responded more slowly to nonadjacent versus adjacent events ($p<0.05$), regardless of cluster. Finally, controls responded faster to nonadjacent events when one was the initial story event ($p<0.05$), an effect magnified in patients ($p<0.01$).

Conclusions: PD patients show impaired processing of hierarchical story organization, related to executive limitations. Performance is governed instead by linear characteristics, such as distance between events. This linear processing style may contribute to slower, less accurate performance among more impaired patients. As story-telling is a prominent part of daily interaction, impaired narrative processing can substantially impact patients' ability to communicate with others. Facilitation by the initial story event suggests potential strategies to help patients process narratives more efficiently.

Tu-214

Self-complexity in Parkinson's disease is predicted by depression

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Objective: The aim of the present study was to test the hypothesis that SC would be impaired in PD patients relative to a group of individuals with major depressive disorder.

Background: Self-complexity (SC) refers to the cognitive organization of the Self. It is assumed that the complexity of the Self reflects a) the number of roles we play and b) the number of traits that describe us in each of these separate roles. The greater the number of roles that exhibit minimal overlap of traits, the greater the SC. SC has been previously found to mediate overall general well-being and be protective against depression, anxiety, and other stress-related illnesses. Between 20-90% of patients with Parkinson's disease (PD) suffer some form of major depressive illness as well as an altered sense of self due to dysexecutive prefrontal function.

Methods: 12 PD patients and 11 depressed control participants were assessed with a modified measure of SC. Our revised measure consisted of 26 traits. We used the SC formula, $SC=\log 2n - (\Sigma i\ ni \log 2ni)/n$, to calculate a maximum SC score of 4.70. Participants completed a mood measure (DASS), a measure of apathy, and a test of prefrontal function (the Stroop). Disease severity was assessed by the Unified Parkinson's Disease Rating Scale (UPDRS).

Results: Mean SC score was marginally greater for depressed controls (mean=3.10(1.06)) than for PD patients (mean=2.44(0.81), $p=0.13$). Greater disease severity among PDs did not predict lower SC scores ($r=-0.31$, $p=0.33$). Greater overlap for depressed controls marginally predicted lower SC ($r=-0.54$, $p=0.11$). This same relationship was not found among PD patients ($r=-0.08$, $p=0.81$). Higher scores on the Stroop color-word interference card were not correlated with lower SC score for PDs ($r=-0.33$, $p=0.30$), or depressed controls ($r=0.07$, $p=0.83$). Greater depression among PDs was significantly and strongly correlated with lower SC ($r=-0.66$, $p=0.02$) but not depressed controls ($r=0.10$, $p=0.84$). Greater total apathy scale score was not correlated with higher SC scores among PDs ($r=0.32$, $p=0.31$) or depressed controls ($r=-0.43$, $p=0.22$).

Conclusions: Prefrontal dysfunction and apathy were not related to the role component of SC, but depression was related. Depression of PD critically involves the self.

Tu-215

Defective visual perception in patients with Parkinson's disease: The impairment of preattentive visual processing

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Objective: Occipital hypometabolism is a common feature of Parkinson's disease (PD). And it has been to underlie the development of hallucinations. In our previous study, occipital hypometabolism was observed in FDG-PET in PD patients with long duration of their illness, while any visuocognitve deficits were not detected on the Visual Perception Test for Agnosia (VPTA). To evaluate the disturbance of visual cognition, we explored the possibility of whether preattentive visual processing is impaired in PD.

Methods: Twenty-eight patients of idiopathic PD and 15 age matched controls without CNS or eye disease were included in this study. To evaluate preattentive visual processing, visual discrimination thresholds for orientation texture stimuli and subjective contour stimuli were determined in five separate measurement sessions. These five separate measurement sessions were as follows: 1. Detection of the gradient, 2. Detection of the regional form that gradients are different, 3. Detection of the form of X in L versus X, 4. Detection of a subjective contour of Kanizsa type, 5. Detection of a boundary subjective contour of a line. As a quantitative psychometric procedure, we applied the Best-PEST algorithm to estimate the threshold. The threshold presentation time in each session was evaluated, and statistic examination was performed between the PD group and the control group.

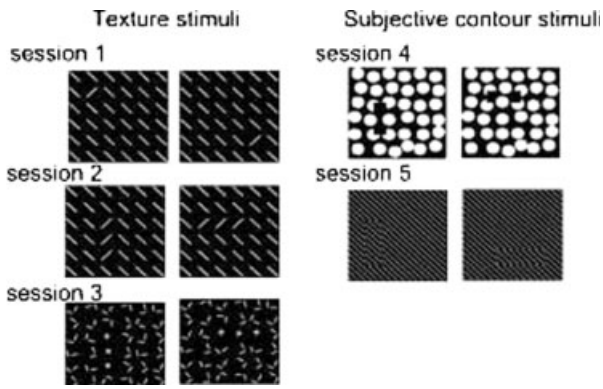

FIG. 1 (Tu-215). Examples of the stimuli used in this study.

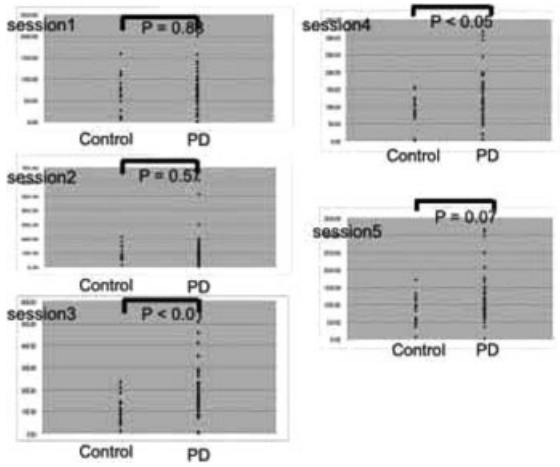

FIG. 2 (Tu-215). Threshold presentation times for patients with PD and controls.

Results: The thresholds of PD patients were significantly higher than those of the control subjects in session 3, 4, and 5.

Conclusions: These findings suggest that preattentive visual processing is impaired in PD patients. Estimation of preattentive visual processing function may be useful in early diagnosis of PD.

Tu-216

Is there a link between lower and higher order visual deficits in early Parkinson's disease: A case-control study?

G. Hipp, M. Vaillant, V. Pieri, N.J. Diederich (Luxembourg, Luxembourg)

Objective: To investigate lower order visual deficits (LOV) and higher order visual deficits (HOV) and possible links between both at an early IPD stage.

Background: Lower order visual deficits (LOV), namely reduced colour and contrast discrimination, have been demonstrated in early idiopathic Parkinson's disease (IPD), while higher order visual deficits (HOV), namely impaired object and face recognition, have mainly been found in advanced IPD. There has been no study exploring possible links between both.

Methods: We prospectively recruited 29 patients with early IPD defined as $\leq$3 years of disease duration and matched them with 29 healthy controls. LOV was tested by Farnsworth-Munsell Test (FM), Vis-Tech 1.5 cpd (VT) and binocular Pelli-Robson (PR). HOV was tested by Visual Object and Space Perception test (VOSP) and Ekman 60 Faces Test (E60FT). The E60FT was only applied to 11 IPD patients and 8 controls. Statistical analysis used, as appropriate, Chi 2 test, Mann-Whitney test, ANOVAs, log-transformed values, correlation coefficients.

Results: Gender distribution and mean age were similar in both groups. IPD patients performed significantly worse on all LOV tests than controls: FM 150.5 ± 62.3 versus 79.0 ± 58.4, $p<0.001$; VT 5.00 ± 0.76 versus 5.97 ± 0.98, $p<0.001$; PR 1.44 ± 0.15 versus 1.6 ± 0.2, $p<0.001$. IPD patients performed also worse on HOV tests, but the difference was significant only for the VOSP screening test: 19.7 ± 0.5 versus 19.9 ± 0.3; $p=0.05$. There was a weak correlation between the different LOV tests, but none between the LOV and the HOV tests.

Conclusions: At an early stage IPD patients show reduced performances of color and contrast discrimination, but not (yet) of object and face recognition. Thus lower order visual dysfunction does not (yet) induce higher order visual dysfunction. These data reinforce the hypothesis that retinal visual dysfunction, but not extrastriate cortical visual dysfunction may be a specific early marker of IPD.

Tu-217

Is there a link between olfactory dysfunction and recognition of facial disgust in early Parkinson's disease?

G. Hipp, M. Vaillant, V. Pieri, N.J. Diederich (Luxembourg, Luxembourg)

Objective: To investigate possible links between EFR and OI in patients with early stages of IPD and in elderly healthy controls.

Background: Deficits of odour identification (OI) are an early marker of idiopathic Parkinson's disease (IPD). Possibly, low performances in emotional face recognition (EFR), especially concerning disgust and fear are another non-motor feature of IPD, linked to disease involvement of the rhinencephalon and the amygdala. EFR and OI, as archaic brain functions, may be interdependent.

Methods: We prospectively recruited 16 patients with early IPD (67.2+/-9.9 years), defined as $<$ 3 years of disease duration, and compared with a group of 25 healthy controls (59.9+/-6.9 years). OI

was tested with the University of Pennsylvania Smell Identification Test (UPSIT) and EFR with the Ekman 60 Faces Test (E60FT), which discriminates recognition of six facial emotional expressions: disgust, fear, anger, sadness, happiness and surprise. Statistical analysis used, as appropriate, ANOVA, Chi2 test, Pearson correlation coefficients and log-transformed values.

Results: Gender distribution was similar in both groups ($p>0.75$) and mean age was higher in the IPD group ($p<0.013$). IPD patients showed more deficits than control subjects on the UPSIT (56.3 vs12%; $p=0.04$), and on the E60FT (37.5 vs 4%; $p=0.009$). The highest differences were found for the recognition of disgust (18.7 vs 0%; $p=0.053$). Subjects with OI deficits had more frequently EFR deficits than subjects without OI deficits. (41.7 vs 6.9%; $p=0.015$). In the IPD group there was a correlation trend between EFR and OI ($r=0.49$; $p=0.054$). The emotions concerned were: disgust, fear and sadness.

Conclusions: Our results show hyposmia *and* deficits in emotional face recognition in patients with early IPD. They further suggest a relationship between both items, possibly because these ontogenetically ancient functions are modulated by the same brain structures.

Tu-218

Decision making, risk and dopamine in sub-groups of Parkinson's disease

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Objective: To investigate responses to novelty and risk taking on a gambling task in sub-groups of patients with Parkinson's disease (PD).

Background: Recent studies implicate dopaminergic medication in pathological risk-taking in PD, yet most patients do not develop such symptoms. The role of dopamine in modulating decision making and risky behaviour was investigated in patients with different presentations of PD: predominantly akinetic-rigid or tremor dominant types.

Methods: 28 PD patients were assessed on how they responded to novelty and their willingness to take risks, compared to healthy controls. Participants were assessed on two versions of an oddball task, each containing 3 types of infrequently occurring visual stimulus: targets, perceptually salient standard stimuli and novel stimuli. In one version of the experiment (task N) subjects were instructed to respond (by button-press) only to targets and novels; while in another version (task P) responses to targets and perceptually salient stimuli were required.

Results: Akinetic-rigid PD patients were significantly quicker to respond on task N compared to task P. By contrast tremor dominant PD patients and controls performed equally across the two tasks. Faster responses on task N correlated with greater risk-taking behaviour on the Iowa Gambling Task for akinetic-rigid patients only. Importantly, there was an interaction between dose of dopaminergic medication and subgroup of PD. In tremor dominant patients higher L-dopa equivalent doses were associated with quicker responses on task P – to perceptually salient, non-novel stimuli. But dopaminergic dose did not correlate with either performance measure in the akinetic-rigid group. Both patient groups were matched in terms of motor impairment and cognitive performance.

Conclusions: Dopaminergic modulation might have differential effects in the two subgroups of PD patients. Moreover, novelty-seeking correlates with risk-taking behaviour but only in akinetic-rigid PD.

Tu-219

α-synuclein pathology in the claustrum is associated with dementia in Parkinson's disease

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Objective: To examine the incidence and extent of α-synuclein (αSyn) pathology in the claustrum in relation to the presence of dementia in Parkinson's disease (PD).

Background: While dementia is a common neuropsychiatric complication and is found in up to 50% of PD sufferers the anatomical and pathological basis remains incompletely defined. The claustrum, a neuronal 'hidden' structure below the inner surface of the neocortex, is reciprocally interconnected with neocortical, allocortical and limbic regions that are known to subserve cognitive function in humans, while its exact function remains enigmatic.

Methods: Thirty nine cases were included in this study comprising 20 PD, 12 PD with dementia (PDD) and 7 cases with Dementia with Lewy bodies (DLB). Semi-quantitative assessment (0-3+; absent to severe) of αSyn immunostaining in the claustrum was carried out blind to clinical diagnosis. Differences between diagnostic subgroups were analyzed with the non-parametric Mann-Whitney U-test.

Results: αSyn positivity was observed in 75% of PD cases and in 100% of PDD and DLB cases. Compared to PD cases, PDD cases demonstrated a significantly greater αSyn burden in the claustrum ($p=0.0003$). In addition, DLB cases showed a significantly increased αSyn deposition in the claustrum when compared to PDD ($p=0.02$) and PD ($p=0.0002$) cases.

Conclusions: We demonstrate for the first time that pathology in the claustrum, a region of largely obscure physiological function, strongly relates to the presence of dementia in Parkinson's disease.

Tu-220

Parkinson's disease dementia (PDD) diagnosis according the new movement disorders task force recommendations: Clinical and cognitive characteristics

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Objective: To compare the clinical and cognitive features of patients with Parkinson's disease Dementia (PDD) and PD without dementia, as defined by the new *Movement* Disorder Society (MDS) recommendations.

Background: Clinical features evoking dementia according to the DSM IV criteria include old age, symptoms severity with a high Hoehn & Yahr stage(H&Y), hallucinations and cognitive disorders.

Methods: Amongst 22 patients fulfilling DSMIV criteria for PDD we distinguished the patients also fulfilling MDS criteria (group I) from the other ones (group II). We compared the both groups for clinical and cognitive characteristics using seven backwards, pentagons, 3- words recall sub tests of MMSE, Free and Cued Selective Reminding Test (FCSRT), 3 Free Recall subtest, copy of the Rey-Osterrieth Complex Figure Test (ROCFT), Mattis Dementia Rating Scale (MDRS)total score and Initiation and Perseveration, Construction subtests.

Results: In group I (14 patients) mean age was 77 +/− 4.57 (versus 79 +/− 4.17 in group II, 8 patients), sex ratio M/W 0.55 (vs 0.33), PD duration 9.5 +/−3.83 years (vs 12 +/− 6.78), age at beginning of PD 68+/−7.09 (vs 68 +/− 9.70), H&Y stage 3.1 +/ −0.51 (3.1 +/− 0.70), anti-psychotic treatment was present in 35 % of patients (vs 25%), there was 2.1 antiparkinsonian treatments (vs 2.5). Seven backwards was normal in 2 patients(14%) in group I versus 7(87 %) in group II, pentagons in 2(14%) vs 5(62%), 3-words recall in 3(22%)vs 5(62%), 3FCSRT was normal (≥ 40) in 3(21%) vs 6(75%), 3 Free Recall was normal in 0 versus 2(25%)and at the border of statistically significance for this score; ROCFT was under the 3-5 percentiles in all group I and 5(62%) were over 19-28 percentiles; MDRS total score was normal for none in group I versus 5(62%) in group II, subtests Initiation and Perseveration in 1(7%) versus 6 (75%) see Table.

Table (Tu-220). PDD (I) and PD without dementia (II) : cognitive testing

Test	MMSE mean score	Seven backwards % normal score	MDRS total score	MDRS IP score	3 FRCSRT score	ROCFT score
group I	22+/−3 DS	14%	102.7 +/− 14.5	23.5+/− 5.3	33.5+/−8.2	5.5+/−5.7
group II	27+/−61 DS	87%	121.6+/−12.6	31.38+/−5.7	38.8 +/−6.6	24.43+/−2.2
P value	0.001*	0.004*	0.008*	0.02*	0.11	0.001*

*p value statistically significant if < 0.05.

Conclusions: Age at PD onset, sex, PD duration, H&Y stage appear related to PDD but no significant difference was found. Seven backwards, MDRS total score, copy of ROCFT score seem useful to characterize cognitive disorders with significant values between cognitive disorders related to PDD and PD without dementia.

Tu-221

Effects of cognitive-linguistic load on spatial and temporal gait parameters during on-off medication cycles in Parkinson's disease

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(Tallahassee, Florida)

Objective: To determine (1) effects of cognitive-linguistic loading on stability of selected spatial-temporal gait parameters during peak and off medication cycles, (2) changes in an established measure of predicted fall risk (Functional Ambulation Profile [FAP]) relative to medication cycle, and (3) interaction effects of medication cycle and cognitive loading on fall risk.

Background: Previous research from our center has begun to define the relationships between cognitive loading and changes in gait that signal an increased risk for falls. The influence and cycle of dopaminergic agents on fall risk and specific temporal-spatial parameters of gait have not been determined however.

Methods: We tested 27 participants with idiopathic Parkinson's disease (UDPR Mean =26; Hoehn-Yahr 2,3,4) during peak and off peak medication cycles across four counterbalanced conditions of cognitive-linguistic loading (1, [gait only]; 2 low [simultaneous walking and counting by ones]; 3, medium [walking and subtracting by 3s]; 4, high [walking and alphanumeric sequencing]). Temporal-spatial step-by-step gait parameters were measured, recorded, and analyzed using the GAITRite walkway system. FAP was determined across all conditions and cycles as were measures of velocity, stride length, ambulation time, and double support time.

Results: Significant differences were found when the cognitive load walking conditions including the FAP were compared to the control condition ($p<.05$). Surprisingly, few differences in parameters of gait were found across conditions during peak and off peak medication cycles.

Conclusions: In our study, significant changes in temporal-spatial parameters of gait, including the FAP measure of fall risk were found across medium and high cognitive load conditions. Measured gait paramenters did not appear to be influenced by dopaminergic agents or medication cycle however. These findings have important pharmacologic and clinical implications related to fall risk and cogntive resource allocation.

Tu-222

Executive dysfunction in Parkinson's disease

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(Singapore, Singapore)

Objective: To evaluate the diagnostic utility of the Chinese version of Frontal Assessment Battery (FAB) in Parkinson's disease (PD) and to study its correlation with motor symptoms.

Background: In PD, executive function (EF) is impaired early in the disease process as a result of frontal lobe dysfunction. EF has also been reported to be associated with gait disorders such as freezing. The utility of the FAB as a valid screening tool for executive dysfunction and its correlation with motor symptoms, among Asian patients with PD has not been established.

Methods: 100 PD patients were recruited from the PD and Movement Disorders Centre, National Neuroscience Institute over a 4-month period. Patients were prospectively evaluated with the MMSE, FAB, UPDRS, Hoehn and Yahr staging. All patients met the National Institute of Neurological Disorders and Stroke criteria for the diagnosis of PD and did not meet DSM-IV criteria for dementia. PD patients with limb deformities or contractures were excluded from the study. Parametric, non-parametric tests and correlation statistics were performed with statistical significance taken at $p\leq0.05$.

Results: Mean age of the non-demented PD patients was 66.1 years (SD5.6) with mean education level of 7.9 years (SD5.6). The mean duration of PD disease was 52.1 months with mean H & Y stage of 2.2. A greater percentage failed the education-adjusted FAB (53%) compared to the memory-based MMSE test (21%). There was a statistically significant trend of decreasing FAB scores with increasing H& Y stage (FAB score 14.9, 12.5, 11.25, 9.25 with H&Y Stage 1,2,3,≥4 respectively), ($p=0.05$ with Bonferroni correction). UPDRS bradykinesia and gait subscore were significantly correlated with FAB (-0.17, $p=0.02$; -0.17, $p=0.04$ respectively). Comparing FAB subscores, only conceptualisation subscore correlated with bradykinesia (-0.15, $p=0.05$) and inhibitory control subscore correlated with gait bradykinesia (-0.21, $p=0.01$). FAB was not correlated with freezing of gait (UPDRS Qn 14) (0.08, $p=0.33$).

Conclusions: The FAB was more sensitive than the MMSE in detecting cognitive impairment among PD patients without dementia, and significantly correlated with bradykinesia and gait subscore. Our findings support the possible utility of the FAB as a useful adjunct to MMSE in the cognitive evaluation of PD patients without dementia.

Tu-223

Can silent ischemic cerebral lesions clinically affect cognitive impairment in patients with Parkinson's disease accompanied by mild dementia?

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Objective: We conducted this study to evaluate the relationship between silent cerebrovascular lesions and cognitive decline in Parkinson' disease with dementia.

Background: Several studies have shown that the presence of cerebrovascular lesions may play an important role in determining the severity of the clinical symptoms of dementia. However, no study to date has explored the clinical effects of cerebrovascular disease on Parkinson's disease with dementia (PDD), although cerebrovascular disease is a common cause of dementia in the elderly population.

Methods: Only 27 patients with PDD were selected for participation in this study. Seventeen patients had PDD with silent cerebral ischemic lesions(PDDI), and 10 patients had PDD without silent cerebral ischemic lesions (pure PDD). All subjects underwent global cognitive function testing and were evaluated using detailed neuropsychological tests, including tests of attention, memory, language, and visuospatial and frontal functioning.

Results: There were no significant differences between the pure PDD and PDDI groups on general cognitive function tests. The mean duration of suffering from the motor symptoms of Parkinson's disease was longer in the pure PDD group than in the PDDI group, but the difference between the two groups was not significant. Furthermore, there were no significant differences in detailed neuropsychological test scores between the two groups.

Conclusions: We concluded that silent cerebrovascular lesions do not contribute to the neuropsychological severity of PDD, even though vascular disease is a common cause of cognitive impairment in the elderly. Thus, the results of the present study suggest that factors other than cerebrovascular disease contribute to the severity of PDD.

Tu-224

Performance over time on two brief cognitive screening measures in Parkinson's disease (PD) and Huntington's disease (HD)

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Objective: To compare performance on brief cognitive screening instruments in two subcortical dementias.

Background: The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) are brief screening instru-

ments of 30 points which take about 10 minutes to administer. Performance on these measures in subcortical dementias (such as PD and HD) has not been extensively examined. In addition, little is known about the annual rate of change in either disease.

Methods: 61 PD and 50 HD subjects were tested on the MMSE and MoCA in counterbalanced order. Performance on these tests were compared by total score and domain. A subset of these patients was tested approximately 12 months later.

Results: PD subjects were older (mean age=71.3y) than HD subjects (mean age=50.8y) although well matched with regard to education (PD=14.8y, HD=14.2y). In both groups, mean score on the MoCA was lower than on the MMSE and showed greater variability (MMSE:PD=27.6(2.5),HD=26.0(2.3); MoCA:PD=22.9(4.2);HD=21.6(3.6)). Mean total scores were similar between PD and HD on the MoCA ($p=0.073$); however, there were statistically significant differences on the MMSE ($p=0.001$). When analyzed by domain, only serial 7s were significantly different between patient groups (MoCA:$p=0.007$;MMSE:$p=0.001$). Annualized rates of change (points per year) were similar in PD and HD subjects on both the MoCA (PD=0.97,HD=1.0) and MMSE (PD=0.84, HD=0.8). However, approximately 30% of patients in each group did not decline over time. In those who did, annualized rates of change on both tests were significantly higher, approximately 2-3 points per year.

Conclusions: Both the MMSE and MoCA appear to have utility as brief cognitive screening instruments in subcortical dementia and may be useful for tracking disease progression over time.

Tu-225

Influence of different classification criteria on the interpretation of group differences in PD-MCI

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Objective: We determined the prevalence of PD-MCI in a large cohort of PD patients and examined, whether it may be influenced by different cut-off values. Additionally we questioned if the statistical mean group comparisons (e.g. PD-MCI vs. PDD, or between varying MCI groups) concerning behavioural abnormalities or daily living function might be affected by the chosen cut-off value.

Background: Recently recommendation for the diagnosis of dementia in Parkinson's disease (PDD) were proposed. For mild cognitive impairment in PD (PD-MCI) the classification of Petersen and colleagues are commonly used. However different authors dispose varying cut-off values for the categorisation of MCI in different neuropsychological tasks. This may have a great impact on the interpretation of the assessed data.

Methods: 100 consecutive patients with Parkinson's disease (mean age 67.9 ± 6.7, 65 male) were recruited, 12 were found to have dementia (PDD). Besides a comprehensive neuropsychological battery, patients and caregivers completed a questionnaire for the assessment of daily living functions, the PDQ-39, the BDI and the Neuropsychiatric Inventory. Different cognitive domains covered by the neuropsychological tests were identified by using explorative factor analysis including all 100 patients. Patients were classified accordingly into four MCI-categories, single-amnestic or non-amnestic or multiple- amnestic or non-amnestic.

Results: The prevalence of cognitive dysfunction (0.42-0.96) varied dramatically depending on the cut-off value of 1, 1.5 and 2 standard deviations below the normative mean of healthy subjects. However, interpretation of mean group differences between PD-MCI and PDD patients regarding the variables assessed did not depended on the chosen cut-off value. In contrast, interpretation of mean group differences among e.g. amnestic/non-amnestic or single/multiple PD-MCI was strongly affected by the choice of the cut-off value.

Conclusions: Interpretation of test results between different PD-MCI groups seems to be highly depending on the chosen cut-off value for cognitive disturbances. Therefore, a standardization for the diagnosis of PD-MCI is needed.

Tu-226

Prediction of cognitive impairment associated with Parkinson's disease by short latency afferent inhibition

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Objective: To use short latency afferent inhibition (SAI) testing 1) evaluate the degree of cholinergic deficits in the brain of Parkinson's disease (PD) patients 2) compare the result of SAI tesing with their cognitive test to confirm whether the cholinergic deficits is proportional to the degree of cognitive decline in patinets with PD.

Background: In vivo evaluation of cholinergic circuits in human brain had recently been using SAI testing with coupled peripheral nerve stimulation with following contralateral motor cortex transcranial magnetic stimulation (TMS). SAI is reduced in deficient cholinergic brain condition and reversed by cholinesterase inhibitor.

Methods: Fifteen patients with PD were recruited to receive minimental state examination (MMSE), UPDRS and SAI with 22 ms (SAI-22) and 25 ms (SAI-25) interval in off-medication situation.

Results: Ten patients had normal MMSE (27-30) and Five patients had mild cognitive impairment (MMSE: 24-26). In the group of normal MMSE, SAI-22 was 34.73% and SAI-25 was 38.97%. In the group of mild cognitive impairment, SAI-22 was 54.47% and SAI-25 was 81.32%. The reduced SAI had been observed in the mild cognitive impairment group. Statisticaaly significant difference was found in SAI-25 between these two groups (Student T test).

Conclusions: Our data suggest cholinergic deficits contribute the cognitive decline in PD and SAI-25 is more sensitive in evaluating the mild cognitive impairment of PD.

Tu-227

Assessment of the progression of cognitive impairment in Parkinson's disease using the MDS-UPDRS

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Objective: To explore the ability of the Part I, Cognitive Impairment (CI) item of The *Movement* Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), to assess the progression of CI in a prospective and representative sample of PD patients.

Background: The UPDRS is the most widely used clinical assessment tool for PD. A revised version, the MDS-UPDRS, has been recently published. Up to date, no studies using the MDS-UPDRS have yet been published. Thus, the construct validity of the Part I, CI item of the MDS-UPDRS as a useful tool to assess CI progression needs to be further clarified.

Methods: Prospective study of 115 PD patients (age 68±10, H&Y 2.1±0.6). The construct validity of the MDS- UPDRS-I, CI item was assessed against the Clinical Dementia Rating scale (CDR). A neurologist administered the MDS-UPDRS-I, and a blinded neuropsychologist administered the CDR. To test for the MDRS-UPDRS-I as a marker of CI progression, one-way ANOVA analyses were performed between the MDS- UPDRS and the CDR, Parkinson's Disease-Cognitive Rating Scale (PD-CRS), Mattis Dementia Rating Scale (MDRS), the Mini Mental State Examination (MMSE).

Results: The MDS-UPDRS-I CI scores showed a high concurrent validity with the CDR scores (CCI = 0.84). Scores on either the MDS-UPDRS ($F;p<0.001$), PD-CRS ($F;p<0.001$), MDRS ($F;p<0.001$) and MMSE ($F;p<0.001$) significantly differentiated PD cognitive groups as assessed by the CDR [0=cognitively intact (CgInt); 1 = mild cognitive defects (MCD); ≥1 dementia]. In the post- hoc analyses (Scheffé), the MDS-UPDRS significantly captured the progression of CI, differentiating CgInt patients from those with MCD ($p<0.001$), and MCD from demented patients ($p<0.001$). Both the PD-CRS and the MDRS distinguished also CgInt from MCD

($p=0.016$) and demented patients ($p<0.001$), while MMSE scores did not help to differentiate CgInt from MCD patients ($p=0.756$).

Conclusions: The MDS-UPDRS-I CI item appears as a valid tool to capture the progression of CI in PD. The comparable ability of the MDS-UPDRS with both the PD-CRS and the MDRS to detect changes from intact cognition to dementia warrants further studies aiming to determine the discriminative validity of this scale in the screening of the mild cognitive defects associated with PD.

We-206

Urate correlates with cognitive performance in Parkinson's disease

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Objective: To explore the relationship between cognition and urate levels in 104 patients diagnosed with idiopathic Parkinson's disease (PD) from the Suzhou region of China.

Background: Cognitive dysfunction is common in PD. Recently lower levels of urate have been linked to a higher risk of developing PD,as well as to a faster rate of clinical decline in PD. Less is known about the relationship between urate and cognition.

Methods: Subjects were divided into two groups: those with cognitive impairment and the those without, based on performance on the Montreal Cognitive Assessment. Fasting plasma urate was measured, and demographic features as well as results of a depression assessment were also recorded.

Results: In the independent-sample t test analysis the plasma urate levels amongst PD subjects with cognitive impairment was found to be significantly lower than in those in the normal range of cognitive function ($P<0.001$). In multiple linear regression, the cognitive scores were related to plasma urate level, education, age, H-Y stage and the depression level, but no obvious correlation is found between the cognitive score and gender, smoking habit, body mass index (BMI) or disease duration.

Conclusions: In the PD population, higher plasma urate levels correlate with higher cognitive performance, which is also related to education, age, H-Y stage and depression level.

We-207

Psychometric attributes of the Parkinson's disease-cognitive rating scale

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Objective: To check out independently the psychometric properties of the Parkinson's Disease–Cognitive Rating Scale (PD-CRS).

Background: Assessment of cognitive impairment in Parkinson's disease (PD) requires specific and valid instruments. The PD-CRS has been developed at this aim and the first validation study was recently published (Mov Disord 2008; 23: 998-1005).

Methods: Fifty PD patients (age 63.65±9.33 y.; 66%, males; PD duration, 9.04±5.7 y.) participated in the study. The following assessments were applied: Hoehn and Yahr staging, Clinical Impression of Severity Index-PD, Scales for Outcomes in PD-Motor (SCOPA-Motor), MMSE, SCOPA-Cognition, Non-Motor Symptoms Questionnaire, and the PD-CRS. For the latter scale, acceptability, internal consistency, construct validity, and precision were explored.

Results: PD-CRS mean scores were: Fronto-subcortical subscale (FS), 60.9±16.5; Cortical subscale (C), 27.88±4.4; PD-CRS total score, 88.7±19.8. Ceiling effect was observed for the PD-CRS C (complete sample, 52%; non-demented, 60.5%; demented, 25.0%), which also showed a high skewness (2.98). PD-CRS Cronbach's alpha was 0.85. Item homogeneity resulted 0.36. PD-CRS convergent validity was high with MMSE ($r_s=0.53$) and with SCOPA-Cognition ($r_s=0.77$), moderate with the other PD measures ($r_s=0.30$-0.40), and weak with the number of declared non-motor symptoms ($r_s=0.14$). Internal validity was 0.59. PD-CRS discriminated significantly between patients with and without dementia, as per the CISI-PD Item Cognition ($p=0.04$). The standard error of measurement was 1.98 (1/2 SD=2.56).

Conclusions: There was a coincidence with the original study in finding a ceiling effect for PD-CRS C, but also a discrepancy since that effect was not cancelled for demented patients in the present one (which included only 12 patients with dementia). Internal consistency resulted similar and satisfactory. The convergent validity (including the PD specific SCOPA-Cognition) and the discriminative validity were adequate, as they were in the first study. This independent validation study showed that PD-CRS is a consistent, valid, and precise measure for evaluation of cognitive impairment in PD.

We-208

Relating neuropsychological test performance to everyday cognitive functioning in Parkinson's disease

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Objective: To evaluate cognitive functioning in people with Parkinson's disease and a healthy age-matched control group, in order to be able to relate the findings to self-report measures of every-day cognition.

Background: In the first phase of this research, we found that people with Parkinson's disease report more attention-related, attentional switching and verbal memory difficulties in their day-to-day lives than healthy controls, while reporting similar levels of planning ability and long-term memory function. Little is currently known about the relationship between such self reports and performance on neuropsychological tests.

Methods: Two sub-groups from the earlier questionnaire phase completed a battery of neuropsychological tests: 41 adults with mild to moderate Parkinson's disease (Hoehn & Yahr stage II-III; mean age 62.68 years, mean illness duration 5.97 years) and 19 age-matched controls (mean age 64.95 years). The groups did not differ significantly in age, gender, years in education or National Adult Reading Test score.

Results: Significant differences between the two groups were found in spatial span (CANTAB), selective attention (flanker) and continuation timing tasks. Differences between the two groups approached significance for spatial working memory tasks (CANTAB) and sustained attention to response tasks. No differences were found in simple rule reversal or set-shifting tasks (CANTAB), or in digit span, Stroop and simple reaction time tasks.

Conclusions: As in previous research, the group with Parkinson's disease demonstrated impairments on some cognitive domains and not others, including one in which performance is typically affected in early stage Parkinson's disease (set-shifting). The group differences in the selective attention task and trend in the sustained attention task parallel the self-reported everyday attentional problems encountered by the Parkinson's disease group in the first phase of the study. In contrast, no group differences were observed in the set-shifting task despite self-reported attentional switching difficulties. Ongoing work involves relating individual differences in self-reported cognitive problems to neuropsychological test scores.

We-209

Verbal recall is impaired in Parkinson's disease without dementia

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Objective: To evaluate verbal recall in patients with PD without dementia.

Background: Growing evidence support the presence of cognitive impairment in patients with Parkinson's disease (PD) without dementia. Frontal lobe functions have been shown as the most frequently

impaired in PD. However, cognitive dysfunctions located out of frontal lobe are not usually recognized as involved in PD.

Methods: We developed two simple tasks to evaluate verbal learning: during the first task we verbally presented participants ten characteristics of a person; then participants were asked to enumerate those characteristics twice: the first time just after stimulus and the second one 5 minutes later, after a distracting task. During the second task participants were asked to learn and immediately recall in the same way a list of objects (daily shopping list) just after deliver.

Results: Patients with PD scored significantly lower both in the immediate verbal recall ($p<.05$ in both tests) and in delayed verbal recall ($p<.05$).

Conclusions: In addition to frontal lobe dysfunction, cognitive impairment involving other functions such as verbal recall is present in PD without dementia.

We-210

Olfactory function as a predictor of cognitive impairments in Parkinson's disease

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Objective: To test the involvement of cognitive processes in olfactory tasks that require different mental resources in twenty non-medicated PD patients and 20 healthy controls. The hypotheses were: a) performance of PD patients would be significantly different from that of healthy older adults in sensorial and cognitive assessment; b) olfactory scores would predict performance in cognitive tasks.

Background: Olfactory dysfunction is a preclinical sign of Parkinson's disease (PD), caused by abnormalities of the central olfactory system. However, results from odour detection, discrimination and identification tests have questioned whether the nature of such deficits is sensorial and to what extent cognition influences odour processing. Cognitive control could be determining, at least partially, the effects of pathology in odour tasks.

Methods: Olfactory testing included odour detection, discrimination and identification with Sniffin'Sticks. The cognitive assessment included a Stroop task, category fluency and vocabulary, WCST and matrices.

Results: Olfactory scores from PD patients were significantly lower than controls. Patients were also impaired in all cognitive tasks. Regression analysis showed that results from odour tasks predict a great percentage of variance in cognitive tasks in all participants.

Conclusions: The first conclusion is that deficits from odor tasks are not only sensorial, revealing an influential role of cognitive processes in odor discrimination and identification. More longitudinal studies are needed in order to investigate the predictive value of odor deficits on cognitive impairments in PD. Moreover, and most important, odor scores could predate the onset of dementia.

We-211

Appreciation of indirect requests in Parkinson's disease

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Objective: This study evaluated how adults with idiopathic Parkinson's disease (PD) understand the non-literal intentions of a speaker.

Background: Individuals with PD are known to have difficulties understanding pragmatic aspects of language, such as metaphors and inferences. However, the understanding of non-literal speech acts has never been evaluated in this population. Non-literal utterances require the ability to process the speaker's utterance beyond its literal meaning in order to allow one to grasp the speaker's intention by reference to the contextual information. Thus, the capacity to communicate does not only rely on an intact language system but also on the knowledge of a specific communicative exchange context and high-level capacities. A strong link has been previously made between the ability to understand "complex" and pragmatic forms of language and executive functions.

Methods: 17 PD patients and 12 HC all matched for age and educational level, were evaluated using the indirect request subtest of the MEC (Montreal evaluation of communication) and a short battery of neuropsychological tests designed to evaluate executive functions. All the data were analyzed using a descriptive cluster analyses, ANOVA's comparisons and Pearson correlations.

Results: Preliminary results show that even when the processing of indirect requests was not different from that of control individuals, one subgroup of PD showed specific problems understanding direct requests. Moreover, correlations were found between the understanding of indirect request and frontal lobe functions deficits (flexibility and working memory).

Conclusions: This results show that frontal lobe dysfunction seems to be the major reason for pragmatic language deficits observed in PD patients. Moreover, these results share similarities with those observed in the right hemisphere damaged population using the same task, that can be explained by a lack of flexibility and by a perseveration strategy in their pattern of performance.

We-212

Dopaminergic medication exaggerates the experience of voluntary motor control in Parkinson's disease

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Objective: To investigate the experience of voluntary motor control in Parkinson's disease (PD), as well as changes in this experience as a consequence of dopaminergic medication.

Background: Little is known of the impact that motor impairments in PD have on the subjective experience of voluntary action. Furthermore, dopaminergic medication used to treat motor impairments might change this experience. For example, side-effects of dopaminergic medication can include impulse control disorders, in which the experience of control over one's actions is altered. We wanted to determine whether PD in the "off" state is characterised by altered experience of voluntary action, compared to healthy controls. Furthermore, we wanted to investigate changes in this experience in the "on" state.

Methods: Previous studies in healthy volunteers have shown that the experience of voluntary motor control is associated with a subjective shortening in the interval between a voluntary movement and its consequence (termed "Intentional binding"). Using this paradigm we tested 9 patients both off and on dopaminergic medication, as well as 9 age-matched healthy controls.

Results: The subjective shortening of the interval between movements and their consequences was similar in controls and patients in the "off" state. However, patients in the "on" state showed the shortening effect significantly more strongly than in the "off" state.

Conclusions: Our results suggest that PD itself may not be associated with changes in the experience of voluntary motor control. However, our results also suggest that medication used to treat motor impairments might exaggerate the experience of voluntary control. We propose that this could be an important factor in the development of impulse control problems as a side-effect of medication.

We-213

Relationship between apathy and cognitive abilities in depressed PD patients

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Objective: To examine the relationship between degree of apathy and cognitive functions in Parkinson's disease (PD) patients with depression.

Background: In PD, apathy can be one of the clinical expressions of a depressed state, but it may also occur without depression, suggesting that features of apathy may not be secondary to the mood state. In fact, the "apathy" noted in these patients may be more cognitively- than affectively-based. Given that apathetic behavior may reflect frontal type initiation deficits, we explored if the degree of apathy had a relationship to "frontal" type cognitive functions in depressed patients with PD.

Methods: Study participants were 27 (age: M=66.96 SD=10.67) with a Hoehn and Yahr stage ranging between I and IV. Inclusion criteria were the presence of depression as revealed by a Hamilton Depression Scale-17 score>12 (range 14-17), and the absence of dementia (MMSE score>24). A k-means cluster analysis based on the Apathy Scale total score resulted in two groups: those with a low (L) or high (H) degree of apathy features. Performance of the two groups on the neuropsychological measures (CVLT-II short form; D-KEFS Trails; WCST-64) was then compared using t-tests.

Results: 12 patients constituted the H-apathy group (cluster center=55) and 15 the L-apathy group (cluster center=42). The groups did not differ in terms of age, years of education, and Hoehn and Yahr stage ($p>0.45$); there was a trend for longer disease duration in the H-apathy group ($p=0.07$). The H-apathy group showed worse visual scanning speed (Trails Trial 1 $p<0.03$), verbal recall (long delay free and cued recall $p<0.04$), and problem solving skills (WCST-64 NPE $p<.04$) compared to the L-apathy group.

Conclusions: Despite similar levels of depression, there appear to be subtypes of this mood disorder in PD patients; that is, those with more or less symptoms of apathy. The PD group with more pronounced apathy symptoms showed significantly poorer performance on tasks exploring attention, verbal memory retrieval, and problem solving ability. These cognitive skills rely on fronto-subcortical circuits suggesting that in this subgroup, apathy may reflect cognitive dysfunction (e.g., impairment in initiating goal-directed behavior often associated with disruption of prefrontal cortex), rather than symptoms of an affective disorder.

We-214

Hallucinations/vivid dreams in Parkinson's disease patients. Preliminary results from the French PARKMIP/COPARK cohort study

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Objective: To assess the prevalence, associated factors and progression of HVD in the first 329 patients of the PARKMIP/COPARK cohort who reached the 24-month visit.

Background: Hallucinations/vivid dreams (HVD) are common problems in Parkinson's disease (PD).

Methods: Inclusion criteria: ambulatory outpatients randomly selected by 28 neurologists, UKPDSBB diagnostic criteria, MMSE>24, no deep brain stimulation. Data collection: demographics, UPDRS and Hoehn & Yahr, antiparkinsonian treatments, anxiety and depression symptoms (HADS), sleep quality (PSQI) and quality of life (PDQ39). Presence of HVD was defined as UPDRS I item $2 \geq 1$. Statistical analysis: bivariate and logistic regression analysis.

Results: Data could be analyzed in 280 patients [49 could not be assessed at 24 month because of death (19 cases) and UPDRS missing data (30 patients)]. At baseline 72/280 patients (25%) had HVD. The main factors associated with the presence of HVD at baseline were: longer PD duration ($p<0.0002$), lower MMSE score ($p<0.0001$), greater UPDRS score and Hoehn & Yahr stage ($p<0.001$ for both), greater depression score ($p<0.0005$), worse PSQI score ($p<0.02$), longer duration and greater dose of levodopa therapy ($p<0.001$), amantadine treatment ($p<0.01$) and poorer PDQ39 score ($p<0.01$). Logistic regression showed that PD duration $>$ 5 years, MMSE $\leq$ 28 and presence of depression symptoms (HADS $>$ 7) were independently associated with the presence of HVD ($p<0.05$ for all factors). At 24-month 98/280 patients (35%) had HDV. Sixty-five patients (23%) showed a worsening of HVD score after 24-months follow up. Patients with HVD score worsening had higher frequency of depressive symptoms ($p<0.001$) and of cardiovascular disease ($p<0.001$) at baseline. The logistic regression analysis found that cardiovascular disease (OR= 2.1, 95%CI=1.2-3.8) and depressive symptoms (HADS-D $>$ 7, OR= 2.9, 95%CI=1.6-5.3) were independent predictors of HVD worsening.

Conclusions: In the PARKMIP/COPARK PD cohort, 25% of the patients exhibited hallucination/vivid dreams at baseline. After 2 years of follow-up 23% of the patients showed some deterioration in HVD score (UPDRS I item 2), which was associated with older age and presence of depressive symptoms at baseline.

We-215

Effect of cognitive dual-task on balance in Parkinson's disease

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Objective: Determine the effect of a concurrent cognitive task on balance in Parkinson's disease.

Background: It has been hypothesized that people with Parkinson's disease (PD) attempt to compensate for poor automatic balance control by using more cognitive attention than control subjects. In this study, we examined the effect of distraction with a concurrent cognitive task on recovery of equilibrium and postural preparation in a forced-stepping task.

Methods: Ten subjects with PD and freezing of gait (UPDRS Motor score 36±7 "OFF" medication, and 17±12 "ON" medication) and 10 control subjects participated. Subjects stood on a backwards-translating platform, forcing the subjects to step or fall into a harness. Subjects performed trials while focusing on either their balance or a concurrent cognitive task (listing items). Changes in the ground-reaction forces were recorded with a dual force plate, yielding data on the number, amplitude, and latency of anticipatory postural adjustments (APAs) before a step. The number falls were also recorded.

Results: Falls were more frequent when PD subjects were distracted by a cognitive task than when focusing on their balance ($p=0.032$). When OFF, PD subjects fell in 52% of trials with a cognitive task compared to 32% when focused on balance (Fig. 1A). When ON, PD subjects fell in 22% of trials with a cognitive task and 11% of trials when focused on balance. In contrast, control subjects never fell. The latency to the postural response was longer when the PD subjects were distracted by the cognitive task ($p=0.042$ ON; $p=0.045$ OFF). During a cognitive task, the APA onset latency was 543 ms longer for PD ON and 825 ms longer OFF (Fig. 1B). Control subjects did not increase the latency of their APAs during dual tasking. Anti-parkinsonian medication did not change the number, peak amplitude or APAs latencies.

Conclusions: Our results suggest that PD subjects use more cognitive attention than control subjects to recover equilibrium in response to an external perturbation. Distraction with a cognitive task delays

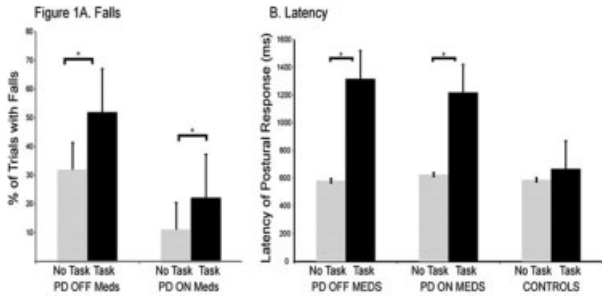

FIG. 1 (We-215).

APA onset, resulting in more falls. This effect of the cognitive task does not change with anti-parkinsonian medication, suggesting that nondopaminergic pathways are involved and that falls when responding to slips and trips will remain prevalent while attending to a secondary task in the on state.

We-216

Implicit sequence learning on the serial reaction time in Parkinson's disease: The effects of training hand and repeated testing

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Objective: To examine the effect of hand used for training and repeated testing on implicit sequence learning on the probabilistic serial reaction time task (SRTT) in Parkinson's disease (PD).

Background: Relative to age-matched controls patients with PD show attenuated implicit sequence learning on a probabilistic SRTT (Wilkinson & Jahanshahi, 2007). There is some suggestion that implicit learning tasks are subject to proactive interference (interference of previous learning with new learning) effects similar to explicit memory tasks, but little evidence on such transfer effects is available for the probabilistic SRTT.

Methods: 8 (5 males) PD patients (mean age=53.2 years, SD=7.8) and average duration of illness of 9.0 years, assessed "on" medication, and 15 (8 males) healthy controls, (mean age= 60.8 years, SD=6.8) took part in the study. None of the participants were depressed or demented and all were right-handed (Edinburgh handedness inventory, PD=75.2%, controls=87.1%). All participants performed 15 blocks of 100 trials of a probabilistic SRTT, with the right and the left hand, using parallel sequences and with the order of assessment of the two hands counterbalanced in each group.

Results: Both groups showed implicit sequence learning on the SRTT, but the learning was significantly greater for controls than the PD patients. Across the two groups, the extent of sequence learning on the SRTT did not differ for the right and left hands. Sequential training on two parallel forms of the SRTT with the right and left hands was associated with proactive interference effects, i.e. reduced learning of the second sequence for the controls and to some extent the patients.

Conclusions: Relative to controls PD patients showed significantly attenuated implicit sequence learning on the probabilistic SRTT. Training with the right and left hands did not influence the extent of learning. The results suggest that learning on the probabilistic SRT is susceptible to proactive interference effects, observed for controls and to a lesser extent the patients.

We-217

Decision-making in Parkinson's disease patients with and without pathological gambling

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Objective: To analyze decision-making processes in Parkinson's disease (PD) patients with and without pathological gambling (PG).

Background: Pathological gambling in PD patients is a frequent impulse control disorder associated mainly with dopamine replacement therapy. Decision-making impairments have been described independently in PG and PD, yet decision-making processes in PD patients with PG has seldom been studied.

Methods: Seven PD patients with PG (defined by DSM-IV, South Oaks Gambling Screen and the Minnesota Impulsive Interview) and 7 age-, sex-, education- and disease severity-matched PD patients without PG or any other impulse control disorder were enrolled in the study. All patients were assessed with a comprehensive neuropsychiatric and cognitive evaluation, including tasks used to assess decision-making abilities under ambiguous or risky situations, like the Iowa Gambling Task (IGT), the Game of Dice Task and the Investment Task.

Results: PD patients with PG were younger at PD onset (52.0±5.6 vs 59.4±4.5, $p<.026$). PG patients obtained a lower score than non-PG patients in the IGT (-20.3±12.4 vs. 3.7±6.6, $p=.001$) and in the Social Behavior Questionnaire (3.1±0.5 vs 4.1±0.5, $p=.009$). No significant differences between groups were found for the GDT and the Investment Task.

Conclusions: Low performance in decision-making under ambiguity and abnormal social behavior distinguished PD patients with PG from those without this disorder. Dopamine replacement therapy may induce dysfunction of the ventromedial prefrontal cortex and amygdala-ventral striatum system, thus increasing the risk for developing PG.

We-218

Neuropsychological differences between Parkinson's disease patients with and without mild cognitive impairment

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Objective: To determine the specific differences in the cognitive profile between Parkinson's disease (PD) patients with and without mild cognitive impairment (MCI).

Background: PD is often associated with cognitive impairment and dementia. The presence of mild cognitive impairment in PD (PD-MCI) was found to be associated with increased risk of subsequent dementia. Furthermore, the mild cognitive changes in nondemented PD patients were also determined to affect quality of life. However, the differences in the neuropsychological profile between PD patients with and without MCI are still unclear.

Methods: We investigated 40 cognitive intact PD patients, 35 patients with PD-MCI (modified Petersen's criteria) and 42 normal elderly controls. All subjects underwent a comprehensive neuropsychological assessment.

Results: Relative to controls, PD group showed significant deficits in digit span backward ($p<0.02$), TMTA ($p<0.01$), TMTB ($p<0.03$), phonemic fluency ($p<0.01$), Stroop test ($p<0.05$) and Wisconsin card sorting test ($p<0.02$). Compared to PD group, patients with PD-MCI demonstrated significantly lower scores on much more cognitive measures, including also immediate ($p<0.01$) and delayed free recall ($p<0.001$), as well as immediate ($p<0.02$) and delayed total recall ($p<0.04$) of the Free and Cued Selective Reminding Test, digit span forward ($p<0.02$), and semantic fluency ($p<0.001$). However, this group was unimpaired on recognition memory, Boston naming test, Clock Drawing test and copy of complex designs.

Conclusions: Slight impairments in psychomotor speed, selective attention, initiation and strategic searching, cognitive flexibility, concept formation and inhibitor control were observed even in patients, who did not come to the stage of MCI. Moreover we found, that the PD-MCI exhibited broader cognitive impairment with short-term and episodic memory domains affected, alongside the more profound attention and executive deficits. More prospective studies are needed to understand the longitudinal course of early cognitive changes in PD and to determine which of them represent a precursor to MCI and eventually dementia.

We-219

Dementia in Parkinson's disease – Correlation with phenotype of the disease and behavioral changes

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Objective: To estimate the prevalence of mild cognitive impairment (MCI) and dementia in patients with Parkinson's disease (PD) and correlation with age, severity of the disease, behavioral changes.

Background: The frequency of dementia in patients with PD is about 30- 35%. The etiology are not known, but old age, severity of

the disease and behavioral and personality changes are predictive factors for cognitive impairment.

Methods: Three hundred and sixteen consecutive patients with PD were included in the study. The assessment included comprehensive neurological and psychiatric examinations and a battery of neuropsychological test.

Results: The frequency of dementia is 8,32%, mostly is mild dementia. Whereas 19,7% were diagnosed with MCI (amnestic multiple domains is frequently). Age, presence of behavioral symptoms were shown to be significant predictive factors, as well as axial parkinsonian signs.

Conclusions: These data suggested that PD patients with more prominent axial signs, older age and behavioral changes are in higher risk for developing cognitive impairment.

We-220

Deficiency to divide in patients with Parkinson's disease: Correlation with gait and balance dysfunction

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Objective: The aim of this study was to investigate the correlation between ability of patients with Parkinson's disease (1) to divide attention between two stimuli; and (2) to sustain attention during one extensive task, with gait and balance performance.

Background: Of all PD motor symptoms, postural instability is one of the most incapacitating, where loss of motor independence by patients. Physiotherapy, in conjunction with medication, plays an important role in the treatment of this symptom, although no consensus has been reached on the best approach to the problem. Recently, several studies have proposed that deficiency in dividing attention associated to the disease, may be one of the factors responsible for this postural instability.

Methods: A total of 30 PD patients participated in this study, having a mean age of 68.08 years, at stages 2 and 3 of Hohen and Yahr, along with 30 healthy subjects, paired for age, gender and schooling. Initially, all subjects were submitted to the Mini-mental State Exam, Beck Depression Inventory and Apathy Scale from Starkstein, UPDRS to assess general cognitive functions, depression, apathy, gait and balance performance respectively. In the first psychophysical experiment the ability to divide attention and in a second experiment, the ability to sustain attention. In both experiments, the subject had to respond as fast and correctly as possible to the presentation of the stimulus (Reaction Time -RT).

Results: PD patients showed significant impairment in the dividing attention experiment in terms of coincident correct responses ($p<0.01$), and the sustaining attention experiment in terms of total number ($p<0.01$) of correct responses, and correct responses in the final blocks ($p<0.01$). No significant differences in terms of RT were found between groups for either experiment. Additionally, the hampering of divided attention correlated with gait and balance dysfunction ($p<0.01$).

Conclusions: PD patients showed a deficiency in dividing and sustaining their attention, independent of mental and cognitive status, suggesting an important relationship between dopamine circuits and these modules of attention, which contribute which gait and balance deficiency these patients.

We-221

Dual task training enhances motor and attentional deficits in patients with Parikinson's disease

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Objective: The present study matched the effects of two motor trainings performed with perceptual tasks of different complexities (visual and auditory distracters). Supposedly, these tasks performed together would demand more attentional resources and would impair the task performance in the: (1) steps task evaluated separately and in dual-task condition; (2) both visual and auditory perceptual tasks; (3) neuropsychological and psychophysical tests, which verifies the attentional control and; (4) gait itself.

Background: The Parkinson's disease (PD) is one of the degenerative disorders of the Central Nervous System that has been discussed both in clinical and experimental researches. Despite the motor symptoms, and not less important, subjects with PD may suffer from impairment in the cognitive functions, such as memory and attention. Then, subjects with PD have shown a significant difficulty in performing two tasks simultaneously, known as "dual-task". Due to the great effort of these subjects in managing the attention into more than one task at the same time, the main procedure within physical therapy is training with external cues and attentional strategies, besides the approach to avoid dual-task situations.

Methods: Forty three subjects were divided in four groups that performed a step task (alternating feet) associated with visual and auditory tasks of different complexities, alternating on each block of training. The study was divided according with the complexity of the distractive tasks, and was carried out in two days, with a 48 hours interval, composed of 8 blocks of 100 steps each day.

Results: The results displayed that the training, disregarding its complexity, increased the outcomes ($P < 0,001$) of the: (1) motor task when tested separately or in addition with perceptual tasks; (2) perceptual tasks when tested separately or concurrently with the motor task; (3) attentional neuropsychological and psychophysical tests and; (4) gait speed when tested alone and concurrently with cognitive tasks, both in patients with PD and healthy elders.

Conclusions: This study's outcome implies that training on dual-task situation has been efficient to enhance the motor and cognitive deficits in patients with DP, being generalized to tasks that demand the same skills.

We-222

Deficiency to divide attention in patients with Parkinson's disease: Psychophysical results

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Objective: Thus, the aim of this study was to investigate the ability: (1) to divide the attention between two stimulus; and (2) to sustain the attention during one extensive task.

Background: The attention has the function to select the relevant information for a specific behavior, allow that this information can be process faster and better. The basal ganglia have an important function for recruitment and selection of attention stimulus. Parkinson's disease (PD) there is a severe harm of basal ganglia functions consequently of dopamine depletion, patients can develop impairment of attention.

Methods: Participated this study a Experimental Group (EG) 50 patients with PD, mean age of 68,08 years (SD=6,29), in stage 2 and 3 Hohen and Yahr Classication, and a Control Group, with 30 health subjects, age, gender and school level pared, with mean age of 63,17 (SD=9,61 years). All patients signed the term of consent. Initially, all subjects were submitted by Mini-mental Exam, Beck Inventory and Starkstein Apathy, to assess general cognitive functions, depression and apathy, respectively. The symptoms of PD were evaluated by Unified Parkinson's disease Rating Scale (UPDRS) only in the EG. In a first psychophysical experiment was studied the ability to divide the attention and in a second experiment, was studied the ability to sustain the attention.

Results: PD patients showed significant prejudice in divide attention experiment in terms of coincident correct responses (ANOVA, group effect: $F= p<0,01$), and sustain attention experiment in terms of total number and correct responses and correct responses in the late blocks (ANOVA, group effect $F=$, $p<0,01$; $F=p<0,01$, respectively). In both experiments was not found significant differences in terms of RT, between groups. Additionally, the hamper of divided attention was correlated with progression if disease (Pearson, $p<0,01$).

Conclusions: PD showed a deficiency to divide and to sustain their attention, independent of mental and cognitive status, o that suggest a important relation between dopamine circuits and this modules of attention.

We-223

Impairment in communicative effectiveness in Parkinson's disease

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Objective: 1) Evaluate patient-reported communication abilities in those with idiopathic Parkinson's disease (IPD); 2) Investigate the degree of concordance between IPD patient perceived communication effectiveness and clinician rated speech intelligibility; and 3) Determine the relationship between IPD disease duration and severity with patient reported communication effectiveness and clinician intelligibility ratings.

Background: A reported 90% of individuals with IPD develop dysarthria during the course of their disease (Sapir et al., 2008), but the impact on functional communication abilities from the patient's perspective and across different stages of the disease progression is unstudied. The Communication Effectiveness Survey (CES) (Donovan, Velzo & Rosenbek, 2007) comprising 8 questions affords a functional index of communication abilities.

Methods: One hundred and twenty-seven patients diagnosed with IPD completed the CES and an experienced Speech-Language Pathologist rated conversational speech intelligibility. Descriptives and a series of Spearman's Rho correlations between the CES score and: 1) clinician rated speech intelligibility; 2) disease duration; 3) Hoehn and Yahr Score; and 4) UPDRS 'on' score were calculated.

Results: Mean CES score was 29.4 (sd=9.42) suggesting perceived difficulties with communication across a variety of situations. Order of difficulty was: 1) conversations with family at home; 2) conversing with a familiar person over the telephone; 3) talking with strangers in a quiet place; 4) speaking in a traveling car; 5) conversing with a stranger on the telephone; 6) speaking with a friend when emotionally upset; 7) having a conversation with someone across the room; and 8) talking in a noisy environment. On average, clinician intelligibility ratings were 82.5% (sd=20.8). CES scores were significantly correlated with clinician intelligibility ratings and IPD disease duration, while clinician rated speech intelligibility was significantly correlated with the UPDRS 'on' score and Hoehn and Yahr stage.

Conclusions: These data highlight important issues IPD patient's have with communicative effectiveness and offer interesting notions about the implications for evaluation and treatment of dysarthria in IPD. Future investigations will need to focus on novel ways to improve impaired domains.

We-224

Motor imagery in Parkinson's disease

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Objective: The aim of the study was to investigate the influence of cognitive function on Motor imagery (MI).

Background: In recent years MI has been included in rehabilitation programmes. There is some evidence that MI is dependent on cognitive function. Since executive dysfunction occurs early in Parkinson's disease (PD), we wondered whether MI can be used in rehabilitation of PD.

Methods: 40 PD-patients (Ø age: 62,7 ± 9,6 years; H&Y stage: 2-4) and 20 controls (Ø age: 62,5 ± 8,2 years) participated in the study. All subjects completed the Vividness of Movement Imagery Questionnaire (VMI). Cognitive function was assessed using the Mini Mental State examination (MMSE) and the SCOPA-COG. Patients and controls were asked to walk 6m, 12m, 24m with turn (w.t.) and without turn and to imagine walking the same distances. The patients had 10 sessions for practising MI prior to the test.

Results: Demographic data and MMSE-scores did not differ between patients and controls. There was a significant difference (t=–10,05, df = 58, p< 0,001) in the SCOPA-COG between PD-patients (26,9 ± 4,40 pts) and controls (37,8 ± 2,84 pts). PD-patients scored higher in the VMI-Questionnaire (lower performance). There was a significant inverse correlation between the results of the SCOPA-COG and the VMI questionnaire ($r = -0{,}666$, $p < 0{,}001$). The time to walk the distances did not differ between PD-patients and controls. However, in contrast to the controls PD-patients needed significantly more time for the imagined than for the physical walks. The percentaged time difference between real and imagined walking correlated inversely with the results of the MMSE (all distances between $r = -0{,}314$ and $r = -0{,}411$, $p < 0{,}001$) and those of the SCOPA-COG (6m: $r = -0{,}432$, $p < 0{,}001$; 12m: $r = -0{,}668$, $p < 0{,}001$; 24m w.t.: $r = -0{,}761$, $p < 0{,}001$; 24m: $r = -0{,}819$, $p < 0{,}001$) in both groups. The results of the VMI score correlated positively with the percentaged difference between real and mental walking (all distances between $r = 0{,}821$ and $r = 0{,}892$, $p < 0{,}001$).

Conclusions: The time needed for imagined walking differed more from the time needed for walking in PD-patients and controls with lower performance in executive function tests and the VMI. Since PD-patients showed a lower performance in both tests they also had more difficulties in MI. However, all patients managed to adopt MI. Thus, MI seems to be applicable for rehabilitation of PD.

We-225

Executive function based on semantic memory is impaired in Parkinson's disease without dementia

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Objective: To evaluate verbal recall in patients with PD without dementia.

Background: Cognitive impairment plays a role in Parkinson's disease (PD) and has important consequences for patient management. The dysexecutive syndrome has been extensively shown as the typical cognitive disturbance in PD. However, the detailed profile of cognitive impairment remains unclear since several functions have not been properly assessed yet.

Methods: We developed a simple test to explore executive function based on semantic memory: the stimulus consisted of ten sheets with 4 pictures of objects each, three of these objects had number, shape or colour features in common and the fourth one had totally different features. Participants were asked to point out the different one.

Results: Patients with PD scored significantly lower than controls (Parkinson: 14,57 (DT 4,34), controls: 16,63 (DT 2,40) being this difference statistically significant (p<.005).

Conclusions: In addition to other cognitive functions, executive function based on semantic memory is impaired in PD without dementia.

We-226

Prevalence of Parkinson's disease dementia according to the clinical diagnostic criteria proposed by Movement Disorders Society

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Objective: The goal was to describe the prevalence of Parkinson' disease Dementia in a Brazilian sample of PD patients according to The *Movement* Disorders Society diagnostic clinical criteria.

Background: Dementia associated to Parkinson's Disease prevalence (PDD) is aproximately 30% and annual conversion rate to dementia in Parkinson's disease is about 15%. *Movement* Disorder Society (MDS) has recently developed clinical diagnostic criteria for Parkinson's disease dementia.

Methods: Ninety PD patients were submitted to neurological evaluation to assess clinical aspects of disease by using UPDRS, Hoehn & Yahr and Schwab & England scales. All patients were submitted to comprehensive neuropsychological evaluation that included memory tests (RAVLT, Logical Memory, Visual Reproduction, Figure Complex of Rey, semantic verbal fluency category animals, digit span), executive functions (Trail Making, FAB, FAS test) and attention tasks (Trail Making test). Functional activities were evaluated by Disability Assessment for Dementia scale. MMSE and Beck Depression Scale were used as screening tools.

Results: The study group consisted of 55 women, with mean age of 67.4 years (SD 11.22), mean age at on onset of disease was 57.22 years (SD 17.7), mean diase duration of 7 years (SD 5.48) and mean years of schooling was 4.3 years (SD 3.57). MMSE mean score was 23 (SD 4.19), BDI mean score were 12.3 (SD 8.7). Hoehn &Yahr score mean was 3,5 (SD 7,6), Schwab & England mean score of 74,4 (SD 19,2) and UPDRS mean score of 50,8 (SD 21). The prevalence for PDD was about 30,2 % for probable PDD and 29,2 % for possible PDD. ANOVA analysis compared performance of PD X PDD groups, revealing group effect for age ($p < 0.003$; PDD > PD 64.5 +-10 years), age at onset of PD ($p < 0, 03$; PDD > PD), years of schooling ($p < 0,003$; PDD < PD) and quality of life scores ($p = 0.03$; PD > PDD). There were no group effects for disease duration of PD and severity of disease.

Conclusions: The prevalence of PDD on this sample was similar to those reported by others studies. Age and age at onset of disease was identified as risk factors for PDD. On the other hand, years of schooling seemed to have a protective effect on PDD incidence, reinforcing cognitive reserve concept.

We-227

Parkinson's disease dementia prevalence rates according to diagnostic levels proposed by Movement Disorder Society

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Objective: This study aimed to evaluate the sensibility of Level I testing as a screening tool for the diagnosis of Parkinson's disease dementia.

Background: *Movement* Disorder Society has recently developed clinical diagnostic procedures for Parkinson's disease dementia (PD-D), establishing diagnosis on two levels process. Level I consists in a brief evaluation conduced by a clinician while Level II consists in neuropsychological evaluation which is more suitable to specify the severity of dementia.

Methods: Ninety PD patients were submitted to diagnostic procedures proposed by MSD for PD-D. At level I, cognitive functioning were measured by performance on lexical fluency tests, subtests of MMSE and activities for dailing living was evaluated using Pill questionnaire. Level II was composed by comprehensive neuropsychological evaluation that included memory tests, executive functions and attention tasks. Functional activities were evaluated by Disability Assessment for Dementia (DAD) scale. MMSE and Beck Depression Scale (BDI) were used as screening tools on both of the procedures.

Results: The study group consisted of 55 women and 45 men with a mean age of 67.4 years (SD 11.22), mean age at on onset of disease of 57.2 years (SD 17.7), mean disease duration of 7 years (SD 5.5) and mean years of schooling was 4.3 (SD 3.6). MMSE mean score was 23 (SD 4.2), BDI and DAD means scores were 12.3 (SD 8.7) and 71 (SD 7.2), respectively. The prevalence for PD-D varied according to diagnosis procedures adopted. According to Level I procedures, 5 % of patients evaluated were demented while Level II diagnosed 30% of the sample as having PD-D.

Conclusions: The rates of Parkinson's disease dementia diagnosis were different according to the process levels adopted, suggesting that the diagnosis of dementia is very low when the Level I is used as diagnostic criteria or screening tool. It could means that Pill questionnaire and cognitive assessment by MMSE subtests and others screening tests are not sensible enough to ascertain dementia in Parkinson's disease. Moreover, it shows the importance to evaluate basic and instrumental aspects of daily living activities. Educational and cultural aspects must also be considered in cognitive domains functioning evaluation.

We-228

Action verbal fluency in DP patients

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Objective: To evaluate the performance of Parkinson's disease (PD) patients in the action (verb) fluency task.

Background: Several neuroimaging and clinical studies have shown that verb retrieving requires a privileged participation of the pre-frontal structures which are dysfunctional in PD. Furthermore some studies suggested that the action (verb) fluency was more sensitive to the integrity of fronto-subcortical circuits and it was a valid measure of the linguistic and executive functions.

Methods: We compared the performance in semantic, phonemic and action verbal fluency tasks of 31 Parkinson's disease patients against 61 healthy controls. Changes of behavioral dysfunction were evaluated with the "The Frontal Behavioural Inventory (FBI)" and cognitive impairment was screened with MMSE. The Evaluation of depression was made with "The Center for Epidemiologic Studies Depression Scale (CES-D)". All patient were on dopaminergic medication.

Results: Mean disease duration of PD was 9.8 years (SD 6.13). There were no age ($U=899.5$, $p=0.616$) gender (Chi-Square$=0.00$; $p=1.00$) or literacy ($U= 956$; $p=0.96$) differences between the two groups. The action verbal fluency task was the only fluency task that showed statistical significant differences between the groups ($U=406.5$ $p=0.00$). The education level was the only biographic variable that affected the action (verb) fluency so there was no effect of gender, age or years of disease duration.

Conclusions: Our findings suggest the existence of a relationship between the diseased mechanisms in PD and a specific verb deficit, and also that this deficit may emerge before patients show clear signs of a cognitive decline. Moreover, our results did not find any verbal fluency deficit in the traditional verbal fluency tasks. The results support the validity of the action (verb) fluency as an executive function measure and suggest that this task provides some unique information not contemplated in traditional executive function tasks.

Th-207

Gender specific impact of antiparkinsonian medication on mood and cognition

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Objective: We aimed to analyse the impact of antiparkinsonian drugs on mood and cognition of Parkinson's disease (PD) patients, as well as a putative association of mood and cognition and the clinical phenotype.

Background: A variety of non-motor symptoms, in particular depression and dementia, are associated with PD.

Methods: 125 PD patients, who attended the PD clinics, were included in the analysis. All patients were examined using the Parkinson Neuropsychometric Dementia Assessment (PANDA), Mini-Mental State Exam (MMSE) and the Hamilton Depression Scale (HAMD). Crystalline intelligence was estimated by the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B). PD patients were grouped according to clinical subtype: tremor-dominant, akinetic-rigid and equivalent type, antiparkinsonian medication and Hoehn and Yahr. Multivariate analysis of covariance was controlled for duration of disease and age of patients.

Results: Our preliminary analysis includes 100 patients with idiopathic PD (67 male/33 female) with a mean duration of disease of 62,5 months (SD=56,5). Mean age was 69 years (SD=8,8). No sig-

nificant differences between male and female patients with regard to psychological parameter (MMSE male m(SD)=28(2)/female 29(2)) and the variables "age" (male and female m(SD)=69(9)) and "duration of disease" (male m(SD)=63(56)/ female 63(59)) were found. MANCOVA revealed a positive effect of amantadine and amantadine in combination with dopaminergic drugs in the MMSE and PANDA. Mood was affected positively by amantadine, too, but only in combination with MAO-B-inhibitors. Mood parameters in female patients depended on the clinical phenotype. Patients with an akinetic-rigid type had significant higher scores in the scales measuring depressive symptoms compared to female patients with tremor-dominant or equivalent type.

Conclusions: The results suggest that amantadine exerts a favorable effect on cognition. In combination with MAO-B-inhibitors, amantadine also improved mood in female PD patients. Gender specific differences of metabolization of levodopa and gene expression profiles in CNS tissues have already been established, but little research under consideration of these findings was conducted. The preliminary results of our study suggest that optimization of PD patients treatment must consider gender specific phenomena.

Th-208

Detecting functionally significant cognitive impairment in PD

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Objective: To evaluate the ability of the Montreal Cognitive Assessment (MoCA) to detect functionally significant cognitive impairment in patients with Parkinson's disease (PD).

Background: The MoCA has demonstrated high sensitivity to cognitive impairment in PD. Whether or not it is sensitive specifically to cognitive impairment affecting activities of daily living (ADLs) has not been determined.

Methods: Parkinson's disease patients over 60 years of age were tested for cognitive status using two brief assessments, the Mini-Mental State Examination (MMSE) and the MoCA, and one longer assessment, the Mattis Dementia Rating Scale-2 (DRS-2). Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) data were obtained from a knowledgeable informant as a measure of daily function. Analyses were adjusted for potential confounders including age, gender and motor impairment as rated by the Unified Parkinson's Disease Rating Scale (UPDRS).

Results: After adjustment for age, gender and motor impairment, the MoCA and the DRS-2 totals both correlated with ADCS-ADL score, while the MMSE total showed a weaker, non-significant correlation ($r = 0.356$; $p = 0.081$). Of the three tests, the MoCA correlated most strongly ($r = 0.473$; $p = 0.017$), followed closely by the DRS-2 ($r = 0.443$; $p = 0.027$). The MoCA explained 22.4% of the variance in ADCS-ADL score, compared with 12.7% for the MMSE.

Conclusions: Our data suggest that the MoCA, a brief cognitive measure appropriate for routine clinical use, is a significant predictor of cognitive impairment contributing to ADL dysfunction. It is a better predictor than the MMSE, a tool of similar length, and at least on par with the more time-intensive DRS-2.

Th-209

^{1}H MRS for determination of therapeutic efficacy in PIRIBEDIL-treated patients with Parkinson's disease (PD)

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Objective: The concept of dementia in patient with PD implies a direct association between brain damage from PD and degree of cognitive dysfunction sufficient to cause of dementia.

Background: We propose the quantitative indicators for the characteristics of the therapeutic efficacy in patients with PD and cognitive dysfunction after two month course monotherapy treatment by Piribedil (150 mg/day)–nonergolinic dopamine agonist's receptors.

Methods: Three groups of patients are studied by 1H MRS with 1.5T SIGNA EXCITE (GE). The 1st group (TPG) includes 14 Piribedil-treated subjects with PD and cognitive dysfunction. The 2nd group (PG) includes 15 untreated subjects with PD. The 3nd group (VG) consists of 20 healthy volunteers. For subjects of TPG and PG the spectra are obtain in the putamen, in the central part of hippocampus, in the gray matter of brain (occipital lobe), and in the substantia nigra.

Results: We found a significant reduction in NAA/Cho ratios from the putamen contralateral to the most affected side in the PG, but not in the TPG group compared with VG. In untreated patients reduced putaminal NAA/Cho ratios may reflect loss of nigrostriatal dopamine terminals or alternatively indicate a functional abnormality of striatal putaminal neurons, such as membrane dysfunction due to striatal deafferentation. In patients with PD the content of Cho in the SN is substantially above, and NAA are below in comparison with the subjects of VG. For all patients with PD before the beginning of treatment the decrease of NAA/Cr ratio in the central part of hippocampus is characteristic, but there is no dependence between the decrease of NAA/Cr ratio, with the degree of movement disorders and with the duration of disease. In occipital lobe the value of NAA/Cho and Cho/Cr for the patients with PD and subjects of the VG the nonsignificantly differences, and in the region of basal ganglia–it is substantial. Increase of the NAA and Cr concentration and decrease of Cho content can be used for the comparative estimation of the efficiency of Piribedil.

Conclusions: Quantitative characteristics of various brain structures integrity, provided by MRS data, may serve to derive markers of therapeutic efficacy of Piribedil which aim at slowing or even stopping the progression of cognitive dysfunction in patients with PD.

Th-210

Cognitive improvement after duodenal levodopa infusion in Parkinson's disease

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Objective: To study the effects of continuous duodenal levodopa infusion therapy (DLI) on the cognitive performance of two patients affected by Parkinson's disease (PD).

Background: Dementia is considered an exclusion criteria for PD surgery and apomorphine pump, but the efficacy and safety of DLI in patients with PD and cognitive impairment has not been assessed.

Methods: A 73-year-old man with 17 years of PD and a 75-year-old woman with 10 years of PD, both with uncontrolled severe motor fluctuations and a progressive cognitive decline in the last months, were assessed through a neuropsychological battery, MMSE and UPDRS before and after DLI.

Results: Both subjects presented a general impairment in all cognitive functions before treatment. After DLI both experienced a great motor improvement and all the cognitive functions were normalized except for motor sequences and perseverations in patient 1, and working memory and cognitive flexibility in patient 2. Patient 1: pre-treatment levodopa daily equivalent dose (DED) 1250mg, motor UPDRS score "on" 31/"off" 42, total daily "off" time 50%, MMSE 17/30, total Mattis score 102; at 24 months follow-up after DLI, levodopa DED was 1558mg, motor UPDRS "on" score 10, daily "off" time 12%, MMSE 23/30, total Mattis 124. Patient 2: pre-treatment levodopa DED 1700mg, motor UPDRS "on" 19/"off" 33, total daily "off" time 56,25%, MMSE 25/30; 2 months after DLI, levodopa DED was 1960mg, motor UPDRS "on" score 6, total daily "off" time 9.4%, MMSE 28/30.

Conclusions: DLI seems to improve cognitive performance in some PD patients through unknown mechanisms, probably including "off" time reduction, higher dose and stability of levodopa plasma

levels. The results must be interpreted with caution, as cognitive decline could be influenced by prolonged "off" periods, psychotic states, drug effects and other possible unrecognised factors. Further studies should be addressed to confirm these preliminary observations.

Th-211

Selective attention in Parkinson's disease: An investigation with the priming-of-popout paradigm

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Objective: This study investigated selective attention in people with Parkinson's disease (PD) using the Priming-of-Popout (PoP) paradigm.

Background: Attentional deficits have been previously reported in PD. The aim of this study was to investigate attentional deficits in PD with a new experimental Priming-of-Popout (PoP) paradigm that controlled for response selection deficits as a confounding variable, rarely done in previous studies.

Methods: 12 nondemented and non-depressed PD patients (64±6.5years, self-assessed Hoehn &Yahr: 2.4 (range:1-3.5)) and 12 age-matched controls (63±5.7years) participated. The PoP paradigm is a speeded reaction time task, and the participants were instructed to respond to the shape of an odd coloured target (singleton) while ignoring three distractors displayed in another second colour. By design, this task is well- suited to examine attentional pop-out effects, because it is possible to disambiguate the effect of colour, which is an attention-driven feature, from the effect of shape, which defines a specific response. There were two conditions in the experiment. In one (mixed) condition, the singleton colour varied randomly being either red or green. In the other (pure) condition, the participant was told at the beginning of the block which singleton colour (e.g. red) would occur throughout the entire block. We predicted that the RT difference between the mixed and the pure conditions would be greater for PD patients than age-matched controls. Furthermore, in the mixed condition, group differences in colour repetition/alternation effects were investigated.

Results: PD patients were generally slower in performing the PoP task ($p<.015$). Both controls and PD patients had increased reaction times in the mixed compared to the pure condition. The difference between these two conditions was 62ms larger in the PD than in the control group, and this group difference was marginally significant ($p<.08$). No difference was found between PD patients and controls when comparing colour repetition and alternation in the mixed condition.

Conclusions: These preliminary results suggest that selective attention deficits may be present in PD, even after controlling for the confounding effects of response selection.

Th-212

Stochastic sequence learning in Parkinson's disease

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Objective: Previous studies have shown that in a probabilistic selection task, learning from positive or negative feedback is differentially affected by PD and the dopaminergic medication used to treat it. However, previous studies have not directly examined these effects during learning, but rather have shown deficits after learning during transfer. The aim of the present study was to examine stochastic sequence learning in PD patients.

Background: A growing body of evidence suggests that dopamine plays a key role in reinforcement learning. Animal studies have shown that phasic bursts of dopamine neurons are observed after reward, whereas the firing of dopamine neurons drops below baseline after choices that do not result in reward. Therefore, disruption of the midbrain dopamine system as in PD may lead to deficits on tasks that require learning from positive and negative feedback.

Methods: A group of medicated PD patients and age-matched healthy controls were assessed. Participants were required to learn sequences of four button presses from a choice of two buttons. After each button press, participants received feedback whether or not it had been correct. Importantly, the feedback was probabilistic (85% correct feedback). Thus, on 15% of the trials, even if the participants had pressed the correct buttons, the feedback informed them that they were incorrect. Their task was to use this "noisy' feedback to learn the correct sequence of button presses and then repeat it eight times. After participants had executed the sequence correctly eight times, a new sequence was introduced and the participants once again had to learn the new sequence by trial and error. We used a randomized block design with six sequences in each block, eight blocks in total.

Results: Both medicated PD patients and age-matched controls were biased to preferentially learn from positive feedback relative to negative feedback. We found that the medicated PD group required more trials to learn the sequences. Interestingly PD patients had a higher working memory than the control.

Conclusions: Our finding that medicated patients with PD showed increased sensitivity to positive feedback in stochastic sequence learning, may reflect a dopamine 'overdosing' effect in the fronto-striatal circuits which are less affected in PD. Future assessment of PD patients in the "off" medication state would be of interest.

Th-213

Defining the neurocognitive profile of an Ashkenazi Jewish (AJ) Parkinson's disease (PD) population with the LRRK2 G2019S mutation

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Objective: To assess the cognitive profile in PD patients having a LRRK2 G2019S mutation.

Background: Expression of the LRRK2 G2019S mutation is considered pleomorphic, with clinical and pathological descriptions including frontotemporal dementia, diffuse Lewy body, and Alzheimer's disease. However, most systematic studies do not find an association between this mutation and atypical parkinsonism/dementia. Further, clinical investigation of patients with LRRK2 G2019S PD support a profile of typical "idiopathic" disease. Whether this extends to cognitive function is unclear as this clinical sphere has not been well defined in the LRRK2 population. We hypothesize that PD patients with mutations will not differ from those without mutations on cognitive testing.

Methods: Consecutive Ashkenazi Jewish PD patients were recruited in an outpatient setting by movement disorder specialists, blinded to genotype, who performed a history and standardized clinical assessment. Mutation carriers were case-matched with mutation negative patients by age of disease onset, sex, and disease duration. All participants completed a battery of neuropsychological tests assessing frontal, temporal, and parietal lobe function. Tests included the Mini-Mental Status Exam (MMSE), Frontal Assessment Battery (FAB), Benton Judgment of Line Orientation (JLO) and the Hopkins Verbal Learning Test-revised (HVLT-R). Statistical analyses compared the test scores in the mutation positive and negative groups.

Results: Twenty-six LRRK2+ and 24 LRRK2- patients participated in the study. Mean scores in the LRRK2+ patients were MMSE =28.8, FAB =16.2, JLO =23.2, and HTLV-R = 5.92, 8.35, 9.38, 8.52, respectively for each of the trials. Mann-Whitney analysis showed no significant difference in testing performance between the mutation positive and negative group across all neuropsychological tests, although the LRRK2- performed slightly worse on all tests.

Conclusions: Neuropsychological assessment of 26 LRRK2+ patients revealed performances similar to a matched non-LRRK2 G2019S mutation. Our study suggests that PD patients with the

LRRK2 G2019S mutation do not have a significantly different neurocognitive profile compared to mutation negative PD.

Th-214

CSF biomarkers of AD in PD patients with and without cognitive impairment suggest a subset with concomitant AD

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Objective: To determine if established CSF biomarkers of AD pathology could detect the presence of co-existing AD pathology in a subset of PD patients with and without cognitive impairment.

Background: Up to 80% of elderly patients with Parkinson's disease (PD) develop meaningful cognitive impairment. The clinical profile is dominated by reduced cognitive processing speed and other measures related to subcortical and frontal lobe impairment. Decreased memory and cognitive functions that overlap with domains typically associated with AD may also be impaired. Additional overlap of these two late-life neurodegenerative conditions is documented by the co-existence of pathologic aggregations of synuclein, neuritic plaques, and hyperphosphorylated tau in as many as 2 out of 3 patients with Parkinson's disease and dementia.

Methods: Standardized clinical evaluations, including cognitive assessments and lumbar spinal fluid analysis were performed in 83 subjects; 38 PD, 7 PD dementia (PDD), and 38 elderly controls, participating in a longitudinal study of biomarkers of late-life neurodegenerative dementia.

Table (Th-214).

	PD	PDD	Control
N	38	7	38
Age*	71 (7.3)	77 (7.5)	71 (10.0)
UPDRS-motor score*	22 (10.2)	30 (7.9)	3 (5.4)
MMS*	28 (1.7)	22 (2.6)	29 (1.0)
DSM*	138 (4.3)	116 (6.5)	139 (6.1)

*Mean (SD)

CSF levels of total tau, p-taup181 and β-amyloid42 were determined using x-MAP Luminex technology.

Results: Applying neuropathologically confirmed AD diagnostic CSF threshold values to the biomarkers in the PD subjects revealed that 31% had a CSF Aβ42 level that was <192 pg/mL (consistent with a biomarker diagnosis of AD). The proportion was lower for p-tau181 and t-tau.

Table (Th-214).

	N (%)
Aβ42 pg/mL	14 (31%)
p-tau 181 pg/mL	10 (22%)
t-tau pg/mL	4 (9%)

There was no consistent relationship between the biomarker levels and global measures of cognitive function (DSM, MMS).

Conclusions: In an overwhelmingly non-demented cohort of PD patients, CSF Aβ42 levels associated with the diagnosis of AD was found in roughly one-third of PD patients. Global measures of cognitive function did not correlate with this finding, suggesting it may be possible to detect the presence of co-existing AD pathology in patients with PD prior to the expression of global cognitive impairment as measured by standard clinical tools. Expanding the study cohort, longitudinal follow-up, and the detection of amyloid using newly developed PET ligands may provide additional information.

Th-215

Three-dimensional analysis of gait of patients with Parkinson's disease during the accomplishment of the dual task

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Objective: The aim of this study was investigate the motor-cognitive dual task performance in Parkinson's disease patients during the gait.

Background: It is known that in Parkinson's disease (PD) occurs the depletion of the nigroestriatais neurons, producing of dopamina, causing loss of automatism of the movement. The Dual Task (DT) is prerequisite for a normal life since it allows the individual to walk and to direct its attention for motor and cognitive tasks.

Methods: Group PD (GPD) was composed for 14 patients, with DP Idiopatic with score between 2 and 3 in the scale of Hoehn & Yahr; control group (CG) had 9 subjects; both the groups had that to have a MMSE ≥24. For three-dimensional analysis of the gait System FALCON–Motion Analysis® was used. The angular and linear kinematics in two conditions were evaluated: Normal gait (NG), that is, without the DT and gait 500 (G500), where the individual was submitted to the one has tested arithmetical regressive (500–7). For statistics analysis used Mann Whitney test and Wilcoxon test.

Results: During the DT the GDP showed a lower step and stride length, increase in cadence. For cinematic angle during the M500 in the GDP reduction of pelvic anteversion, increased knee flexion during support and reduction of the angular plantar flexion movement in ankle during the gait cycle.

Conclusions: DT changed the kinematics and linear parameters compared to control group.

Th-216

Working memory and emotional face processing in Parkinson's disease

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Objective: We aimed to study visual working memory for faces with emotional expressions (angry, happy, neutral, sad and fearful) and also the ability to identify, rate intensity, arousal and valence of the emotions (disgust and surprise along with the other emotions) in PD patients on and off medication.

Background: Studies have shown that some patients with Parkinson's disease (PD) have difficulty identifying emotions of anger, fear and disgust.

Methods: Task 1. A visual working memory task was used–the subject was to remember and then recall the identity of faces with emotional expressions. Task 2. Faces with different emotional expressions were presented–the subject was to identify the emotion, state the intensity, arousal and valence of the emotion. 22 PD patients(fulfilling the UK PD Brain bank criteria) had carried out the above tasks on medication (Tasks 1b and 2b) and 20 of the same patients did the same tasks again while they were off medication (12 hours after last dose) (Task 2a and 2b). 22 age matched controls were included.

Results: Task 1. 1a. The visual working memory task showed that when off medication PD patients with a longer duration of illness seemed to be worse overall when compared to the controls but particularly for faces with expressions of anger, neutral and fear while those with a shorter duration of illness where as good as the controls except for neutral. 1b. When on medication PD patients with a longer duration of illness showed an improvement in their working memory for faces with expressions of anger, neutral and fear but were significantly worse remembering sad faces when compared to controls. Those with a shorter duration of illness were worse in their working memory for sad faces. Task 2a and b. Results from the face processing task showed that patients on and off medication had difficulty

identifying expressions of anger and were less aroused when compared to the controls.

Conclusions: From the above results we can conclude that patients with PD have disease related difficulty with visual working memory for faces with some emotions (anger and fear), which worsens as the disease progresses, but there is improvement with medication. But memory for sad faces seems to be impaired due to medication from early in the disease and this impairment continues later on in the disease.

Th-217

Detecting cognitive impairment in patients with Parkinson's disease by use the Addenbrooke's Cognitive Examination Revised (ACE-R)

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Objective: The aim of this study was to investigate whether the ACE-R is capable of detecting cognitive impairment in patients with Parkinson's disease and to compare the ACE-R with the Mini-mental State Examination (MMSE).

Background: Parkinson's disease (PD) is regarded as a disorder of movement, but approximately 40% of the patients are affected by cognitive impairment, even among the first 1-2 years after onset of disease. Cognitive deficits have important consequences for the patient management, but there is no brief cognitive tool to identify these cognitive problems.

Methods: A total of 56 nondemented patients with mild to moderate stages of PD were studied. Patients were evaluted for the clinical condition (Unified Parkinson's disease Rating Scale, Hoehn and Yahr), as well as for demographic and disease related characteristic. The assessment of the cognition was based on the MMSE and the ACE-R.

Results: The prevalence of cognitive impairment in this study sample was 10,8% by the MMSE and 44,7 % by the ACE-R PD patients showed more difficulties in the memory and verbal fluency subdomains. The patients did not have problems with language, attention and orientation subdomains.

Conclusions: The higher proportion of PD patients with cognitive impairment was detected by the ACE-R over the MMSE. ACE-R appears to be a useful screening tool for cognitive impairment in PD.

Th-218

Comparison of cognitive dysfunction in Parkinson's disease and Machado-Joseph disease

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Objective: The aim of this study is to compare cognitive functions including verbal learning in patients with Parkinson's disease (PD) and Machado-Joseph disease (MJD).

Background: Previous studies indicated that mild cognitive impairments concerning executive functions were found in both PD and MJD, but detailed comparative investigations on neuropsychological deficits between these groups have not been done yet.

Methods: We tested 15 PD and 15 genetically confirmed MJD patients, comparing with each 15 control subjects matched for age, education, and global cognitive status. Free and Cued Selective Reminding Test (FCSRT), consisting of three consecutive series of free and semantic cued recall, delayed free and cued recall, and recognition, was administered to these patients. The other cognitive tasks were verbal fluency, digit span, visual span, Trail Making Test (TMT) and copy of a cube.

Results: The PD group showed significantly lower scores in digit backward span, TMT-A,B, and in the free recalls in the FCSRT, but well performed delayed cue recall was observed. While, the MJD patients performed significantly lower scores in category and letter fluency, digit backward span, copy of a cube and in the free recalls in the FCSRT. Dramatic improvements in delayed free recall following interference cognitive tasks in the MJD group were observed, contrasting with those of the control and PD subjects who showed a decline. Both groups displayed preserved performance of cued recalls and recognition.

Conclusions: The different neuropsychological dysfunctions including verbal learning impairments were found between the PD and the MJD group. The cognitive dysfunctions is involved with striato-prefrontal loop modulated by the nigrostriatal dopaminergic pathway in PD, and with cerebello-thalamo-cortical circuitry from the cerebellum to the prefrontal cortex in MJD. We considered that the differences of cognitive impairments between the PD patients and the MJD group were corresponded to each of the neural dysfunction.

Th-219

Bilateral subthalamic nucleus deep brain stimulation for the treatment of medically refractory Parkinson's disease: Effects on neuropsychiatric tests

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Objective: To (1) analyze the effects of bilateral subthalamic nucleus deep brain stimulation (STN-DBS) on patient performance in neuropsychiatric testing and (2) describe our patient population with regard to demographics, age of onset, duration of symptoms, Unified Parkinson's Disease Rating Scale, Motor Part III scores (UPDRS III) on-off meds, and outcomes.

Background: STN-DBS for the treatment of medically refractory Parkinson's disease has become an accepted mode of treatment in patient's not optimally controlled on medications alone. Previous studies that analyze the outcomes of STN stimulation, address neuropsychological changes with either the Mini-mental status exam (MMSE), Neuro-Psychiatric Inventory (NPI), or Hamilton Depression scores. We analyzed and discuss our results and findings in 32 patients with complete pre- and postoperative neuropsychiatric (Mattis DRS) data.

Methods: We reviewed the charts of over 100 patients undergoing DBS-STN (1 unilateral). Complete data including demographics, results of neuropsychiatric testing (Mattis DRS) and the outcomes in a smaller population was analyzed. Patients without obvious complications (ischemic or hemorrhagic stroke) were included in this evaluation.

Results: Complete data was available on 32 patients. Mattis DRS scores changed from pre-surgery score of 139 to post-surgery score of 138 (p-value 0.0752). The average age at surgery was 60, symptom onset of 48 years, with an average duration of symptoms at time of surgery of 12 years. Pre-surgery UPDRS-III on-off evaluation found the following: Off-medication – 42; On-medication – 22, with a change of 47%. Post-surgery the UPDRS-III evaluation found the following values: ON-stimulation and Off-medication of 33, six months after implantation (change of 23%). Complications: patient with bilateral lead breaks requiring replacement; hypersexuality and impulsiveness in one patient not noted on previous preoperative testing; one patient with transient postoperative confusion; and one patient who sustained a thalamic stroke manifesting as post-operative confusion.

Conclusions: At our institution, postoperative neuropsychiatric scores, demonstrated no statistically significant change from preoperative scores, after STN-DBS for the treatment of Parkinson's disease, when assessed by Mattis DRS.

Th-220

Sentence production in Parkinson's disease: Effects of conceptual and task complexity

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Objective: Test the effects of increased conceptual/task complexity on language production in persons with Parkinson's disease (PD).

The influence of cognitive impairment and severity of disability on expressive language was also assessed.

Background: Language use in PD is not well-studied. More is known about comprehension than production. Sentence production is a complex task that taxes linguistic and cognitive resources, particularly working memory (WM) and executive function. Expressive language deficits in PD include impaired word fluency and confrontation naming. The few researchers who have studied complex sentence production abilities in PD, report deficits in information content, grammaticality, and syntactic complexity.

Methods: We tested the sentence production of 19 non-demented persons with PD and 19 gender, education, and age (62 to 85 years) matched healthy older adults (HOAs). Participants completed sentence repetition and sentence generation (i.e. picture description) tasks, and measures of WM and executive function. Responses were digitally recorded, transcribed verbatim, and coded on four language dimensions: completeness, grammaticality, gist meaning, and fluency.

Results: No difference was noted between PD and HOA participants on WM and executive function scores. Participants with PD performed more poorly on both sentence production tasks. PD and HOA participants produced more errors in sentence generation than repetition. As conceptual complexity increased, errors increased in both tasks. Results were exaggerated in the PD group, which produced significantly fewer complete, grammatical, and fluent responses than HOAs. Fluency was disproportionately impaired. Severity of disability correlated with overall performance.

Conclusions: These results suggest that there are pervasive changes to complex language in persons with PD. Specifically, language functioning is particularly impaired when the ideas to be communicated are novel and complex. The magnitude of the effects on language is predictable from disability scores in PD, memory, and executive function scores. These deficits of language production in people with PD could significantly impact everyday communication and quality of life.

Th-221

Internally-guided executive functioning predicts memory impairments in Parkinson's disease

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Objective: To determine relationships between executive dysfunction and memory impairment in Parkinson's disease (PD).

Background: Impaired memory and executive dysfunction are commonly observed in PD. Several studies suggest memory impairment may be secondary to executive dysfunction. However, the nature of this relationship remains unclear.

Methods: Participants were PD patients followed in a university hospital clinic. All had subjective memory complaints and underwent neuropsychological evaluation. Data were collected via retrospective chart review. The sample consisted of 33 participants (27 male), with mean age of 66.0 years (SD=9.5), mean education of 14.9 years (SD=3.2), and mean disease duration of 9.5 years (SD=6.3). Mean total Mattis Dementia Rating Scale score was 132.3 (SD=15.3). The California Verbal Learning Test II (CVLT-2) assessed verbal recall and recognition memory. Psychomotor speed, verbal fluency, inhibition, set-switching, and concept formation were examined using subtests from the Delis-Kaplan Executive Functioning Scale (D-KEFS). Step-wise linear regression was performed to determine which aspects of executive functioning predicted verbal recall and recognition.

Results: Psychomotor speed and verbal fluency, but not concept formation, predicted recall and recognition memory performance. Poor set-switching ability during Verbal Fluency, an internally-guided function, predicted impaired recall, $F(1,29)=13.70$, $p=0.001$, and recognition memory, $F(1,29)=8.03$, $p=0.008$. Inhibition and set-switching demands with external cues did not.

Conclusions: Recall memory on the CVLT-2 and verbal fluency with switching both require internally-guided set-switching in the absence of external cues. CVLT-2 recognition requires accurate source memory for target words, which also requires internally-guided set-switching. With external cues, concept formation, set-switching, and response inhibition appear unrelated to memory. Results suggest that in addition to psychomotor slowing, disrupted internally-guided executive functioning may explain memory impairments in PD. Findings have clinical implications with regard to compensatory strategies. Future studies examining cognitive and neuroanatomical measures in prefrontal regions would further elucidate relationships between executive dysfunction and memory impairment in PD.

Th-222

Increased rear-end collisions in drivers with Parkinson's disease

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Objective: To assess rear-end collision (REC) avoidance in drivers with Parkinson's disease (PD).

Background: Drivers with cognitive and visual impairment are at increased risk for vehicular crashes. Patients with PD suffer from cognitive, visual, and motor dysfunction. Rear-end collisions (REC) are among the most common crash types.

Methods: Licensed, active drivers with mild-moderate PD ($n=83$, age$=67.4\pm7.9$, median Hoehn-Yahr stage$=2$) and elderly controls ($n=52$, age$=65.3\pm7.5$) drove on a 2-lane rural highway in a simulator scenario in which the driver became trapped behind a lead vehicle that remained inexplicably stopped at a green traffic light and proceeded forward only after the light turned red.

Results: Compared to controls, drivers with PD experienced more rear-end collisions (7 vs. 0, $p=0.04$). No subject except one PD driver with poor cognitive test scores proceded throught the red light. Within the PD group, significant univariate predictors of RECs were scores on tests of visual processing speed and attention (Useful Field of View, $p<0.01$), motion perception (Structure-From-Motion, $p<0.01$), visuospatial perception (Judgment of Line Orientation, $p<0.05$) and construction abilities (Complex Figure Test-Copy, $p<0.01$), visual working memory (Benton Visual Retention Test-BVRT, $p<0.01$), contrast sensitivity ($p<0.05$), and rigidity ($p<0.05$) measured by motor examination on the UPDRS. Multivariate analysis using stepwise regression revealed BVRT and rigidity as the most important predictors of crashes.

Conclusions: Drivers with PD were significantly more likely than controls to have an REC when a vehicle was stopped unexpectedly ahead of them. PD drivers with impaired visual perception and cognition, and worse parkinsonism may be at a higher risk of safety hazards under complex or ambiguous traffic situations.

Th-223

Prospective memory in de novo Parkinson's disease patients

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Objective: To investigate event based PM in patients with Parkinson's disease (PD) and Mild Cognitive Impairment (MCI).

Background: Prospective memory (PM), which is memory for actions to be performed in the future, have been reported to be impaired in patient with PD. To the best of our knowledge this cognitive function has not yet be investigated in very early, drug naïve patients with PD.

Methods: Fourteen drug naïve PD patients, 21 MCI patients and 21 age matched controls have been enrolled in this study. All subjects have been tested with an extensive neuropsychological battery including MMSE, Stroop Test, Rey auditory verbal learning test,

Trail making test A/B, Progressive matrix Raven 47, Modified card sorting test, digit span and an experimental event-based prospective memory tasks. Statistical analysis has been performed with Mann Whitney U test.

Results: All PD patients were very early stage disease (disease duration 11±5 months, Hohen&Yahr 1.5, UPDRS III 11.5±4.7). All but 2 PD patients were cognitively unimpaired. Two patients showed executive dysfunction. Prospective memory was not different as comparing PD patients and control while all MCI patients showed prospective and retrospective memory impairment.

Conclusions: Our results suggest the sparing of prospective memory in very early drug naïve PD patients. The different results with previous studies could be due to longer disease duration of those PD patients which were also on dopaminergic therapy. However, the role of the dopaminergic therapy on PM is still controversial since some evidences suggest that levodopa could restore prospective memory in PD patients. It should be also taken into account that most of our patients were Tremor-Dominant PD, a phenotype that is related to a less cognitive impairment. Finally it is worth to note that both PD patients of our series with executive dysfunction showed also impaired prospective memory.

Th-224

CHIP mediates PINK1 ubiquitination, degradation and aggregation

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Objective: To determine whether PINK1 is a substrate for the ubiquitin ligase–chaperone protein,CHIP.

Background: Molecular chaperones, ubiquitin ligases and proteasome impairment have been implicated in Parkinson's disease, which are characterized by accumulation of abnormal protein aggregates (e.g. tau and a-synuclein respectively). CHIP (carboxyl terminus of Hsc70-interacting protein), is a molecule which was previously shown as a cochaperon protein and a U-box-dependent E3 ligase. PINK1(PTEN-induced kinase 1)-related parkinsonism is the second most common cause of autosomal recessive parkinsonism and in our other studies, we found that PINK1 degraded through ubiquitin-proteasome pathway(UPP). The goal of this work was to elucidate the correlation between CHIP and PINK1, focusing on the role of UPP.

Methods: We first conducted co-immunoprecipitation experiments to determine the interation of CHIP and PINK1. Using co-immunoprecipitation and in vitro binding assays,we next examined which regions of CHIP are necessary for the interaction with PINK1. To ascertain whether CHIP ubiquitinates PINK1, COS-7 cells were transfected with V5-tagged CHIP, myc-tagged tau and HA-tagged ubiquitin. Two days later, immunoprecipitation was performed with an antibody against myc and probed with an antibody against HA to assess the degree of tau ubiquitination. To examine the impact of CHIP-mediated ubiquitination on PINK1 aggregation, COS-7 cells were transfected with PINK1 expression construct in the absence or presence of either CHIP or Hsp70. Total PINK1 was extracted and then detected by western blot analysis with the myc antibodies.

Results: PINK1 was found to co-immunoprecipitate with CHIP and it was conceivable that the interaction with PINK1 requires both domains of CHIP. Immunoprecipitated PINK1 showed prominent anti-HA (ubiquitin) immunoreactivity in CHIP transfected cells, with ubiquitin positive species appearing as mulitple higher molecular weight species, possibly representing oligomeric and multimeric ligations. Transfection of CHIP dramatically decreased the accumulation of PINK1.

Conclusions: In the current study, we identified PINK1 as a substrate for the ubiquitin ligase–chaperone protein CHIP and found that CHIP mediated ubiquitination, degradation and aggregation of PINK1.

Th-225

Validity of the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) for detection of cognitive impairment in Parkinson's disease

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Objective: To determine the discriminant validity of the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE) for the detection of cognitive impairment in Parkinson's disease (PD).

Background: Dementia in PD (PDD) occurs in up to 80% of patients long-term, and mild cognitive impairment (MCI) is also common. Thus, routine cognitive screening in the context of clinical care is important for the optimal management of PD patients. The MoCA is more sensitive than the MMSE for detecting cognitive impairment in non-PD patients, but its validity in PD has not been formally assessed.

Methods: 128 patients with PD were administered the MoCA, the MMSE, and a detailed neuropsychological battery. MCI and new DSM-IV style PDD criteria were applied by a rater who was blinded to the MoCA and MMSE results.

Results: The population was 77.6% male, age =64.5 (10.0) years, PD duration =6.2 (5.3) years, and Hoehn and Yahr stage =1.9 (0.7). A total of 27.3% of the sample met criteria for cognitive impairment (14.1% PDD and 13.2% MCI). Mean MMSE and MoCA scores were 28.3 (1.9) and 25.1 (3.7), respectively. The AUCs for detection of dementia were .707 for the MoCA and .677 for the MMSE. At the point of maximum sensitivity and specificity (26/27 for the MoCA and 27/28 for the MMSE), the sensitivities for detection of dementia were 83.3% for the MoCA and 61.1% for the MMSE.

Conclusions: Although the MoCA is more sensitive than the MMSE for detecting dementia in PD, there is no single cutoff point for either instrument that provides high sensitivity and specificity. A larger sample size and additional analyses will be presented at the MDS meeting.

Th-226

Dance for Parkinson's disease: Eight years of collaboration of Brooklyn Parkinson group (BPG), a chapter of National Parkinson Foundation and Mark Morris Dance Group (MMDG), a renowned company

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Objective: Present *Dance for PD* concept and potential neurobiological links.

Background: In 2001 BPG and MMDG started *Dance for PD* classes. Rationale: 1) Perception that PD patients and caregivers participating in a social, joyful activity unrelated to therapy in the community would combat depression, frustration and isolation discussed in support group meetings. 2) Expectation that persons with PD would benefit by learning and practicing, cognitive strategies dancers use to guide movement. 3. Awareness that structure and teaching method of a traditional dance class is easily adapted for persons with PD.

Methods: Classes are taught by professional dancers (Heginbotham, Leventhal and Owens) with live accompaniment (Wade) to persons with PD and caregivers.

Results: It is reported and obvious from observations (see video) that PD participants enjoy the **socialization, watching the teachers and each others' movements.** PD participants mention being with others, improved mood and feeling vigorous as main reasons for continued class attendance. (Westheimer, Topics in Geriatric Rehabilitation;Vol. 24, 2008) Classes grew from 3 to 9 persons once a month to 25 to 30 every week. Training workshops are offered by BPG and MMDG. Dance for PD classes are now replicated in Washington DC, Chicago, California (Berkeley, Oakland, San Jose), Massachusetts (Boston, Stockbridge) South Carolina, Tennessee, Toronto.

Others are in development throughout the U.S. Discussion in the context of neurobiology: **Feeling** the emotions of others requires empathy and social cognition (Gallese et al 2004) **Observing** the state of others activates specific mirror neurons in the observer's brain, as if they were acting (Glaser 2006) **Imitation** requires early visual description, detailed motor planning and the goal of the action to be copied (Hurley & Chater 2005)**. Reward for planned action** involves oculomotor caudate Lau & Glimcher 2008), midbrain dopamine neurons (Bayer& Glimcher 2005) **Executive processing** (striatal and mesocortical dopaminergic mechanisms. (Monchi et al 2007)

Conclusions: Self-reports and observations that patients enjoy socialization, watching the teachers and each other perform movements in dance class fits with current views of select brain circuits of relevance to PD.

Th-227

Patients with Parkinson's disease learn to control complex systems via procedural as well as non-procedural learning

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Objective: The aim of this study was to test the hypothesis that patients with Parkinson's disease who have striatal dysfunction, are impaired on complex dynamic control (CDC) tasks only when learning involves procedural learning.

Background: The striatum is considered to mediate some forms of procedural learning. CDC tasks involve an individual having to make a series of sequential decisions to achieve a specific outcome (e.g. learning to operate and control a car), and they involve procedural learning.

Methods: 26 patients with Parkinson's disease (PD) and 26 age-matched controls performed two CDC tasks, one in which training was observation-based (non-procedural), and a second in which training was action-based (procedural).

Results: Both groups were able to control the system to a specific criterion equally well, regardless of the training condition. However, when reporting their knowledge of the underlying structure of the system, both groups showed poorer accuracy when learning took place through observation-based compared with action-based training. Moreover, the controls' accuracy in reporting the underlying structure of the systems was superior to that of PD patients.

Conclusions: The findings suggest that the striatal dysfunction in Parkinson's disease is not associated with impairment of procedural learning, regardless of whether the task involved procedural learning or not. It is possible that the learning and performance on CDC tasks are mediated by perceptual priming mechanisms in the neocortex.

Th-228

Effects of STN DBS on antisaccade and frontal lobe function in Parkinson's disease

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Objective: To investigate the effects of subthalamic nucleus deep brain stimulation (STN DBS) on antisaccade (AS) performances and frontal lobe functions in Parkinson's disease (PD).

Background: STN DBS for PD improves motor symptoms and reduces some adverse effects of antiparkinsonian drugs such as fluctuation of symptoms and drug induced dyskinesia. On the other hand, it has been argued whether STN DBS may lead to changes in memory, cognition, and behavior, particularly executive functions. Some neuropsychological tests are used for evaluating them. In addition, some saccade performances are also thought to reflect activities of frontal cortices, especially the AS task. There, however, have been few studies which tried to evaluate frontal lobe functions using AS task in PD patients with STN DBS.

Methods: 29 PD patients (Hoehn-Yahr II-III, age 58.5 $\pm$ 7.9, 13 men, 16 women) treated with STN DBS were recruited. Their frontal lobe functions were evaluated by neuropsychological batteries, such as the "Kanahiroi" multi-cancellation test and the verbal fluency test (VFT) before DBS surgery and at DBS on state after surgery. In addition, the AS task was evaluated with DC EOG when DBS was on and off. The onset latency, accuracy, peak velocity of saccades, and the frequency of directional errors (prosaccades) were measured. We investigated correlations among the scores of neuropsychological tests at pre- and post-surgery, and AS parameters when DBS was on and off.

Results: (1) The scores of "Kanahiroi" multi-cancelation test and VFT did not change from pre- to post-surgery. (2) STN DBS improved the latency and accuracy of AS. The frequency of directional errors (prosaccades) was unchanged by STN DBS. (3) No correlations were found between the saccade parameters, such as latency, accuracy, and frequency of prosaccades, and scores of the "Kanahiroi" multi-cancelation test or of VFT.

Conclusions: DBS surgery did not affect scores of the "Kanahiroi" multi-cancelation test or VFT. In contrast, STN DBS improved AS performances, although both of these are thought to reflect frontal lobe functions. This suggests that neuropsychological tests and AS performances reflect distinct aspects of frontal lobe functions.

Th-229

Comparative study about cognitive performances on patients with Parkinson's disease

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Objective: The aim of our study was to evaluate the cognitive performances in patients with Parkinson's disease in stage I and II on Hoehn and Yahr Scale.

Methods: We studied 50 patients (29 men and 21 women) diagnosed with idiopathic Parkinson's disease. Twenty-five patients (14 men and 11 women) were in stage I Hoehn and Yahr (group A) and 25 patients (15 men and 10 women) were in stage II Hoehn and Yahr (group B). The patients were selected to meet the following inclusion criteria: age between 51-60 years and at least 8 years of education. The both groups were compared regarding the cognitive performances with a control group (group C) composed of 25 healthy subjects (11 men and 14 women) aged between 51-60 years and at least 8 years of education. In all groups we used Mini Mental State Examination (MMSE) and The Verbal Fluency Test (FAS Test and Category Fluency) to assess the cognitive performances. The results were statistically analyzed using Student's Test.

Results: The average scores in patients in stage I were: 27,6 at MMSE, 15,8 at Category Fluency and 7,8 at FAS Test. In patients in stage II we obtained 27,01 at MMSE, 14,3 at Category Fluency and 7,02 at FAS Test. In control group the average scores were: 28,9 at MMSE, 17,4 at Category Fluency and 9,2 at FAS.

Conclusions: The patients in stage II had smaller values obtained at all test in comparison with values obtained in stage I and in control group.

PARKINSON'S DISEASE: DYSAUTONOMIA

Mo-226

Global alteration in postganglionic neuronal function affects whole body kinetics of MIBG in patients with Parkinson's disease

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Objective: To verify whether global alteration of postganglionic autonomic nervous system (ANS) affects the whole body kinetics of 123I-Metaiodobenzylguanidine (MIBG).

Background: The differential diagnosis between idiopathic Parkinson's disease (PD) and multiple system atrophy (MSA) may be

difficult in early stages. In PD postganglionic involvement of ANS predominates, whereas in MSA the preganglionic structures are prevalently affected. MIBG imaging of myocardial innervation has been proposed as a potential tool to differentiate between these two entities. The computation of heart to mediastinum ratio (H/M) early after MIBG injection was identified as an index able to differentiate PD from MSA. However, recent studies argued against this criterion because of a significant overlap between data in the two diseases.

Methods: Eighteen patients with clinical suspicion of PD (n = 11) or MSA (n = 7) underwent MIBG whole body planar imaging. The clinical diagnosis was confirmed at one year of follow up. Images were collected 30 minutes and 4 hours after tracer injection and myocardial MIBG retention was normalised for the whole body MIBG behaviour.

Results: In early images H/M was lower in PD than in MSA (1.33 ± 0.16 vs. 1.74 ± 0.33, $P<0.05$). Early myocardial MIBG uptake expressed in % of the injected dose (calculated from the whole body scan) documented a markedly larger difference between PD and MSA (0.7 ± 0.4% vs. 1.7 ± 0.4, $P<0.01$). Heart washout was similar in the two groups (35 ± 11% vs. 35 ± 21%, ns); by contrast the tracer loss from the body was remarkably higher in PD than in MSA (33 ± 15% vs. 7 ± 4%, $P<0.01$). Moreover a significant correlation was observed between whole body washout and heart washout in PD but not in MSA ($r = .78$, $P<0.01$).

Conclusions: MIBG imaging provides direct evidence of a global postganglionic dysfunction in PD. Analysis of images accounting for tracer kinetic in the whole body might improve the differential diagnostic accuracy of this test in patients with suspected PD or MSA.

Mo-227

Paroxysmal sympathetic storm in a patient with Parkinson's disease with dementia: Case report

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Objective: We report a case of paroxysmal sympathetic storm in a patient with Parkinson's disease with dementia.

Background: Sympathetic storm is known a profound autonomic dysreflexia, consisting of paroxysmal hyperhidorosis, tachycardia, tachypnea, hyperthermia, hypertension and dystonic posture. It has been suggested that sympathetic storm occurs by disturbance of central autonomic network (CAN) which regulates the sympathetic nervous system in inhibitory manner. Sympathetic storm usually occurs in patients in patients with central neurological disorders such as stroke, amyotrophic lateral sclerosis and diencephalic seizure, but it has not been reported in patients with Parkinson's disease.

Methods: This case report describes an 81-year-old woman with Parkinson's disease with demenita presented with paroxysmal unconsciousness, hypertension, hyperthermia and hyperhidrosis.

Results: Brain atrophy in MRI, diffuse slow electrical activity in EEG, urinary tract infection, dehydration and severe hyponatremia were revealed at the initial investigation. During her admission, we confirmed paroxysmal autonomic symptoms as hyperthermia, hypertension and severe consciousness disturbance with hyponatremia and the level of increased plasma norepinephrine. Malnutrition was considered as a cause of hyponatremia, because SIADH was excluded by laboratory data. The paroxysmal sympathetic storm was diminished with correction in serum sodium concentration and administration of antiepileptic agent.

Conclusions: We consider that the paroxysmal sympathetic storm in this patient was induced by hyponatremia and its pathophysiology was mimicking diencephalic seizure.

Mo-229

Correlation between odor identification and MIBG myocardial scintigraphy in patients with Parkinson's disease: Preliminary results

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Objective: to evaluate the correlation between olfacory system and myocardial sympathetic nerve system in patients with Parkinson's disease (PD).

Methods: a series of 20 outpatients diagnosed as PD according to the Brain Bank Clinical Diagnosis Criteria was studied. None of the patients had a story of neuropathy or previous relevant cardiac disease. Additionally none of the patients suffered from otorhino-laryngeal disorders. For assessing olfactory function the Sticks Sniffin' Test (SST), a widely used test in Europe for odor identification was administrated to the patients. ^{123}I-MIBG was performed in the patients and the heart to mediastinum uptake ratio was condsidered 15' and 4 hours after the injection. Spearman correlation coefficients were obtained.

Results: we found a significant positive correlation between the SST score and the cardiac MIBG uptake in the PD patients both at 15' ($r = 0.51$; $P = 0.010$) and at 4 hours ($r = 0.57$; $P = 0.004$) after the injection of the tracer. This correlation remained significant also after adjusting of age.

Conclusions: our findings indicate that the dysfunction of the olfactory and cardiac sympathetic systems are closely coupled in Parkinson's disease. A larger study in PD patients and a comparison with other parkinsonisms will clarify weather the involvement of these non motor systems may be a biomarker for the detection of PD.

Mo-230

Heart rate variability as a biomarker for Parkinson's disease

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Objective: To explore heart rate variability as a potential biomarker for Parkinson's disease.

Background: A cure for Parkinson's disease (PD) may depend upon an intervention much earlier in its course than we presently have the ability to detect. Presymptomatic diagnosis is a critical undeveloped area of research in the field. Autonomic dysfunction may occur at the earliest stage of PD without overt signs. Heart rate variability (HRV) is one autonomic index that may be measured with great sensitivity, and aberrations of HRV in PD have previously been reported. We measured HRV in early untreated PD patients and age-matched controls.

Methods: Six subjects diagnosed with PD with symptoms less than 1 year and not on symptomatic medication, and three age-matched control subjects, were recruited. At the baseline visit, a UPDRS was obtained, physical activity was assessed with the Physical Activity Scale for the Elderly (PASE), and subjects underwent a resting electrocardiogram for 45 minutes with normal breathing effort. The exam, PASE and resting ECG was repeated at 6 and 12 months. HRV metrics were calculated as specified by task force standards using both time- and frequency-domain methods including mean heart rate, low-frequency (LF) power, high-frequency (HF) power and the LF/HF power ratio.

Results: Baseline LF was 509.4 ms^2 in PD and 413.9 ms^2 in controls. Baseline HF was 269.5 ms^2 in PD and 221.8 ms^2 in controls. Change from baseline to six months in LF was -242.2 ms^2 in PD and +89.4 ms^2 in controls, and in HF -94.6 ms^2 in PD and +10.7 ms^2 in controls. The difference between the mean of the PD subjects and the mean of the controls was never greater than the standard deviation across individuals in either group. PD and control subjects had equivical physical activity histories based on their PASE scores.

Conclusions: This preliminary analysis based on a limited number of subjects thus far in the study has not demonstrated a significant

difference in HRV between early PD subjects and age-matched controls at baseline. Although a trend was seen in the difference in change of LF and HF HRV values over six months, this failed to reach statistical significance. These results may be due to the small sampling size in this analysis. Further analysis when all subjects have completed the 1 year followup may yield more significant results, which would prove useful as part of a preclinical screening test battery.

Mo-231

Incidence of quantitative sudomotor axon reflex test (QSART) abnormalities in patients diagnosed with idiopathic Parkinson's disease

J. Cristini, P.A. Hanna, M. Rosenberg (Edison, New Jersey)

Objective: To evaluate the incidence of postganglionic autonomic dysfunction as assessed by the quantitative sudomotor axon reflex test (QSART) abnormalities in patients with idiopathic Parkinson's disease (PD).

Background: Patients with PD are known to have a high incidence of autonomic symptoms, including abnormal sweating. The pathophysiology of sudomotor abnormalities is not completely understood with regard to peripheral or central nervous system involvement. QSART is performed at the following standard four sites: forearm, proximal leg, distal leg and foot in order to evaluate postganglionic function of sympathetic axons innervating sweat glands.

Methods: All patients with PD who had undergone autonomic function testing (AFT) including QSART and who had in their records quantitative clinical evaluations (Activities of Daily Living (ADL), Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn & Yahr (H&Y) rating scores) were included in this study. All of the patients tested were in the "on" Parkinson-medication state. The results of QSART testing were quantified based on the number of sites that were abnormal (0-4). The results of QSART testing were compared to each of the rating scales for disease state and epidemiologic data.

Results: Twenty patients were entered into the study. Mean age was 63.4 (range 38–82) with 4 females and 16 males. Five patients had subthalamic nucleus deep brain stimulation surgical implants. Mean duration of disease was 13.75 years. Fifteen patients (75%) had abnormal QSART testing. Ten were mildly abnormal (1 or two sites abnormal) and 5 were more markedly abnormal (3 or 4 sites involved). There was no relationship between QSART and age, gender, duration of disease, or severity of symptoms.

Conclusions: QSART abnormalities are common in patients with idiopathic Parkinson's disease. This indicates that peripheral pathology may play an essential role in the etiology of autonomic symptoms in these patients. In contrast to a few studies using sympathetic skin response, we found no correlation between these abnormalities and disease severity. This may be secondary to our sample size or perhaps to physiologic differences in these testing methods.

Mo-232

An evaluation of autonomic function in idiopathic Parkinson's disease using wavelet analysis

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Objective: To quantitatively estimate both sympathetic and parasympathetic function at baseline and in response to autonomic stimulation in idiopathic Parkinson's disease (PD).

Background: Although it is well known that the autonomic nervous system (ANS) is commonly affected in PD, specific evaluation of baseline autonomic tone is difficult to obtain with current techniques. Using wavelet analysis, one can use variability in both the cardiac and respiratory cycles to estimate sympathetic and parasympathetic tones simultaneously and continuously.

Methods: Twenty patients who fulfilled standard clinical criteria for a diagnosis of PD underwent ANS function testing (AFT). Mean age was 63.4 (range 38–82) with 4 females and 16 males. Five patients had subthalamic nucleus deep brain stimulation surgical implants. Mean duration of disease was 13.75 years. Our AFT protocol includes an assessment of heart rate variability (hrv), low-frequency area (Lfa); high frequency area (Rfa) at baseline and in response to deep breathing, Valsalva, and stand. Lfa and Rfa are estimates of sympathetic and parasympathetic tones respectively. All of the patients tested were in the "on" Parkinson-medication state.

Results: Only two subjects had normal baseline function. Baseline deficits in Rfa, Lfa, as well as hrv were found in 85%, 75%, and 60% of subjects, respectively. 35% had critical deficits in baseline Rfa (<0.01) and 30% had hrv of < 5 beats/minute. The Lfa response to stand was abnormal in 70%. 40% had abnormal responses to deep breathing and Valsalva. Orthostatic hypertension (defined by a systolic increase of >20 mm Hg) was documented in three subjects.

Conclusions: This study confirms that autonomic abnormalities are prevalent in PD. There was no statistical difference between the degree of Lfa (sympathetic) and Rfa (parasympathetic) loss. The degree of baseline loss of autonomic tone and heart rate variability was often severe. The incidence of orthostasis was high and documented in a number of patients even without a significant drop in blood pressure. Interestingly, there was an unexpectedly high incidence of orthostatic hypertension, a relatively rare condition. The significance of these correlations needs further evaluation in larger numbers of patients with PD.

Mo-233

Do anosmia, orthostasis, and constipation progress differently in Parkinson's disease?

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Objective: To compare the prevalence of anosmia, orthostasis, and constipation between Parkinson's disease (PD) versus age-matched controls, and to determine the factors associated with these autonomic features.

Background: Braak has recently hypothesized that, based on Lewy body pathology, PD may start from the lower brainstem progressing rostrally, potentially explaining early autonomic symptoms.

Methods: We surveyed 58 PD patients and 51 age-matched controls and measured blood pressures while seated and standing, administered the University of Pennsylvania smell test (UPSIT), and performed a constipation survey. We then performed a regression analysis to look at the factors associated with each autonomic feature including: age, disease duration, UPDRS ADL and motor scores, and levodopa equivalent daily doses (LEDD).

Results: Our PD patient population had a mean age of 69.27 (SD 6.85), disease duration is of 10.96 years (SD 8.66), the UPDRS on motor score of 30.76 (SD 10.57), levodopa equivalent daily dose (LEDD) of 692.47 mg (SD 544.03). Our age-matched controls had a mean age of 66.45 (SD 9.17). Our PD patients had a significantly different average decrease in systolic BP from seating to a standing position compared to their age-matched controls (5.90 mmHg (SD 17.03) vs. 2.6 mmHg (SD 11.28); $p=0.05$). Similarly, more PD patients had anosmia ($P<.001$) and constipation (67.3% vs. 21.6%; $p<0.001$) compared to their age-matched cohort. The PD patients' anosmia scores were significantly correlated with age ($p=0.002$) and disease duration ($p=.038$). Regression analyses of constipation and orthostasis did not reveal any significant associated factors.

Conclusions: While anosmia, orthostasis, and constipation were found to be more prevalent in PD compared to age-matched controls, the significant association of anosmia (but not orthostasis and constipation) to disease duration suggest a difference in timing of presentation among these three autonomic features. Longitudinal studies will need to be performed to clarify our findings in this cross-sectional study.

Tu-228

Is rhinorrhea an intrinsic symptom of PD?

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Objective: To compare the prevalence of idiopathic rhinorrhea in PD patients vs. controls, and to determine the correlation between rhinorrhea and anosmia, and the factors associated with rhinorrhea.

Background: Anosmia is now increasingly recognized as an intrinsic early symptom of PD. There have been recent reports of increased incidence of rhinorrhea in PD, and we wondered if this may, in part, explain the increased incidence of anosmia.

Methods: A cohort of 61 PD patients and 51 age-matched non-PD controls completed a survey about rhinorrhea and underwent the University of Pennsylvania Smell Identification Test (UPSIT). We classified each subject as having no, mild to moderate, or severe rhinorrhea. We compared the prevalence of idiopathic rhinorrhea in the PD patients vs. controls, examined the correlation between rhinorrhea and anosmia in PD patients, and studied the factors associated with rhinorrhea in the PD patients.

Results: Our patient cohort had a mean: age of 69 (SD 6.85) years; disease duration of 11 years (SD 8.66); UPDRS on motor score of 30.76 (SD 10.57), and a levodopa daily dose equivalent (LEDD) of 692.47mg (SD 544.03). Our controls had a mean age of 66.45 (SD 9.17). In total, 94% of controls vs 75.9% of PD patients had no rhinorrhea ($p=0.03$); moreover, only 2% of controls vs. 14.8% of PD patients had severe rhinorrhea. However, no difference in age, disease duration, UPDRS ADL and motor scores, QOL scores, levodopa equivalent daily doses, and UPSIT (assessing anosmia) scores were found between PD patients with rhinorrhea and those without.

Conclusions: Rhinorhhea was more prevalent in PD patients compared to controls and it did not significantly impact performance on a smell test. Longitudinal studies need to be performed to determine whether rhinorrhea is a pre-diagnostic, early, or late symptom of PD.

Tu-229

Botulinum toxin A injection in the detrusor muscle to treat overactive bladder syndrome and detrusor muscle overactivity in patients with Parkinson's disease and multiple system atrophy

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Objective: to investigate the effectiveness and safety of botulinum toxin type A (BoNT/A) injected into the detrusor muscle in patients with PD and MSA all of whom had refractory overactive bladder symptoms and detrusor overactivity.

Background: urinary disturbances are common in patients with Parkinson's disease (PD) and multiple system atrophy (MSA).

Methods: all participants underwent clinical and urodynamic assessment and completed a quality-of-life questionnaire before BoNT/A treatment and at one and three months thereafter. Four PD patients and two MSA patients were enrolled in the study. All patients received 200 U of BoNT/A injected into the detrusor muscle at 20 sites under cystoscopic control, in a single session on an inpatient basis. Outcome measures were clinical assessment (a voiding diary included the recording of daytime and night-time urinary frequency and episodes of urgency and urge urinary incontinence) and urodynamic assessment (first volume and maximum pressure of uninhibited detrusor contractions and maximum cystometric capacity) and pressure-flow studies.

Results: one and three months after BoNT/A injection all patients reported that daytime and night-time urinary frequency had diminished, their quality-of-life scores improved, and none of the patients had further episodes of urgency and urge urinary incontinence during the five month follow-up. Urodynamic assessment showed that all the urinary function variables tested improved. No systemic side effects were recorded during or after treatment. In all patients the post-void urinary residual volume increased and intermittent catheterization was required only in patients with MSA.

Conclusions: the new beneficial effect we report in a small study sample encourage larger trials to confirm BoNT/A injections into the detrusor muscle as an effective and safe treatment option for patients with refractory overactive bladder symptoms and detrusor overactivity related to PD and MSA.

Tu-230

A case series of peripheral neuropathy (PN) and Parkinson's disease (PD)

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Objective: To describe the clinical, laboratory and electrodiagnostic findings of peripheral neuropathy (PN) in Parkinson's disease (PD) patients.

Background: PN has been described in patients with PD, as a potential complication of levodopa therapy or as a peripheral manifestation of PD (Toth et al. 2008).

Methods: We retrospectively evaluated the clinical, laboratory and electrodiagnostic findings of PN in PD patients seen in a tertiary Neuromuscular oupatient Clinic from Fortaleza, Brazil. This study was approved by the IRB from the Universidade Federal do Ceara, Brazil.

Results: Ten patients were identified (5 women and 5 men). Their mean age was 76.8 ± 3.2 years. PN was diagnosed 1-9 years after the diagnosis of PD. Three patients were in stage 2 (Hoehn and Yahr staging of PD), 3 in stage 3 and 4 in stage 4. Most of the patients had minor positive sensory complaints ($N=7$). PN was suspected because of worsening gait impairement and/or atrophy or other signs of neuropathy present on the neurological exam. All patients were taking levodopa, with moderate-good clinical response to levodopa. Axonal sensorimotor or sensory PN was documented by EMG in all, but one patient. Laboratory and electrodiagnostic tests were suggestive of immune-mediated disorders in half (3 with MGUS, 1 with positive ANA and 1 with CIDP). The patient who met the criteria for CIDP had high CSF protein (90 mg/dl). Two patients had hypothyroidism and 4 had additional nutritional/metabolic dysfunction (4 with vitamin B12 deficiency and 1 with low serum Cu levels). High homocysteine levels were seen in 4 patients, and was related to levodopa treatment in 2. Immunotherapy was proposed for 2 patients. Only 1 patient was treated with IVIg and had mild response (gait improvement). One patient had transient orthostatic hypotension with increased doses of levodopa and 2 had erectile dysfunction and constipation late in the disease course.

Conclusions: The diagnosis of PN in PD patients is challenging. It may be suspected in the presence of worsening gait impairment or sensory complaints. MGUS and immune-mediated disorders should be evaluated in addition to nutritional, endocrine and metabolic dysfunction due to levodopa therapy.

Tu-231

Clinical features of idiopathic Parkinson's disease and their correlation with autonomic function testing

P.A. Hanna, J. Cristini, M. Rosenberg (Edison, New Jersey)

Objective: To quantitatively evaluate autonomic function variables with clinical symptoms in patients with idiopathic Parkinson's disease (PD).

Background: It is well recognized that patients with PD experience significant autonomic nervous system (ANS) dysfunction. A correlation with disease state has not been well documented. We evaluated the results of autonomic function testing (AFT) and compared these to different clinical characteristics and disease course.

Methods: Twenty patients with PD underwent AFT. Our lab uses wavelet analysis to estimate tone in both the sympathetic and parasympathetic systems simultaneously and continuously. Quantitative sudomotor axon reflex testing (QSART) was performed to demonstrate involvement of the peripheral sympathetic sudomotor axons. AFT protocol includes an assessment of heart rate variability (hrv), low-frequency area (Lfa), high frequency area (Rfa) at baseline and in response to deep breathing, Valsalva, and stand. Lfa and Rfa are estimates of sympathetic and parasympathetic tones respectively. Baseline values of standard high (HF), low (LF) and very low frequency (VLF) activity were also evaluated. AFT findings were compared with clinical features obtained as part of the participants' routine clinical evaluation. These included age, duration of disease, dementia, dystonia, freezing of gait, motor fluctuations, as well as rating scales of activities of daily living (ADL), Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn & Yahr (H&Y) scores.

Results: The UPDRS and H&Y scores correlated with loss of heart rate variability ($p=0.05$) but no other baseline measures. Freezing of gait (FOG) correlated well with the deficit in baseline Lfa ($p = 0.013$), VLF ($p=0.008$) and LF ($p<0.008$) power. Rfa at baseline and in response to deep breathing both showed a suggestive but not significant correlation with dementia ($p = 0.051$).

Conclusions: Several interesting correlations were found comparing specific ANS tests with clinical parameters. Specifically, FOG correlated highly with low frequency parameters at baseline (Lfa, LF, and VLF). There was a suggestion that Rfa (a parasympathetic estimate) was linked to the severity of dementia. Heart rate variability was correlated with disease severity scores. Further evaluation of these associations with a larger group of patients is ongoing.

Tu-232

Autonomic dysfunction in Parkinson's disease and multiple system atrophy: Evaluation with eye drop test and MIBG scintigraphy

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Objective: The aim of this study is to elucidate characteristics of autonomic disturbance in Parkinson's disease (PD), comparison with those in multiple system atrophy (MSA).

Background: Autonomic disturbance is common in PD, as well as in MSA. Recent studies on metaiodobenzylguanidine (MIBG) scintigraphy revealed that cardiac postganglionic sympathetic terminal deteriorates in even early stage of PD although it shows quite normal in MSA. There were several reports that similar postganglionic sympathetic denervation could be detected in PD using eye drop test. We investigated both MIBG scintigraphy and eye drop test using phenylephrine (direct alfa-adrenergic receptor stimulator) and tyramine (enhancer for the release of stored noradrenaline) in PD patients and MSA patients.

Methods: Sympathetic nerve function in pupils was assessed as response to the directly acting receptor agonist, phenylephrine, and to tyramine, causing the release of stored noradrenaline. The pupil diameter of both eyes was recorded using an infrared digitalcamera. 0.5% phenylephrine or 5% tyramine was applied to an eye of each patient and pupil diameter was measured. Pupillary response value of each drug was calculated as subtraction pupil diameter before from after the eye drop. MIBG was administered intravenously and determined using gamma camera. The ratio of the MIBG cardiac accumulation to the upper mediastinum accumulation (H/M ratio) was calculated.

Results: In MIBG scintigraphy, all PD patients showed reduction in H/M ratio, while no MSA patient had abnormal findings. The mean$\pm$SD of H/M ratio in PD patients and that in MSA patients were 1.45 ± 0.22 and 2.52 ± 0.41, respectively. Normal mydriasis was observed after tyramine administration in both PD patients (2.29 ± 0.51 mm) and MSA patients (3.00 ± 0.79 mm). Phenylephrine administration revealed marked mydriasis in MSA patients (3.20 ± 0.91 mm) but not in PD patients (1.71 ± 1.05 mm).

Conclusions: MIBG scintigraphy revealed postganglionic sympathetic denervation in PD patients' heart, but not in MSA patients. Eye drop test, however, indicated postganglionic sympathetic denervation not in MSA, but not in PD patients.

Tu-233

The frequency of autonomic failure symptoms in Parkinson's disease: Is initial presentation sympathetic or parasympathetic?

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Objective: To investigate presentation of autonomic dysfunction in PD patients.

Background: There is disagreement regarding prevalence and autonomic dysfunctions in Parkinson's disease (PD) patients.

Methods: We examined 72 PD patients- 25 patients who were drug naïve (group I), 25 patients with good therapeutic response (group II) and 22 patients with complications of levodopa treatment (group III), as well as 35 age-matched controls using specially designed questionnaire. Additionally, autonomic nervous system dysfunction was diagnosed by applying cardiovascular reflex tests according to Ewing. We used Student's t-test and $\chi 2$ test for statistical analysis.

Results: Genitourinary, gastrointestinal, secretomotor abnormalities and postprandial symptoms were statistically significantly more frequent in PD patients in comparison with control group. The tests for evaluation sympathetic (SNS) and parasympathetic nervous system (PNS) function showed statistically significant distinction between PD patients and control group. However, comparing *de novo* patients and control group statistical significance has been shown in all tests for SNS, while for PNS the significance is irrelevant. The patients from group II and group III differed from the controls in both SNS ($p<0.0001$), and PNS dysfunction ($p<0.0001$). The existence of autonomic neuropathy has been established in 44% of *de novo* patients, 88% in group II and in all patients in group III (average 76% of PD patients). Complete autonomic neuropathy (CAN) has not been determined in group I, while 36% in group II and 50% in group III showed dysfunction of both SNS and PNS (average 28% of PD patients). The persistence of autonomic neuropathy differed significantly ($p<0.0001$) between the groups, as well as CAN ($p<0.0001$).

Conclusions: Our results confirm high prevalence of autonomic nervous system disturbances among PD patients from the very beginning of the disease, with predominant sympathetic nervous system involvement. Patients who developed CAN were individuals with considerable level of functional failure, more severe clinical presentation, marked postural instability and bradykinesia.

Tu-234

Can the EKG be used to identify prodromal PD? Assessment of heart rate variability (HRV) during wakefulness in patients with RBD

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Objective: To test the hypothesis that patients with REM sleep behavior disorder (RBD) have significant alterations in heart rate variability (HRV) during wakefulness as measured by EKG recordings compared to a group of age-matched controls without RBD.

Background: It is now well established that RBD can precede clinical symptoms of PD by a number of years. Based on the assumption that many patients with RBD likely have prodromal PD, we hypothesized these patients might have alterations in HRV similar to those with fully-developed PD and that this dysautonomia can be identified using a standard EKG. The long-term goal of this research is to identify tools that could be used to screen the general popula-

tion for the earliest signs of PD, well before motor features are manifested.

Methods: Data from polysomnograms performed between the years 2000 to 2008 in 10 RBD patients and 10 age- and sex-matched controls were retrieved and the pre-sleep segments of EKG channel analyzed for changes in HRV.

Results: A wide variety of HRV measures, including standard deviation of N-N intervals (SDNN) and heart rate (SDHR), root mean square difference of successive RR intervals (RMSSD) percentage of number of pairs of adjacent RR intervals differing by more than 50 ms (pNN50), short term HRV (SD1) and long term HRV (SD2) obtained from the Poincaré plot, RR triangular index, triangular interpolation of NN (TINN), spectral powers in the Very Low Frequency (VLF), Low Frequency (LF) and High Frequency (HF) bands as well as Total Spectral Power, were significantly lower in RBD patients than controls (see Table). The LF/HF ratio, normalized LF (LF nu) and HF (HF nu) also showed a trend in the same direction. These changes indicate that sympathovagal balance is impaired in RBD patients who do not have a diagnosis of PD.

HRV parameters between control and RBD groups

	RBD patients	Control group	p value
RR (ms)	941.5 ± 95.8	945.3 ± 188.98	NS
SDNN (ms)	17.6 ± 6.49	29.8 ± 11.14	**p < 0.01**
HR (bpm)	64.437 ± 6.14	65.84 ± 12.1	NS
SDHR (bpm)	1.784 ± 0.75	2.77 ± 1.01	**p < 0.03**
RMSSD (ms)	16.21 ± 5.62	27.27 ± 13.20	**p < 0.03**
pNN50 (%)	2.03 ± 2.18	10.24 ± 10.61	**p < 0.03**
SD1 (ms)	11.81 ± 4.11	19.73 ± 9.50	**p < 0.03**
SD2 (ms)	43.89 ± 20.93	70.26 ± 33.44	**p < 0.05**
RR triangular index	0.038 ± 0.01	0.052 ± 0.016	**p < 0.03**
TINN (ms)	92 ± 30.43	157 ± 61.78	**p < 0.01**
VLF (ms²)	11.2 ± 8.12	24.6 ± 17.37	**p < 0.04**
LF (ms²)	104.3 ± 72.56	382.1 ± 289.02	**p < 0.01**
LF (nu)	62.97 ± 16.66	74.91 ± 10.62	p < 0.08
HF (ms²)	45.3 ± 29.40	134.6 ± 118.22	**p < 0.03**
HF (nu)	37.03 ± 16.66	25.09 ± 10.62	p < 0.08
Total Power (ms²)	160.8 ± 102.85	541.3 ± 398.30	**p < 0.01**
LF/HF	2.26 ± 1.39	3.60 ± 1.77	p < 0.08

Data is presented as mean ± SD. Parameters showing statistical significance are shown in bold

FIG. 1 (Tu-234).

Conclusions: HRV during wakefulness in idiopathic RBD patients is markedly altered as compared to control subjects. This alteration can be measured by a standard EKG. Because a significant proportion of those with RBD develop parkinsonism, this observation raises the possibility that routine EKG recording could be a useful preliminary screening procedure for prodromal parkinsonism. This could be very important should disease modifying therapies become available.

Tu-235

Pilocarpine-induced myotic response is greater in PD than in MSA patients

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Objective: To evaluate the basal pupil diameter and the amplitude of response to pilocarpine in 10 patients with Parkinson's disease (PD), six patients with MSA and 10 healthy controls.

Background: PD patients often complain of visual disturbances. Only few studies have evaluated ocular dysautonomias in PD patients while, to our knowledge, no studies have compared the pupil response to pilocarpine between PD and MSA patients.

Methods: Pupil diameter was assessed using an infrared videocamera in darkness. Dilute pilocarpine (0,143%) was administered in one eye. The pupil diameter was recorded at baseline and every 15 minutes up to 60 minutes. The diameters of the pupil were blindly measured on the PC display. The pupil response was quantified by the percentage of the following ratio: (D2-D1) X 100/D1, where D1 and D2 represent the baseline diameter and the minimum drug-treated diameter, respectively.

Results: The myotic response to 0,142% pilocarpine administration was significantly greater in PD patients than in MSA and control subjects ($p < 0.05$). In addition, the basal pupil diameter in darkness was significantly greater in PD group than in both MSA and healthy subjects ($p < 0.05$).

Conclusions: These data suggest a pupil postganglionic autonomic dysfunction in Parkinson's disease and, if confirmed by larger studies, pilocarpine-induced myotic response should represent a useful tool in the diagnostic approach of PD.

We-229

Alterations of enteric neurons in Parkinson's disease assessed by colonoscopy biopsies

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Objective: (1) To develop a method to analyze the submucosal plexus (SMP) from standard colonic biopsies acquired during the course of a routine colonoscopy, and (2) to identify in the SMP of living Parkinson's disease (PD) patients the putative presence of neuronal inclusions and changes in the neurochemical coding.

Background: There is currently an increasing interest for the non-motor symptoms of PD, among which gastrointestinal dysfunction is the most common. Gastroparesis and constipation affect most of the patients and can even precede motor signs. Recent autopsy studies showed that Lewy bodies and Lewy neurites are present in theenteric nervous system (ENS).

Methods: 13 age-matched patients and controls were included in this study approved by the Ethics Comitte of the University Hospital of Nantes. 5 patients had PD and suffered from constipation; 3 control patients had chronic constipation; 5 controls underwent colonoscopy for colorectal cancer screening. 4 standard biopsies from the ascending colon were taken. Submucosa was microdissected from the mucosa, and whole mounts were stained with antibodies against tyrosine hydroxylase (TH) dopamine-beta-hydroxylase (DBH), phosphorylated alpha-synuclein, neurofilament (NF220kDa) or Hu (used as a general neuronal marker).

Results: Biopsies contained a similar number of ganglia in control, constipated or PD patients. No change was observed in the number Hu-IR neurons per ganglion when comparing PD patients (7.0+/−1.6) with constipated patients (5.5+/-0.6; p=0.19), nor with healthy controls (5.6+/-1.9, p=0.22). In addition, we found no change in the proportion of TH-IR neurons between PD (12.3+/-3.3%) and constipated patients (8.2+/-2.7%; p=0.12), nor between PD patients and healthy controls (12.3+/-3.3%; p=0.80). No TH-IR neurons in the SMP were DBH-IR. Finally phospho-alpha-synuclein-immunoreactive fibres similar to Lewy neurites were present in 4 out of 5 PD patients but in none of the controls.

Conclusions: The method developed permits an accurate analysis of the SMP obtained from standard colonic biopsies. With respect to PD, the identification of alterations in the ENS paralleling CNS pathology could allow a neuropathological diagnosis in the living patient. Our results validate the concept considering the ENS as a window toward the CNS.

We-230

MIBG scintigraphy for differentiating Parkinson's disease with autonomic dysfunction from parkinsonism predominant multiple system atrophy

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Objective: This study aimed to analyze the validity of MIBG scintigraphy for Parkinson's disease (PD) with autonomic dysfunction and parkinsonism predominant multiple system atrophy (MSA-p).

Background: PD with autonomic dysfunction is difficult to differentiate from MSA-p. MIBG scintigraphy is a useful tool for differentiating PD from MSA. However, study on validity of MIBG scintigraphy for differentiating between PD with autonomic dysfunction and MSA-p has not been reported.

Methods: Thirty-nine patients (PD: 27 patients, MSA-p type: 12) and 12 age-matched controls were prospectively enrolled and underwent MIBG scintigraphy and autonomic function test (AFT). We separately calculated early and delayed heart to mediastinal (H/M) ratio, and washout rates (WR). AFT was composed of sympathetic skin reflex (SSR) and parasympathetic tests based on heart rate variability (HRV).

Results: Abnormal AFT was observed in 17 (63%) of PD and 10 (83%) of MSA-p. On comparing PD with abnormal AFT with MSA-p, either the early or delayed H/M ratio in PD was not different from that in MSA-p ($p > 0.05$). Only the WR could differentiate PD with abnormal AFT from MSA-p (47.07 ± 57.48 vs. 31.39 ± 31.52, respectively) ($p = 0.026$). Among the patients with PD, there were no significant correlations between the MIBG uptake and age at examination, age of onset, disease duration, or Hoehn and Yahr stage ($p > 0.05$).

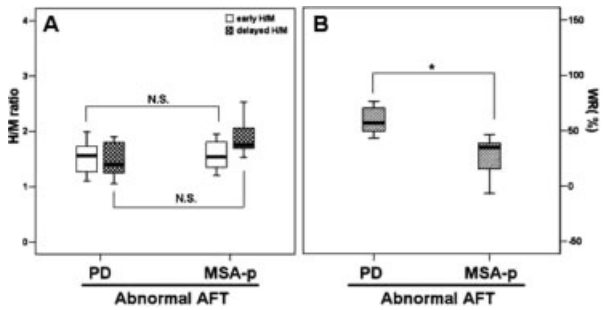

FIG. 1 (We-230).

Conclusions: According to the results, WR may be more useful than the early and delayed H/M ratio to distinguish MSA-p from PD with abnormal AFT. Furthermore, the MIBG uptake did not reflect the disease duration or severity.

We-231

Parkinson's disease is associated with a decreased risk of hypertension

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Objective: To assess whether Parkinson's disease (PD) is a protective factor against a subsequent diagnosis of hypertension.

Background: The relationship between PD and hypertension has been evaluated in previous epidemiological studies with inconsistent results. Because subclinical sympathetic dysfunction is a common feature of early PD, PD patients might have a lower risk of hypertension.

Methods: In this retrospective cohort study, we selected 35 consecutive PD patients and 35 control subjects (respective partners of similar age ($\pm$ 5 yrs) who have lived with the patients since the diagnosis). Clinical data were collected at around the time of the diagnosis and at the present time on history of hypertension, diabetes, smoking and drug use. We also measured blood pressure and administered the SCOPA questionnaire for dysautonomic symptoms.

Results: PD patients were 26 men and 9 women (controls: 26 women and 9 men) with a mean age of 58 yrs at the diagnosis and 68 yrs at the present time. No significant differences in the prevalence of hypertension were found at the diagnosis or at the present time. However, the accumulated incidence of newly diagnosed hypertension at 10 yrs after the diagnosis was significantly higher in controls (43%) vs. PD patients (18%; relative risk = 2.4; $p = 0.042$). PD patients had lower systolic and diastolic blood pressure vs. controls (127/76 vs. 142/83; $p = 0.002$) and a higher SCOPA score for cardiovascular dysautonomic symptoms (1.2 vs. 0.6; $p = 0.011$).

Conclusions: In this study, the diagnosis of PD was associated with a decreased risk of hypertension, probably due to the presence of sympathetic dysfunction and the effects of dopaminergic drugs.

We-232

A mathematical model from heart rate variability analysis to distinguish between de novo Parkinson's disease patients and controls

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Objective: To develop a mathematical model from HRVA parameters that distinguishes between individual de novo PD patients and controls.

Background: Parkinson's disease (PD) usually affects the autonomic nervous system (ANS). Heart rate variability analysis (HRVA) is considered a useful tool to assess both sympathetic and parasympathetic cardiac function. In previous reports, HRVA has shown its ability to distinguish between de novo PD patients and controls as groups but not on an individual basis.

Methods: 8 de novo untreated PD patients and 8 controls were enrolled in the study. Holter recordings were made in the supine position, breathing at 6 c/min in the supine position, in the upright position and walking normally. A mathematical model based on logistic binary regression was constructed to distinguish between patients and controls.

Results: The mathematical model obtained after logistic binary regression is useful to distinguish between PD patients and controls with a sensitivity of 0.91, specificity of 0.88, positive predictive value of 0.87 and negative predicitive value of 0.91 ($p<0.05$).

Conclusions: This mathematical model appears to be useful to distinguish between controls and de novo PD patients on an individual basis and could be used when there are clinical doubts as to diagnosis at onset of the illness.

We-157

Autonomic and sensory symptoms are frequent and of mild severity in patients with incident, untreated PD

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Objective: To investigate the frequency and severity of a selection of autonomic and sensory symptoms in a population-based cohort of patients with newly diagnosed and untreated PD.

Background: Non motor symptoms are an important part of the clinical picture in Parkinson's disease. Their frequency is reported as relatively high even in early disease stages, while the severity is highlighted insufficiently. Most reports are based on selected populations in specialised clinics.

Methods: 207 patients with untreated, incident PD and 175 controls were included. Investigations were based on structured and semi-structured interview, comprising i.a. the UPDRS score. Dysphagia, drooling and sensory complaints were rated with UPDRS part II

(score 0-4), urinary problems, constipation and increased sweating with a questionnaire ranging the severity from 0-3 (absent, slight, moderate, severe). Scoring ≥1 indicated the presence of the particular symptom. Orthostatic hypotension was defined as ≥20mmHg decrease in systolic bloodpressure measured after 2min standing, preceded by 10min supine. Smell was tested with vanilla and coffee presented separately in open flasks.

Results: Patients were at mean 67.9 years, 122 (58.9%) were men, the disease duration was 2.3 years. The 175 controls were group matched for age and gender. The most frequent symptoms in patients were olfactory dysfunction, urinary problems, drooling and constipation, ranging from 58.9% to 39.1%. Less frequent were sensory complaints, sweating, dysphagia and orthostatic hypotension, ranging from 33.8% to 17.9%. The severity was rather low. In 85.9% to 94.4% of cases the respective symptom was either not present, or in the slightest expression (score 0 or 1). Only 4.8% to 11.7% scored moderate degree (score 2), and less than 4% reported the most serious degrees (scores 3 and 4). All symptoms but sweating were significantly more frequent in patients compared to controls. Only for dysphagia (patients vs. controls 1.41 vs. 1.00, p=0.032) and constipation (1.33 vs. 1.08, p=0.47) the scores were significantly higher in patients.

Conclusions: Autonomic and sensory symptoms in patients with incident and untreated PD are frequent, but mild. Nevertheless they might influence the quality of life.

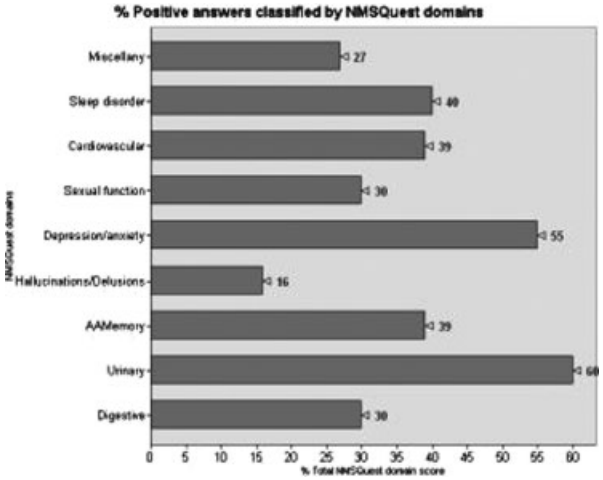

FIG. 1 (We-233).

seem to be more prevalent in men but this may be only a cultural bias. No correlation was found with treatment, age or age at onset.

We-233

Non-motor dysfunction prevalence among Mexican Parkinson's disease patients

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Objective: To describe non-motor symptoms prevalence in Mexican PD patients and analyze correlation with demographic and disease factors.

Background: Prevalence of non-motor dysfunction in Parkinson's disease is high but mostly remains undiagnosed. This dysfunction includes neuropsychiatric, dysautonomic and sleep disorders that have an important effect on patient's quality of life. NMSQuest is a self-completed questionnaire used to assess the presence of non-motor symptoms in PD patients. Prevalence of motor symptoms in Mexican PD patients has not been reported.

Methods: A transversal analytic study was carried out in 110 PD subjects at the outpatient movement disorder clinic from april 1st to december 16th, 2008. NMSQuest was applied, clinical and demographical data was collected. Statistical analysis tests included descriptive statistics, Spearman's correlation, Mann-Whitney and one-way ANOVA (or Kruskal-Wallis when needed).

Results: From the 110 patients, 43% were female and 57% were male, mean age was 63.7 ± 11.3 years, mean age at PD diagnosis was 57.1 ± 11.3 years, PD duration of 6.5 ± 5 years and median HY stage was 2.5. 75% were treated with L-dopa, 56% were on dopaminergic agonists, 14% received MAO inhibitors and 7% COMT inhibitors. All patients had at least one NMSQuest positive answer, mean total score was 10.5 ± 5.6 with a range from 1 to 26. No statistically significant difference was found between age group and L-dopa use and with total score but significant differences were found by gender for total and sexual domain score with men having a scoring higher. A weak but significant correlation was found with HY score (r=0.21). Frequency of positive answers classified by domain (% on the maximum) was as follows: gastrointestinal symptoms 30%, urinary symptoms 60%, memory/attention/apathy 39%, hallucinations/delusions 16%, depression/anxiety 55%, sexual symptoms 30%, cardiovascular 39%, sleep disorders 40% and miscellany 27%.

Conclusions: Prevalence of non-motor symptoms in our population do not differ from international published data. Sexual disorders

We-234

Lewy body diseases spectrum by myocardial sympathetic degeneration

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Objective: To investigate clinical spectrum of myocardial sympathetic denervation disease as detected by ^{123}I-metaiodobenzylguanidine (MIBG) cardiac scintigraphy.

Background: In the last two decades MIBG scintigraphy is well known to detect myocardial denervation, originally described in dilated cardiomyopathy. However, pathology studies showed that myocardial denervation is common in Lewy body diseases (LBD) of various forms, e.g., Parkinson's disease (PD), dementia with Lewy bodies (DLB), and pure autonomic failure (PAF), which is unrelated with cardiac failure in those patients. Therefore, it turned out to be an excellent biomarker. Using this, LBD could present itself in a more clear-cut manner than in the past.

Methods: Among 1229 new outpatients in our university clinic last year, most of whom were referred patients, and in whom 230 patients had undergone MIBG scintigraphy, 116 patients were enrolled. All patients had the heart to the mediastinum (H/M) ratio of less than 2.0 in delayed planar images. All patients underwent neurological examination, systematized interview of autonomic and sleep disorders, MRI, SPECT, and laboratory examination. Fifty-two of the patients underwent cognitive tests. None had apparent heart failure, had history of repeated strokes, use of neuroleptics, antidepressants, or substance abuse.

Results: Our cohort included 47 men and 69 women; mean age, 73 years; mean duration of disease, 6.0 years; median Hoehn and Yahr motor grade, 3. At the time of referral, levodopa was administered in 77 patients, with a mean dose, 200 mg per day. They were diagnosed with PD in 81; DLB in 32; PAF in one, and undermined in two. In drug-naïve subcohort, 'PD' patients (median HY grade 2) lack rest tremor in 76% and rigidity in 19% (pure akinesia); these features simulated those of 'DLB'. Hallucination was more common in medicated subcohort. Among autonomic disorder in drug-naïve subcohort, bowel dysfunction (86%) was the most common. Insomnia and sleep attack were more common in medicated subcohort. Two with undetermined type had severe constipation, bladder dysfunction, and REM sleep behavior disorder alone.

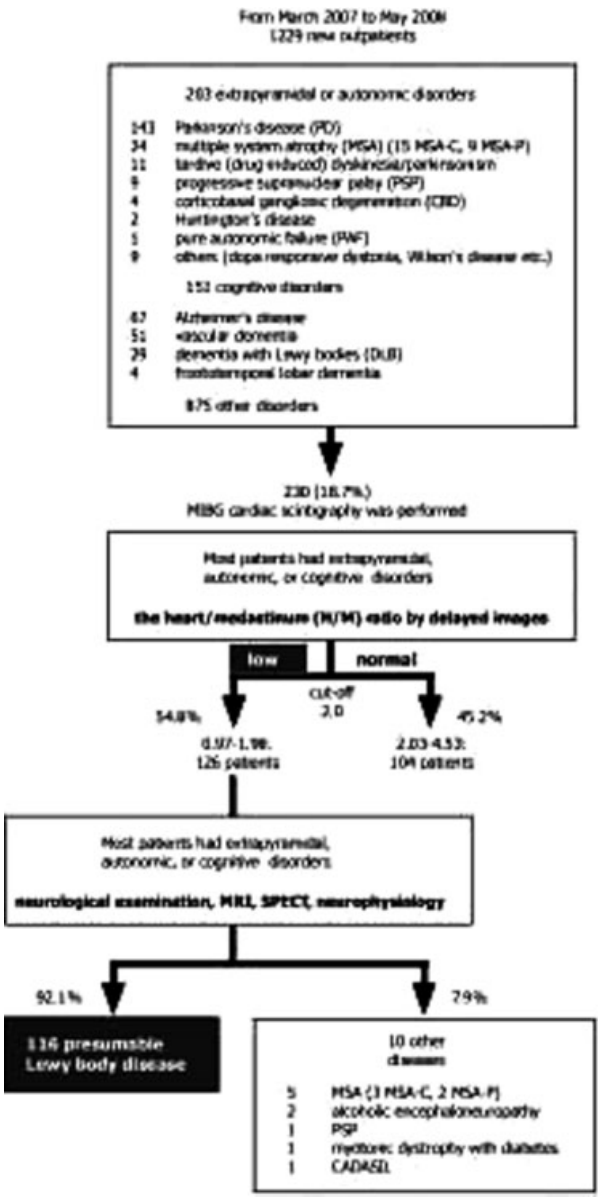

FIG. 1 (We-234).

diagnosis	levodopa mg/day	No. of patients	motor grade HY	rigidity %(No. of patients)	tremor rest %	tremor postural %	akinesia slowness %	akinesia short step %	akinesia festination diadocho kinesis %	akinesia gait %	disturbed postural reflex %	dyskinesia %
PD	-	21	2(1-3)	81(17)	24(5)	41(11)	57(12)	48(10)	48(10)	38(8)	57(12)	0
	+ [400(100-900)]	60	3(2-5)	77(46)	32(19)	43(26)	62(37)	60(36)	32(19)	60(36)	75(45)	20(12)
	total	81	3(1-5)	78(63)	30(24)	46(37)	60(49)	57(46)	52(42)	54(44)	70(57)	15(12)
DLB	-	15	2(0-4)	33(5)	7(1)	27(4)	67(10)	40(6)	27(4)	33(5)	73(11)	0
	+ [300(200-500)]	17	3(2-4)	82(14)	29(5)	29(5)	65(11)	65(11)	29(5)	59(10)	88(15)	0
	total	32	3(0-4)	59(19)	19(6)	28(9)	66(21)	53(17)	28(9)	47(15)	81(26)	0
PAF	-	1	0	-	-	-	-	-	-	-	-	-
	+	0										
undetermined LBD	-	2	0	0	0	0	0	0	0	0	0	0
	+	0										

FIG. 2 (We-234).

Conclusions: The results of this study suggest that clinical spectrum of myocardial sympathetic denervation disease (possible LBD) is wider than in the past.

We-235

Reduced bowel movements preceding Parkinson's disease: A case-control study

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Objective: To investigate the association of reduced bowel movement (constipation) with Parkinson's disease (PD) using a case-control study design.

Background: Non-motor manifestations have been considered part of PD since first described in 1817. Several studies have reported an association between constipation and PD, but few studies have explored the relationship of constipation prior to the onset of motor symptoms of PD. In addition, small sample size and methodological limitations of previous studies make the interpretation of the evidence difficult.

Methods: We used the medical records-linkage system of the Rochester Epidemiology Project to identify 196 subjects who developed PD in Olmsted County, MN, from 1976 through 1995. Each incident case was matched by age (± 1 year) and sex to a general population control. We reviewed the complete medical records of cases and controls to detect the occurrence of constipation preceding the onset of PD (or index year). All of the analyses were adjusted by smoking and coffee-consumption.

Results: Constipation was significantly more common in cases than in controls (odds ratio [OR] 2.18; 95% confidence interval [CI] 1.32 to 3.61; $p = 0.003$), and the association remained significant after excluding constipation occurring as a side effect of medications (OR 1.77; 95% CI 1.04 to 2.98; $p = 0.03$). Although the differences were not statistically significant, the association was stronger in women (OR 3.18; 95% CI 1.45 to 6.98; $p = 0.004$) than in men (OR 1.86; 95% CI 0.94 to 3.68; $p = 0.07$; p for interaction $= 0.35$) and in patients with tremor-predominant PD (OR 2.33; 95% CI 1.31 to 4.17; $p = 0.004$) than in patients with akinetic-rigid PD (OR 1.43; 95% CI 0.41 to 4.98; $p = 0.58$; p for interaction $= 0.68$). The association was similar for constipation starting within 20 years of PD onset or index year (OR 1.86; 95% CI 1.01 to 3.44; $p = 0.047$) and for constipation starting 20 or more years before PD onset (OR 2.70; 95% CI 1.33 to 5.50; $p = 0.006$; p for interaction $= 0.39$).

Conclusions: Our findings support the hypothesis that constipation is an early premotor manifestation of PD, occurring even 20 or more years before the development of motor symptoms. In addition, our results suggest a stronger association in women and in patients with tremor-predominant PD.

We-236

Long term blood pressure in Parkinson's disease

S. Sommer, B. Aral, W. Jost (Wiesbaden, Germany)

Objective: We studied long term blood pressure measurements in patients with Parkinson's disease, especially to evaluate non dipper patients.

Background: Parkinson's disease is a multi-system degeneration with motor symptoms as well as psychiatric and autonomic dysfunction. The most common autonomic symptom beside constipation is orthostatic hypotension. MIBG-szintigraphy shows abnormalities even in the early and non-motor stages. Until now the effect of degeneration of central and peripheral components of the autonomic nervous system on blood pressure is not well understood.

Methods: We performed long term blood pressure measurements in 20 non-selected patients with idiopathic Parkinson's disease. 10 of them were male (50%), 10 were female (50%); they were aged 43 to 83 years; disease duration was 4 months to 15 years. 13 of the patients (65%) werde diagnosed with arterial hypertension and received anti-hypertensive drugs. Long term blood pressure measurements werde performed with 'Mobilograph' (I.E.M. GmbH, Stolberg, Germany).

Results: Long term blood pressure measurements showed 11 patients with arterial hypertension (defined as increase of systolic blood pressure > 140mmHg and/or increase of diastolic blood pressure > 90mmHg), one patient with low blood pressure and 8 patients with normal blood pressure. We identified 17 non dipper patients (85%), defined as nocturnal decrease of mean systolic and diastolic blood pressure < 10%, among 20 examined patients with idiopathic Parkinson's disease. Actually 9 of them (45%) showed nocturnal increase of blood pressure.

Table (We-236). Long term blood pressure measurements

Long term blood pressure	Patients with idiopathic Parkinson's disease n = 20
Day	
Mean systolic BP [mmHg]	130,6
Mean diastolic BP [mmHg]	75,3
Arterial hypertension: systolic BP > 140mmHg and/or diastolic BP > 90mmHg	55% [11/20]
Night	
Mean systolic BP [mmHg]	127
Mean diastolic BP [mmHg]	72,5
Pathologic mean nocturnal BP: BP > = 125/80mmHg	60% [12/20]
Cumulative measurement period (17 to 24h)	
Mean systolic BP [mmHg]	129,2
Mean diastolic BP [mmHg]	74,3
Nocturnal BP fall	
Non dipper patients	85% [17/20]
Nocturnal increase of BP	45% [9/20]
Mean systolic nocturnal decrease of BP [%]	3,0 (-16,7; 28,5)
Mean diastolic nocturnal decrease of BP [%]	3,4 (-7,6; 23,9)

BP = blood pressure, − = increase of BP.

Conclusions: Our results show that most of our examined patients with Parkinson's disease were non dipper (85%). This was a surprising result given the fact that this hasn't been observed in former studies. There was no correlation to age, disease duration, presence of arterial hypertension or antihypertensive medication. These results should be considered in therapy of Parkinson's disease, especially when arterial hypertension is present and anti-hypertensive drugs are used.

Th-230

Dysautonomia frequently occurs prior to the onset and diagnosis of tremor dominant Parkinson's disease (PD)

M.K. Sanghera, R.J. Buchanan, R.M. Stewart (Dallas, Texas)

Objective: To evaluate the temporal relationship of dysautonomia to motor symptoms in typical PD.

Background: Traditionally PD involves degeneration of dopaminergic (DA) nigra neurons resulting in motor symptoms. Braak et al. (Neurobiol. Aging 24:197,2003) reported that PD starts with brainstem Lewy body pathology in non DA neurons and ascends to the cortex. These data suggest the possibility that nonmotor symptoms including autonomic symptoms might be used in the early detection of PD.

Methods: Twenty-five cognitively intact PD patients were independently rated by two raters on two differently occasions (time interval 2 days to 2 weeks) using the Presbyterian Hospital Autonomic Profile for the presence and intensity of dysautonomia in the following domains: (i) orthostatic hypotension (ii) cardiovascular (iii) thermoregulatory (iv) vision (v) secretions (vi) upper and lower gastrointestinal and (vii) urogential tract. All patients answered the questionnaire in the presence of a spouse who verified the autonomic and motor symptom time line. Only symptoms occurring up to 16 yrs prior and up to 10 yrs after diagnosis were included. Subjects with MSA were excluded.

Results: Seventeen patients met the inclusion criteria of complete compatibility of time line of events between the 2 raters. Thirteen patients were tremor dominant and 4 were gait dominant. All tremor dominant patients reported having one or more autonomic dysfunctions 1-16 years prior to Dx. Average age of onset (years) were cardiovascular (13±4.5), GI (7.6±4.7), GU (7.2±5.6), thermoregulation (6.0±3.7), and secretions (3.5±3.5). GI was the most reported and secretory dysfunction the least. Three out of four gait dominant patients reported no autonomic dysfunction prior to Dx but did report autonomic dysfunction at the onset or shortly after (1-5 yrs) Dx. One remaining patient with 16 years of PD continues free of autonomic deficits.

Conclusions: Autonomic dysfunction is frequent prior to onset of motor symptoms in tremor predominant PD and does not automatically signify an atypical PD such as MSA. The temporal pattern of clinical symptoms of autonomic dysfunction may not strictly follow the ascending pattern of neuronal involvement recently proposed.

Th-231

Clinical characteristics of a family with Perry syndrome due to a DCTN1 mutation

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Objective: To characterize the clinical features of the Fukuoka-1 family with Perry syndrome due to a mutation in *DCTN1*.

Background: Perry syndrome is a familial parkinsonism associated with central hypoventilation, depression and weight loss. To date, 9 families with this syndrome have been reported worldwide.

Methods: The pedigree contains 20 family members spanning 3 generations, with 8 affected individuals. We obtained detailed medical records from 5 affected patients.

Results: Mean age at onset was 43.6 years (38 to 49 years). Mean disease duration was 5.6 years (3 to 9 years). All affected patients exhibited rapidly progressive parkinsonism characterized by bradykinesia, tremor, postural instability, and rigidity. Some patients benefited from levodopa therapy during the initial stages, however with early wearing off and dyskinesia. Because of central hypoventilation, three affected patients needed ventilatory assistance, which helped prolong survival. Severe weight loss and depression were seen in 2 patients. In addition, marked reduction of cardiac uptake of meta-[^{123}I] iodobenzylguanidine (MIBG) was seen in 2 examined cases, indicating significant autonomic dysfunction. Genetic study revealed a point mutation, c.212G>C (p.G71A) in the *DCTN1* gene.

Conclusions: This study demonstrates for the first time marked autonomic dysfunction (abnormal cardiac MIBG scintigraphy) in a family with genetically-proven Perry syndrome. Affected individuals also presented the classical symptoms of parkinsonism, hypoventilation, depression and weight loss.

Th-232

Urinary disturbances precede the classical motor symptoms of Parkinson's disease?

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Objective: To investigate whether urinary disturbances precede the classical motor symptoms of Parkinson's disease, and duration of the prodromal phase.

Background: There is growing evidence that some symptoms can precede the classical motor features of Parkinson's disease. Premotor symptoms in Parkinson's disease include constipation, loss of smell, sleep disturbances such as REM sleep behavior disorder, and mood disturbances like depression. Urinary disturbances in Parkinson's disease are also a well-known non-motor feature. A recent report of one case with long standing urinary disturbances and orthostatic hypotension diagnosed as pure autonomic failure (PAF) but evolving into Parkinson's disease later on, suggest that urinary disturbances may occasionally precede motor symptoms of Parkinson's disease. However the preceding symptom and duration of urinary disturbances were not investigated in detail.

Methods: Forty-nine de-novo Parkinson's disease patients with a mean age of 68 years were recruited. We questioned the existence and duration of their urinary and motor symptoms. The questionnaire for urinary disturbances concerned the storage symptoms such as daytime frequency, night time frequency, urgency and urge urinary incontinence, and the voiding symptoms such as hesitancy, slow stream, intermittent stream, straining and feeling of incomplete emptying.

Results: Forty-three patients out of 49 (88%) complained of urinary symptoms. Their Initial symptoms were daytime frequency (19%), night time frequency (33%), urgency (14%), daytime frequency + urgency (21%), nighttime frequency + urgency (7%), nighttime frequency + voiding difficulty (hesitancy or slow stream) (5%). These incidence rates were significantly higher than the previous studied rates in healthy subjects. In 15 patients out of 49 (31%), onset of urinary symptoms preceded motor symptoms by an average time of 35 months (6 – 120 months).

Conclusions: Urinary disturbances, in particular storage symptoms, may precede the motor disturbances of Parkinson's disease, which might reflect particular brain pathology relevant to the lower urinary tract function.

Th-233

Dysautonomy in patients with Parkinson's disease (PD)

A.F. Vasilenko (Chelyabinsk, Russian Federation)

Objective: The assessments of peripheral autonomic disorders in patients with PD.

Background: In PD heart denervation, which is manifested in heart rate stabilization and orthostatic hypotension, has an unfavorable clinical course.

Methods: 47 patients with parkinsonism and 25 healthy persons, as control, were included into the study groups. Besides the general clinical examination and neuroimaging studies, for evaluation of the autonomic regulation in the heart sinus node (SN) all patients were examined by analysis of heart rate variability (HRV) by rhythmocardiography. Three types of the HRV waves were defined in the next average indices: VLF, LF, HF and their statistic analogues – σl, σm, σs and SDNN.

Results: In patients with PD was decreased HRV–SDNN=0.024±0.012 vs 0.053±0.043 sec in the healthy control on account of amplitudes reduction of σl, σm, σs, especially high frequency waves, which reflected the parasympathetic influence in SN (σs =0.012±0.008 vs 0.044±0.02 sec, correspondingly). In Frequency-Domain analysis we found that the most share of spectral density was in VLF-range (VLF% =48.89±14.27% vs 17.10 ±6.02%, correspondingly), which was the evidence of the decrease of rapid autonomic regulation in the SN rhythm and one's transition to the very low humoral-metabolic level. There were sites of the HRV stabilization in 42 patients, which were equivalent of myocardial ischemia episodes, proving the coronary artery disease and stenocardia in them. Evaluating HRV by various stimuli tests confirmed the pathological autonomic SN regulation too.

Conclusions: Thus, in patients with PD were found to have autonomic dysregulation in SN pacemaker activity. Rhythmocardiography HRV study is sensitive method to evaluate the peripheral autonomic system in patients with PD.

Th-234

Heart rate variability as a measure of autonomic dysfunction in Parkinson's disease: Clinical correlates

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Objective: To evaluate (1) the association between heart rate variability (HRV), a measure of autonomic function, and autonomic symptom burden in idiopathic Parkinson's disease (PD) and (2) the relationship between HRV and standard PD-related variables.

Background: HRV is a non-invasive measure of autonomic function. Studies applying HRV to PD (largely young patients with early PD) have confirmed autonomic dysfunction, but few have compared degree of dysautonomia with symptom severity. SCOPA-Aut is a validated PD-specific tool for measuring autonomic symptom severity.

Methods: An autonomic symptom survey of PD patients under the Northumbria PD service (an all-age, geriatrician-lead service) took place over 17-months from 01/09/2006 (n=160). All subjects were invited to undergo HRV. Subjects were excluded if they had a history of ischaemic heart disease, arrhythmias or were using anti-arrhythmic drugs (n=56). Standard tools were applied (Hoehn and Yahr, MMSE, SCOPA-Aut). A 10-minute supine HRV measurement in standardised conditions was undertaken using the Task Force monitor (TFM). A portable monitor was used where the subject was too unwell to attend the hospital (n=25: results not presented). Frequency-domain HRV parameters were used. Standard statistical tests were applied.

Results: 35 subjects underwent TFM HRV. 6 excluded (2 previously-undiagnosed arrhythmias, 4 tremor artefact). 19 male, median age 71 years (55-85), median disease duration 3 years (1-17), median H&Y 2 (1-3), median MMSE 29 (25-30) and median SCOPA-Aut 17 (6-42). 26 (89.7%) were on anti-parkinsonian drugs (median time from last medication to HRV 63 minutes (47-110)). Univariate analyses (Spearman's rho) suggested negative correlations between HRV and age ($r_s=-0.45$, $p<.05$), H&Y ($r_s=-0.40$, $p<.05$), disease duration ($r_s=$-0.42, $p<.05$) and levodopa dose ($r_s=$-0.44, $p<.05$). There was no significant association between total SCOPA-Aut and HRV ($r_s=$-0.14, $p=.475$). Considering individual SCOPA-Aut domains, there were significant negative correlations between total HRV and cardiovascular symptoms ($r_s=$-0.46, $p<.05$), and high frequency HRV and pupillomotor symptoms ($r_s=$-0.41, $p<.05$).

Conclusions: Autonomic function worsens with advancing age, levodopa dose, disease duration and severity, in patients with PD. There is no relationship between overall autonomic symptom burden and dysautonomia (HRV).

Th-235

Screening for orthostatic hypotension in patients with Parkinson's disease may help to decrease morbidity and mortality: Database analysis from acute rehabilitation facility

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Objective: To determine the frequency of orthostasis in patients with Parkinson's disease admitted to an acute rehabilitation facility.

Background: Some patients with Parkinson's disease develop autonomic dysfunction during the course of their disease.

Methods: Database from an acute rehabilitation facility for Parkinson's disease patients admitted from January 2007 to August 2008 was analyzed and information on diagnosis, severity of Parkinson's disease as indicated by Hoehn and Yahr stage, and orthostasis was collected. Daily blood pressure data collected in the first three days of admission was used to determine orthostasis. Orthostasis was defined as a drop in systolic blood pressure of 20 points or a drop in diastolic pressure of 10 points from sitting to standing.

Results: Of the 119 patients with a diagnosis of idiopathic Parkinson's disease admitted from January 2007 to August 2008, forty-nine percent were orthostatic. Patients with orthostatic hypotension were not always symptomatic. Of the orthostatic idiopathic Parkinson's disease patients, thirty-six percent had Hoehn and Yahr stage 3, forty-five percent had Hoehn and Yahr stage 4, and sixteen percent had Hoehn and Yahr stage 5.

Conclusions: Orthostatic hypotension occurs with frequency in individuals with more advanced Parkinson's disease and patients may be asymptomatic. Routine orthostatic blood pressure screening during Parkinson's disease office visits will likely identify some of these individuals. Orthostatic hypotension may contribute to falls in

patients with Parkinson's disease. Optimizing blood pressure may decrease morbidity and mortality in these individuals.

Th-236

Body weight dynamics in Parkinsonan patients

A.Y. Yablonskaya, N.V. Fedorova (Moscow, Russian Federation)

Objective: To estimate body weight dynamics in parkinsonian patients at different clinical stages; to evaluate associated clinical condition's (quality of life and depression scores, grade of autonomic disorders) importance.

Background: Magnitude of weight loss in most patients with Parkinson's disease since first appearance of symptoms is about 52-65%. Weight loss associated with depression, advanced age and stage of disease. Levodopa may lead to weight loss by means of side effects (nausea, vomiting). Rigidity and dyskinesias are main causative factors of weight loss on advanced stages of disease. Swallowing disorders, diet, associated with levodopa administration are also means. Weight gain in parkinsonian patients is rare (6,7%), and often follows on dophamin agonists administration.

Methods: Twenty patients with PD, M: F=18:7, age (62,13 ± 9,45 years), duration of disease (6.2±0.4 years). Anthropometric data (weight, growth) were estimated and its dynamics were compared with therapy compound. Autonomic disorders were estimated with Levin & Amosova (2003) scale. Life quality was evaluated by means of PDQ-39 scale. UPDRS and Hoehn-Yahr scales were applied to estimate movement disorders. Depression was evaluated by means of Hamilton scale. Character of antiparkinsonian therapy was estimated.

Results: Average Hoehh-Yahr stage of Parkinson's disease is 2,77±0,7, UPDRS score is 58,68±17,65. Prevalence of weight loss in study group was 68%, average magnitude 4,13±2,1 kg; weight gain was stated in 23% patients; average magnitude 2,12±1,7 kg. Weight loss was more frequent among women (86%). Body weight changes correlate with UPDRS (r = 0,55, p = - 0,003), autonomic disorders scores (r = 0,36, p = 0,03) and age (r = 0,52, p = 0,04). Weight loss was not associated with duration of disease, life quality scores and depression. All patients received combination of levodopa, amantadines and dophamin agonists. Weight gain since beginning of treatment was observed in 24% parkinsonian patients, average magnitude 3,4±1,9 kg.

Conclusions: Weight loss is typical in early stages and advanced of Parkinson's disease. Weight loss grade depends of sex, age and presence of autonomic disorders. Effective therapy of disease leads to body weight stabilization.

Th-237

Salivary composition in Parkinson's disease

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Objective: To evaluate the salivary composition and production in Parkinson's disease (PD)

Background: Hypersialorhea occur in more than 70 % of PD patients and may be an early symptom of the disease. Dysphagia has been suggested as a causative factor for hypersialorhea because of the decrease in the frequency and the efficacy of swallowing of saliva in PD patients. Furthermore in previous studies significantly lower secretion rate of saliva in advanced PD has been shown.

Methods: A total of 22 patients with PD and age matched 14 control subjects were participated in this study. The Hoehn and Yahr (HY) disability scale was used to determine the severity of the disease. Salivary collection was performed according to a methodology described in the literature and salivary composition was determined. Between group comparisons were performed using the independent t test and chi-square.

Results: There were no significant difference in age and gender distribution between the PD and control groups (p=0.187, p=0.304, respectively). PD patients produce less saliva compared to the control group. In PD patients salivary concentrations of potassium and chloride but not of sodium were higher than in controls (p=0.004, p=0.029, p=0.686, respectively). There were no significant difference in amylase levels between PD and control groups (p=0.129). Also the severity of PD has no effect on the composition and production of saliva.

Conclusions: PD is associated with decreased salivary flow and abnormally high electrolyte concentrations and drooling of saliva is caused by concomitant swallowing difficulties. Thus, using botulinum toxin or anticolinergic drugs in treatment of drooling may cause xerostomia.

PARKINSON'S DISEASE: ELECTROPHYSIOLOGY

Mo-234

Pedunculopontine and subthalamic deep brain stimulation affects motor cortex network function

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Objective: To compare the effects of deep brain stimulation (DBS) of the pedunculopontine nucleus (PPN) and subthalamic nucleus (STN) on motor cortex (MCx) network function in a rodent model of unilateral Parkinson's disease (PD).

Background: High frequency (>100 Hz) DBS of the STN reduces PD motor symptoms possibly via antidromic enhancement of resonant MCx activity (Li *et al*., 2007). DBS of the PPN at lower frequencies (10-20 Hz) has been shown to ameliorate medically intractable axial symptoms of PD.

Methods: Local field potentials (LFPs) were recorded from the MCx while stimulating the ipsilateral PPN or STN at 13 Hz or 130 Hz in control or hemi-parkinsonian urethane-anesthetized rats 2-3 weeks after a unilateral injection of 6-OHDA into the medial forebrain bundle. MCx recordings were obtained incrementally between 0.05 mm and 2.15 mm below the MCx surface for each block of stimulation. Current source density (CSD), the second spatial derivative of MCx LFP activity along the range of depth recordings, was computed during stimulation as were MCx LFP amplitude and spectral power.

Results: Stimulation of the PPN or STN at 13 Hz or 130 Hz reduced MCx LFP amplitude and delta frequency power (layer V) in control and lesioned rats. Changes in MCx current flow (as revealed by CSD analyses) differed between PPN and STN stimulation. Typically, STN stimulation at 13 Hz was associated with a pattern of alternating sink/source in layer V that moves dorsally over ~6 ms. Consistent with the observations of Li *et al*., this pattern is repeated with STN stimulation at 130 Hz. PPN stimulation at 13 Hz induced a similar sink/source pattern that moved dorsally less rapidly over the 77 ms inter-stimulation period.

Conclusions: These results suggest that DBS of the PPN or STN can effectively desynchronize slow wave cortical activity in the urethane-anesthetized rat and that both PPN and STN stimulation predominantly affect MCx layer V. Differences between the effects of PPN and STN stimulation on the duration and range of current flow changes in the MCx network may be relevant to the relative benefits of high frequency STN versus lower frequency PPN DBS in PD.

Mo-235

Lack of efficiency of levodopa treatment on motor cortex excitability in dyskinetic patients with Parkinson's disease

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Objective: To compare the motor cortex excitability in both dyskinetic and non-dyskinetic patients with Parkinson's disease (PD) before (OFF state) and after (ON state) the administration of levodopa in order to detect changes linked to levodopa-induced dyskinesia (LID) that might reflect maladaptive plasticity.

Background: Plasticity could have negative or positive effects. LID appear as the PD progress and with long term dopaminergic treatment and could be linked to dysfunctional plasticity. Previous works showed that LID are associated to abnormal synaptic plasticity.

Methods: Ten dyskinetic PD patients (dys), 10 non-dyskinetic PD patients (N-dys) and 10 healthy subjects were included. Transcranial magnetic stimulation (TMS) was performed through a 9 cm circular coil over the motor cortex contralateral to the more affected side of PD patients and to the dominant hemisphere of healthy subjects. TMS measurements included resting motor threshold (RMT), short and long intracortical inhibition (respectively SICI and LICI). For SICI, the conditioning stimulus (CS) was set at 0.8RMT and followed 3 ms after by the test stimulus (TS) set at 1.2RMT. For LICI, CS and TS were set at 1.2RMT and the interval between CS and TS was 100 ms. Motor signs were assessed with motor UPDRS scale.

Results: Levodopa improved the motor signs ($p<0.01$) to the same extent in both dys (69±4%) and N-dys (66±4%). In the OFF state, the 2 groups of patients showed a similar SICI (dys:49.5±7.6% vs N-dys:48.05±7.6%) and LICI (dys:51.1±23.1% vs N-dys: 23.5±9.6%) and compared to the healthy subjects a significant reduced SICI (28.8±4.7%, $p<0.05$) reversed by levodopa. LICI was weaker in the dys than in the healthy subjects (10.9±5.8%, $p<0.05$). Levodopa enhanced SICI only in the N-dys patients (OFF:48.05±7.6% vs ON:30.9±4.01%, $p<0.05$). Under treatment, LICI was weaker in the dys (27.6±7.7%) than in the N-dys patients (6.8±4.9%, $p<0.05$) and the healthy subjects (10.9±5.8%, $p<0.05$).

Conclusions: Despite the improvement of the motor deficit the levodopa failed to activate effectively the inhibitory systems in the dyskinetic patients suggesting that a deficiency in the cortical inhibitory circuits, perhaps due to maladaptive changes, when levodopa acts might be one of the mechanisms underlying LID.

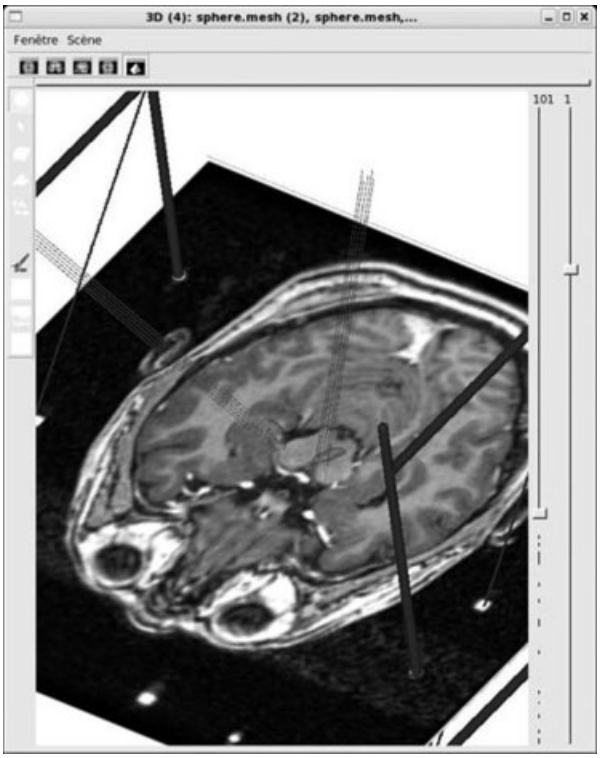

FIG. 1 (Mo-236).

Mo-236

An atlas-based computerized method to estimate the anatomical localization of peroperative electrophysiological recordings in deep brain stimulation of parkinsonian patients

S. Fernandez Vidal, M.-L. Welter, E. Bardinet, A. Buot, A. Teillant, L. Mallet, C. Karachi, J. Yelnik (Paris, France)

Objective: Develop an automated method to associate a posteriori accurate atlas-based anatomical labelling to peroperative recording sites visited during electrophysiological exploration in deep brain stimulation of parkinsonian patients.

Background: DBS is a surgical procedure that consists of implanting stimulating electrodes in the basal ganglia. It is used to treat symptoms of Parkinson's disease. DBS is done under stereotactic conditions. To more specifically identify the precise brain target that will be stimulated, the neurosurgeon uses microelectrode recordings around the area that has been defined preoperatively. We have developed an histological, three-dimensional and deformable atlas of the basal ganglia (Bardinet et al 2008) that has been used to study the position of the definitive electrodes in DBS patients.

Methods: All data acquired before and during a DBS procedure have their own specific referential: MRI, AC-PC for the preoperative target or the stereotactic frame for microelectrode recordings. The 3D atlas has also its own one. In order to merge these data, bridges between these referentials had first to be defined. This was done by successive image processing pipelines. The stereotactic frame, that is visible in the preoperative MRI, was detected and registered with a theoretic template of the frame. AC and PC points (anterior and posterior commissural points) were identified on the preoperative MRI. The atlas was adapted onto the patient's head by MRI-based registration. After surgery, stereotactic angles as well as information related to the electrophysiological exploration (consisting of depth values and firing rate levels) were collected. A template of the 5 microelectrodes was built and used to merge all these data in the patient's preoperative MRI.

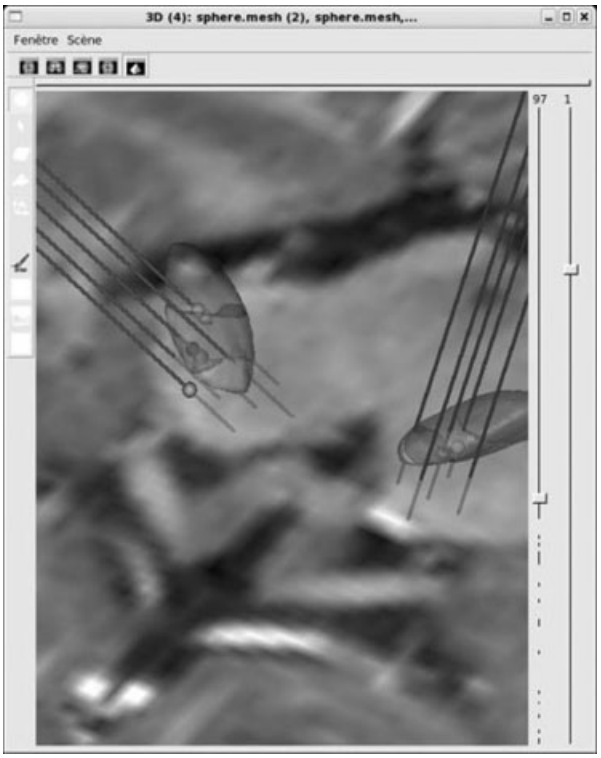

FIG. 2 (Mo-236).

Results: A systematic prospective study has been started that includes all parkinsonian patients implanted in our hospital. Its goal is to compare electrophysiological recordings location, given by the atlas, and parameters such as firing rate extracted from them.

Conclusions: This new method will allow to better understand the physiopathology of the STN area in parkinsonian patients. Bardinet et al, J. Neurosurg, 2008.

Mo-237

Interlimb coordination in Parkinson's disease during split belt locomotion

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Objective: To investigate interlimb coordination, asymmetry of arm and leg motion, and stride time variability during split belt locomotion in PD.

Background: Gait asymmetry and stride-to-stride variability are factors associated with gait disturbances and freezing of gait in Parkinson's disease (PD) (Hausdorff J.M. et al. Exp Brain Res. 149:187-194, 2003; Plotnik M. et al. Ann Neurol. 57 :656-663, 2005). A split belt can be used to artificially generate stride length asymmetry.

Methods: 15 PD patients (8 with freezing of gait) walked on a split belt at different speeds and with variable differences in speed between both legs (velocity belt most affected side –less affected side: 2-2 km/h, 1.5-2 km/h, 2-1.5 km/h, 3-2 km/h, 2-3 km/h). This was recorded using a video motion analysis system for off-line computation of spatio-temporal gait parameters and synchronization between the arms and legs. Differences were compared between conditions using a repeated measures ANOVA with within-subjects factor 'Condition' and between-subject factor 'Group' (to distinguish freezers from non-freezers).

Results: PD subjects were able to adapt to split belt walking by modulating stride length, while keeping a constant stride duration. The arm swing also changed in length, which was generally linked to the change in ipsilateral stride length (Figure 1. ANOVA effect 'condition' $F = 10.1$, $p=0.002$ for arm swing length, $F = 46.3$, $p < 0.001$ for stride length). However, split belt locomotion did not affect stride time variability or arm-leg synchronization. There was no difference between freezers and non-freezers for any of the parameters. There was no freezing of gait during the split belt walking in freezers.

Conclusions: We used split belt walking in patients with PD to generate an asymmetry in stride length. The arm swing length reacted mostly the same way as the ipsilateral stride length. This artificially generated gait asymmetry had no effect on stride time variability, nor did it influence the synchronization between hands and feet. As split belt walking induces only spatial asymmetry and does not increase stride-to-stride variability, we propose that the split belt can be used for training gait flexibility. Another implication is that split belt walking is unlikely to induce freezing of gait.

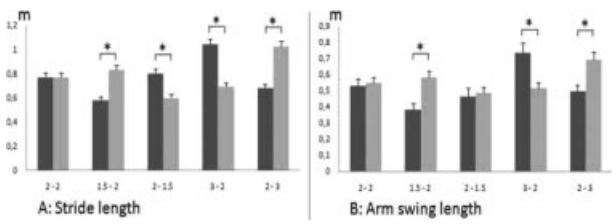

FIG. 1 (Mo-237). Stride and arm swing length in different split belt conditions. Conditions x-axis: belt speed in km/h on the most affected − less affected side. With Standard Errors of the Mean. •=significant difference between the two sides, $p < 0.01$. ■ Most affected side. ■ Less affected side.

Mo-238

Relationship between essential tremor and Parkinson's disease – Clinical and neurophysiological study

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Objective: We discuss the relationship between Essential tremor (ET) and Parkinson's disease (PD) after follow up of out-patients with ET between 1990-1997–2008 year in University Hospital of Neurology and Psychiatry "St. Naum", Sofia, Bulgaria.

Background: The Essential tremor is recognized as the most common movement disorder in the world. In contrast to parkinsonism, which is polysymptomatic hypokinetic disorder, ET is a monosynaptic hyperkinetic disorder that primarily affects the distal upper extremities, as well as the head and the voice. Although up to 20% of patients with ET develop Parkinson's disease (and 10% report a family history of PD, whether ET is a risk factor for PD remains unresolved and is still controversial.

Methods: One hundred and fourteen patients with clinical diagnosis ET were reevaluated after more than 10 years. In more patients neurological examination and electromyorgaphic investigation of tremor were performed. In some patients a questionnaire by telephone was used. The patients were diagnosed using strict anamnesis, clinical and electromyographic diagnostic criteria. Statistical evaluation of data were performed.

Results: The diagnosis ET was confirmed in all patients with sporadic ET and in more patients with familial ET. Eight of the patients with ET type B were found to have parkinsonian features (7 % of all patients and 13.5% of patients with ET type B).

Conclusions: The results confirmed the results of previous studies about the relationship between ET and PD. A clear relationship between ET type B and PD was suggested.

Mo-239

Emotional processing within the subthalamic nucleus in human

A. Buot, M.-L. Welter, C. Karachi, J.-B. Pochon, E. Bardinet, J. Yelnik, L. Mallet (Paris, France)

Objective: To determine the implication of the subthalamic nucleus (STN) in emotional processing and to study the integration of emotional and motor information in this basal ganglia structure.

Background: Basal ganglia receive projections from the cortex that are thought to be segregated into three circuits: motor, associative and limbic. In recent animal and human studies, the STN has been implicated in emotional processing. Recent data obtained in parkinsonian (PD) patients treated by STN stimulation suggest that this nucleus operates some kind of motor, cognitive and emotional integration (Mallet, 2007).

Methods: Subthalamic local field potentials (STN-LFP) were recorded in 10 PD patients that underwent surgery for bilateral STN electrodes implantation. Recordings were performed while the subjects executed an emotional and decisional task. The task was based on a "Go"/"No Go" paradigm, with emotional (positive and negative) and neutral pictures as stimuli. Subjects had to indicate the emotional picture ("Go" condition) or the neutral picture ("NoGo" condition) by a motor response. The STN-LFP location was assessed with a 3D deformable atlas of human basal ganglia.

Results: The presentation of the picture evoked a potential (EP) within the STN, starting 150 ms after the picture presentation and reaching its maximum at 350 ms. For contacts located into the ventro-medial part of the STN, the EP amplitude was significantly higher for negative pictures than for neutral pictures ($p<0.01$). This difference was not related to ocular movement or to the motor response.

Conclusions: This study confirms that some STN neuronal assemblies are implicated in emotional processing in human, in particular the ventro-medial part (associative-limbic), in line with the Parent's model (Parent 1990). Stimulation of this part of the nucleus could be responsible for the behavioral modifications observed in some PD patients following deep brain stimulation.

Mo-240

Abnormal cerebellar inhibition by transcranial magnetic stimulation in Parkinson's disease

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Objective: The aims of this study were to investigate the connections between the cerebellum and intracortical circuits in motor cortex by transcranial magnetic stimulation (TMS) in Parkinson's disease (PD) and to evaluate the role of dopaminergic treatment.

Background: The cerebellum takes part in several motor functions through its influence on the motor cortex and corticospinal outputs. The activity in the cerebellothalamocortical pathway has been demonstrated non-invasively trough electrical or transcranial magnetic stimulation of the cerebellum. A single TMS pulse applied over the lateral cerebellum 5–7 ms before magnetic stimulation of the motor cortex causes inhibition of the motor-evoked potential produced by motor cortical stimulation.

Methods: Fifteen PD patients with (ON) and without dopaminergic treatment (OFF), and fifteen control subjects with similar age and sex distribution were included in the study. A TMS conditioning stimulus (CS) was applied over the lateral right cerebellum, localizated 1 cm under and 3 cm right to the inion. The intensity of TMS test stimulus applied over the left motor cortex was adjusted to evoke a motor-evoked potential (MEP) of approximately 1 mV peak to peak in the relaxed right first dorsal interosseous. We evaluated the cerebellar inhibition (CBI) at two CS intensities, set at 80% and 90% of resting motor threshold (RMT), using different interstimulus intervals (ISIs) at 3, 5, 7, 9 and 15 ms.

Results: We observed in controls subject a reduction in MEPs amplitudes following cerebellar magnetic stimulation at ISIs of 3, 5 and 7 ms with both CS intensities. However, PD patients in OFF compared to controls did not show a decrease in MEPs amplitudes at ISIs of 3 and 5 ms when CS intensity was 90% of RMT. This defect tended to normalize in PD patients in ON. There were no significant differences between groups of PD patients in ON and OFF and control subjects at 80% RMT CS intensity.

Conclusions: PD patients have an abnormal CBI which tends to normalize by dopaminergic therapy. Dopamine deficit in PD leads to a change in functional connectivity between cerebellum and intracortical circuits in motor cortex.

Mo-241

Cortical plasticity in Parkinson's disease (PD) with levodopa-on

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Objective: Evaluate the time and the effect of cortical plasticity after neurophysiological perturbation by using the transcranial magnetic stimulation (TMS) in patients of Parkinson's disease (PD) with medication.

Background: Alternation of cortical plasticity in PD is already manifested by various methods. The abnormality may cause functional perturbation as impaired connectivity among cortical level. It is suggestive that plasticity of the human cortex is partially controlled by dopamine.

Methods: We performed TMS with intermittent theta burst stimulation (iTBS) to the primary motor cortex (M1) on eleven patients with PD and 11 age-matched normal controls. We assessed the short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) using paired-pulse method, and measured the change of motor evoked potential (MEP) amplitude of single pulse, time needed to complete the pegboard, before and after the iTBS.

Results: The mean age was 62.1(SD 10) years and the mean disease duration was 8.1(SD 3.1) years in these eleven PD patients. iTBS on the M1 showed no contribution of increasing intensity of SICI in norms but demonstrated the decreasing amplitude of SICI, normal ICF in PD patients. iTBS could not induce the synaptic plasticity as long-term potentiation (LTP)-like effect in PD patients as that in normal controls. There was no difference in the speed executing the pegboard of PD patients after the iTBS.

Conclusions: Our data confirmed that iTBS on M1 is capable to enhance motor cortex excitability for at least 30 minutes in health and demonstrate a trend of normalizing the intracortical inhibitory pathway. Cortical synaptic plasticity of primary motor cortex is impairment in PD even after levodopa treatment.

Mo-242

Decrease of beta frequency power in the subthalamic nucleus (STN) after pallidotomy in patients with Parkinson's disease (PD)

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Objective: To investigate whether surgical lesions of the GPi (pallidotomies) influence electrical activity in the ipsilateral or contralateral STN in patients with PD.

Background: Some PD patients with unilateral pallidotomy undergo bilateral STN deep brain stimulation (DBS). Data on the electrical activity in the STN in such patients is scarce. The results of two studies suggest that on the side ipsilateral to pallidotomy, overall firing activity in the STN might be reduced, however in another study this finding could not be confirmed.

Methods: All the microelectrode recordings acquired during STN DBS surgery up to June 2007 were included in the study. Multi-units microrecordings from the channel where the permanent electrode was implanted were blindly analyzed. The absolute and normalized power spectral density, divided into 6 frequency bands (3-8, 8-12, 12-20, 20-30, 30-60, and 60-100 Hz), and the normalized RMS (root mean square) of the recordings were averaged across the whole STN in each patient. Recordings were then subdivided in 3 groups: tracks ipsilateral to pallidotomy (IP), contralateral to pallidotomy (CP) and tracks from patients without prior pallidotomy (Non-P). Multivariate analysis of variances (MANOVA) was used to compare results between groups.

Results: There were 36 patients (64 STN tracks) with no prior pallidotomy and 7 patients (14 tracks) with prior unilateral pallidotomy. There were no significant differences in clinical or demographical characteristics between patients with or without prior unilateral pallidotomy, apart from longer disease duration in patients with prior pallidotomy. Absolute total power inside STN, as well as absolute power in the 3-8, 12-20 and 20-30Hz, was significantly smaller in IP with respect to Non-P ($p<.04$). After normalization, only power in the 20-30Hz was significantly smaller in IP with respect to Non-P ($p<.03$). Power in the CP tracks was not significantly different from IP or Non-P tracks. Differences in normalized RMS were not significant.

Conclusions: Results confirm that prior pallidotomy decreases the overall electrical activity in the ipsilateral STN and suggest that this is due to influence on the power in the beta frequency band.

Mo-243

Modulation of sensorimotor integration by intermittent theta-burst stimulation in Parkinson's disease

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Objective: Intermittent theta burst stimulation (iTBS) is known to have an excitatory influence on primary motor cortex (PMC) excitability. We studied the influence of iTBS on akinesia in Parkinson's disease (PD) and on modulation of sensorimotor integration (SMI) by conditioning a transcranial repetitive stimulation (TMS) test pulse with a subthreshold electrical stimulation delivered over the median nerve. Our hypothesis was that iTBS could change SMI processes and improve akinesia.

Background: Several studies have reported an improvement of akinesia in PD after repetitive TMS. Although, it remains unclear whether SMI abnormalities reflect motor impairment in PD, some studies have also shown that SMI is deficient in PD. For example, short (20 ms) and long (200 ms) afferent inhibition can be altered, and iTBS can potentially normalize cortical network excitability. A facilitatory interstimulus interval (ISI) was noted in controls between 40 and 70 ms.

Methods: A subthreshold TMS test pulse was applied over PMC after an electrical stimulus delivered at the median nerve. ISI ranging from 19 to 200ms were tested with a special attention to ISIs between 40 and 70ms. At each ISI, motor evoked potentials (MEP) from *abductor pollicis brevis*, *extensor carpi radialis,* and *first dorsal interosseus* muscles were averaged. Peak-to-peak amplitude was measured and expressed with reference to control unconditioned MEP. The protocol was repeated before and after iTBS train (600 shocks) delivered over the primary motor cortex in 10 patients suffering of PD and under levodopa usual treatment and in 10 age matched controls subjects.

Results: A significant improvement of akinesia was demonstrated after iTBS (38.8% in finger tapping, 54% in rigidity and 15.6% in pointing test). Rest and active threshold, short and long afferent inhibition, intracortical inhibition and facilitation were not modified after iTBS in both populations. In contrast, a strong (75%) significant increase of afferent induced facilitation was demonstrated at intervals from 40 to 70 ms after iTBS in PD patients but not in control subjects.

Conclusions: ITBS over PMC seems efficient in akinesia in PD. A restoration of an excitatory effect of sensory afferents at intervals around 55ms could be in relation with the improvement of akinesia.

Mo-244

Objective detection of freezing of gait elicited by obstacle avoidance during treadmill walking in Parkinson's disease

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Objective: To evaluate which quantitative gait parameters identify subtle FOG episodes.

Background: Freezing of gait (FOG) is a clinically defined phenomenon of Parkinson's disease (PD). Detailed electrophysiological studies of the underlying pathophysiology are difficult, because FOG is notoriously difficult to elicit in the gait laboratory. However, recent work showed that obstacle avoidance during treadmill walking can elicit subtle FOG episodes.

Methods: We included 10 patients with PD and clinically certified 'OFF-state' FOG. Patients were tested in a practically defined OFF condition. Patients were asked to walk on a motorised treadmill and to avoid unexpectedly appearing obstacles. FOG episodes during treadmill walking were defined based upon review of videotaped gait performance by two independent experts. Gait was also analysed using detailed kinematics, and knee joint signals were processed using time-frequency analysis with combinations of sliding Fast Fourier transform (FFT) and wavelets transform.

Results: 20 FOG episodes occurred during treadmill walking in five patients, predominantly in relation to obstacle avoidance. FOG occurred mainly just before or after obstacle crossing and was characterised by short rapid steps. Frequency analysis showed an increase in power in the 3-8 Hz band (2) and a decreased power in 0-3 Hz band during the FOG episode (3), and was preceded by an increase in dominant frequency in the 0-3 Hz band (1) (festination). These methods detected FOG with acceptable sensitivity (79%) and specificity (94%).

Conclusions: Obstacle avoidance provokes subtle FOG episodes during treadmill walking. Time frequency analysis is an appropriate approach to analyse biomechanical gait signals. This approach can reliably detect even subtle FOG episodes, possibly even beyond those detectable by expert clinicians. Therefore these methods invite further studies aimed at better understanding and describing the underlying pathophysiology of PD FOG.

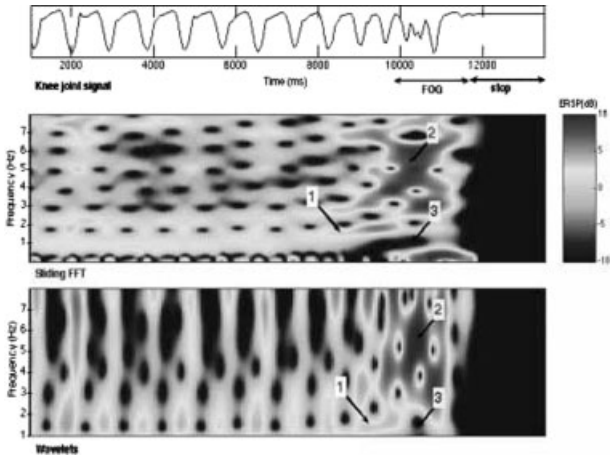

FIG. 1 (Mo-244).

Mo-245

Reflex inhibition following electrical stimulation of muscle tendons is not influenced by different motor tasks in healthy subjects and parkinsonian patients

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Objective: to analyse the significance of different motor tasks on the SP after electrical tendon stimulation.

Background: Electrical stimulation over muscle tendons inhibits EMG-activity of the voluntary contracting muscle, a phenomenon known as silent period (SP, Bourne and Lippold, 1996, Priori et al. 1998). In patients with Parkinson's disease (PD) SP's are significantly altered. In these patients, a significant discrepancy between voluntary muscle activation and involuntary control of muscle activation during walking on a treadmill has been described. (Fuss et al. 2000).

Methods: Silent period was analysed after electrical stimulation of the patellar tendon and the Achilles tendon respectively. EMG was recorded by surface electrodes from vastus medialis (VM) muscle and the medial gastrocnemius (GM) muscle. The stimulus intensity was adapted to obtain a clearly visible silent period. Stimulation of peripheral nerves was carefully avoided. We analysed duration and latencies of the SP. With voluntary innervation, 13 parkinsonian patients (mean age 57.3 years, SD 8.7) and 16 healthy controls (mean age 23.9 years, SD 2.5) were studied. SP's in muscles contracting involuntarily were investigated during walking with individual normal gait velocity on a treadmill in 10 parkinsonian patients (mean age 58.6 years, SD 14) and 10 healthy controls (mean age 52.1 years, SD 10.6).

Results: With voluntary innervation, SP's could be recorded from the VM and the GM muscles with significantly prolonged latencies and durations in parkinsonian patients. During walking on a treadmill, good reproducible SP's were recordable. Latencies and duration showed similar differences between healthy subjects and parkinsonian patients. The comparison of latencies and duration of the SP's between the both motor tasks revealed no significant differences.

Conclusions: Our data show that the SP after electrical stimulation over muscle tendons is not influenced by different motor tasks, neither in healthy controls nor in parkinsonian patients. This suggests that the silent period is generated within a probably spinal reflex circuit which is not influenced by different motor tasks. The alterations

of the SP found in parkinsonian patients may be due to disturbances within this reflex circuit.

Mo-417

Effects of deep brain stimulation on sensory evoked fields of parkinsonian patients

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Objective: To observe the effects of deep brain stimulation (DBS) of subthalamic nucleus (STN) on the somatosensory evoked fields (SEFs) in parkinsonian patients.

Background: DBS of STN relieves the symptoms of advanced Parkinson's disease (PD) effectively. The mechanism of DBS action is unknown and difficult to study with conventional brain imaging methods. Huge stimulator artifacts have previously rendered magnetoencephalography (MEG) measurements of DBS patients impossible.

Methods: We measured 11 medicated PD patients with STN DBS using a 306-channel MEG-system (Elekta Neuromag®) both when the stimulator was on and off. SEFs were elicited by electrical pulses delivered to the median nerve at both wrists, with an intensity producing a visible thumb twitch. The magnetic artifacts caused by DBS were removed by spatiotemporal signal space separation (tSSS) - method. The averaged signals were lowpass filtered at 100 Hz. Three SEF deflections (N20m, P35m and P60m) were identified over the contralateral primary somatosensory cortex (SI). A single dipole model for SI activity of each patient was constructed, and the source strengths and latencies of N20m and P60m were calculated when DBS was on and off.

Results: Mean UPDRS motor scores ± SD (n=9) were 22±9 when stimulator was on and 31±16 when off ($p<0.05$). tSSS allowed reliable analysis of data from 21 of 22 measured hemispheres. The mean source strengths of P60m were stronger when DBS was on than off (51 nAm vs. 45 nAm, n.s.). Peak latencies of N20m or P60m did not differ across conditions.

Conclusions: tSSS makes MEG studies of DBS effects feasible. Motor symptoms were significantly relieved by DBS, and there was a trend for increased P60m source strengths by DBS. Larger sample size and discontinuation of antiparkinsonian medication during DBS testing may produce more robust electrophysiological changes.

Mo-418

Discrete wavelet transformation in gait analysis: Comparison of methods in healthy subjects and parkinsonian patients

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Objective: To estimate significance of discrete wavelet-transformation for analysis of parkinsonian gait.

Background: The standard parameters used in analyzing gait allow a restricted classification due to a broad variability. We were interested in the capability of discrete wavelet-transformation, an analysis method providing frequency and time information simultaneously, to separate parkinsonian patients from a control group.

Methods: We studied 15 parkinsonian patients (mean age 64.1 years, SD 6.0 years) and 16 normal controls (mean age: 60.4 years, SD 3.7 years). The groups were measured with three gait-velocities (slow, individual normal, fast) during 10 minutes each. Data acquisition was made using a ultrasound system for gait measurement (Zebris Medical GmbH). As standard parameters, we investigated total angular excursions, and their minima and maxima of the right and left arm, elbow, leg and knee as well as the side-differences. The groups in our study were also tested for differences in gait by analyzing the values of these parameters, according to the study of Zijlmans et al. (Mov Disord. 1996; 11:501-8.) For detection of differences between both groups, we compared (Mann-Whitney-U-Test) the significance of our standard parameters with the significance of discrete wavelet transformation using a custom made program based on Labview™ (National Instruments).

Results: By analyzing the collected parameters we were able to identify significant differences in the most of our parameters except the total angular excursions of the left elbow and knee. Using the discrete wavelet-transformation the parameters used in this study showed significant differences in many wavelet coefficients of the motion patterns. This applied to all three gait-velocities. The thresholds for the collected wavelet coefficients showed high values for specificity and sensitivity (range 80-100%).

Conclusions: Our results show the capability of the wavelet-transformation to detect significant differences between the parkinsonian group and the control group.

Tu-236

Resonance in subthalamo-cortical circuits in Parkinson's disease

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Objective: To test the hypothesis that resonance phenomena favors the propagation of synchronized activities within the basal ganglia – cortical network in Parkinson's disease.

Background: Neuronal activity within and across the cortex and basal ganglia often synchronizes at ~20 Hz in patients with Parkinson's disease (PD) and is linked to impaired movement. Defining how activities in spatially distributed brain regions overtly synchronize in narrow frequency bands is critical for understanding disease processes like PD.

Methods: We recorded cortical responses to electrical stimulation of the subthalamic nucleus at various frequencies between 5 and 30 Hz in two cohorts of eight PD patients from different surgical centers. The cortical evoked activity consisted of a series of diminishing waves with a peak latency of 21ms for the first wave in the series. The evoked potentials averaged in each group were well fitted by a damped oscillator function ($r \geq 0.9$, $p < 0.00001$).

Results: Fits suggested that the natural frequency of the subthalamo-cortical circuit was around 20 Hz. When the system was forced at this frequency by stimulation of the subthalamic nucleus at 20 Hz, the undamped amplitude of the cortical response increased relative to with 5 Hz stimulation in both groups ($p \leq 0.005$), consistent with resonance. Restoration of dopaminergic input by treatment with levodopa increased the damping of oscillatory activity (as measured by the damping factor) in both patient groups ($p \leq 0.001$). The increased damping would tend to limit resonance, as confirmed in simulations.

Conclusions: Our results show that the basal ganglia – cortical network has a tendency to resonate at ~20 Hz in parkinsonian patients. This resonance phenomenon may underlie the propagation and amplification of activities synchronized around this frequency. Crucially, dopamine acts to increase damping and thereby limit resonance in the basal ganglia – cortical network.

Tu-237

Deep brain stimulation can suppress pathological synchronisation in Parkinson's disease

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Objective: To explore whether deep-brain stimulation of the subthalamic nucleus reduces pathological synchronisation in Parkinson's disease.

Background: Although deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a highly effective therapeutic intervention in severe Parkinson's disease, its mechanism of action remains unclear. One possibility is that DBS suppresses local pathologically

synchronised oscillatory activity. To explore this we recorded from DBS electrodes implanted in the STN of patients with Parkinson's disease during simultaneous stimulation of the same target using a specially designed amplifier.

Methods: 15 patients were studied after implantation of bilateral electrodes in the STN in the few days before their connection to the stimulator. Local field potentials at rest were recorded bipolarly from two contacts surrounding the contact used for monopolar stimulation (pulse-width 60μs; frequency 130 Hz) both before and during stimulation applied with increasing voltage. We analysed data only from the 23 sides showing at least one spectral peak before stimulation. Spectral peaks were divided into three frequency bands: 4-6 Hz, 7-10 Hz and 11-30 Hz.

Results: We found that DBS applied at 2.0 or more volts suppressed the power in peaks over the 11-30 Hz band (n of observations = 138, $\chi^2 = 53.2$, $p < 0.00001$; Kruskal Wallis Test). This threshold compared favourably with the median threshold for the therapeutic effect of stimulation (2.0 V, range 1.5 to 3.5 V). There was no such effect upon peaks at 7-10 Hz ($n = 64$, $\chi^2 = 5.1$, $p = 0.515$).

Conclusions: The findings suggest that DBS can suppress pathological 11-30 Hz activity in the vicinity of stimulation in patients with Parkinson's disease. This suppression is frequency selective and occurs at stimulation voltages that are clinically effective.

Tu-238

Gait analysis in healthy subjects and parkinsonian patients: Analysis of side asymmetries

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Objective: To compare asymmetry of gait parameters in Parkinson's disease.

Background: The asymmetry of the affection of limbs is a main sign in Parkinson's disease (PD). To quantify the asymmetry as a possible marker of therapeutic approach, we analyzed gait parameters in patients with PD.

Methods: We studied 15 parkinsonian patients (mean age: 64.1 years, SD 6.0) and 16 normal controls (mean age: 60.4 years, SD 3.7). Gait was analyzed during walking on a treadmill using three velocities (slow, individual normal, fast) during 10 minutes each. Data acquisition was made by a ultrasound system (Zebris medical GmbH). The following standard parameters were measured simultaneously on both sides: the maxima and minima of the angular excursions in arms, elbows, legs and knees and the amplitudes of their total angular excursion according to the study of Zijlmans et al. (Mov Disord. 1996; 11:501-8). The differences between right and left side, respectively the more or less affected side, were analyzed for each person. The Mann-Whitney-U-Test was used to compare the groups.

Results: The gait velocities were clearly slower in parkinsonian patients. The absolute values of our parameters also showed significant differences. Concerning the side asymmetries, however, we found no differences between both groups with individual normal gait velocity. With fast and slow velocities, the amplitudes of the total angular excursions of upper and lower extremities showed no differences either. Only the minima and maxima of the angular excursions of the elbow were significantly altered in parkinsonian patients.

Conclusions: A main result of our study is that side differences in patients with PD were not increased compared with healthy controls which contradicts the clinical impression. A possible explanation may be the altered position of extremities in PD as expressed by the different maxima and minima of the angular excursions. In addition, more sophisticated approaches of analyses such as wavelet transformation may be necessary.

Tu-239

Camptocormia: neurophysiological pattern in Parkinson's disease and parkinsonisms

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Objective: To characterize clinical and electrophysiological patterns of camptocormia and head drop in 12 patients with PD or parkinsonism, in order to detect a possible different pathogenesis and to choose the most appropriate treatment.

Background: Camptocormia is an abnormal flexion of the trunk that appears when standing and usually disappears in supine position. Head drop is characterized by marked anterior curvature or angulation of the cervical spine and results from weakness of the neck extensor or increased tone of the flexor muscles. They are associated with various neuromuscular and extrapiramidal disorders, in which they worse gait and determine spondyloarthrotic changes and pain. In PD camptocormia can be the first, disclosing sign, mostly in patients with prominent levodopa-unresponsive axial symptoms. The pathogenesis of these disorders is debated. EMG finding, MRI abnormalities and biopsies of paraspinal muscles suggest myopathic changes in extensor muscles, though it could be an atrophy leaded to under-use, because of rigidity of the spinal flexor muscles. Rigidity may also induces spinal deformities, leading to a neurogenic syndrome via compression of the spinal nerves. Camptocormia might represent a type of dystonia of the trunk or even action dystonia, from striatal damage. Levodopa have usually minimal or no effect on the camptocormia and head drop. Other therapeutic options are: injections of BTX in contracted flexor muscles, intratecal baclofen, immunosuppressive agents and corticosteroids, pallidal deep brain stimulation. Such treatments are often unsatisfactory.

Methods: We studied 12 patients, 5 male and 7 female, mean age 54 ± 14 DS. 5 patients had clinical diagnosis of idiopathic PD based on the NIH criteria, 7 patients had parkinsonism. In addiction to neurologic examination, patients were rated on the UPDRS and videotaped. We perform neurophysiological study in all patients.

Results: We finded 3 different electromyographic patterns: 1) tremorigen pattern; 2) hypoactivity on the extensor muscles; 3) hyperactivity on flexor muscles.

Conclusions: Various mechanisms may contribute to the development of camptocormia and head drop in parkinsonian patients. The detection of the main contributing factor in every patient could support to choice of the appropriate therapy.

Tu-240

Low-frequency repetitive transcranial magnetic stimulation and off-phase motor symptoms in Parkinson's disease

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Objective: To check whether four consecutive daily sessions of low-frequency repetitive transcranial magnetic stimulation (rTMS) can bring improvement of off-phase motor symptoms in Parkinson' disease.

Background: rTMS can modulate cortical excitability and activation and consequently may affect clinical symptoms in neurological conditions characterized by altered motor cortex functions. There are conflicting reports in the literature whether low-frequency rTMS has any clinical effects in PD.

Methods: In a placebo-controlled, single blinded, crossover study we assessed the effect of "real" versus "sham" rTMS (placebo) on UPDRS Part 3 (Motor Scale) score in practically defined off-phase in ten patients with Parkinson's disease (PD). Patients had medium severity of PD (mean Hoehn and Yahr stage 3.3 ± 0.7) and manifested prominent dyskinesias. They had rTMS (1800 pulses; 1Hz rate) delivered over the motor cortex for four consecutive days twice, once real stimuli and once sham stimulation were used; evaluations were done at the baseline and one day after the end of each of the treatment series.

Results: UPDRS Part 3 scores showed a trend toward lower values after real rTMS (Baseline: 46.6±11.7; real rTMS: 44.7±11.9; sham rTMS: 45.2±14.0), but the difference was not significant. Subscores for rigidity, bradykinesia, and tremor did not show significant difference either.

Conclusions: The results do not confirm presence of residual beneficial clinical after-effects of consecutive daily applications of low-frequency rTMS on motor symptoms in PD. Different results obtained in some of the published studies may be due to differences in severity and clinical presentation of patients examined. This is an issue that needs to be explored further.

Tu-241

Differential connectivity between subthalamic area and forearm muscle in Parkinson's patients with tremor

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Objective: The treatment of patients with Parkinson's disease (PD) using deep brain stimulation (DBS) in the subthalamic nucleus (STN) is well established. However, the exact mechanisms underlying DBS remain elusive. To gain further insight into STN pathophysiology in PD, we analyzed the directionality between forearm muscles and the subthalamic area.

Background: While tremor is one of the cardinal symptoms of Parkinson's disease its genesis remains to be elucidated. Previous studies detected oscillatory coupling at tremor frequency between the STN und affected muscles, but did not identify the directionality of this coupling (Volkmann et al., Neurology 46(5),1996; Timmermann et al., Brain 126(1), 2003).

Methods: During DBS electrode implantation, we recorded local field potentials (LFPs) in the subthalamic region and the EMGs of the M. extensor digitorum communis and M. flexor digitorum superficialis in 14 PD patients. 6 patients were diagnosed to have an akinetic-rigid subtype, 8 patients were tremor dominant. All patients showed periods of tremor during the recordings. We conducted an offline analysis of the directionality between the LFPs and EMGs during tremor episodes using the squared partial directed coherence.

Results: We identified differential directionality-patterns for patients of the akinetic-rigid subtype and for those of the tremor dominant subtype during tremor episodes. In accordance with the standard model of the basal ganglia and classical accounts of PD pathophysiology, akinetic-rigid patients showed more efferent connections between LFPs and the tremor EMG. In contrast, however, tremor-dominant patients exhibited significantly more afferences.

Conclusions: The contrasting patterns of predominantly efferent directionality for akinetic-rigid and mainly afferent directionalities for tremor-dominant patients, suggest differential pathological mechanisms of tremor generation or maintenance in these two PD subtypes. Furthermore, the observed data call for a more critical appraisal of the classical basal ganglia model in PD.

Tu-242

An integrative approach to characterize coordination-stabilographic profile in Parkinson's disease and non-parkinsonian patients versus healthy control subjects

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Objective: To study the coordination-stabilographic pattern in Parkinson's disease (PD) and non-parkinsonian patients and compare them with healthy control subjects.

Background: There is not evidence for an integrative approach to characterize coordination-stabilographic pattern in PD and non-parkinsonian patients versus (vs) healthy control subjects.

Methods: An original complex methodological approach to quantitative assessment of static and dynamic motor coordinations is presented. Using an original apparatus set, the equilibrium stability during open and closed eyes with Romberg's sign derivation, and the central and motor times of symmetrical ballistic, controllable, complex and serial movements with the asymmetry coefficient derivation, are investigated. Study participants are 24 PD and 36 non-parkinsonian patients and 30 healthy control volunteers (age: M=59.7yrs, SD=7.4). Performances on used tests are compared in PD and non-parkinsonian patients, and healthy control subjects by Student's t-test. A non-parametrical statistical analysis is used.

Results: Disturbances in the dynamic and static motor coordination indices are established ($p<0.001$), more pronounced in PD patients ($p<0.001$). The most informative parameters are postural stability ($p<0.001$), reaction (central) ($p<0.001$) and motor ($p<0.002$) times of the complex movement.

Conclusions: A complex constellation map portraying the overall motor coordination status is obtained with good ($p<0.05$) prospects of its reliable computerization for differential-diagnostic ($p<0.002$) and drug, resp. antiparkinsonian therapy monitoring ($p<0.001$) purposes.

Tu-243

Lack of facilitation by a triad-conditioned TMS at 40Hz in PD

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Objective: To detect abnormal rhythm generation in the primary motor cortex (M1) in patients with Parkinson's disease (PD) using transcranial magnetic stimulation (TMS).

Background: Abnormal synchronizations of neuronal activities at the basal ganglia or the cortex, such as enhancement of ß-synchronization, have been revealed in PD by studying local field potentials. This abnormality is suggested to be correlated with parkinsonian symptoms. However, the physiological meaning of the abnormal synchronization is unknown. Previously, we reported that a triad-conditioning TMS at a frequency of 40Hz can enhance motor evoked potentials (MEPs) to succeeded test TMS in normal subjects and that the facilitation was generated at the cortical level. This finding may reflect an intrinsic oscillatory rhythm of the motor cortex. We studied this intrinsic motor cortical rhythm in PD patients.

Methods: Subjects are 10 PD patients (44-77 yrs old, UPDRSIII 4-24) and 10 normal volunteers (30-53 yrs old). Three subthreshold conditioning TMS pulses were applied over M1 to test TMS setting to elicit an MEP in the relaxed hand muscle at various interstimulus intervals (ISIs) corresponding to 10-200Hz. We analyzed the amplitude change of MEPs at different intervals.

Results: In PD patients, a triad-conditioning TMS at ISI of 25 ms (40Hz) did not induce any facilitation which was elicited in normal volunteers, whereas a 7 or 8 ms interval triad-conditioning TMS induced a significant facilitation in both groups.

Conclusions: The lack of 40Hz triad conditioning facilitation may support a previous hypothesis of cortical gamma oscillation abnormality in PD.

Tu-244

Repetitive transcranial magnetic stimulation in complex treatment of Parkinson's disease patients

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Objective: To estimate rTMS efficiency in complex PD patients treatment.

Background: Pattern of movement disorders in patients with Parkinson's disease (PD) is formed by hypokinesia and stiffness. Repetitive transcranial magnetic stimulation (rTMS) has recommended itself as effective therapeutic tool for several nervous system disorders treatment including PD.

Methods: 40 PD patients of the main group (25 men and 15 women, mean age 65.12±9.37 years) have received standard drug therapy (L-DOPA or/and dofamin receptors agonists) and underwent

rTMS by circular coil (outer diameter 12 sm.) over Cz according to the following regime: field strength just below motor threshold, train length 7.0 sec., pause between trains 1.0 sec., session duration 5 min., number of sessions 10. 20 PD patients of the control group (11 men and 9 women, mean age 65.33±12.73 years) have received only standard drug therapy. Whole patients had 2.0-3.0 stage (Hoehn and Yahr). Treatment efficacy was assessed according to the Unified PD Rating Scale (UPDRS) (Fahn C., Elton S. et al).

Results: Due to the complex treatment significant symptoms reduction according to the UPDRS was notified in main group from 58.4±4.4 to 50.1±6.8 points ($p<0.001$). Positive dynamic in control group from 55.2±6.1 to 52.6±7.2 ($p<0.05$) wasn't so evident and significant. Hipokinesia symptoms (gait, handwriting, specific hypocinetic tests) evaluation also has revealed more evident reduction in main group from 13.7±2.2 to 8.1±1.9 ($p<0.001$) in comparison with control group where hypokinesia grade reduction was less: from 12.7±2.3 to 9.1 points ($p<0.05$).

Conclusions: rTMS is an effective additional therapeutic tool for PD patients treatment. Movement status improvement was reached first of all due to hypokinesia symptoms reduction.

Tu-245

Lack of plasticity in the motor cortex (M1) is a primary marker of Parkinson's disease (PD) and is L-dopa sensitive only when motor dysfunction sets in: A TMS study

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Objective: To test if cortical plasticity is different between the asymptomatic and symptomatic sides in L-dopa-naïve patients with PD and how it is modulated by L-dopa.

Background: Intermittent theta burst stimulation (iTBS) with TMS on the M1 region induces plasticity in normal subjects. Plasticity of the motor cortex is reduced in PD.

Methods: Seventeen patients (50.8 ± 9.2 years) with PD, who were L-dopa-naïve and symptomatic only on one side, were selected from the movement disorder clinic of SCTIMST. UPDRS III motor subset scores were measured on both sides. Twelve patients had received dopamine agonist (DA) and 5 were untreated. They had 2 sessions of iTBS; one 24 hrs after withdrawal of DA in those who were on it and the second after intake of a uniform L-dopa dose (100/25 mg). iTBS was delivered on M1 region of the first dorsal interosseous muscle, at 80% aMT (3 pulses @ 50 Hz x 10 bursts @ 5Hz x 10 trains @ 8 seconds interval). Ten controls (47.1, ± 8.6 years) underwent the same iTBS protocol. MEPs were measured immediately (T0), 10 (T1), 20 (T2) and 30 (T3) minutes after iTBS.

Results: Mean UPDRS scores were 10.3 (SD 4.4) and 2.7 (SD 2.7) for the symptomatic and asymptomatic sides respectively. In controls, MEPs were strongly increased after iTBS at T0, T1 and T2. In patients, in the untreated state, iTBS was less effective than in controls on both sides with a complete loss of induced plasticity on the asymptomatic side (ANOVA: TIME *SIDE $p<0.002$; At T0, controls vs. asymptomatic side $p<0.0001$; controls vs. symptomatic side $p< 0.04$). After intake of L-dopa, plasticity was still null on the asymptomatic side while it was partially restored on the symptomatic side (ANOVA: TIME $p<0.01$) SIDE $p = 0.05$; At T0, controls vs. asymptomatic side $p<0.006$, controls vs. symptomatic side $p< 0.03$) There was no correlation between effect of iTBS and UPDRS scores. There was no significant effect of prior treatment with agonists.

Conclusions: The lack of excitatory plasticity on the asymptomatic side in early PD may represent a primary disorder, as it precedes the cardinal motor symptoms and is not corrected by L-dopa. On the symptomatic side, an adaptive excitatory plasticity may develop to compensate for the motor dysfunction and is enhanced by L-dopa.

Tu-246

The characteristics of sequence effect in Parkinson's disease: Placebo-controlled, four-way crossover study of levodopa and rTMS

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Objective: To provide new insights into sequence effect (worsening of bradykinesia during repetitive movements) that is unique feature in Parkinson's disease (PD).

Background: The sequence effect in PD is characterized by progressive slowness in speed and decrease in amplitude during continuing, repetitive movements. This phenomenon was reported many years ago, but its physiology is still unclear. We hypothesized that the sequence effect may be related to dopaminergic deficit and altered cortical excitability and may be one aspect of clinical fatigue, a common symptom in PD.

Methods: We measured bradykinesia and the sequence effect with a modified Purdue pegboard, a computer-based device, in eleven advanced PD patients. The modified Purdue Pegboard test can detect start and stop times for individual peg insertion and for the task in its entirety. We conducted a placebo-controlled, four-way crossover study to investigate if levodopa and repetitive transcranial magnetic stimulation (rTMS) could improve bradykinesia and the sequence effect in PD patients. We also examined the correlation between the sequence effect and fatigue, which we assessed with the Fatigue Severity Scale (FSS) and Multidimensional Fatigue Inventory (MFI).

Results: Levodopa and rTMS administration both improved bradykinesia, but rTMS did not show an additive effect on levodopa treatment. We did not find any evidence that levodopa and rTMS could alleviate the sequence effect. There was no correlation between the sequence effect and fatigue.

Conclusions: This study suggests that dopaminergic mechanisms and motor cortex excitability are not relevant for the sequence effect. Additionally, the sequence effect is not a component of clinical fatigue. Further work is needed to establish its physiology and clinical relevance. (This abstract was presented as a poster at Third International Conference on Transcranial Magnetic and Direct Current Stimulation, October 1-4, 2008)

Tu-247

Non-linear surface EMG indices as determinants of UPDRS motor scores in Parkinson's disease patients

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Objective: To assess the value of novel non-linear surface EMG (SEMG) characteristics as determinants of UPDRS motor scores (total score, tremor, rigidity and bradykinesia) in Parkinson's disease patients (PD).

Background: It has been postulated that non-linear characteristics of SEMG would reflect the deficiencies of central processes in PD patients. Earlier studies have shown that non-linear SEMG parameters are capable of detecting PD induced neuromuscular manifestations. However, the relationship between the non-linear SEMG parameters and clinical signs of PD are not well defined.

Methods: 30 PD patients participated in the study. Bipolar surface EMG was measured over the biceps brachii muscles bilaterally while subjects were standing and isometrically holding their elbows in 90 degree angle palms up without any additional loads. Surface EMG was analysed by non-linear analysis tools [correlation dimension (CD), RQA %recurrence (REC) and %determinism (DET)]. The UPDRS motor score (part III) was obtained prior to the measurements. The linear regression procedures were used to define the relationships between combined left – right SEMG non-linear indices and UPDRS total score. UPDRS components (rest tremor, action tremor, rigidity and finger taps) and SEMG indices were combined as regarding the left and right side, and Pearson correlation coefficients were defined.

Results: The linear regression analysis revealed that non-linear SEMG parameters correlated significantly with UPDRS total motor score (r=0.528-628). The correlation between tremor parameters and SEMG indices ranged from r = 0,363–0,554. The best correlations were defined between finger tapping and SEMG indices (r=0.457 – 0,535). Rigidity did not have any significant relationship with SEMG non-linear indices.

Conclusions: These results indicate that non-linear SEMG analysis have some explanatory power in clinical signs of PD as expressed by UPDRS motor score and its components. This would suggest that non-linear SEMG analysis gives a measure of complexity and deterministic structure of the underlying central attractors of the neuromuscular system in PD patients. Further studies regarding the non-linear EMG analysis in PD patients are suggested.

Tu-248

Sensory temporal discrimination and mental rotation of corporal objects in patients with early-onset parkinsonism, positive or negative for mutations in the parkin gene, compared to healthy controls

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Objective: To test whether sensory temporal discrimination and mental rotation can reveal differences between patients with early-onset parkinsonism, positive or negative for mutations in the parkin gene compared to healthy controls.

Background: Abnormalities in temporal discrimination and mental rotation have been described in various studies in primary dystonia and Parkinson's disease (PD) supporting the hypothesis of impaired sensory processing and sensorimotor integration in those disorders. So far these methods have not been applied to patients with early-onset parkinsonism and mutations in the parkin gene.

Methods: 6 parkin positive and 6 parkin negative patients with early-onset parkinsonism, and 6 age matched controls were asked to discriminate whether pairs of unimodal (visual, tactile) and cross-modal (visuo-tactile) stimuli were simultaneous or sequential (temporal discrimination threshold, TDT) and which stimulus preceded the other (temporal order judgement, TOJ). In the mental rotation task subjects had to judge the laterality of hands, feet, and a patch in a face which covered the left or right eye. Reaction times (RT) and accuracy were measured.

Results: Patients with mutations in the parkin gene showed significantly higher thresholds for cross-modal TDT and TOJ, whereas parkin negative patients were only impaired in cross-modal TOJ. Accuracy in mentally rotating feet was significantly lower in parkin positive patients than in controls, whereas RT revealed no differences between the groups.

Conclusions: Since temporal discrimination of cross-modal stimuli in contrast to unimodal stimuli requires the integrity of multisensory integration in addition to temporal processing our results rather point to a dysfunction of the former than to defective timing per se. Parkin positive patients were less accurate in rotating feet and interestingly there is a higher frequency of foot dystonia in these patients. However, we did not find significant differences between patients with and without mutations in the parkin gene, thus rather pointing to a more general deficit of sensory processing and sensorimotor integration in PD than to an association between the deficits and specific genes or pathological processes.

Tu-249

The effects of levodopa and the posterior subthalamic DBS on the task-related EEG theta activity in patients with Parkinson's disease

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Objective: To examine the task-related EEG theta power in patients with Parkinson's disease (PD) and normal controls, and to evaluate the effect of levodopa and deep brain stimulation (DBS) of the posterior subthalamic region (pST) on theta power.

Background: pST DBS can improve parkinsonian symptoms including gait disturbances. In rodents, hippocampal theta activity was recorded during locomotion while subthalamic locomotor region and posterior hypothalamus were electrically stimulated. However, to our knowledge, theta activity of EEG during locomotion has not been systematically examined in humans.

Methods: Eleven PD patients with pST DBS (mean age 62.3 years, five females) and nine age-matched healthy controls (mean age 61.2 yeas, four females) were studied. EEG was recorded during resting with eyes closed, self-paced slow repetitive wrist extension/flexion movements, saccadic eye movements, standing with eyes closed, and slow gait with eyes opened. EEG recordings in PD patients were performed at three different conditions; off-medication without pST DBS, off-medication with pST DBS and 1 hour after administration of levodopa/carbidopa (100–200 mg). The absolute spectral power of theta, alpha and beta bands of EEG from the C3/C4 derivation was calculated. Task-related theta power changes were also evaluated by the ratio of theta power during each task and theta power during saccade (task/saccade ratio).

Results: As compared to controls, PD patients had higher absolute EEG theta activity in all tasks but gait. pST DBS significantly increased the gait-related absolute theta power ($p<0.05$). The mean gait/saccade ratios with and without pST DBS were 1.2 and 1.9, respectively. Levodopa did not influence the task-related theta changes.

Conclusions: pST DBS may influence EEG theta power associated with gait in PD patients. Task-related changes in EEG spectral power may be useful to study the pathophysiology of parkinsonian symptoms.

Tu-415

Objective quantification of neuromotor symptoms in Parkinson's disease: A feasibility study for the implementation of a portable, computerized measurement tool

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Objective: To test the feasibility of the computer based, portable Coordination Ability Test System (CATSYS®, Danish Product Development Ltd. Denmark) in Parkinson's disease neuromotor symptom registration.

Background: Quantification of neuromotor symptoms such as tremor, bradykinesia, and imbalance using objective, device-based measures provides a powerful supplement to traditional subjective approaches of clinical evaluation. Research using the CATSYS has established its utility as a computerized measurement system to quantify neuromotor function.

Methods: Forty-four patients with idiopathic Parkinson's disease (PD) and 28 healthy controls were prospectively recruited from the Movement Disorders Clinic at the University of Miami Miller School of Medicine. CATSYS, a portable, Microsoft Windows-based system that consists of a data logger and four different sensors: a tremor pen, a touch recording plate, a reaction time handle, and a force plate for balance (static posturography) recording was utilized to quantify neuromotor functions including tremor (rest and postural/action), reaction time, bradykinesia, and postural sway.

Results: CATSYS clearly discriminated between PD and controls on measurements of rest/postural tremor, pronation/supination, finger tapping, simple reaction time, and postural sway intensity and velocity. CATSYS measurements were associated with clinician-rated UPDRS items assessing tremor and bradykinesia.

Conclusions: Supplementing current subjective methods used in patient evaluation with a simple objective electronic symptom registration test may enhance treatment outcomes and provide alternative, objective end-points for clinical trials.

We-237

Movement related potentials in Parkinson's disease patients

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Objective: The aim of the study was to investigate the association of clinical progression of Parkinson's disease (PD) and Movement related potentials (MRP).

Background: MRP is a slow, negative potential preceding the onset of self-paced movements and has been implicated in movement preparation. Impaired initiation and slowed execution of movements are two of the principal characteristics of PD. Electrophysiological studies have shown that MRP are affected in PD patients but with inconsistence results regarding the influence of disease progression.

Methods: Twenty PD patients and 20 controls (matched for age and gender) were enrolled in the study. Teen PD patients were "de novo" drug-naïve PD patients with unilateral clinical presentation. The subjects were asked to press a button at their most comfortable rate. The electrophysiological signals were recorded and analyzed using 40 channels Brain Products–Brain Vision System, 29 for EEG, 3 for eye movements artifacts removal, 2 for EMG and 1 for accelerometer. The mean amplitude of Bereitschaftspotential (BP), negative slope (NS) and the motor potential (MP) were compared among the groups. Data were presented by individual curves for each electrode and by using brain mapping topography.

Results: A well-recordable movement related potentiales were observed in PD patients and controls with maximal amplitude over the contralateral central electrode (C3/C4). There were significant amplitude difference between the PD patients and control group. In the unilateral PD the amplitudes were markedly reduced over the contralateral hemisphere of the affected side. Also, the prolonged cortical activation over the ipsilateral motor cortex of the side engaged in movement was observed suggesting that the inhibition process was delayed. Diminishing of the BP and NS potential was positively correlated with the illness duration as well as the ipsilateral motor cortex inhibition. In bilateral PD patients MRP amplitudes were bilaterally reduced and prolonged MP phase was prolonged. This prolongation can be due to the increased tremor and has to be further analyzed.

Conclusions: Experimental results showed the clear difference between PD patients and the control group of healthy subjects. Moreover changes in MRP correlated with affected size in PD suggesting that this could be use for early detection of PD.

We-239

Specificity and sensitivity of routine neurophysiological tremor analysis as a diagnostic tool for parkinsonian tremor

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Objective: The aim of the present study was to evaluate the diagnostical potential of tremor analysis for the diagnosis of parkinsonian tremor syndromes.

Background: The clinical differential diagnosis of various tremor syndromes is troublesome at the early stage of the disease.

Methods: 124 consecutive outpatients attending for undiagnosed tremor was included in the study. Simultaneous accelerometry and surface electromyography (sEMG) was performed and each recording was named by a unique alphanumerical ID to allow blinded analysis. The final clinical diagnosis was made 48.1 $\pm$ 5.2 months after the electrophysiological investigation according to the Consensus Statement of The *Movement* Disorder Society on Tremor and the British Brain Bank Criteria for Parkinson's disease. Six neurophysiologic criteria were applied to establish the electrophysiological diagnosis of parkinsonian tremor: (1) rhythmic burst activity of rest tremor on sEMG; (2) tremor frequency less than or equal to 8.5 Hz; (3) absence of postural tremor or, if present, its frequency is similar to that of the rest tremor (difference $<$0.5 Hz); (4) presence of tremor latency from rest to postural position; (5) changes of the frequency less than 1 Hz after load test and (6) increase in tremor amplitude (intensity) during/after mental concentration.

Results: The applied electrophysiological criteria have a sensitivity of 92.2% and specificity of 80.1% for the diagnosis of parkinsonian tremor.

Conclusions: In the differential diagnosis of tremor syndromes the routine tremor analysis has a high predictive value.

We-240

Relation between abnormalities of prepulse inhibition of blink reflex and levodopa resistant freezing of gait in Parkinson's disease

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Objective: To compare inhibition of the blink reflex by prepulse stimulus in Parkinson's disease (PD) patients with or without levodopa resistant freezing of gait (FOG).

Background: Severe gait disorders including FOG resistant to optimal dopaminergic treatment often occur in advanced Parkinson's disease. They have a deep impact on autonomy and quality of life. Upper brainstem nuclei with the mesencephalic locomotor area are thought to be responsible for the anatomical basis of gait dysfunction. Parts of these structures are known to be involved in the circuit of prepulse inhibition of the blink reflex.

Methods: Blink reflexes to the supraorbital nerve were preceded in test trials by auditory or somatosensory prepulse stimuli with randomized inter-stimuli intervals (ISI) of 50 to 110 milliseconds (ms). We compared the percentage inhibition induced by the prepulse stimulus in the R2 component of the orbicularis oculi response in seven PD patients with severe gait disorders with levodopa resistant FOG, twelve PD patients without gait disorder and nine age-matched healthy subjects.

Results: We found R2 inhibition was significantly decreased in PD patients with FOG compared with control subjects at the ISI of 100 ms with auditory prepulse stimulus and 110 ms with the two modalities of prepulse stimuli. There was a significantly decrease of prepulse inhibition in PD patients without gait disorder only at the ISI of 110 ms with the auditory modality. Levodopa did not improve these abnormalities.

Conclusions: The decrease of R2 inhibition by prepulse stimulus seems to depend on the levodopa resistant FOG in PD patients. These findings underline the possible role of functionally disturbed inputs and loss of neurons in mesencephalic structures, like the pedunculopontine nucleus, on FOG in advanced PD. Our method could be a useful and physiological tool to evaluate new treatments concerning these axial symptoms.

We-241

Nonlinear features of basal ganglia neurons in Parkinson's disease patients

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Objective: To characterize nonlinear features in the discharge patterns of basal ganglia (BG) neurons in Parkinson's disease.

Background: The characteristics of inter-spike interval (ISI) sequences using time- and frequency domains have been described. However, these measures are not sensitive to the nonlinear features of ISI sequences (Darbin et al. 2006. Brain Res., 1118, 84-93). In this study we characterized the spontaneous activity of BG neurons using parameters indicative of statistical irregularity (i.e. Sample entropy, SampEN) and self-similarity (i.e. Allan factor).

Methods: Thirteen, 12, and 11 neurons in the globus pallidus externa (GPe), interna (GPi) and the subthalamic nucleus (STN) respectively, were recorded in PD patients undergoing implantation of deep brain stimulating electrodes in the GPi or STN. One thousand ISIs were analyzed using linear (coefficient variation, CV and

dispersion index, DI), and nonlinear (SampEN and Allan factor) analyses. We calculated SampEN and Allan factor from the original ISIs and compared them to the random 100 times shuffling of the original data.

Results: Values for CV and DI indicated a greater variability in the standard deviation of the ISI for GPe and STN neurons compared to GPi neurons. That is, GPi neurons discharge with a more regular pattern than GPe and STN.

Table 1 (We-241). Linear Analysis

Types of Cells	N	Mean ISI	SD ISI	CV	DI
GPe	13	22.30 (16.80–27.30)	26.90 (14.90–43.90)	1.17 (0.86–1.59)	30.60 (12.60–69.60)
GPi	12	14.80 (9.28–20.30)	14.35 (8.89–26.10)	0.98 (0.83–1.33)	15.35 (6.89–27.90)
STN	11	17.40 (15.90–34.10)	21.40 (16.80–35.10)	1.02 (0.91–1.41)	29.10 (16.20–47.70)
P value between nuclei		0.0538	0.1396	0.6195	0.1603

Medians with 25th-75th percentiles.

In the non-linear analysis however, 92% of GPe, 92% GPi and 82% of STN neurons, the SampENs calculated from the original ISIs were lower than the first percentile of SampENs of the shuffled data.

Table2 (We-241). Nonlinear Analysis

Types of Cells	N	Samp EN_raw	Median of SampEN_shuffled	Lower than 1st percentile of SampEN_shuffled	Allan_raw	Outside of the interval between 1st and 99th percentiles of Allan_shuffled	McNemar Test : P value
GPe	13	1.06 (0.75–1.35), P*=0.0002	1.16 (0.89–1.63)	12/13 (92%)	0.29 (0.25–0.34)	12/13(92%)	1
GPi	12	1.22 (0.84–1.37), P*=0.0005	1.40 (1.06–1.60)	11/12 (92%)	0.29 (0.23–0.35)	10/12(82%)	1
STN	11	1.10 (0.92–1.56), P*=0.0020	1.32 (1.05–1.68)	9/11 (82%)	0.27 (0.18–0.34)	6/11(55%)	0.2500
P value between nuclei		0.4877	0.4344	0.6650	0.7844	0.1035	
All cells	30	P*<0.0001		32/36		28/36	0.1573

Medians with 25th-75th percentiles, P* value : SampEN_raw vs. Median SampEN_shuffled, McNemar test:see if two decisions agree with each other ($p>0.05$) or if not ($p<0.05$).

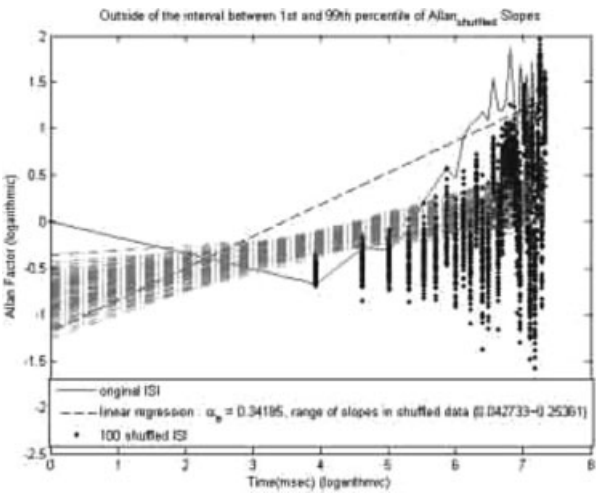

FIG. 1 (We-241).

Calculation of the Allen factor revealed similar features: 92% of GPe, 82% of GPi and 55% of STN neurons displayed self-similarity (evidence for self-similariy in Fig1, not in Fig2). McNemar's test showed no significant difference between the SampEN and Allen factor values for the three nuclei indicting an agreement between data with the two analyses. These data suggest that non-linear analysis reveals a temporal organization in the original ISI sequence in the majority of neurons.

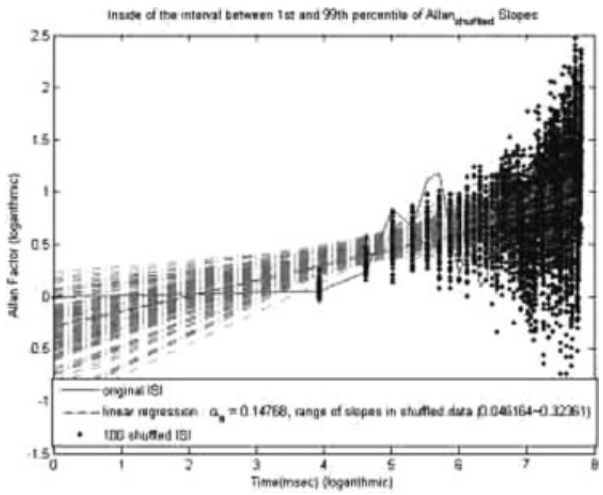

FIG. 2 (We-241).

Conclusions: SampENs and Allan factors showed evidence for a temporal organization and self-similarity of the ISIs which could not be captured by the conventional measures of variability. Nonlinear features in basal ganglia may be important for information processing and may reflect an operational mode that is related to different behavioral functions in PD.

We-242

Towards adaptive DBS: LFP recordings during levodopa and DBS administration

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Objective: To implement adaptive deep brain stimulation (DBS) retroacted through local field potentials (LFPs), we tested how subthalamic LFPs are modulated during the administration of electrical and pharmacological stimulation in patients with Parkinson's disease (PD) undergoing DBS in the subthalamic nucleus (STN).

Background: Complicated PD is a fluctuating condition and DBS could be optimized adapting moment-by-moment to the clinical condition of the patient. Because LFPs reflect the clinical condition of the patient, adaptive DBS (aDBS) could be based on LFPs.

Methods: 12 patients were studied at rest in four conditions: without DBS and without levodopa (StimOFF,MedOFF), with DBS ON and without levodopa (StimON,MedOFF), with DBS ON and levodopa (StimON,MedON), and without DBS with levodopa (StimOFF, MedON). LFPs were recorded during stimulation from the same electrode thanks to a new patented apparatus (FilterDBS). Rhythms and their synchronizations were evaluated through spectral and bispectral analysis and changes in the beta band during the transition OFF to ON and ON to OFF DBS were studied.

Results: In the StimOFF,MedOFF condition, the activity was concentrated in the low-frequency, in the low-beta and in the high-beta bands and there was a synchronization between the low- and the high-beta. In the StimON,MedOFF condition, despite a small reduc-

tion of the beta activity, the beta rhythm was not disrupted, nor the low- and the high-beta rhythms were completely desynchronized, even though the patient was in a good clinical state. The administration of levodopa (StimON,MedON) completely destroyed the beta activity, increasing the low-frequency activity and producing an increase of the low-frequency synchronization and a decrease of the other synchronizations. In the StimOFF,MedON the beta activity slightly increased and the low-frequencies decreased, together with the low-frequency synchronization. In the OFF to ON DBS transitory the beta oscillation decreased, whereas, during the ON to OFF transitory it did not change.

Conclusions: These results suggest that, because LFPs are specifically modulated during DBS and levodopa administration, they can be successfully used to retroact new aDBS systems.

We-243

Inadequate modulation of cortical excitability with voluntary contraction in Parkinson's disease

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Objective: Modulation of cortical excitability with voluntary contraction in Parkinson's disease (PD) was evaluated as a recruitment property of motor evoked potential (MEP) evoked with transcranial magnetic stimulation (TMS).

Background: Performing smooth voluntary contraction is impaired in PD patients, but its pathophysiology is still unclear. Authors previously reported impairment of selective execution of voluntary contraction of targeted muscle and loss of reciprocity in soleus muscle (Clin Neurophysiol 2002:113;1316-24).

Methods: 9 patients with PD and 8 normal subjects participated with informed consent for the study. MEP was recorded from tibialis anterior muscle under three conditions: at rest, during tonic contraction (TDF), and at onset of contraction with an audio cue signal. Stimulus intensity was systematically and randomly changed below threshold and up to 80% of stimulus output of Magsitm 200 with double corn coil. The MEP was recorded 10 times in each stimulus intensity and situation and averaged. The size of MEP was expressed as a percentage of the maximal M-response. The relationship between the stimulus intensity of TMS and the size of MEP (MEP-gain) was expressed as a slope of linear regression line.

Results: Motor threshold decreased with voluntary contraction in both PD and normal subjects, but threshold at rest and TDF in PD was lower than that of normal. (at rest: normal 61.7±2.6%, PD 51.1±10.4, $p < 0.05$; TDF normal 51.7±5.2, PD 38.0±12.5, $p < 0.05$; onset normal 40.0±8.9, PD 36.7±10.6, ns). The size of MEP with maximal stimulus intensity increased with voluntary contraction in both group, and this tendency was more obvious in normal subjects (normal at rest 12.7±10.6%, TDF 56.0±14.9, onset 60.5±18.5; PD at rest 37.7±21.3, TDF 51.6±26.4, onset 58.3±24.7). The MEP-gain during contraction was steeper than that at rest in normal subject (rest 0.53±0.18, TDF 1.79±1.13, onset 2.12±0.99). However, there was no such increase in patients with PD (at rest 2.42±1.87, TDF 2.53±2.15, onset 2.45±2.00).

Conclusions: There was no increase of MEP-gain with voluntary contraction in PD, which was obvious especially at onset of voluntary contraction in normal subjects. Because the increase of the gain should reflect the increase of cortical excitability, modulation of cortical excitability with voluntary contraction was impaired in PD.

We-244

Apomorphine-induced changes in the oscillatory activity of the cortex and basal ganglia from control rats

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Objective: To study the changes in oscillatory activity in the cortex and basal ganglia of control rats after apomorphine administration.

Background: 6-OH lesioned rats show abnormal beta activity in the cortex and STN, which is reduced after apomorphine administration. These changes are similar to those observed in patients with Parkinson's disease (PD) recorded in the STN in the "off" and "on" motor states. In addition, PD patients also show an increase in gamma activity in the STN in the "on" state. However, the effect of dopaminergic agonists on the activity of the normal motor circuit of the basal ganglia has not been assessed.

Methods: We recorded LFP from the motor cortex, subthalamic area, caudate-putamen and substantia nigra pars reticulata in 13 awake Wistar male rats before and after the administration of apomorphine (5 mg/Kg ip), through screws placed in the skull (motor cortex) and bipolar needle electrodes (basal ganglia). The animals were recorded a minimum of 6 days after the electrode implantation, in a custom recording cage that allowed free movement during the whole procedure. The recording session lasted a minimum of 80 min (20 before and 60 after apomorphine injection. The power spectra from artefact-free long fragments from both periods were compared in separate frequency bands (theta (4-7), beta (low: 11-20, high 20-30) and gamma (65-90)) by means of non-parametrical paired statistics.

Results: After apomorphine, a definite peak of gamma activity was observed in the power spectra from most of the animals in the cortex (10 of 13 rats), CPU (10 out of 12), STN (9 out of 10) and SNr (5 out of 9 rats). The statistical comparison showed significant differences in gamma activity after apomorphine administration in the four structures (mean increases ranging from 27 to 61% of baseline). A significant reduction in low beta activity was also observed in the motor cortex (14% reduction, $p=0.01$), but not in the other structures.

Conclusions: Apomorphine administration generates changes in control rats which are similar to those described in 6-OH lesioneds animals and in the STN of patients with PD after L-DOPA administration. These results suggest that these changes may be related to dopaminergic stimulation, independently of the motor state.

We-245

Disturbed large-scale brain networks in Parkinson's disease

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Objective: To examine the large-scale structure of resting-state brain networks in Parkinson's disease, using concepts from graph theory.

Background: In Parkinson's disease (PD) excessive cortico-cortical coupling has been demonstrated and may reflect a disturbed activity of functional interactions between neuronal assemblies of the brain. Recent neuroscientific studies have stressed the importance of network architecture for adequate brain function, in healthy subjects as well as in patients with various brain pathologies. It is unknown whether the changes in strength of functional coupling in PD are associated with an abnormal network architecture.

Methods: Magnetoencephalographic recordings were performed in an eyes-closed resting-state condition in 70 PD patients with varying disease duration (including 18 untreated, de novo patients) as well as in 21 controls. Graph theoretical analysis was applied to matrices of functional connectivity, as computed by synchronization likelihood, within six standard frequency domains. Resulting connectivity networks were characterized by a weighted clustering coefficient (C, an index of local network structure) and a weighted path length (L, a index of global network integration). All results were compared with reference data from ensembles of random networks.

Results: In the de novo PD patients, resting-state brain networks showed an increase in C/L ratio for theta and alpha1 frequency bands when compared to control subjects. This was due to an increase in clustering coefficient, while path length remained constant. Within the total group of PD patients, correlational analysis revealed a positive association between subjective disease duration and alpha2 and

beta C-values. Disease severity, as expressed by UPDRS motor scores, was positively correlated with alpha1 and alpha2 as well as beta C/L-ratios.

Conclusions: Large scale brain networks are altered in the earliest clinical stages of PD, as indicated by increased local clustering in theta and alpha1 frequency bands. Over the course of PD similar changes also occur in adjacent frequency bands. The increased clustering coefficient in absence of a change in path length suggests an alteration towards more ordered, possibly less flexible, brain networks in PD.

We-246

Analysis of random saccades in early-to mild-stage Parkinson's disease

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Objective: To evaluate the visually-guided random saccades in early- to mild-stage Parkinson's disease using ratatory chair system.

Background: The most consistent oculomotor abnormality in Parkinson's disease is the saccadic hypometria in which the primary saccade undershoots. However, other components of saccadic eye movement in Parkinson's disease are not consistent. We studied the three main components of random saccades in Parkinson's disease, which may contribute to understanding the role of basal ganglia in saccadic eye movement control.

Methods: Twenty one patients with early to mild stage idiopathic Parkinson's disease (Hoehn and Yahr, grade 1-2) were compaired with the same number of age-matched normal controls. They did not have signs or symptoms of dementia or coexistent cerebrovascular disease. Their mean age was 64.7 years (range 49-79). Eye movements were recorded using rotatory chair system for random saccade. Target (red spot) appeared randomly between 0 and 25 degree on the screen. The time interval between each target was also random. The subjects were told that the target would jump randomly on the screen and were instructed to follow it as accurately as possible. Fifteen random saccades per each subject were recorded. The mean velocity, accuracy and latency of saccadic eye movements in Parkinson's disease group were compared with the values of the control group. SSPE 13.3K was used for statistical analysis.

Results: The value of random saccade velocity was significantly higher in control group than patients group ($Z=-2.209$, $p=0.027$; Mann-Whitney U test). The percentile of saccadic accuracy of patients was significantly lower than control (84.8 ± 6.2 and 89.5 ± 3.3 respectively, $F=5.4$, $p=0.05$; student's t test). However, the latencies showed no significant difference between the two groups.

Conclusions: Our study and the review of literature shows that some component of saccadic eye movements are more vulnerable to dopamine deficiency in basal ganglia. Saccadic latency may be the most resistant parameter to the derangement of basal ganglia-superiorcollicular connections.

We-247

Impaired bilateral coordination of gait and upper extremity rhythmic movements in Parkinson's disease: Association with freezing of gait

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Objective: To study the hypothesis that patients with Parkinson's disease (PD) and freezing of gait (PD+FOG) have a generalized deficiency in the bilateral coordination of rhythmic movements.

Background: Recent studies indicate that bilateral coordination of gait is impaired in PD patients and that it may be related to FOG.

Methods: 19 PD+FOG patients, 11 patients without freezing (PD-FOG) during "OFF" state, and 16 elderly subjects were tested. Bilateral coordination of gait was assessed during a 100 m walk while the subjects were wearing force sensitive insoles. We defined the stride duration of one foot as a gait cycle or 360°, determined the relative timing of contra-lateral heel-strikes, and defined this as the phase, φ (ideally, φ=180° in each step). The sum of the coefficient of variation of φ (φ_CV) and the mean absolute difference between φ and 180° (φ_ABS) was defined as the Phase Coordination Index (PCI), representing variability and inaccuracy, respectively, in φ generation. Subsequently, subjects performed left-right alternating tapping on a flat board with two force sensitive rectangles as if they were "walking with there hands." PCI values were calculated for hand tapping using the inter tap interval (ITI) instead of stride duration.

Table 1 (We-247). Demographic, clinical and bilateral coordination parameters (mean ± SD)

Demographic & Clinical Parameters	PD+FOG (n=19)	PD-FOG (n=11)	Elderly (n=16)
Age (y)	64.3 ± 8.5 (p=0.83)†	65.1 ± 9.6 (p=0.93)‡	64.7 ± 9.1
Gender (F/M)	6/13	6/5	13/3
PD duration (y)	10.7 ± 5.9 (p=0.26)	8.5 ± 4.5 (NA)	–
Hoehn and Yahr Scale	3.1 ± 0.7 (p=0.02)	2.5 ± 0.4 (NA)	–
UPDRS part III	41.5 ± 12.0 (p=0.05)	31.9 ± 11.4 (p<0.001)	2.6 ± 1.4
Coordination Parameters			
Errors: hand tapping (%)	3.9 ± 5.3 (p=0.02)	0.7 ± 1.5 (p=0.18)	0 ± 0
PCI hand tapping (%)	29.8 ± 21.8 (p=0.52)	24.6 ± 19.3 (p=0.02)	11.0 ± 6.6
PCI gait (%)	9.7 ± 5.6 (p=0.08)	6.9 ± 3.2 (p=0.003)	3.7 ± 1.2
Hand tapping CV (%)	17.6 ± 11.0 (p=0.27)	13.1 ± 8.4 (p=0.001)	5.0 ± 1.9
Gait CV (%)	6.3 ± 4.8 (p=0.04)	3.1 ± 1.4 (p=0.02)	2.2 ± 0.6

†and ‡p-values based on t-test comparison between PD+FOG and PD-FOG and between PD-FOG and healthy elderly, respectively; UPDRS- Unified Parkinson's Disease Rating Scale; CV-coefficient of variation of the stride/ITI time, i.e., variability.

Results: PD+FOG patients had more errors (i.e., disruption in the alternating pattern) than PD-FOG while performing the hand tapping task (Table 1). PCI values for alternating hand tapping were increased (reduced coordination) among PD patients as compared to elderly subjects ($p=0.005$), with no significant distinction between the PD+FOG and PD-FOG groups. Gait PCI and variability were increased in PD+FOG as compared to PD-FOG, but hand tapping variability was not.

Conclusions: Regardless of FOG status, PD patients have difficulties maintaining an alternating pattern of hand tapping. Patients with FOG make more errors during hand tapping, compared to non-freezers. PCI values of hand tapping also tend to be higher among PD+FOG patients, compared to PD-FOG, however, in contrast to gait, these are not significantly different. While further research is required to differentiate the effects of disease severity, the present findings suggest that walking places unique demands on the bilateral coordination among patients with FOG.

We-406

MEG before and after implantation of deep brain stimulator in a parkinsonian patient

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Objective: To elucidate the therapeutic mechanisms of deep brain stimulation (DBS).

Background: DBS of subthalamic nucleus (STN) relieves symptoms of Parkinson's disease (PD) although the mechanism of action

is disputed. Artifacts produced by DBS have precluded magnetoencephalography (MEG) studies of these patients.

Methods: We measured MEG of one 68-year old female patient with PD for 14 years, displaying bradykinesia, left-predominant tremor, off states and dyskinesia. Levodopa challenge test was positive. Bilateral STN DBS electrodes were implanted. Medication was kept stable. MEG was done with a 306-channel magnetometer (Elekta Neuromag®) half a year before and 18 days after the operation. Auditory evoked fields (AEFs) were elicited by 1-kHz tones and somatosensory evoked fields (SEFs) by electrical pulses to the median nerves at the wrists. Spontaneous MEG was recorded in combination with EMG from extended left arm. The magnetic artifacts from DBS were suppressed by spatiotemporal signal space separation method (tSSS). Single dipole models for AEFs and SEFs were constructed. The source strengths of SEF P60m, AEF N100m and coherence spectra between MEG signals and wrist extensor EMG were calculated preoperatively, and postoperatively with DBS on and off.

Results: In the right hemisphere, the source strengths of AEFs and SEFs were strongest when DBS was on. In the left hemisphere the preoperative responses were strongest and postoperative stimulator off-responses were weakest. MEG-EMG coherence at beta frequency (12-30Hz) was clear preoperatively, and absent after the operation.

Conclusions: MEG-studies of DBS patients are feasible when employing tSSS. Further studies are needed to address mechanism of action of DBS.

Th-238

Automated biofeedback assistance for freezing of gait in patients with Parkinson's disease

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Objective: To test if a wearable device can recognize in real-time an occurrence of freezing of gait (FOG) episode in patients with Parkinson's disease (PD) and provide auditory cueing to help resuming gait.

Background: FOG is a disabling gait disturbance commonly seen in patients with advanced PD. It has been suggested that external cuing may help the patient to negotiate the FOG episode and to resume functional walking.

Methods: 10 PD patients (66.5±4.8 y; H&Y in "ON";2.7±0.6) with a history of FOG were studied. 8 patients were examined in the "OFF" state (>12h from last medication uptake) and 2 patients ("ON freezers") were examined in the "ON" state. Patients wore a miniature 3D accelerometer attached to one of their ankles. Time series of acceleration were transmitted (64Hz) wirelessly to a wearable device placed on the trunk for real-time identification of FOG (using an algorithm based on a set of frequency content criteria). Earphones placed around the subject's neck and connected to the wearable device produced a 1 Hz ticking sound whenever an episode was identified and lasted until the subject resumed walking. The subjects walked twice for about 10 min in paths representative of normal daily walking (straight line, turning, and moving around rooms) with and without the earphones connected. Real time annotation and simultaneous video taping were used to determine the number of FOG episodes.

Results: 96.2% of the identified FOG episodes (n=237) were detected online by the wearable device which started the auditory cuing. The 'technological' sensitivity and specificity of the device were 73.1% sensitivity and 81.6%, respectively (based on 0.5 sec moving window). Post-hoc optimization analysis suggested that these figures could have been 88.6% and 92.8%, respectively; if the device would have been 'calibrated' for each of the patients based on their gait characteristics (figure1).

Conclusions: Wearable devices can measure leg movements with acceleration sensors to identify FOG in real-time and produce a response that alleviates this paroxysmal gait disturbance. **Fig.1** Sensitivity and specificity plots for online automated detection of FOG for all individuals prior (left) and post (right) adjusting algorithm parameters based on individual gait characteristics. Each point denotes one subject.

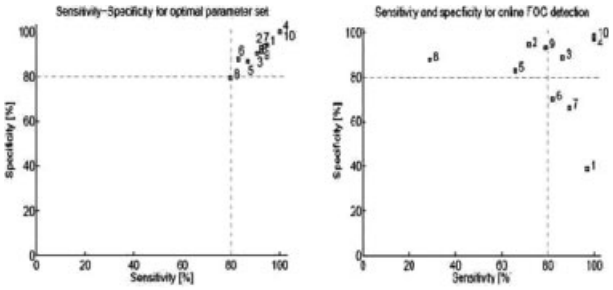

FIG. 1 (Th-238).

Th-239

Bladder dysfunction in an acute experimental model of unilateral medial forebrain lesion

C.C. Santos, C. Fuellhase, R. Soler, S. Vishwajit, G. Badlani, K.-E. Andersson (Winston-Salem, North Carolina)

Objective: To evaluate the acute cystometric findings in an animal model of Parkinson's disease (PD) by creating unilateral medial forebrain lesion using 6-OHDA.

Background: Parkinson's disease is one of the most common neurologic condition associated with voiding dysfunction. Up to 70% of patients report lower urinary tract symptoms ressulting from detrusor overactivity and impairment of urethral sphincter relaxation.

Methods: Female Sprague-Dawley rats (200 -250 g) underwent a stereotaxic injection of 6-OHDA (8 μg) into the medial forebrain bundle on the right side (n=8). At the same time, PE 50 tubes were inserted into the dome of the bladder and held in place with a purse string suture, which is then tunnelled subcutaneously and anchored to the skin of the back. Healthy controls (n=6) underwent bladder catheterisation, without the stereotaxic brain lesion. Three days later, urodynamic evaluation was performed in all animals, without anesthesia.

Results: In 6-OHDA lesioned rats, cystometric analysis revealed higher threshold pressure (33.6±15 vs. 19.1±3 cmH_2O; $p<0.05$) and maximum pressure (50.3± 19 vs. 27.9±4.6 cmH_2O; $p<0.05$) compared to controls, as well as higher spontaneous activity (7.9±8 vs. 2.2±1; $p<0.05$). The inter-micturition pressure was also higher in the 6-OHDA group, but without statistical significance.

Conclusions: Our data suggest that 6-OHDA lesion in the medial forebrain bundle induces detrusor overactivity, characterized by higher spontaneous activity and inter-micturition pressure, with a possible sphincter dyssynergia, reflected by higher micturition pressures. Even though this is an acute model of dopaminergic lesion, abnormalities in the bladder function could be detected as early as 3 days. This model of PD may be useful to study the evolution and pathophysiology of bladder dysfunction in a chronic model of PD.

Th-240

L-dopa and STN stimulation effects on pneumophonic coordination in parkinsonian dysarthria: Intra-oral pressure measurements

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Objective: To evaluate L-dopa and STN stimulation effects on pneumophonic coordination (PC) in Parkinson's disease (PD), by studying the temporal progression of intra-oral pressure (IOP) during the expiratory phase of a sentence production.

Background: Effects of L-dopa and STN stimulation on parkinsonian dysarthria still remain erratic and challenging for the clinician.

As the PC plays a crucial role in the sound pressure level production, then contributing largely to speech intelligibility, it is important to assess this aspect of speech in PD and to quantify the changes that may be expected following treatments.

Methods: Using a dedicated system (EVA2, SQLAb, Aix-en-Provence), 24 PD patients were recorded preoperatively on and off L-dopa, as well as postoperatively ON and OFF STN stimulation. IOP on six measurement points (every "p" consonants) during realisation of the French sentence *Papa ne m'a pas parlé de beau-papa* (Daddy did not speak to me about daddy-in-law) was calculated. Fifty control subjects were recorded in parallel in order to define the reference. A linear mixed model was estimated ("R" software, version 2.6.2, http://www.r-project.org) for group analyses integrating patient and "p" consonant as random terms and treatment nature (L-dopa *vs.* STN stimulation) and state (off *vs.* on) as fixed effects.

Results: UPDRS motor scores and IOP measurements displayed significant differences ($p<0.025$) between off and on states, either with L-dopa or STN stimulation. Differences between on and off states could not be distinguished from L-dopa and STN stimulation treatments. Regards to IOP measurements, significant differences were found between control subjects and patients OFF stimulation, ON stimulation and off L-dopa. No difference was revealed between controls and patients on L-dopa.

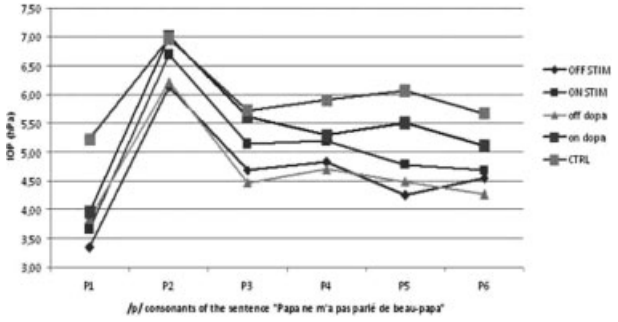

FIG. 1 (Th-240). IOP measurements (means) of PD patients during the four treatment conditions [off dopa and on dopa preoperatively, OFF STIM and ON STIM postoperatively) and control subjects

Conclusions: L-dopa administration led to patient IOP values closer to controls in comparison with the STN stimulation ON state: this point deserves attention since it confirms the frequent need for treatment combination following surgery. However, the levels of PC improvement by L-dopa preoperatively and STN stimulation postoperatively are not statistically different, highlighting the controversial effect of treatments on axial signs.

Th-241

Stretch reflex gain in Parkinson patients studied during a dynamic tracking task

V. Stanislaus, J.A. Burne (Lidcombe, Sydney, NSW, Australia)

Objective: To study the possible contribution of the stretch reflex (SR) to the dyskinetic movement disorder of Parkinson's disease (PD), we obtained estimates of SR gain and coherence during a tracking task requiring dynamic muscle contractions.

Background: A detailed study of the relationship between SR gain and a range of constant background contraction levels is reported for normals and PD patients in the accompanying poster. SR gain was reported to be significantly reduced in patients relative to controls at all contraction levels to 50% of maximum.

Methods: The metacarpophalangeal joint of the index fingers of 11 Parkinson patients was perturbed sinusoidally (1-2 deg,10 Hz), while they voluntarily modulated the contraction level of the first dorsal interrosseous muscle by tracking a triangular waveform displayed at different frequencies (0.1, 0.2 and 0.3 Hz) The range of the modulation corresponded to 0-50% of each subject's maximum. Joint angle and surface EMG data were collected. Cross correlation analysis was performed between stretch and EMG for sequential 1s data intervals and SR gain and coherence was estimated for each 1s interval. The estimates for each of six different contraction levels were then averaged.

Results: A linear relationship between SR gain and the background contraction level was established for each of the dynamic tasks. This dynamic gain data was pooled for all patients and compared with the static data (see accompanying poster) as shown in Figure 1. The relation between SR gain and contraction level was similar in the static and dynamic conditions.

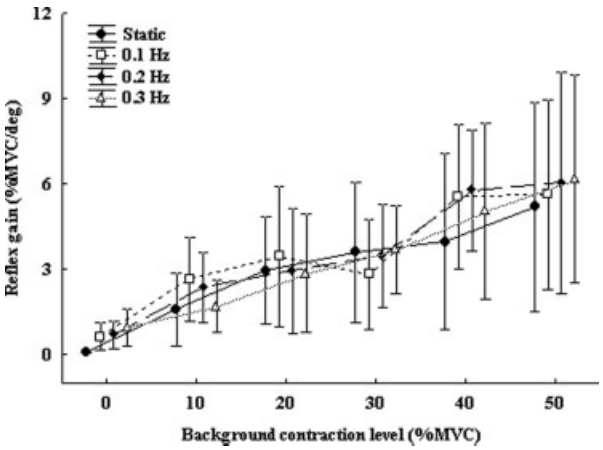

FIG. 1 (Th-241).

Conclusions: The results indicate a similar reduced range of reflex modulation in static and dynamic contraction tasks in PD. This reduced central reflex gain modulation is likely to contribute to the dyskinesia of PD.

Th-242

Stretch reflex gain and biomechanical measures of joint stiffness show no correlation in Parkinson's disease

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Objective: We here report on the correlation between parallel measures of stretch reflex (SR) gain and the mechanical stiffness of the same joint (which is related to the clinical feature of muscle rigidity) in Parkinson's disease (PD) patients.

Background: We previously reported (Stanislaus and Burne, 2007) that SR gain was reduced by 50% in PD patients compared to age-matched controls, inferring that the SR does not contribute significantly to rigidity in PD. Here we assessed this further through biomechanical measures of joint stiffness.

Methods: The metacarpal joint of the index finger was perturbed sinusoidally at several frequencies up to 40Hz while patients and age-matched controls maintained constant background contractions of the first dorsal interrosseous muscle (rest to 50% of maximum). SR and resistive joint torque gain, coherence and phase with respect to the stretch perturbation were determined by correlation analysis.

Results: (1) Mean maximal voluntary EMG levels (MVC) were reduced by 35% of the average age matched control value. (2) Joint mechanical stiffness was increased by a factor of 6-10 in PD but angle-torque gain was not correlated with stretch frequency or contraction level as observed in controls (3) Angle-torque gain was not correlated with simultaneous measures of SR gain (4) Angle-torque phase difference showed an increased lag behind stretch compared with controls. Hence parallel investigation of the SR and joint biomechanics found no evidence of a significant correlation between these

variables. A small background EMG persisted in the resting PD muscle however it was not strongly modulated by sinusoidal stretching.

Conclusions: This study provides further evidence that the origin of the rigidity of PD does not lie in increased SR activity. PD can be differentiated from stroke spasticity (Burne et al, 2005) by reduced modulation of the resting EMG. References: 1. Burne JA, Carleton VL & O'Dwyer NJ. (2005). The spasticity paradox: movement disorder or disorder of resting limbs? Journal of Neurology Neurosurgery and Psychiatry 76, 47-54. 2. Stanislaus V, Burne J.A. Movement Disorders, Vol. 22, Suppl. 16, 2007, S37.

Th-243

Neurophysiological correlates of muscolar pain in Parkinson's disease

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Objective: Patients with PD often complain of painful sensations that may involve body parts affected and unaffected by dystonia. Pain in non-dystonic body parts may have features of muscular or neuropathic pain. The recording of CO_2 laser evoked potentials (LEPs) is an useful tool to explore the functional status of some cerebral structures involved in nociceptive input processing. The aim of the present study was to assess in the off state LEPs in PD patients with muscular pain to one arm and to compare the results with those obtained in pain-free PD patients and in controls.

Background: In pain-free PD patients with hemiparkinson, we have recently reported that the amplitude of the N2/P2 complex, originating from the cingulate cortex and insula, was significantly lower (regardless of the clinically affected body side) than in controls, and that acute L-dopa administration yielded no significant change in N2/P2 amplitude as compared to the *off* state (Tinazzi et al. Pain 2008; J Neurological Sciences 2008).

Methods: We recorded LEPs to arm stimulation (skin over deltoid muscle) in 12 pain-free and 11 PD patients complaining of muscular pain to one arm with hemiparkinson during the off state. Results were compared with those obtained in 11 normal subjects matched for age and sex.

Results: N2/P2 peak-to-peak amplitude was significantly lower in both group of PD patients than in controls, regardless of the clinically affected body side. Comparisons between the two groups of PD patients showed that the N2/P2 amplitude obtained following stimulation of the painful arm was significantly reduced compared to the one obtained on the non painful arm and those obtained in pain-free PD patients. In PD patients with muscular pain, the N2/P2 amplitude did not change after acute L-dopa administration.

Conclusions: The present results suggest an abnormal nociceptive input processing which appears to be independent of clinical expression of parkinsonian motor signs. These alterations appears greater in presence of muscular pain and are not modified by dopaminergic stimulation.

Th-244

Modulation of neural activity during mental simulation and imitation of a motor task on young, elderly and Parkinson's disease subjects: A comparison of simple vs complex task

L.E. Tremblay, C.M. Tardif (Ottawa, Ontaio, Canada)

Objective: The aim of this study was to measure cortical activation during motor imagery (MI) and imitation in the course of a simple task (one leg knee extension) and a complex task (standing-up on both legs) on young, elderly and PD subjects.

Background: Parkinson's disease (PD) is known to affect the ability of generating adequate movement due to decreased Basal Ganglia activity. Mentally simulating and imitating a motor task activates several cortical areas, including M1, as revealed by transcranial magnetic stimulation (TMS) (Tremblay et al. 2007).

Methods: 75 subjects (25 young, 22 elderly and 28 medicated PD) participated in two experiments. Cortical excitability was measured using motor evoked potential (MEPs) (surface electrodes) induced by TMS with the double cone coil of a Magstim 200. The MEPs were recorded from the motor point of the dominant rectus femoris muscle (RF). The subject imitated a simple task (subject executing knee extension, 90 to 180°) or a complex task (a subject standing-up to chair) depicted on a video timed with the stimulator. The same task was mentally simulated with eyes closed following verbal instructions. Facilitation of MEPs amplitude (peak-to-peak) was expressed in % of baseline values.

Results: MEPs facilitation decreased significantly during MI of knee extension task (290±12%, 245±15% and 215±10%) and during imitation (1320±90%, 1190±80% and 545±60%) respectively for young, elderly and PD subjects. MEPs facilitation also decreased during MI of standing-up task (190±8%, 170±8% and 140±6%) and during imitation (810±60%, 610±100% and 240±30%) respectively for young, elderly and PD subjects.

Conclusions: The type of task showed a significant difference in relationship to EMG activity. In PD, the neural system is operational, while deficit or impairment in explicit MI is related to mirror neurons (Rizzolatti and Fabbri-Desto, 2008) and deficit in imitation is related to energization (McAuley, 2003), when compared to young and elderly subjects. These results suggest a possible implication of MI in rehabilitation of PD subjects. MI is a simple, easy and non-costly way to activate the motor cortex during practice of motor programs' or exercises' MI.

Th-245

Force-dependent interhemispheric connectivity in Parkinson's disease (PD)

G. Tropini, J. Chiang, S. Palmer, Z.J. Wang, M.J. McKeown (Vancouver, Canada)

Objective: To investigate modulation of cortical connectivity in PD subjects during production of different force levels.

Background: PD is associated with difficulties in modulating force output. Patients' movements are characterized by prolonged times to peak force and irregular force-time curves. As recent research has suggested that production of force requires appropriate modulation of cortical rhythms via the basal ganglia, we used EEG techniques to investigate how modulation of cortical connectivity is affected in PD at different levels of force output.

Methods: 10 PD subjects (ON and OFF L-dopa medication) and 9 age-matched controls participated in our study. Subjects were asked to squeeze a pressure responsive bulb for 2 seconds in order to match "Low" and "High" levels of force amplitude (5% and 25% of maximum voluntary contraction) that were presented on a computer screen. Targets were presented every 10 seconds in a randomized order. We utilized partial directed coherence (PDC), a frequency-dependent measure related to Granger causality, to identify EEG patterns of connectivity between 4 electrode regions: Fronto-Central (Fc), Left Sensorimotor (L_SM), Right Sensorimotor (R_SM), and Central(C).

Results: Controls showed significantly increased directional connectivity from the L_SM to the R_SM for the "Low" force condition at frequencies <25Hz, which is suggestive of interhemispheric inhibition (IHI). Increased connectivity in the opposite direction of information flow (R_SM → L_SM) was instead observed for the "High" force level in the same frequency range, suggestive of interhemispheric facilitation (IHF) normally associated with higher force levels. PD patients OFF medication instead showed decreased connectivity in both directions of information flow and for both force levels. In PD patients ON medication, a pattern of connectivity similar to that of controls was restored in the R_SM → L_SM direction, but only for the "High" force condition.

Conclusions: In healthy subjects, the observed patterns of IHI and IHF were consistent with prior studies. However our results suggest

that PD patients are unable to appropriately modulate connectivity. Most significantly, L-dopa medication does not restore normal patterns of information flow. Thus, deficits in IHI and IHF might contribute to altered force production in PD.

Th-246

Different wave conformations of movement-related cortical potentials in de novo Parkinson's disease with and without rest tremor

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Objective: To investigate the movement-related cortical potentials (MRCP) conformations in PD with and without tremor.

Background: Resting tremor is a distinct hallmark of idiopathic Parkinson's disease (PD); however, the development and severity of resting tremor in PD patients is not uniform. It is intriguing whether the presence of tremor will cause different manifestations of MRCP.

Methods: Movement-related cortical potential was studied in 6 untreated PD patients with prominent resting tremor (PDt group), in 6 without prominent tremor (PDnt group), and in 8 normal individuals (control group). We compared the mean amplitude of early Bereitschaftspotential (BP), late BP and the frontal peak of motor potential among the patient and control groups.

Results: There was no significant difference between the PDt group and the control group. However, the mean amplitude of early BP was significantly reduced on Cz and C4 in the PDnt group ($P<0.05$ by Mann-Whitney). The late BP was also significantly reduced on Cz, CP3, P3 and O1 ($P<0.05$) with tendency of reduction on C3 and CPz in the PDnt group ($P=0.05$).

Conclusions: The current data suggest that there is electrophysiological heterogeneity between PD patients with and those without prominent resting tremor.

Th-247

Gait pattern of Parkinson patients at different treadmill-induced walking speeds

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Objective: To analyse, how Parkinson patients adapt their gait pattern to a given walking speed by a treadmill and how timing and scaling could be modified by visual cues.

Background: When people walk, each of them has their optimal walking speed, where the consumption of energy is best related to the effect of covered distance. The gait of parkinsonian patients, however, is characterized by reduced speed, short step length and prolonged stance phase, thus providing a low effective energetic balance. This results in disturbance of gait rhythmicity, untimely fatigue and increased risk of falls.

Methods: Gait pattern was analysed in 35 patients with Parkinson's disease and 15 aged matched volunteers. Patients and volunteers had to walk an a treadmill (Zebris Systems) using dynamic pressure sensors with a given velocity of 1, 2,3 and 4 km/h. They performed 3 turns, the first without and two turns with visual cues (white stripes in a distance of 30 cm and 60 cm respectively). Subjects had to walk for 2 – 3 minutes before a 15 second period was recorded and analysed. The following parameters were measured: cadence, step and stride length, percentage of stance and swing phase, stride to stride variability and the groundforce dynamics during a walking cycle.

Results: In normals, the 4 fold increase of velocity results in a doublication of step length and cadence. The swing phase increases slightly. There is only limited variance with visual cues. In Parkinson patients, nearly 200% increase of step length can be achieved at 4,0 km/h as compared to 1,0 km/h while the cadence only increases by 65%. Additionally step length becomes larger when visual cues are used. We could observe that patients could preserve an increased walking speed and larger step length of over-ground walking as compared as to before the treadmill session. (Data will be shown in detail).

Conclusions: Our results support the idea of optimizing gait pattern in Parkinson patients with treadmill training.

Th-248

Electromagnetic articulography assessment of tongue function in non-dysarthric speakers with Parkinson's disease

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Objective: The present study investigated lingual kinematics in a group of seven participants diagnosed with idiopathic Parkinson's disease (PD) using the electromagnetic articulography (AG-200 EMA Carstens).

Background: Articulatory imprecision in PD has been attributed to reduced range of movement, rigidity and abnormal speed of movement of the articulatory structures. Most of the previous studies provided acoustic and kinematic evidence of lip muscle rigidity, reduced amplitude and velocity of lip and jaw movement. Although reduced tongue strength in PD has been reported, to date very limited studies have documented the effects of PD on lingual kinematics.

Methods: Seven participants with idiopathic PD were rated as non-dsysarthic on the basis of a perceptual assessment. A group of seven age and sex matched non-neurologically impaired participants served as controls participants. While fitted with the EMA system, each participant was required to read aloud one sentence loaded with alveolar consonants, /t/, to examine movement of the tongue tip and one sentence loaded with velar consonants, /k/, to examine movement of the tongue back. Three repetitions of each sentence by each participant were analyzed.

Results: There was no difference between the PD and control groups on the distance of tongue movement during either the approach or release phases of either alveolar or velar consonants. However, the PD did showed significant reduced acceleration ($p<.05$) and deceleration ($p<.01$) of the tongue movement during the approach phase of alveolar consonant production. Duration of tongue movement was also significantly longer for the PD group than controls during production of both alveolar ($p<.01$) and velar ($p<.01$) consonants.

Conclusions: Findings suggest "articulatory undershoot" may be the cause of articulatory impairment in PD. The implications of the presence of subclinical changes in lingual kinematics for the management of persons with PD are discussed.

Th-249

Pain threshold and tolerance in parkinsonian patients with and without pain

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Objective: To assess pain threshold and tolerance in patients with Parkinson's disease (PD) with or without pain.

Background: Patients with PD can experience pain of various categories such as dystonic and non dystonic pain. A recent case-control study recruiting a large number of subjects, reported a significant association between PD and non-dystonic pain with features of muscular or neuropathic pain starting at or after the onset of parkinsonian symptoms (Defazio G, Arch of Neurol 2008). Moreover, we reported abnormal pain-evoked responses to laser stimulation in hemiparkinson pain-free patients suggesting alterations of nociceptive inputs processing (Tinazzi M, Pain 2008).

Methods: 70 patients affected by PD were selected. These included 45 patients without pain, and 25 patients with muscular or neuropathic pain to one body part present at the time of the study, developing at/after the onset of parkinsonian motor symptoms. Patients with headache or other facial pain, medical conditions asso-

ciated with or predisposing to painful symptoms, cognitive impairment and depression were excluded from the study. In all patients, pain threshold and tolerance were assessed after overnight withdrawal of dopaminergic medications, using electrical stimulation delivered to the little finger and big toe. Both right and left hand and foot were tested separately in each patient. Results were compared with those obtained in 40 aged-matched controls.

Results: Pain threshold and pain tolerance were significantly lower in PD patients for both right and left hand and foot than in normal subjects. In PD patients with pain, pain threshold and tolerance obtained on the painful limb (regardless of muscular or neuropathic pain) were lower compared to those obtained on the non painful limb and in pain-free PD patients.

Conclusions: These results extend previous data indicating that the processing of nociceptive inputs is altered in PD patients and this abnormality appears to be greater in presence of muscular or neuropathic pain.

Th-250

Coexistence of altered firing patterns in the basal ganglia and thalamus in patients with Parkinson's disease

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Objective: To explore neuronal activity in the basal ganglia nuclei and thalamus in Parkinson's disease (PD).

Background: According to the classic model of the basal ganglia dysfunction, the parkinsonian state is associated with excessive inhibition output from GPi, whereas chorea-ballism as well as L-dopa induced dyskinetic (LID) state in PD are associated with reduced and altered firing pattern in basal ganglia output activity.

Methods: Ten patients with idiopathic PD were studied in the off state. Their mean age was (56.1±6.9) years and mean disease duration was (10.1±4.6) years. All patients had tremor, rigidity and bradykinesia. All had motor fluctuations and five had dyskinesia related to L-dopa therapy. Their Hoehn and Yahr scores were 2 to 4, and mean total Unified Parkinson's Disease Rating Scale (UPDRS III) score off medication was 28.6 ± 6.4. Microelectrode recording in the GPi, the STN and the Vop/Vim and electromyogram of the contralateral body side to surgery were recorded simultaneously. Single unit analysis was performed. The interspike interval (ISI) and coefficient of variation (CV) of ISI were calculated. ISI histograms were constructed to evaluate the neuronal firing pattern. One-way ANOVA and Chi Square test was employed.

Results: One hundred and fifty-four neurons were identified from 12 trajectories of GPi (n=4), STN (n=4) and Vop/Vim (n=4). In addition to 25.6% tremor related neuronal activity, 35.2% rapid tonic neuronal discharge, and 26.6% irregular neuronal activity which are often seen in the PD state, there were 11.7% neurons (STN:6/38;GPi:8/53;VL:4/63) with highly irregular bursty firing. The pattern was characterized by intermittent grouped discharges separated by periodic pauses, a similar firing pattern to that seen in the drug-related dyskinetic state in PD and dystonic patients. Their CV ranged from 1.1-2.1 (with mean 1.6±0.4) indicating a high degree of irregularity. There were significant differences of ISI and CV of ISI among different types of neuronal discharges ($P < 0.05$).

Conclusions: It appears that the highly grouped discharge patterns that coexist in the basal ganglia nuclei and thalamus in the off-medication state are apparently not directly involved in the involuntary movements in response to L-dopa administration such as LID.

Th-410

Alterations of the visual pathway in Parkinson's disease patients: Understanding visuospatial abnomalities in this condition

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Objective: To evaluate, define and quantify the presence of alterations in the visual pathway in PD carriers without concomitant affliction.

Background: Parkinson's disease (PD) is a neurodegenerative disorder, wich is primarily due to depletion of dopamine at the Central Nervous System (CNS). However, the CNS involvment is more extensive as evidence by several manifestations that can accompany PD development such as visuospatial disorders.

Methods: In a prospective study we selected 31 patients with diagnosed mild to moderate PD (stages I and II of Hoehn and Yahr - HY- scale) who were derived to specialist polyclinic consultation. In every patient we are interesed in performing and assesing: i) HY scale and Webster evaluation, ii) comprehensive clinical ocular evaluation, false positive: deterioration due to glaucoma, opacity of the lens or retinal disorders, iii) electroretinogram and iv) visual evoked potentials.

Results: In construction.

Conclusions: As in a previous work alterations of visual evoked potentials (VEP) were postulated to be linked to the existence of dopaminergic neurons within the retina, in this study we want to addressed wether VEP is associated with PD. To this end, we first rule out of false positives caused by prior ocular alterations that could lead to VEP misinterpretation; we then identify, through VEP, the existence of alterations in the visual pathways in patients with PD. In cases of finding VEP alterations we will observe electroretinogram alterations. Our results may reveal that the visuospatial abnormalities in PD, could be explained by the involvment of dopaminergic retinal cells. In cases of inconsistencies between the results of electroretinogram and VEP (normal and altered, respectively) we suggest that alternate causes, such as neurodegeneration of the visual pathway, may explain the altered VEP. Overall, our results could indicate that early detection of VEP alteration in patients with emerging PD can be useful to predict visuospatial disorders.

PARKINSON'S DISEASE: NEUROPHARMACOLOGY

Mo-246

Do different pharmacological treatments have different effects on saccadic eye movement abnormalities in Parkinson's disease?

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Objective: To examine the extent to which abnormalities in saccadic eye movements in Parkinson's disease vary with drug treatment.

Background: One of the most promising clinical biomarkers that we are working with is eye movement abnormalities and in particular visually guided horizontal saccades. As with other measures, from simple clinical rating scales such as UPDRS to quantitative measures such as hand tapping, saccadic latencies are affected by the medication the patient takes. Disentangling the effects of disease and medication is difficult. Here we examine the extent to which the type of medication a patient is on determines the nature of the changes in latency of saccadic eye movements.

Methods: We have used a specialized portable non invasive infrared oculometer to record horizontal visually-guided saccadic eye movements. 300 trials can be obtained in less than 15 minutes and large amount of data be produced. The latency distributions are analyzed using the LATER model and analysis of variance was primarily used to robustly distinguish the various groups.

Results: We have examined a cohort of 70 PD patients who have been taking different medication regimes. The medication groups were matched for age, sex, and where possible UPDRS scores. Here we present the changes in the median saccadic latencies for each individual distribution as a function for their medication.

Conclusions: While the heterogeneity of PD has made the analysis more difficult, this technique has provided a quantifiable and accurate way of measuring eye movement abnormalities (even subtle ones) in PD patients. Measurement of saccadic eye movements may also provide unique insights into the mechanisms of oculomotor control and

its dysfunction in neurodegenerative disorders involving the basal ganglia and more specifically dopamine. We are currently carrying out longitudinal studies to determine whether we can reliably detect disease progression despite the various medical regimes. Reference: Michell et al 2006 Saccadic latency distributions in Parkinson's disease and the effects of L-dopa Funding: This work has been supported by an award from the Medical Research Council, United Kingdom. Aspects of this work were also funded by the Parkinson's Disease Society of the United Kingdom and the NIHR Cambridge Biomedical Research Centre.

Mo-247

Astrocyte-proliferating effect and neuroprotective effect against 6-OHDA-induced dopaminergic neurodegeneration of a novel anti-parkinsonian agent zonisamide

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Objective: Our previous studies revealed that repeated administration of zonisamide (ZNS) dramatically increased glutathione (GSH) levels in the basal ganglia and completely suppressed L-DOPA-induced striatal dopamine (DA) quinone formation in the model of Parkinson's disease (PD) (Movement Disord. 21 Suppl. 15: S467, S493, 2006). Furthermore, we recently clarified that ZNS activates astroglial proliferation and/or astroglial cystine transport system which supply cysteine of GSH synthesis substrate to neurons. In the present study, further examinations were performed to clarify the mechanism of astrocyte-proliferating effect of ZNS and to evaluate its neuroprotective effects against degeneration of DA neurons.

Background: ZNS has been used as an anti-epileptic agent for over 10 years in Japan, and now available in the South Korea, USA and Europe. The recent double-blind controlled study in Japan showed that ZNS improved the cardinal symptoms of PD (Murata et al., Neurology 68: 45-50, 2007).

Methods: Effects of neutralization by anti-S100β antibody on ZNS-induced astroglial proliferation were examined in cultured astroglial C6 cells. We also examined repeated effects of one-week ZNS administration starting 3 weeks after the 6-OHDA lesioning on the progression of dopaminergic neurodegeneration in hemi-PD mice.

Results: Neutralization by anti-S100β antibody completely inhibited ZNS-induced increase in the number of astroglial C6 cells. Compared with the level at 3 weeks after the lesioning, nigral tyrosine hydroxylase (TH)-positive neurons and striatal TH- or DA transporter-immunoreactivity showed slightly or significantly lower levels on the parkinsonian side at 4 weeks after the 6-OHDA injection in the hemi-PD mice. The progression of nigrostriatal neurodegeneration in the lesioned side of hemi-PD mice was somewhat or significantly prevented by one-week administration of ZNS starting 3 weeks after the lesioning.

Conclusions: S100β secreted from astrocytes is known to exert autocrine effects to promote astrocyte proliferation. These results indicate that ZNS may promote proliferation of astrocytes via its enhancing effects of S100β production or secretion in/from the astrocytes. Furthermore, we could confirm that ZNS exerts neuroprotective effects against progressive neurodegeneration in 6-OHDA-induced hemi-PD models.

Mo-248

Efficacy of double-blind, placebo-controlled pramipexole against depression in Parkinson's disease

P. Barone, W. Poewe, E. Tolosa, O. Rascol, D. Massey, C. Debieuvre, S. Albrecht (Naples, Italy)

Objective: To investigate the benefit of double-blind pramipexole (0.125-1.0 mg tid vs placebo) for treating depression in patients with Parkinson's disease (PD), depressive symptomatology, and stable motor function.

Background: Depressive symptoms are common in PD and are possibly related to dopaminergic dysfunction. Exploratory studies found that the dopamine agonist pramipexole may have antidepressive effects. The present study is the first placebo-controlled investigation of depressive symptoms in PD to use the Beck Depression Inventory (BDI) as its primary endpoint.

Methods: In a multicenter international trial, each patient's 12-week treatment began with ≤5 weeks of titration to optimal therapeutic effect and mood response. At baseline, all patients had PD at modified Hoehn-Yahr stage I-III, with stable motor function and stable PD treatment but no dopamine agonist for ≥30 days. They also had depressive symptoms, with baseline scores ≥5 on the Geriatric Depression Scale (15-Item GDS) and ≥2 on Unified Parkinson's Disease Rating Scale Part I, question 3. The primary endpoint was change in depression, as measured by BDI-1A total score. BDI responders were defined as patients with a ≥50% reduction from baseline score. Other endpoints included change on GDS.

Results: Of 144 pramipexole and 152 placebo recipients, 139 (96.5%) and 148 (97.4%) provided post-baseline BDI/GDS data. Their baseline mean BDI scores were 18.7 vs 19.2, and their baseline mean GDS scores were 8.4 vs 9.2. On BDI, the mean change, adjusted for baseline and country (and with LOCF for the 20 pramipexole and 19 placebo recipients [13.9% and 12.5%] who discontinued prematurely) was –5.9 vs –4.0 ($P=.0103$, ANCOVA). BDI responder rates were 27.3% vs 18.4%, for an adjusted odds ratio of 1.76 ($P=.0535$). On GDS, adjusted mean change was -2.5 vs -1.7 ($P=.0346$). The change in depressive symptoms by BDI was not related to the change in motor symptoms (correlation coefficients 0.21 and 0.09).

Conclusions: In a large-scale prospective double-blind trial, pramipexole significantly reduced depressive symptoms in PD compared with placebo, as measured by BDI, a widely utilized outcome assessment in depression-treatment trials. GDS, a secondary endpoint, also showed greater antidepressive efficacy for pramipexole than for placebo.

Mo-249

Efficacy of pramipexole for motor function and activities of daily living in Parkinson's disease and associated depression

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Objective: To investigate if benefit of pramipexole for motor function and activities of daily living in early Parkinson's disease (PD) pertains to PD patients with concurrent depressive symptoms in a study investigating treatment effect on depressive and PD symptomatology.

Background: Depression is common in PD and may be directly related to dopaminergic dysfunction. This is the first placebo-controlled study to use the Beck Depression Inventory (BDI) as the primary endpoint in PD patients. The study was designed to clarify evidence from previous studies in which the dopamine agonist pramipexole was shown to have antidepressive effects.

Methods: In a multicenter international trial, 296 patients received double-blind pramipexole or placebo for 12 weeks. At baseline, all patients had PD at modified H&Y stage I-III, stable motor function, stable PD treatment, but no dopamine agonist for ≥30 days. All patients also had depressive symptoms, with baseline scores ≥5 on the Geriatric Depression Scale (15-Item GDS) and ≥2 on Part I question 3 of the Unified Parkinson's Disease Rating Scale (UPDRS). Pramipexole was taken at 0.125-1.0 mg tid, as optimized during the first 5 weeks. At endpoint, UPDRS was re-administered, including Part II (activities of daily living) and Part III (motor examination).

Results: Among an initial 144 pramipexole and 152 placebo recipients, 89.9% received concomitant therapy, including 74.7% on levodopa. Analyzable UPDRS data were provided by 138 (95.8%) and 148 (97.4%), respectively. At baseline, mean UPDRS Part II score was 11.9 vs 11.5; 26.5 vs 25.1 on Part III. Mean change, adjusted for baseline and country (LOCF for 20 pramipexole and 19 placebo recipients [13.9% and 12.5%] who discontinued prematurely), was -

2.4 vs -1.2 on Part II (P=.0030, ANCOVA); -4.4 vs -2.2 on Part III (P=.0034). For Parts II+III, adjusted mean change was -6.8 vs -3.4 (P=.0007).

Conclusions: In activities of daily living (UPDRS Part II) and in motor function (UPDRS Part III), depressed PD patients receiving 12 weeks of pramipexole showed significant improvement, ~double that for placebo. Although this population was already receiving antiparkinsonian medication and had stable motor function at baseline, modest improvement in motor function indicates there is further potential to ameliorate symptoms.

Mo-250

Apomorphine effect on pain threshold in Parkinson's disease: A clinical and positron emission tomography study

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Objective: The aim of this randomized, double blind study was to compare the effect of a dopamine agonist (apomorphine) versus placebo on pain thresholds (subjective and objective) and on cerebral activity (Positron Emission Tomography, PET) during experimental nociceptive stimulation in two groups of patients with Parkinson's disease (PD): with and without neuropathic pain.

Background: PD is a painful disorder. Previous studies have shown that levodopa administration raised pain threshold and reduced pain-induced cerebral activations of PD patients compared with healthy subjects. However, in the central nervous system, levodopa is not only converted in dopamine but also in norepinephrine and noradrenergic system is involved in nociception.

Methods: Subjective pain threshold (using thermal stimulation, thermotest) and objective pain threshold (assessed by the nociceptive flexion reflex) were determined during two randomized conditions: after a subcutaneous injection of apomorphine and after a subcutaneous injection of a placebo. $H_2{}^{15}O$ PET analysis of regional cerebral blood flow were performed on patients while they received alternate noxious and innocuous thermal stimulations during the two conditions.

Results: 25 PD patients participated to this study (12 painful and 13 non painful patients). Subjective and objective nociceptive thresholds were not significantly modified by administration of apomorphine (45.5 $\pm$ 2.7°C and 9.4 $\pm$ 3.7 mA, respectively) in comparison with placebo injection (45.6 $\pm$ 2.8°C and 10.7 $\pm$ 3.6 mA, respectively) in 25 PD patients. In addition, apomorphine did not modify pain thresholds in any groups of PD patients. Neuroimaging results showed that noxious thermal stimulations induced activations of cerebral areas classically involved in pain processing network. Administration of apomorphine did not modify the pain activation profile in non painful nor painful PD patients ($p \leq 0.01$; $k \geq 50$; z-score ≥ 3).

Conclusions: This study shows that, although levodopa reverses abnormal pain processing in PD, administration of apomorphine has no effect. We suggest that, in PD, noradrenergic system could be involved in nociceptive processing and dopaminergic system could only have a minor role.

Mo-251

Neuroprotective effect of glucocorticoids in parkinsonism is mediated by the expression of glucocorticoid receptor in dopaminergic neurons

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Objective: To evaluate the role of glucocorticoids (GCs) and glucocoticoid receptor (GR), in survival of dopaminergic neurons in Parkinson's disease (PD) using different experimental models.

Background: GCs acting through GR have wide variety of functions in brain. Their actions on neuronal survival are complex; both protective and deleterious effects have been reported. These contrasting effects of GR may be direct on neurons or through modulation of inflammatory responses of glial cells. GCs and GR are known to regulate all phases of the inflammatory responses, by controlling the expression of anti- and pro-inflammatory cytokines. Their role in neuronal survival in pathogenesis of PD is not well characterized.

Methods: Tyrosine hydroxylase positive (TH+) neurons, from embryonic rat mesencephalic cell cultures intoxicated with MPP+, were quantified after treatment with or without GCs and RU486, inhibitor of GR. The effect of corticosterone treatment was analyzed in mice injected with MPTP (30 mg/Kg, for 5 days) and the number of TH+ neurons in Substantia Nigra pars compacta (SNpc) quantified. In monkeys, sacrificed two years after chronic MPTP treatment, the proportion of TH+ neurons that express GR was analyzed by fluorescence microscopy at SNpc level.

Results: 1) We observed a significant neuroprotective effect of GCs in vivo (in mice injected with MPTP), and in vitro (mesencephalic cultures treated with MPP+). 2) Importantly, in cell culture the neuroprotective effect of GCs was still present after treatment with antimitotics that inhibit microglía or/and astroglia. 3) The quantitative analysis of TH+ neurons and its relation with the expression of GR in MPTP-monkey brain sections at the SNpc level indicated that the proportion of surviving TH positive neurons expressing GR was significantly higher in monkeys that presented the highest dopaminergic cells loss.

Conclusions: These results demonstrate that GR could have a neuroprotective effect directly on dopaminergic neurons and may be involved in neuronal survival in parkinsonism, suggesting new potential therapies for PD.

Mo-252

Continuous subcutaneous apomorphine infusion (CSAI) in advanced Parkinson's disease: The west Australian experience

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Objective: To describe the patient characteristics and outcomes of a CSAI program for advanced PD and describe our experience in integrating CSAI with an existing DBS program.

Background: CSAI is an established treatment option for PD patients with refractory motor fluctuations and dyskinesias. While GPi-DBS has been available at our Centre for over a decade, our experience with CSAI has been limited and its role as an alternative or adjunctive treatment to DBS uncertain.

Methods: We reviewed our database and identified 19 patients (17M, aged 44-71y at treatment initiation, 16 with young-onset PD) over a 34-mth period since April 2006.

Results: All patients were managed by experienced movement disorders specialists, and failed treatment with L-dopa, DAs and COMT inhibitors. Most were referred for surgery but were offered a trial of CSAI as an alternative or temporary option while awaiting surgery. Four had undergone GPi-DBS with a sustained anti-dyskinetic effect but inadequate anti-PD effect. Oral DAs were ceased at initiation and L-dopa dose reduced during CSAI dose titration. Eight patients achieved a reasonable 'ON' state but stopped CSAI due to severe rhinorrhea (1), unrelated medical conditions or death (3), psychosocial problems (4). Eleven patients were successfully managed with CSAI for a minimum of 6 months achieving a near-continuous waking 'ON' state. Three stopped treatment and underwent GPi-DBS because of dykinesias. Three used CSAI alone with quality continuous 'ON' times and regained independent mobility. Five who needed ongoing oral therapy achieved a good reduction in 'OFF' periods with a 50% drop in L-dopa dose. Overall, UPDRS motor scores dropped 25-50% by 6-8 months of CSAI. Functional gains included near-normal gait pattern, independence in ADLs, and restoration of continence in two cases. Side-effects reported were nausea, mild orthostatic hypotension and rhinorrhea.

Conclusions: Our results confirm the efficacy of CSAI in advanced PD, with marked improvements in 'ON'-time and functional gains. Though patients with marked dyskinesia can be successfully treated with CSAI, GPi-DBS was still necessary in some patients. Due to its relative safety a trial of CSAI should be offered to all patients referred for DBS.

Mo-253

Metabolic profils of the striatum and the NAc detected by proton magnetic resonance spectroscopy (^{1}H MRS) in vivo in the MPTP-intoxicated mouse, before and after levodopa

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Objective: In this study, we assessed the amount of glutamate (Glu), glutamine (Gln) and GABA in structures where dopaminergic (DA) neurons project (dorsal striatum and nucleus accumbens, NAc) after DA denervation and DA replacement.

Background: Parkinson's disease (PD) is characterized by preferential degeneration of DA neurons of the SNc which project to the dorsal striatum, involved in the motor system. In parallel, DA neurons of the mesocorticolimbic system (DA pathway from the ventral tegmental area, VTA to the NAc) also degenerate which could explain psychiatric disorders observed in PD.

Methods: In vivo MRS was performed at 9.4T on control mice (n=16) and MPTP-lesioned mice (n=16). Spectra were acquired in a voxel (8μL) centered in the dorsal striatum, and in the NAc (1.56μL). 3 days after basal MRS acquisitions, new spectra were acquired in striatum and NAc after levodopa (200 mg/kg). The absolute concentrations of metabolites were determined. Tyrosine hydroxylase (TH) immunohistochemistry in SNc and VTA was performed.

Results: Glu, Gln and GABA amounts obtained from NMR spectra acquired in basal state were significantly increased in dorsal striatum of MPTP mice (Glu: 20.2±0.8mM vs 12.9±1.1mM, $p<0.001$; Gln: 5.4±1.6mM vs 2.0±0.6mM, $p<0.05$; GABA: 3.7±0.8mM vs 1.6±0.2mM, $p<0.05$). Levodopa restored the amount of metabolites identical to those obtained in controls. No change was described in the NAc after MPTP. MPTP led to a significant decrease (72%) in the mean number of TH-immunoreactive neurons in the SNpc compared with control values (104±15 vs 370±51; $p<0.001$). The decrease of the mean number of TH-immunoreactive neurons in the VTA was 43% (88±17 vs 50±10, $p<0.05$). Levodopa administration had not impact on the number of TH-immunoreactive neurons in the SNpc of controls and of MPTP mice. Also in the VTA, levodopa had not impact on the number of TH-immunoreactive neurons.

Conclusions: DA denervation around 70-80% in the SNc induces a significant increase of levels of main metabolites of the dorsal striatum. However, a partial DA denervation ("45%) of VTA doesn't change metabolites levels in NAc. Thus psychiatric disorders in PD could be explained by a selective lesion of prefrontal cortex/amygdale and/or a more severe DA denervation of VTA.

Mo-254

Blockade of the translocation and activation of c-Jun N-terminal kinase 3 (JNK3) attenuates dopamine neuronal damage in mouse model of Parkinson's disease

S.-D. Chen, J. Pan, Q. Xiao, Z.-Q. Wang, Z. Hong (Shanghai, China)

Objective: To investigate whether blockade of the translocation and activation of c-Jun N-terminal kinase 3 (JNK3) attenuates dopaminergic neuronal damage in mouse model of Parkinson's disease (PD).

Background: Increasing evidence suggests that c-Jun N-terminal kinase (JNK) is an important kinase mediating neuronal death in PD model induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). JNK3, the only neural-specific isoform, may play an important role in mediating the neurotoxic effects of MPTP in dopaminergic neuronal injury.

Methods: The levels of phospho-JNK3 were measured at the various time points of occurrence of MPTP-induced lesions. The antioxidant *N*-acetylcysteine (NAC), the *N*-methyl-d-aspartate (NMDA) receptor antagonist ketamine, and the α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate (KA) receptor antagonist 6,7-dinitroquinoxaline-2,3(1H,4H)-dione (DNQX) were administered to the mice 30 min after each of the 4 MPTP injections.

Results: During MPTP intoxication, 2 peaks of JNK3 activation appeared at 8 h and 24 h. NAC clearly inhibited JNK3 activation during the early intoxication, whereas ketamine preferably attenuated JNK3 activation during the latter intoxication. DNQX had no significant effects on JNK3 activation during intoxication. Consequently, reactive oxygen species (ROS) and the NMDA receptor were closely associated with JNK3 activation following MPTP intoxication. NAC and ketamine exerted a preventive effect against MPTP-induced loss of tyrosine hydroxylase-positive neurons and suppressed the nuclear translocation of JNK3.

Conclusions: NAC and ketamine can prevent MPTP-induced dopaminergic neuronal death by suppressing JNK activation.

Mo-255

Identification of glial-cell-line-derived neurotrophic factor-regulated proteins of striatum in mouse model of Parkinson's disease

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Objective: To investigate proteome changes in the parkinsonian mouse striatum after Glial-cell-line-derived neurotrophic factor (GDNF) challenge.

Background: GDNF is a potent survival factor for dopaminergic (DA) neurons, hence serves as a therapeutic candidate for the treatment of Parkinson's disease (PD). However, despite the potential clinical and physiological importance of GDNF, its mechanism of action is unclear.

Methods: We employed a state-of-the-art proteomic technique, DIGE (acronym for Difference in two-dimensional gel electrophoresis), along with mass spectrometry and bioinformatics tool of Database for Annotation, Visualization and Integrated Discovery (DAVID).

Results: 51 unique differentially expressed proteins were successfully identified, which were found either up-regulated and/or down-regulated at the two time points 4 h and 72 h compared with the control. Proteins involved in cell proliferation, differentiation and apoptosis formed the largest part of the proteins regulated under GDNF. Furthermore, the aberrant expressions of heat shock proteins and mitochondria-associated proteins were noticeable. Moreover, mtHSP70 and Hsc71, whose relative levels increased significantly in GDNF-treated striatum, was further evaluated with Western blot and RT-PCR, demonstrating a good agreement with quantitative proteomic data.

Conclusions: These data may provide some clues for understanding the mechanisms by which GDNF-promoted survival of DA neurons.

Mo-256

Brain metabotropic glutamate receptor 5 in Parkinson's disease patients with motor complications

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Objective: To investigate metabotropic glutamate receptors type 5 (mGluR5) receptors changes the brain of Parkinson's disease (PD) patients with motors complications.

Background: Glutamatergic transmission overactivity has been implicated in PD and levodopa-induced dyskinesias. Striatal mGluR5 are abundant and provide specific targets to decrease glutamatergic activity.

Methods: We investigated mGluR5 receptors in 11 normal and 14 PD patients in relation to motor complications (dyskinesias and wearing-off) associated with treatment with levodopa the gold standard therapy. Binding autoradiography was performed with [^{3}H]ABP688, a high affinity and selective mGluR5 antagonist.

Results: In normal humans, high striatal and lower globus pallidus [^{3}H]ABP688 specific binding was measured with very low non-specific binding. [^{3}H]ABP688 specific binding was higher in caudate nucleus than putamen of normal controls. This binding was higher in external (GPe) than internal (GPi) globus pallidus of controls. A ventral/dorsal gradient was measured in caudate nucleus, putamen and external globus pallidus with higher ventral values whereas no lateral/medial gradient was found in putamen. No difference of [^{3}H]ABP688 specific binding was obtained in caudate, putamen, GPe and GPi of all PD patients as compared to control subjects. PD patients subdivided according to presence or absence of motor complications showed differences compared to controls with lower [^{3}H]ABP688 specific binding in putamen of PD patients without motor complications compared to controls. PD patients with motor complications had higher [^{3}H]ABP688 specific binding compared to those without motor complications and controls in putamen, GPe and GPi. Both dyskinesias and wearing-off, led to increased [^{3}H]ABP688 specific binding in GPe and GPi; higher increases were observed in putamen of patients with wearing-off compared to dyskinesia. Putamen dorso-lateral, dorso-medial, ventro-lateral and ventro-medial sub regions as well as dorsal and ventral GPe showed similar changes of [^{3}H]ABP688 specific binding due to motor complications.

Conclusions: Our results are the first to show in human PD with dyskinesias and wearing-off elevation of striatal mGluR5 [^{3}H]ABP688 specific binding.

Mo-257

Effects of ropinirole prolonged-release on sleep disturbances in Parkinson's disease

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Objective: To evaluate the effects of ropinirole prolonged-release (RPR) in comparison with ropinirole immediate-release (RIR) on daytime sleepiness and sleep disturbances in Parkinson's disease (PD).

Background: Some of sleep and wakefulness disturbances associated with PD are supposedly related to imbalance in dopamine neurotransmission and thus might be improved by stable plasma levels of a dopamine agonist: REM-sleep behavior disorder (RBD), restless legs syndrome, periodic limb movements in sleep (PLMS), night akinesia and excessive daytime sleepiness with imperative sleep attacks (ISA).

Methods: Five PD patients (1 f, 4 m, age 55-69 yrs, PD duration 6-14 yrs) on a stable dose of RIR were switched to the closest-possible dose of RPR. The following sleep related measures were investigated on RIR and 6 weeks after switching on RPR therapy: Epworth sleepiness scale (ESS), PD sleep scale (PDSS), Pittsburgh Sleep Quality Index (PSQI), and RBD screening questionnaire (RBDSQ). We asked additional questions regarding the occurrence of ISA and sleepiness within one hour after ropinirole dose (1HS). Actigraphy was used as an objective measure of PLMS index–average number of nighttime periodic leg movements per one hour (PLMI).

Results: ISA were reported in 4 and 1HS in 3 patients on RIR. After switching to RPR there were none reports of ISA or 1HS. In parallel, ESS score decreased in all patients (by 1 to 9 points). There was a marked drop in PLMI scores in 2 patients: 56/4 and 26/5 (on RIR/on RPR). Other patients' PLMI scores did not change remarkably. PDSS score improved by 10 and 20 points in two out of five patients and remained virtually unchanged in the others. PSQI and RBDSQ scores did not change remarkably.

Conclusions: These pilot data suggest beneficial effects of RPR compared to RIR on symptoms of excessive daytime sleepiness in PD. RPR may improve PLMS and sleep quality in some patients as well. These observations warrant further investigation. Study support: IGA NR9220, MSM 0021620849

Mo-258

Fluoxetine does not impair motor function in patients with Parkinson's disease

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Objective: To investigate motor performances of patients with Parkinson's disease (PD) treated with fluoxetine (Flu) and to assess a possible correlation between motor performance scores and serum concentrations of Flu and its active metabolite norfluoxetine (NORFlu).

Background: Depression in PD may be accompanied with anxiety, cognitive impairment and may reduce effectiveness of antiparkinson's therapy (Kostic et al, 1995,2003). Some authors confirmed that extrapiramidal side effects of Flu were related to the exacerbation of PD's disability (Leo,1996). On the contrary, it was reported that Flu did not increase PD's disability either in retrospective (Caley et al,1992) or in prospective studies (Dell'Agnello et al, 2001).

Methods: In this prospective, controlled, open-label study, 18 patients with PD and mild depression ($10 \leq$HDRS≤ 23) without dementia ($25 \leq$MMSE) were treated with Flu. Plasma concentrations of Flu and its active metabolite NORFlu were correlated with the results of selected motor performance scores in PD patients. Estimations of motor function and blood sampling for plasma levels of Flu/NORFlu were carried out before Flu medication and 4, 6 and 8 hours after the administration of the drug (days 1 and 5). All tests were repeated in the same patients on days 11 and 18, and in 9 out of 18 patients on days 50 and 80 (droput rate of 50%). Motor functions were estimated with the Unified Parkinson Disease Rating Scale (UPDRS), as well as with the Finger Tapping Test (FTT) and Purdue Pegboard Test (PPT). Severity of PD was evaluated using standard tests for PD (HY, ADL, Hamilton Rating Scale for Depression-HDRS, Mini Mental State Examination-MMSE).

Results: As expected, steady-state for Flu/NORFlu was reached after 18 days of treatment. Such a plateau correlated with significant improvements in both scores of depression and Parkinson's disability (HDRS, UPDRS and ADL, respectively) while HY and MMSE scores did not change significantly. In addition, FTT and PPT scores also increased until day 18, with further slight fluctuations around the plateau. According to the factor analysis, optimal motor performances correlated with Flu concentrations of 60-110 micro g/L.

Conclusions: Flu (20 mg/day) significantly reduced depression in PD patients while it did not impair their motor performances.

Mo-259

Effects of the novel opioid peptide MMP-2200 in rat models of Parkinson's disease

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Objective: In the present study, we have demonstrated that systemic administration of a novel glycosylated opioid peptide MMP-2200 has potent effects in two standard models of Parkinson's disease (PD).

Background: In PD, the consequence of dopaminergic denervation is an imbalance in the activity of the Go and NoGo pathways, which includes important changes in opioid peptides.

Methods: The standard PD models utilized were: 1.) amphetamine-induced rotations in the hemi-parkinsonian 6-hydroxydopamine (6-OHDA)-treated rat and 2.) locomotion in the reserpine-treated rat.

Results: 1.) MMP-2200 reduced amphetamine-induced rotations in hemi-parkinsonian rats. This effect is opioid receptor mediated, since the non-selective opioid receptor antagonist naloxone blocked the effect. The selective delta-opioid receptor antagonist naltrindole only partially blocked the effect of MMP-2200. MMP-2200 alone did not induce rotations. 2.) In reserpinized animals, profound akinesia was induced that was readily reversed with apomorphine. There was a prominent overshoot compared to non-reserpinized animals that received apomorphine, reflecting the well described phenomenon of

dopamine supersensitivity indicating that apomorphine had not only reversed akinesia but induced hyper-kinesia. The opioid peptide MMP-2200 blocked the apomorphine-induced hyper-kinesia. This effect of MMP-2200 was reversed by pre-administration of naloxone. MMP-2200 had absolutely no effect in reversing the reserpine-induced akinesia nor did it affect locomotion in control animals.

Conclusions: Taken together the results from these two models are consistent with MMP-2200 having a potent effect on movements related to dopaminergic hyper-stimulation following striatal dopamine depletion. Based on prior studies of non-peptide delta opioid agonists we had anticipated finding pro-kinetic effects of inducing rotation in the first model and reversal of akinesia in the second model. Instead we found potent effects that are best explained by a reduction in the downstream effects of direct and indirect dopamine agonists in these models. These results suggest that there may be substantial differences between peptide and non-peptide opioid agonists and indicate that the compound under study MMP-2200 could have utility as an anti-dyskinetic rather than a pro-kinetic agent in PD.

Mo-260

The effect of dopaminergic medication on tests of deftness compared to bradykinesia and rigidity in Parkinson's disease

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Objective: We sought to verify previous reports on deftness by performing more objective tasks of deftness, and this time, in the ON and OFF medication state in PD patients.

Background: At least one report suggested that limb kinetic apraxia (deftness) was independent of bradykinesia and rigidity in PD and may not respond to dopaminergic medications. Quencer et al (2007) had treated PD patients and healthy controls perform a coin rotation task as a measure of deftness, and a finger tapping task as a measure of bradykinesia. Because the PD subject's speed of finger tapping was largely comparable yet their ability to manipulate and rotate the coin was slower compared to the healthy controls, they suggested that deftness was independent of bradykinesia and rigidity and may not respond to dopaminergic medications.

Methods: 11 PD patients and 10 healthy age matched controls were included. The bradykinesia items in the UPDRS and the Large Box and Block (LBB) tests were used to measure bradykinesia. The Small Box and Block Test (SBB), Small Coin Rotation Task (SCR), and a Small Lock Rotation Tasks (SLR) were used to measure deftness in the ON and OFF dopaminergic state.

Results: Our PD patients had a mean age of 67.6±9.0 years, while our controls had a mean age of 68.2±8.3 years. Analyses using the Wilcoxon paired t-test showed a significant difference in the OFF and ON states for all measures (LBB, SBB, SLR and the bradykinesia and rigidity items of the UPDRS). Furthermore, our PD cohort's scores were comparable to controls on tests of bradykinesia and deftness (SLR, SBB and LBB) in the ON state, but they performed worse than controls in the OFF state.

Conclusions: The improvement in deftness, bradykinesia and rigidity in the ON state among our PD cohorts (and their comparable performance in the ON but not OFF state compared to healthy controls) suggests uniform response of these motor features to dopaminergic therapy in PD.

Mo-419

The effect of high dose orally disintegrating tablet selegiline (Zelapar®; ODT-S), a selective monoamine oxidase B inhibitor, on monoamine oxidase A and synaptic dopamine re-uptake in the human brain

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Objective: To investigate if the monoamine oxidase B (MAO B) inhibitor ODT-S given at high daily doses 1) inhibits monoamine oxidase A (MAO A) in the human brain measured by positron emission tomography (PET) scans of [^{11}C]clorgyline binding and 2) increases dopamine by inhibiting the synaptic dopamine transporter (DAT) measured by PET scans of [^{11}C]cocaine binding.

Background: Up to 70% of Parkinson's patients experience non motor symptoms, including depression, fatigue, and poor concentration. ODT-S, approved as adjunctive treatment to levodopa in Parkinson's disease, 1) specifically inhibits MAO B at low doses 2) bypasses first-pass metabolism (a significant portion is absorbed buccally) and 3) increases bioavailability of selegiline while decreasing metabolites (Clarke 2003). An alternate formulation of high dose selegiline (selegiline transdermal system) 1) inhibits both MAO A and B in the brain 2) is approved for the treatment of depression and 3) has been shown to be particularly effective in improving these same non motor symptoms in major depressive disorder (Robinson 2008). Previous PET studies showed no MAO A inhibition with conventional selegiline (Eldepryl). We hypothesize that ODT-S will inhibit MAO A at high doses.

Methods: This study is a phase I, open-label, non-randomized, single center, proof-of-concept study of 10, 5, and 2.5 mg/day ODT-S in healthy volunteers (n= 6/dose; 5 and 2.5 mg in progress). All subjects undergo baseline and post-28 day ODT-S dosing [^{11}C]clorgyline PET scans; the first three 10 mg subjects underwent additional [^{11}C]cocaine PET scans.

Results: The mean MAO A inhibition after 10 mg ODT-S for 28 days was 36.7 ± 19.9% (range 10.6 to 70.1%) averaged over all regions of interest in the brains of six healthy human subjects. The mean inhibition of DAT was 12.0 + 5.2% (range 6-15%) in the striatum of a subgroup of three 10 mg ODT-S subjects. ODT-S was well tolerated.

Conclusions: These data show that high dose ODT-S inhibits MAO A in the brain in addition to its known inhibition of MAO B. Further studies are warranted to determine if ODT-S would be an effective treatment of non-motor symptoms in addition to motor symptoms in Parkinson's patients.

Tu-250

The histamine H2 receptor antagonist, famotidine, reduces L-dopa-induced motor complications in the MPTP-lesioned macaque model of Parkinson's disease

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Objective: To assess the ability of the H2 receptor antagonist, famotidine, to modify the actions of L-DOPA in the MPTP-lesioned macaque model of PD.

Background: Long-term L-DOPA therapy in Parkinson's disease (PD) results in motor complications including dyskinesia and shortening of duration of anti-parkinsonian action, 'wearing-off'. We have previously shown that histamine H3 receptor agonists can reduce L-DOPA-induced motor complications in MPTP-lesioned, parkinsonian primates (Gomez-Ramirez *et al*, 2006); an effect that may be due, in part, to a reduction in histamine release, and consequent reduced stimulation of post-synaptic H2 receptor sites.

Methods: Six cynomolgus monkeys (*Macaca fascicularis*) were rendered parkinsonian by repeated administration of MPTP. Animals were then treated with L-DOPA (15 mg/kg p.o. bid) for 3 months, a regime that induces stable dyskinesia and wearing-off. Following this, L-DOPA was co-administered (s.c.), with either vehicle or famotidine (1-30mg/kg, p.o.) and behaviour assessed for 6h via computerised activity monitors and *post hoc* analysis of DVD recordings by an experienced rater, blinded to treatment.

Results: Co-administration of L-DOPA with famotidine (1 mg/kg, p.o.) increased the duration of action of L-DOPA by 36%, (L-DOPA alone *cf.* L-DOPA/famotidine, 102 ± 23 min *cf.* 138 ± 40 min. *P<0.05, ANOVA). Moreover, famotidine (1 mg/kg) reduced levodopa-induced chorea by 21%. At no time did famotidine (at any dose) reduce the anti-parkinsonian efficacy of L-DOPA.

Conclusions: Histamine H2 antagonism increase the duration of anti-parkinsonian action of L-DOPA and decreases L-DOPA-induced dyskinesia in MPTP-lesioned primates.

Tu-251

DJ-1 mediated control of cell death is dependent of its proteolysis

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Objective: The objective of this study was to analize the mechanism by which DJ-1 modulates cell death as well as its influence on p53 pathway at both transcriptional and post transcriptional levels.

Background: Autosomal recessive genetic cases of Parkinson's disease are usually characterized by early onset and aggressive evolution. Several gene candidates have been identified which account for these familial cases, among which DJ-1, a cytosolic oxidative stress regulator. The mechanisms by which mutations on DJ-1 alter its function leading to PD-related pathology are poorly understood.

Methods: The effect of either wild-type or mutated DJ-1 in the control of cell death was assessed in various cell systems including neuronal dopaminergic cells such as SH-SY5Y neuroblastoma cells and mouse embryonic fibroblasts depleted or not in DJ-1 and p53. We have used a various set of techniques that allowing the quantification of cell death processes in vitro. These include caspase-3 determination, western blot and mRNA analysis of key apoptotic pathway players.

Results: Here we show that overexpression of DJ-1 elicits an anti-apoptotic phenotype by negatively regulating the p53-dependent cell death pathway at both transcriptional and post-transcriptional levels. The inverse phenotype is observed when DJ-1 is depleted both in vitro and in vivo. We show that DJ-1 is proteolytically processed by caspase-6 to generate a physiological product harboring its neuroprotective properties. Of most importance, a pathogenic DJ-1 mutation abolishes both DJ-1 cleavage and associated protective phenotype.

Conclusions: Overall, our data show that DJ-1 triggers a p53-dependent antiapoptotic phenotype and that this function is proteolytically regulated by caspase-6 and impaired by pathogenic mutations.

Tu-253

Whether or not amantadine sulfate does prevent to disease progression in Parkinson's disease?

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Objective: To evaluate the AH efficacy in our out patients with PD.

Background: Amantadine hydrocloride AH is one of a NMDA receptor antagonist, which widely uses as a drug for reducing dyskinesia in Parkinson's disease. However, we usually use AH as an initial drug for controlling PD in our out patients. In our observation, our out patients with PD show less frequent and mild degree of motor fluctuations and dyskinesias, so that we think that AH would contribute their disease progression in slowing. Therefore, we retrospectively analyzed our patients with PD on medication with AH to clarify the efficacy of AH.

Methods: 212 cases of PD (female 111, male 101), who came our clinic from 01 Sept. 2009 to 30 Oct. 2009, diagnosed by UK bank PD criteria were included in this study. They were divided into two groups by prescribed AH or not. We checked them in their clinical status such as motor fluctuations, dyskinesia, cognitive impairment and hallucinations.

Results: There were no differences in age, onset of age and duration of illness. In AH group, apparent wearing-off phenomenon are lesser frequent and off severity is milder ($p<0.001$) than no-AH groups. Diskinesia is also lesser frequent and milder degree in AH group ($p<0.01$). There are no different in cognitive function in both groups, however, apparent hallucination is in frequent in AH group.

Conclusions: In our retrospective analysis, AH might prevent the disease progression and overt hallucination in PD.

Tu-254

Factors affecting the time to levodopa-induced dyskinesias

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Objective: To determine which factors affect the time to the appearance of levodopa-induced dyskinesias (LID).

Background: Levodopa-induced dyskinesias are commonly observed during long-term treatment of patients with Parkinson's disease (PD). Several factors have been found to be associated with their occurrence. While the cumulative prevalence of LID increases beginning from the time of treatment onset, the relative impact of other factors affecting the latency to their appearance has not yet been defined.

Methods: A hundred and fifty-five consecutive patients with PD treated with levodopa were included. Patients who experience dyskinesia were included if the time of their onset was known. Demographic and clinical parameters including age of disease onset, gender, smoking habits and other data were obtained. The Student t test and the X^2 test were performed to determine the differences between groups with and without LID. The relationship between possible factors and the time of LID onset was explored using the Kaplan Meier method and the Cox multivariate regression model while controlling for the confounding effects of gender, age of disease onset, time to initiation of levodopa treatment and history of smoking.

Results: The prevalence of LID in the sample was 57.4%. Patients with LID were younger at disease onset ($p<0.00005$) and the time from diagnosis to levodopa treatment was longer ($p=0.046$)**;** however, disease duration prior to LID onset and age had no effect on LID appearance In a multivariate survival analysis the time to LID onset was affected by gender and smoking habits. Female gender (HR=0.599, CI=0.375-0.958, p=0.033) as well as past and present history of smoking (HR=2.491, CI=1.414-4.388, p=0.002) were found to be associated with a shorter time to the onset of LID, but smoking pack years was negatively correlated (HR=0.979, CI=0.960-0.998, p=0.028) with time to LID, that is the more cigarettes the patients had smoked, the later LID appeared.

Conclusions: While female gender is associated with a shorter latency to LID onset, smoking affects the latency to LID dichotomously- a history of smoking hastens their appearance while the more the patient smokes the onset of LID is delayed.

Tu-255

The relationship between daytime sleepiness associated with non-ergot dopamine agonist therapy and renal function in Parkinson's disease

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Objective: To consider the influence of renal dysfunction on emergence of excessive daytime sleepiness (EDS) associated with non-ergot dopamine agonist therapy in Parkinson's disease (PD).

Methods: Eighty-eight patients treated with either non-ergot DA agonist (ropinirole or pramipexole) in combination with levodopa/DCI or non-ergot DA agonist (ropinirole or pramipexole) alone were recruited for the study. The assessment battery included the UPDRS score, modified Hoehn & Yahr scale, and Epworth sleepiness scale (ESS). An ESS score of 10 or greater was defined as EDS. Historical data included age at symptomatic onset, and presence or absence of stereotactic neurosurgery. Estimated GFR (Egfr) was calculated by an equation based on the serum creatinine. Participants with an Egfr less than 60 Ml/min/1.73 m^2 were determined as chronic kidney disease (CKD). The relationship between EDS and gathered data was examined using multiple logistic regression analysis and Spearmen correlation analysis.

Results: In overall sample, older age (≥70 yrs) and presence of CKD were the predictors for expression of EDS ($p = 0.040$ and 0.039, respectively). Additional analyses demonstrated that a negative correlation between ESS score and eGFR was only observed for PD patients treated with pramipexole ($rs = -0.705$, $p < 0.001$).

Conclusions: Whereas ropinirole is metabolized extensively by the hepatic microsomal enzyme system and is excreted in the urine, pramipexole undergoes minimal hepatic biotransformation and is excreted virtually unchanged in the urine. Taken together, results of our study suggest that CKD may be a risk factor of EDS as a drug toxicity in PD patients treated with pramipexole.

Tu-256

The ability of UWA-0101 to enhance anti-parkinsonian actions of L-dopa in the MPTP-lesioned primate may result from mixed, though selective, inhibition of dopamine and serotonin re-uptake

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Objective: To correlate the receptor and transporter binding profiles of UWA-0101 ((RS)-2-(1,3-benzodioxol-5-yl)-1-cyclopropyl-N-methylethanaminium chloride) and three structurally related compounds, UWA-0001, UWA-0104 and MDMA, with their ability to enhance anti-parkinsonian actions of L-DOPA in the MPTP-lesioned primate model of Parkinson's disease.

Background: The benefit of L-DOPA therapy in Parkinson's disease (PD) patients is compromised by motor fluctuations, particularly a progressive shortening of the duration for which L-DOPA alleviates symptoms, i.e. 'wearing-off'. UWA-0101 is a novel molecule with purported ability to enhance monoaminergic transmission and potential to reduce wearing-off.

Methods: Motor complications were induced in MPTP-lesioned marmosets (n=5-6) by daily L-DOPA treatment (Prolopa, 15 mg/kg, p.o.) for 6 months. L-DOPA with benserazide (15/3.75 mg/kg, s.c.) was co-administered with either vehicle, UWA-0101, UWA-001, UWA-104 or MDMA (1 or 3 mg/kg, s.c.). Behaviour, including parkinsonian disability and quality of 'on-time', was assessed over a 6 h period via analysis of DVD recordings by a neurologist blinded to treatment. The ability of each analogue to inhibit the dopamine (DAT), serotonin (SERT) and noradrenaline (NET) transporter was assessed, as was ability to bind to a range of 5-HT receptors.

Results: UWA-0101 (3 mg/kg) dose-dependently increased (by 133%) L-DOPA-induced duration of good quality anti-parkinsonian action i.e. 'on-time' during which dyskinesia was not disabling, compared to that produced by L-DOPA alone (veh *cf.* 3 mg/kg, 54 min ± 17 min *cf.* 126 ± 27 min, $P<0.05$). UWA-0001, UWA-0104 and MDMA had no effect on L-DOPA actions. UWA-0101 inhibited DAT (IC_{50}, 3.6μM) and SERT (2.3μM) with low or no activity at NET and 5-HT_{2A} sites. All other compounds exhibited moderate to high affinity for NET and 5-HT_{2A}.

Conclusions: The actions of UWA-0101 to increase the anti-parkinsonian benefit of L-DOPA may relate to more selective binding to dopamine and serotonin reuptake sites. Mixed DAT/ SERT inhibitors may be of benefit in the treatment of motor complications in PD.

Tu-257

PYM50028, an orally active neurotrophic factor inducer, is neurorestorative following MPTP-administration in a mouse model of Parkinson's disease

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Objective: This study investigated the ability of PYM50028 to reverse dopaminergic loss after MPTP administration in mice.

Background: Oral administration of PYM50028 attenuates dopaminergic loss in MPTP-mice, a model of Parkinson's disease (PD; Visanji *et al*. 2008). However, the effect of PYM50028 on dopaminergic loss when administered several days after MPTP remains unknown.

Methods: 10 week old mice received MPTP (25 mg/kg, i.p.) for 5 days (D1-5). From day 2 (D2) or 7 days after MPTP administration (D12), mice received PYM50028 (10 mg/kg/day, p.o.) until day 72 (D72). On D72, striatal dopamine transporter (DAT) and dopamine (DA) levels and numbers of tyrosine hydroxylase positive (TH^{+ve}) nigral cells were assessed. Three additional groups of mice were used; unlesioned mice receiving vehicle (D2-72; control mice) MPTP-lesioned mice receiving vehicle (D2-72) and unlesioned mice receiving PYM50028 (D2-72). On D72, 2 h after PYM50028 administration, PYM50028 plasma and brain levels were measured. PYM50028 administration, DAT, DA and plasma PYM50028 measurements were performed as previously (Visanji *et al*. 2008). Nigral TH^{+ve} cell counts were assessed stereologically and brain PYM50028 levels were by LC-MS/MS.

Results: MPTP decreased DAT, DA and TH^{+ve} cell counts compared to control mice (veh-veh *cf.* MPTP-veh; DAT: 436 *cf.* 158 nCi/g***, DA: 337 *cf.* 118 pmol/mg***, TH: 2438 *cf.* 1525 cells*, ANOVA). In MPTP-lesioned mice receiving PYM50028 (D12) there was no difference in TH^{+ve} cells compared to control mice (veh-veh *cf.* MPTP-PYM50028 (D12); TH: 2438 *cf.* 1892 cells). Furthermore, PYM50028 increased DAT and DA (MPTP-veh *cf.* MPTP-PYM50028; DAT: 158 *cf.* 280 nCi/g**, DA: 118 *cf.* 208 pmol/mg*). Similar results were obtained in the PYM50028 (D2) group. In unlesioned mice PYM50028 did not alter DAT, DA or TH^{+ve} cell counts. Plasma and brain levels of PYM50028 were 413 ng/ml and 3734 ng/g (D2 group animals) and 439 ng/ml and 3894 ng/g (D12 group animals) respectively.

Conclusions: PYM50028 restores neurochemical correlates of dopaminergic nerve function when administered after a lesion has been established supporting the development of PYM50028 as a disease-modifying treatment for PD. Visanji *et al*. (2008). FASEB J. 22(7): 2488-97.

Tu-258

Antiparkinsonian activities of istradefylline (KW-6002), pramipexole and entacapone in MPTP-treated common marmosets

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Objective: To compare the antiparkinsonian activities of istradefylline with pramipexole and entacapone as both monotherapy and combination therapy with L-DOPA in MPTP-treated common marmosets.

Background: Istradefylline, a non-dopaminergic, first-in-class selective adenosine A_{2A} receptor antagonist, has been shown to have antiparkinsonian activity in rodents, in non-human primate models of Parkinson's disease (PD) as mono- or adjunct therapy with L-DOPA and in several clinical studies in PD patients treated with levodopa.

Methods: In the study with MPTP-treated common marmosets, istradefylline and entacapone were used at 10 mg/kg each and pramipexole was used at the range from 0.01 upto 0.1 mg/kg. In the case of levodopa adjunct therapy, L-DOPA was used at 2.5 or 5 mg/kg. Before and after drug administration, animals were evaluated their motor disability and locomotor activity.

Results: Istradefylline monotherapy induced significant antiparkinsonian activities, which improvement in motor disability was comparable to that of pramipexole at 0.03 mg/kg. Also istradefylline enhanced and prolonged antiparkinsonian activity of levodopa, which potency was almost same as that of pramepexole and superior to enatacopone in levodopa adjunct therapy. However, regarding the maximum antiparkinsonian effect in levodopa adjunct therapy defined to provide side effects, pramipexople showed higher activity than istradefylline. Dyskinesia was seen in 1/8 animals in istradefylline monotherapy and in 1-2/8 animals in adjunct therapy. In pramipexole monotherapy dyskinesia was seen in 1-4/8 animals and the incidence increased to 4/8 animals in adjunct therapy. Pramipexole induced

vomiting and/or stereotyped sideway moving in mono- and adjunct therapy. Dyskinesia was not observed in entacapone monotherapy but was observed in 2-4/8 animals in adjunct therapy. Animals given vehicle exhibited dyskinesia.

Conclusions: The present study has demonstrated that these three tested coumpunds can be ranked as pramipexole > istradefylline > entacapone in antiparkinsonian efficacy potency and however, pramipexole ≥ entacapone > istradefylline in regard with incidence rate of side effects such as dyskinesia and/or vomiting in adjunct therapy with levodopa. This suggested that istradefylline is superior to entacapone and may compatible to pramipexole in overall usefulness in parkinsonian therapy.

Tu-259

Longitudinal study of the levodopa motor response in Parkinson's disease: Effects of cognitive decline on motor function

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Objective: To trace out the pattern of progression of Parkinson's disease (PD) by repeated measurement of the short duration levodopa motor response.

Background: There is a limited amount of longitudinal research on the levodopa motor response in PD. This small study, which has been reported in its previous phases, now has data from a mean levodopa treatment period of almost 15 years.

Methods: Serial measurements of the short duration levodopa motor response in 34 patients have been performed in defined *off* states at three yearly intervals. Cognitive function was assessed by Folstein mini-mental state scoring. Seventeen patients survived to the latest assessment stage.

Results: *Off* phase motor function worsened at a yearly rate of 2.2% of the maximum disability score. The magnitude of the levodopa response is well preserved as the disease progresses, and patients who developed motor fluctuations maintained better *on* phase motor function than non-fluctuators ($P = 0.01$). Midline motor deficits do not actually become less responsive to levodopa, but the mean midline disability sub-score did worsen more quickly than the lateralised sub-score. Ten patients, of whom 5 survive, developed dementia. There was no difference in pre-treatment disability or initial levodopa response between demented and non-demented subjects. However, dementia was associated with worse *on* and *off* motor disability scores after 11.2 and 14.7 years ($P < 0.001$), and a smaller levodopa response magnitude after 14.7 years ($P = 0.008$). The plot of sequential scores shows the association between cognitive decline and accelerating increase in motor disability.

Conclusions: The levodopa motor response is quite durable. The advanced phase of PD, when cognitive function declines, may progress in an exponential rather than linear fashion.

Tu-260

Effect of combination therapy of IV amantadine and drug holiday in PD patients with motor fluctuations: Pharmacodynamic analysis of L-dopa response

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Objective: To verify therapeutic effects of IV amantadine during the drug holiday in patients with Parkinson's disease(PD) and motor fluctuation.

Background: Recently, IV amantadine has become available for clinical use. It has been used during the drug holiday to ameliorate parkinsonian off symptoms. Drug holiday intends to reduce "sensitization" induced by L-dopa treatment. Lack of dopaminergic stimulation, however, will increase glutamatergic activity in the striatum, which is associated with motor complications in PD. Thus, it is theoretically plausible to use IV amantadine-antiglutamatergic agent, during the drug holiday. We analyzed pharmacodynamic changes of L-dopa after iv amantadine treatment during the drug holiday in PD patients.

Methods: We studied 6 PD patients with motor fluctuations(age=54.0±9.7 years; duration=8.83±8.16 years). L-dopa response was obtained on both sides one day before and after a 6-day period of drug holiday by measuring finger tapping rate every 15 min after a single dose of L-dopa. During the drug holiday, 200mg of IV amantadine was infused twice daily. [^{18}F]FP-CIT PET scans were performed for each patient.

Results: L-dopa response before the drug holiday showed that baseline tapping rate was significantly lower on the more affected (p=0.027, 16.5 vs. 19.4). No significant differences were found in the duration, $Ta_{1/2}$($T_{1/2}$ on the ascending limb) and $Td_{1/2}$($T_{1/2}$ on the descending limb). L-dopa response after the treatment period showed significantly longer duration similarly on both sides than before treatment (p=0.001, 292.8±63.6 min vs. 213.1±47.2). Post-treatment $Td_{1/2}$ was significantly longer than pre-treatment $Td_{1/2}$ on both sides (p=0.002, 347.2±69.7 min vs 276.8±47.1). No significant differences were found in baseline tapping rates, latency to the onset, $Ta_{1/2}$, Tmax and Emax.

Conclusions: This preliminary study shows that the most significant effect of IV amantadine treatment during the drug holiday is the prolongation of $Td_{1/2}$ without significant changes in $Ta_{1/2}$ or Tmax. These findings suggest that the effect of the combination therapy is mediated by reversing the mechanisms, which cannot be explained by the presynaptic storage hypothesis, and could be either postsynaptic mechanism or central pharmacokinetics of L-dopa.

Tu-261

Priming for L-dopa-induced dyskinesia is inhibited by blockade of calcium-permeable AMPA receptors in the 6-OHDA-lesioned rat model of Parkinson's disease

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Objective: To characterise the role of calcium-permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA-Rs) in priming for L-DOPA-induced dyskinesia (LID) in Parkinson's disease.

Background: LID commonly complicates L-DOPA therapy of patients with Parkinson's disease. Overactivity of corticostriatal glutamatergic transmission is implicated in the pathophysiology of LID, and blockade of AMPA-Rs has been shown to reduce established dyskinesia. Increased phosphorylation of the GluR1 subunit in animal models suggests a role for calcium-permeable AMPA-Rs in the process of priming for LID.

Methods: Unilateral 6-hydroxydopamine (6-OHDA)-lesions were induced in rats by stereotactic injection (12.5 mcg) under isoflurane anaesthesia. After a 5 week recovery period, rats were treated daily in three groups: (1) vehicle; (2) L-DOPA/benserazide (6/15 mg/kg, i.p.); (3) L-DOPA/benserazide + IEM 1460 (3 mg/kg, i.p.) for 21 days. Abnormal involuntary movements (AIMs) and rotarod performance were assessed weekly. On day 22, all animals were challenged with L-DOPA/benserazide and AIMs were assessed. On day 24, brains were removed and in situ hybridisation for pre-proenkephalin A (PPE-A) mRNA was performed.

Results: L-DOPA alone induced significantly greater axial, limb and orolingual (ALO) AIMs compared to vehicle at all time points; there was no significant difference between vehicle and L-DOPA + IEM 1460. IEM 1460 did not impair rotarod performance when given chronically with L-DOPA. Following an L-DOPA challenge, rats treated with L-DOPA + IEM 1460 displayed significantly lower ALO AIMs (75%) than rats treated with L-DOPA alone. In animals treated with IEM 1460, there was a reversal of L-DOPA-induced upregulation of PPE-A mRNA in the lesioned striatum, to levels comparable to those seen in vehicle-treated animals.

Conclusions: These data suggest that chronic blockade of calcium-permeable AMPA-Rs attenuates the process of priming for LID, without impairing the therapeutic response to L-DOPA. This was associated with a reduction in molecular correlates of priming. These findings support previous data implicating the GluR1 AMPA subunit in priming for LID. Selective targeting of calcium-permeable AMPA-Rs may be a therapeutic strategy to prevent the development of LID.

Tu-262

Change of tapping speed during short examinations of 32 seconds in Parkinson's disease before and under dopaminergic therapy

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Objective: In addition to our former analyses of tapping speed which does not react on dopaminergic therapy in PD, we now alalysed regularity and change of speed of our original data.

Background: From earlier results we know that the rate of fast oscillatory tapping movements is reduced significantly in Parkinson's disease (PD), but nevertheless is not responsive to dopaminergic therapy, while the regularity of such oscillatory movements – although disturbed too – improves under dopaminergic treatment. The current project presents the examination of systematic change during short examinations of 32 seconds – where we expected reduction in speed (exhaustion) in PD.

Methods: We used a motor performance test battery whose tapping examination is a beating with a stylus including measurement of duration of each single interval from tap to tap. Patients were instructed to tap for 32 seconds as fast as possible. We analyzed 101 de-novo-PD-patients at two visits: without medication and after 6 months of optimized dopaminergic therapy.

Results: Patients were able to keep tapping rate stable over 32 seconds. Nevertheless we found a remarkable range from clear acceleration down to severe exhaustion (calculated as slope from linear regression). Non parametric comparison of measures before (initial) and under dopaminergic therapy (6 months) did not show any therapeutic effect of dopaminergic medication. Relations between all parameters were analyzed with non-parametric correlation. For change of tapping rate over 32 seconds (CoTR32) significant correlations were found between collateral as well as contra-lateral CoTR32-measures of both visits but not with any other parameter (i.e. tapping rate or regularity).

Conclusions: The postulated exhaustion during the test duration of 32 seconds could be found only for a part of all patients while about the same number of patients showed an acceleration. Our results for CoTR32 showed resistance to dopaminergic therapy as well as stability of movement over time. Although oscillatory tapping looks like a very simple movement, following our results tapping rate, regularity and systematic change of rate are independent parameters under statistical and pharmacological aspects. Nevertheless we found a complex explanation of relations between all parameters.

Tu-263

A daily dose of dopaminergic medications in Parkinson's disease; clinical correlates and a posteriori equation of the dose

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Objective: To survey daily doses of dopaminergic medications and to draw a posteriori equation of the dose in relation to the various clinical variables in Korean patients with Parkinson's disease (PD) thereby to provide a data to compare with other ethnic groups.

Methods: A multi-center cross-sectional survey was conducted in patients with clinically diagnosed PD over a defined period. Information on patient demographics and clinical features including age at onset, disease duration and Hoehn and Yahr (HY) stage, and daily doses of anti-parkinsonian drugs were obtained from the patients' medical records. The mean $_{L}$-dopa daily equivalent dose (LEDD) was calculated from the daily dosages of administered dopaminergic drugs based on the theoretical equivalence[1,2] as follows; 100mg of $_{L}$-dopa = 130 mg of $_{L}$-dopa in controlled release = 77 mg $_{L}$-dopa with entacapone = 1mg pergolide = 1mg pramipexole = 5 mg ropinirole = 10mg bromocriptine.

Results: A total of 1762 patients were recruited from seven referral centers. The mean LEDD in the whole population was 608.9 mg/day, which increased linearly according to the duration of disease until it reached about 10 years and to HY stage up to 4, at which point the mean LEDD became plateaud and even decreased. LEDD was also correlated with age, gender, and age at onset. We devised a posteriori equation of the LEDD with clinical variables by multiple linear regression analyses (adjusted R^2=0.27 and F=137.60, p<0.0001).

Table (Tu-263). A proposed multiple linear regression model for the LEDD in Korean patients with PD

Variables	Regression coefficient	Coefficient β	Standard error	95% Confidence interval	p-value
Intercept	237.35		56.51	126.50 to 348.21	<0.0001
HY stage, 1-5	172.69	0.34	12.67	147.85 to 197.54	<0.0001
Female gender	-45.97	-0.06	16.31	-77.96 to -13.98	0.0049
Disease duration, yr	35.51	0.27	3.15	29.32 to 41.69	<0.0001
Age, yr	-3.30	-0.09	0.84	-4.95 to -1.65	0.0001

Conclusions: Our linear regression model may allow comparing daily doses of dopaminergic medications in terms of LEDDs among PD populations with different demographics. **References** 1. Grosset KA, Grosset DG. Proposed dose equivalence for rapid switching between dopamine agonists in Parkinson's disease. Clin Ther 2006;28:1063-64. 2. Hobson DE, Lang AE, Martin WR, Razmy A, Rivest J, Fleming J. Excessive daytime sleepiness and sudden-onset sleep in Parkinson's disease: a survey by the Canadian Movement Disorders Group. JAMA 2002;287:455-463.

Tu-264

Systemic L-dopa deplete the striatal serotonin release in rats with nigro-striatal dopaminergic denervation

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Objective: To investigate the striatal serotonin release derived from L-DOPA systemically administered to rats with nigro-striatal dopaminergic denervation.

Background: In the nigro-striatal dopaminergic denervated striatum, the raphe-striatal serotonergic neurons can convert exogenous L-DOPA into dopamine with intrinsic aromatic L-amino acid decarboxylase in rats, which is released from the striatal serotonergic terminals and can contribute to the dopaminergic neurotransmission. However, little is known concerning the effects of systemic L-DOPA on the striatal serotonin release.

Methods: Male Splague-Dawley rats (250 g) were used. The nigro-striatal dopaminergic denervation was induced by 8 mg/4 ml 6-hydroxydopamine into the right medial forebrain bundle and was confirmed by 0.05 mg/kg of apomorphine. L-DOPA was intraperitoneally injected to the intact or the dopaminergic denervated rats 30 minutes after 30 mg/kg of benserazide. L-DOPA doses were arranged to 50, 100 and 200 mg/kg. The striatal dopamine and serotonin release were quantitatively measured per 5 minutes in freely-moving rats using with in vivo microdialysis method coupled to high performance liquid chromatography. Serotonin immuno-staining was also performed in dopaminergic denervated rats with 200 mg/kg of L-DOPA. Brains fixed with 4% paraformaldehyde were cut on a

cryostat into 30 mm sections, which were immuno-stained with anti-serotonin antibody. The immuno-positive area was measured and compared between the intact and lesioned side of the striatum.

Results: Basal releases (mean±SEM fmol/sample) of dopamine and serotonin were 23.60±1.81 and 0.83±0.02 in the intact rats, and were 2.93±0.37 and 1.07±0.05 in the dopaminergic denervated rats. Serotonin release decreased to 60% after L-DOPA in both rats. In 200 mg/kg of L-DOPA, the striatal serotonin release transiently increased to 150% in the intact rats and 130% in the dopaminergic denervated rats, and then decreased to 60%. Immunohistochemistry showed a decrease of serotonin immuno-positive area after L-DOPA in the dopaminergic denervated striatum, which was comparable to an increase of immuno-positive area induced by serotonergic hyperinnervation.

Conclusions: Our results suggests that the raphe-striatal serotonergic neurons can compensate for dopamine release when exogenous L-DOPA is systemically administered in rats.

Tu-416

Clinical and therapeutic aspects in Parkinson's disease

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Objective: Early diagnosis and adequate modern treatment in Parkinson's disease, associated or not with other diseases, increased significantly the life expectancy and its quality.

Background: Parkinson's disease is a progressive neurodegenerative disorder of unknown aetiology. Its main pathological hallmark is the degeneration of midbrain dopaminergic neurons projecting to the striatum, although other neuronal systems are also affected.

Methods: Our study is consisted of 60 patients with Parkinson's disease who are flowed up monthly for last 5 years in Department of Neurology and benefit from free treatment.

Results: Disease age in all cases was between 1 to 25 years. Grouping of patients according to Hoehn and Yahr staging showed a maximum for stage III (40%), followed by stage IV and stage II with easy female predominant in late stages. Introducing of L-dopa (with benserazida or carbidopa) to therapy was done within the period of 1 to 3 years from the diagnosis of the disease. For patients younger than 60 the first drug introduced was pramipexol or ropinirol, followed by their combination with L-dopa in the next 6 month to 2 years period, according to evolution and patient needs. Doses of L-dopa benserazida and respectively L-dopa carbidopa seldom exceeded daily 600 mg respectively 750 mg, in 4, 5 or 6 divided doses. Entacapone were added to treatment in cases after 5 to 15 years from diagnosis according to motor fluctuation and also if they were within the reach of patients (16 cases). For prevention of dyskinesias induced by L-dopa we used amantadine in daily dose of 200 mg. Severe alteration of cognitive function was detected in 2 cases and were treated with rivastigmina 9 mg per day. Hallucination was present in 8 cases and was treated with clozapin. Associated diseases before or after the diagnosis of Parkinson's disease (arterial hypertension, cardiomyopathies with or without arrhythmias, diabetes mellitus, glaucoma, discopathy) were of low incidence. Patients died due to cardio-respiratory complications after period off 9-16 years from the diagnosis of Parkinson's disease being older than 70.

Conclusions: Since used treatment strategies (small doses of L-dopa) and kinetotherapy succeeded to improve movements, thoracic expansion, balance and functional abilities, cognitive and mental status didn't make any problem and dyskinesias were fewer.

We-248

Effect of the metabotropic glutamate antagonist MPEP on levodopa-induced dyskinesias and the striatal regulation of vesicular glutamate transporters

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Objective: We investigated the effect of the mGluR5 antagonist, MPEP on the striatal expression of: a) VGluT1 and VGluT2, as presynaptic markers of glutamate afferents and b) delta Fos-B, as a dyskinetic marker, in levodopa-treated hemiparkinsonian rats.

Background: The striatal glutamatergic hyperactivity is considered critical in the development of levodopa-induced dyskinesias in Parkinson's disease. Pharmacological antagonism of the metabotropic glutamate receptors (mGluRs), in particular the subtype mGluR5, can inhibit the expression of dyskinesia in both rodent and non-human primate models of PD. However, the exact mechanisms underlying the mGluR5 antagonism effects are not completely known. The vesicular glutamate transporters (VGluTs) are localized to synaptic vesicles in striatal glutamatergic axonal terminals. It is still unknown the effect of mGluR5 antagonism modulating VGluT1 and VGluT2, as selective markers for the corticostriatal and thalamostriatal pathways, respectively.

Methods: Male Sprague-Dawley rats received a unilateral 6-hydroxydopamine administration in the nigrostriatal pathway. Rats were treated with: a) levodopa (12 mg/kg/day with benserazide 15 mg/kg, ip) + vehicle; b) levodopa + MPEP (1.5 mg/kg/day, ip) or c) saline for 10 days.

Results: Levodopa treatment did not modify the striatal expression of either VGluT1 or VGluT2. The administration of MPEP significantly decreased the levels of VGluT2, but not the VGluT1, in the striatum ipsilateral to the lesion ($p<0.05$). A significant increase in the striatal levels of deltaFosB protein was observed in the group of animals treated with levodopa ($p<0.05$). MPEP administration significantly decreased deltaFosB levels ($p<0.05$).

Conclusions: Our results suggest that the effects of MPEP on levodopa-induced dyskinesias and on the striatal expression deltaFosB might mediated by a modulating effect on VGLuT 2 expression.

We-249

Extrastriatal dopamine in the basal ganglia: Effect of dopaminergic denervation of the subthalamic nucleus

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Objective: We investigated the effect of STN dopaminergic denervation on the parkinsonian symptoms and dyskinesias and molecular changes induced by levodopa in the 6-hydroxydopamine (6-OHDA) rat model.

Background: In basal ganglia, the pallidal-subthalamic pathway activity (GPe-STN-GPi) is modulated by the dopaminergic afferents from the pars compacta of the substantia nigra. The modifications of this activity are crucial in the development of the parkinsonian symptoms and levodopa-induced motor complications.

Methods: All lesions were performed with 6-OHDA unilaterally. STN surgery was performed in male Sprague-Dawley rats one week before the medial forebrain bundle (MFB, 8 μg) lesion. Three groups were studied: a) STN lesion+MFB sham, b) STN sham+MFB lesion and c) STN lesion+MFB lesion. Rats were treated for 22 days with levodopa (6 mg/kg with benserazide 15 mg/kg, ip, twice at day). A four group of rats with STN lesion+MFB lesion received dopamine (DA) directly into the STN on day 23. Rotational behavior and dyskinesias were weekly evaluated. In situ hybridization was performed measuring striatal expression of preproenkephalin (ENK) and preprodynorphin (PDyn) mRNAs. The expression of the 67kDa isoform of glutamate decarboxylase (GAD) mRNA in the pars reticulata of the substantia nigra (SNr) and cytochrome oxidase (CO) mRNA in the STN were measured as well.

Results: The combined STN lesion+MFB lesion achieved a significant decrease in rotational behavior ($p<0.01$) and in total dyskinesia score ($p<0.05$) in comparison with the group STN sham+ MFB lesion. Orofacial dyskinesias were the ones that achieved the greater decrease ($p<0.01$). The intrasubthalamic administration of DA increased orofacial dyskinesias. A significant decrease in STN CO mRNA expression was observed in the combined lesioned group in comparison with the STN Sham+ MFB lesion group.

Conclusions: Our results show a relevant role for the dopaminergic innervation of the STN and the requeriment of the nigrosubthalamic pathway integrity for the expression of levodopa-induced dyskinesias, in particular the orofacial sub-type.

We-250

Sequential bilateral model of parkinsonism in rats: Behavioral and molecular study

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Objective: We investigated the consequences of sequential nigrostriatal lesions on the parkinsonian symptoms and dyskinesias and on molecular changes induced by levodopa.

Background: Parkinson's disease (PD) symptoms typically begin on one body part and spread bilaterally with disease progression. This sequential timing of the motor symptoms has not been well reproduced in animal models yet. Unilateral DAergic lesion only, might allow more successful compensatory mechanisms, which may be compromised by a second lesion in the intact side Moreover, less is known regarding the effect of this sequential lesioning on levodopa-induced dyskinesias and molecular abnormalities.

Methods: Sprague-Dawley rats received a 6-hydroxydopamine (6-OHDA) (8 μg) into: a) the left medial forebrain bundle (MFB), b) the right MFB, c) the left and three weeks later into the right MFB, d) the right MFB and three weeks later into the left MFB. Animals were then treated for 22 days with levodopa (6 mg/kg, b.i.d) or saline. The cylinder test, and levodopa-induced dyskinesias were evaluated. In situ hybridization was performed measuring striatal expression of preproenkephalin (ENK) and pre-prodynorphin (PDyn) mRNAs. The subthalamic expression of cytochrome oxidase (CO) and entopeduncular GAD67 mRNAs were also measured.

Results: Bradykinesia was similar in all animals. The addition of a contralateral lesion increased dyskinesias ($p<0.01$). A higher degree of dyskinesias were observed in the groups in which lesion (when unilateral), or the initial lesion (when bilateral), was done in the right MFB ($p<0.05$). Regarding unilateral lesions, in the right MFB-lesioned animals a decrease in subthalamic CO mRNA was observed ($p<0.05$). Regarding bilateral lesions, in the first lesioned side, no molecular changes were observed between groups. However, in the second lesioned side, rats with a right initial lesion showed an increase in ENK and PDyn mRNAs ($p<0.01$).

Conclusions: Our results describe a new sequential bilateral model of parkinsonism in rats. Moreover, the additive effects of sequential bilateral dopamine depletion on levodopa-induced dyskinesias and the view of a new pattern of molecular changes provide insight into the possible compensatory mechanisms that may occur through the progression of PD.

We-251

How to avoid skin nodules with subcutaneous continuous apomorphine infusion

M.-H. Marion, A. Leake, S. Gay (London, United Kingdom)

Objective: To present a technique of subcutaneous infusion of Apomorphine in order to minimise the frequency of skin nodules, which can be a limiting factor in the success of the treatment.

Background: Red and itchy skin nodules (panniculitis) are very frequent, occurring in about 70% of parkinsonian patients treated with subcutaneous continuous Apomorphine infusion. They can be a limiting factor in about 38% of the patients because they are painful and swollen, and persist for many weeks, sometimes with superficial necrosis and infection.

Methods: In our department, following initial suggestions from patients with many years of experience of subcutaneous Apomorphine infusion, we have defined a technique of injection which appears to limit the incidence of skin nodules.

Results: We will present 2 patient series from 2004 and 2008 with a follow up from 1 to 7 years, with a frequency of occasional nodules in only 18% and no patient with longterm skin issues. Pictures of the injection sites and sketches for illustrating needle placement will be presented. We will also discuss the nature of the nodules and the possible role of Apomorphine, and Metabisulphite, (the antioxidant in Apomorphine preparations) in the genesis of these skin nodules.

Conclusions: Precise guidelines, given to carers and nurses can reduce local side effects due to the subcutaneous infusion and allowed the infusion to be continue for many years.

We-252

Effect of rotenone toxicity on PINK1 mutated cells

P.M. Mehta, C.M. Sue (Sydney, NSW, Australia)

Objective: To determine the Effect of Rotenone toxicity on primary culture of human olfactory epithelium derived from a patient with mutations in PINK1 gene.

Background: Rotenone is a mitochondrial complex I inhibitor. Mutations in PTEN-induced kinase 1 (PINK1) gene cause recessive familial type 6 of Parkinson's disease (PARK6). The PINK1 gene encodes a putative protein kinase. The protein is targeted to mitochondria and shows a serine-threonine kinase domain with homology to kinases of the Ca2+/calmodulin family. It has been reported that PINK1 exerts protective effects against cellular stress within mitochondria.

Methods: Wild type (Control) and mutant PINK1 cells were cultured at 37°C in DMEM/F12 (Dulbecco's modified Eagle's Medium) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin under humidified atmosphere of 5% CO2. Cultures were treated with 0, 50, 100, 150, 200 and 250 nM rotenone (MP Biomedicals, Australia) for 3 days. Culture medium was replaced every day with the same rotenone concentration. Cell viability was measured by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. The absorbance was measured at 560 nm of wavelength using a spectrophotometer and the results were expressed by a percentage of control values.

Results: Exposure to rotenone for 3 days resulted in decrease in the viability of PINK1 mutated cells, as measured by the MTT assay at highest dose of 250 nM of rotenone (77.27%) compared to the viability of treated controls (100%).

Conclusions: Rotenone exposure for 3 days reduced the cell viability of PINK1 mutant cells. This finding suggests that PINK1 mutations result in enhanced cell vulnerability to complex I inhibition.

We-253

Effect of hemizygotic parkin suppression in APPswe mutant mice

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Objective: We have investigated the relation between APP and parkin in a double transgenic mouse with mutations of these two important proteins in neurodegenerative diseases.

Background: Amyloid plaques and α-synuclein inclusions are present in the brain of patients with neurodegenerative disease such as Alzheimer's disease (AD) and Parkinson's disease (PD) and many authors hypothesized that the accumulation of these proteins is due to defective ubiquitination or abnormal proteosomal processing. Dementia in PD is a common late event of the evolution of this disease and it has been postulated that the risk of dementia is increased in idiopathic PD and in familiar PD related to mutations of α-synuclein and dardarin but not of parkin.

Methods: We produced a double transgenic mouse with overexpression of human mutated APPswe and hemizygotic inactivation of parkin gene (Itier et al 2003). The experiments were performed in 4 experimental groups with identical genetic Wild type (WT),

APPswe over-expressing (APP), hemizygotic deletion of Park-2 (PK+/-) and double mutants (APP/PK+/-). The development and behaviour of the animals were investigated for more than one year and brain histology and biochemistry were analysed in animals sacrificed at the age of 12 and 16 months.

Results: APP and the APP/PK+/- mice had worse exploratory behaviour than WT. APP/PK+/-mice had greater levels of anxiety than WT and APP. There was a small, barely significant, reduction of β-amyloid plaques, soluble and total β-amyloid fractions in APP/PK+/- with respect to those of APP at 12 months and a highly significant difference at 16 months. Surprisingly, the ratio of pro/antiapoptotic proteins and the number of apoptotic cells were smaller in APP/PK+/- than in APP mice.

Conclusions: Hemi-zygotic suppression of parkin ameliorates apoptotic cell death, amyloidosis and neuronal deficits found in APP mutant transgenic mice. These data suggest that the deficit of ubiquitination present in PK+/- mice is compensated by other mechanisms in APP/PK+/-.

We-254

Parkin deletion causes amyloidosis in mice overexpressiong human mutated Tau

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Objective: To study the tau pathology and amyloid deposition in brain and peripheral organs of parkin null, over-expressing human mutated tau (PK-/-/TauVLW) mice.

Background: Deposition of proteins leading to amyloid takes place in some neurodegenerative diseases such as Alzheimer's disease. Mutations of tau and parkin proteins produce neurofibrillary abnormalities without deposition of amyloid.

Methods: We produced a double transgenic mouse with overexpression of human mutated Tau and inactivation of parkin gene. The experiments were performed in 4 experimental groups with identical genetic WT, PK-KO, TauVLW, PK-KO/TauVLW. The development and behaviour of the animals were investigated for more than one year and brain histology and biochemistry were analysed in animals sacrificed at the age of 12 months.

Results: PK-/-/TauVLW mice have abnormal behavior and severe drop-out of dopamine neurons in the ventral midbrain, up to 70 %, at 12 months and abundant phosphorylated tau positive neuritic plaques, neuro-fibrillary tangles, astrogliosis, microgliosis, and plaques of murine b-amyloid in the hippocampus. PK-/-/TauVLW mice have organomegaly of the liver, spleen and kidneys. The electron microscopy of the liver confirmed the presence of a fibrillary protein deposits with amyloid characteristics. There is also accumulation of mouse tau in hepatocytes. These mice have lower levels of CHIP-HSP70, involved in the proteosomal degradation of tau, increased oxidative stress, measured as depletion of glutathione which, added to lack of parkin, could trigger tau accumulation and amyloidogenesis.

Conclusions: This model is the first that demonstrates b-amyloid deposits caused by over-expression of tau and without modification of the amyloid precursor protein, presenilins or secretases. PK-/-/TauVLW mice provide a link between the two proteins more important for the pathogenesis of Alzheimer's disease.

We-255

Enriched environment affects striatal glutamate following dopamine loss

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Objective: To determine the effect of an enriched environment (EE) on striatal glutamate function and dopamine (DA) cell loss in the substantia nigra pars compacta (SN-PC) following exposure of mice to the neurotoxin, MPTP.

Background: It was reported (Bezard et al., 2003) that prior exposure to an EE reduces the loss of DA cells in the SN following treatment with MPTP. We are the first to report the effect of exposure to an EE after MPTP administration on both striatal glutamate function and DA cell loss in the SN-PC.

Methods: Mice (males, C57BL/6J, 10 wks) were injected with MPTP (30 mg/kg/d) or vehicle for 7 days and the following day were placed in an EE or in the home cage [standard environment (SE)] for an additional 21 days. In vivo microdialysis was used to measure extracellular striatal glutamate. Locomotor tests (free vs wall-assisted rears and foot-faults) were carried out prior to MPTP treatment and then 21 days after exposure to the EE. Tyrosine hydroxylase (TH) immunohistochemistry was used to count the number of DA cells in the SN-PC. The density of glutamate immunogold labeling within striatal nerve terminals using electron microscopy was measured.

Results: MPTP resulted in an overall 54% loss of DA cells in the SN-PC. Exposure of the MPTP treated mice to the EE (MPTP/EE) reduced the DA cell loss in the SN-PC to 22%, decreased the number of foot-faults and increased the number of free or unassisted rears compared to the MPTP/SE group. MPTP alone resulted in a decrease in the extracellular level of striatal glutamate. Exposure of mice to EE only 1) decreased the number of foot-faults, 2) increased the extracellular level of striatal glutamate, 3) decreased the density of striatal nerve terminal glutamate immuno-gold labeling, 4) increased the striatal protein level of the glutamate transporter, GLT-1, and the glial protein, GFAP, and 5) reduced the striatal protein levels for TH compared to the SE group.

Conclusions: The data suggests that exposure to an enriched environment after MPTP treatment results in partial restoration of DA labeled cells in the SN-PC, which is associated with an increase in motor function. EE may be beneficial following MPTP due to the effect of EE on increasing striatal glutamate levels and transporter protein and reducing TH protein.

We-256

Effects of zonisamide on experimental parkinsonian tremors in rats

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Objective: To study the effect of zonisamide (ZNS) on tacrine-induced tremulous jaw movements (TJMs), an experimental model of parkinosnian tremor, in rats.

Background: ZNS is a widely used antiepileptic drug. There is growing interest in the therapeutic potential of ZNS on symptoms of Parkinson's disease (PD). A recent, randomized, placebo-controlled study revealed that ZNS could effectively improve symptoms of PD. In addition, zonisamide may be effective for the treatment of tremor disorders. However, the pharmacological mechanisms of ZNS remain uncertain. Tacrine-induced TJMs have been proposed as a pharmacological model of parkinsonian tremors in rats.

Methods: Male adult rats received systemic administration of ZNS (5 or 50 mg/kg) or vehicle at 20 min prior to the administration of tacrine. Ten minutes after the administration of tacrine, TJMs were measured. Animals were sacrificed 2 hours later for immunohistochemial analysis of c-Fos expression in various anatomic sites.

Results: Systemic administration of tacrine induced characteristic jaw movements, previously defined as TJMs. ZNS significantly suppressed tacrine-induced TJMs, and this effect was not lost under conditions of monoamine-depletion or dopaminergic blockade. Immunohistochemically, administration of tacrine induced abundant c-Fos expression in various anatomical sites including the cortex, striatum, and diencephalon, when compared to the control animals. There was no effect of ZNS on tacrine- induced c-Fos expression in the ventrolateral striatum, a primary site of the pharmacological action of tacrine. ZNS suppressed the tacrine-induced c-Fos expression in the cortex, the dorsal striatum, and the nucleus accumbens, which are

involved in the architecture of the cortico-basal ganglia-thalamocortical circuits.

Conclusions: The anti-tremor effects of ZNS may be achieved by a non-dopaminergic mechanism. The anti-TJM effect of ZNS may be related to a more broad inhibitory effect on tremor-related structures such as the cortex or the striatum. This effect of ZNS may be a contributing mechanism underlying its therapeutic efficacy on parkinsonian tremor.

We-257

L-dopa treatment-specific induction of metallothionein in reactive astrocytes in the striatum of parkinsonian model and its neuroprotective effects against dopaminergic neurotoxicity

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Objective: Dopamine (DA) quinone as DA neuron-specific oxidative stress conjugates with functional proteins to form quinoproteins. Metallothioneins (MTs) are cysteine-rich intracellular metal-binding proteins participating in metal homeostasis, antioxidative and detoxification. In this study, we examined effects of L-DOPA treatment on MT expression in the striatal astrocytes in the model of Parkinson's disease (PD) and also examined astroglial MT expression and its neuroprotective effects using primary cultured mixed neurons and astrocytes.

Background: We previously demonstrated the protective effects of MT against DA quinone neurotoxicity: MT exerted protective effects against the excess DA/L-DOPA-induced DA quinone neurotoxicity in dopaminergic cells and PD model mice through its DA quinone-quenching activity (Miyazaki et al., FEBS Lett, 581: 5003-8, 2007). Recently, extracellular MTs have been reported to play a role in the astrocyte-neuron response in the brain injury.

Methods: Changes in MT expression were examined by immunohistochemistry after L-DOPA/DA exposure using 6-OHDA-injected hemi-PD mice and primary cultured mesencephalic neurons and striatal astrocytes. Furthermore, effects of conditioned media from DA-treated astrocytes were examined against DA-induced neuronal death.

Results: MT expression was markedly elevated specifically in the reactive astrocytes in lesioned striatum after repeated L-DOPA administration. DA exposure dramatically produced MT induction in striatal cultured astrocytes but not in mesencephalic neurons. DA-induced reduction of mesencephalic DA neurons was ameliorated by pre-incubation with conditioned media from striatal astrocytes, especially DA-treated astrocytes. These protective effects of conditioned media from DA-treated astrocytes were cancelled by neutralization with anti-MT antibody.

Conclusions: These results suggest that the activation of astrocytes and consequent induction and secretion of MT in/from the reactive astrocytes may play an important role to protect dopaminergic neuron by its quinone-quenching or free radical scavenging property.

We-258

Retrospective statistical analysis of the incidence of serotonin toxicity in patients taking rasagiline and anti-depressants in clinical trials

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Objective: To determine the risk of developing serotonin toxicity in patients taking rasagiline and certain antidepressants in rasagiline clinical trials.

Background: Rasagiline is a novel, potent, selective, irreversible inhibitor of monoamine oxidase type B (MAO-B) effective in the early and moderate to advanced Parkinson's disease (PD) patient. Non-selective MAO inhibitors have a potential to interact with antidepressants causing a severe CNS toxicity known as serotonin toxicity. While there were no reports of serotonin toxicity in rasagiline clinical trials, it is unknown whether these trials represented a sufficient sample size to conclude that the risk is approximately zero.

Methods: A retrospective analysis of all patients enrolled in eight clinical trials and five of their long-term extensions who had taken rasagiline in combination with an antidepressant was conducted to determine the confidence intervals for the incidence of developing serotonin toxicity. A confidence interval for a binomial proportion based on F distribution was calculated for the incidence of serotonin toxicity in all patients taking rasagiline and an antidepressant.

Results: The analysis included approximately 1010 patient-years of experience (316 patients) with patients taking some combination of antidepressants and rasagiline. Antidepressants primarily included amitriptyline, trazodone, citalopram, sertraline and paroxetine. Review of individual patient records for combinations of psychic, autonomic, and neuromuscular symptoms revealed no apparent cases of serotonin toxicity (Panisset, et al. Mov Disord, 2007, Vol. 22, Suppl. 16, 340). The 95% confidence interval of the incidence of serotonin toxicity in the entire group was 0-0.0116.

Conclusions: The results suggest that the population incidence of serotonin toxicity in those taking rasagiline and antidepressants, such as those in the clinical and extension trials, has a 95% probability of being less than 1.2%. This low calculated probability suggests that in the clinical setting, concomitant use of rasagiline and antidepressants is safe.

We-259

Symptomatic efficacy of mucuna pruriens seed extract in rodent model of Parkinson's disease

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Objective: The present study evaluated the antiparkinsonian effects of an extract of *Mucuna pruriens* (MP) seeds that contain 12.5 % L-DOPA, as compared to equivalent doses of L-DOPA. Moreover, the neuroprotective efficacy of MP and its potential reinforcing properties were evaluated.

Background: MP has long been used in Indian ayurvedic medicine in the treatment of Parkinson's disease, however, no systematic preclinical studies are available to date.

Methods: Investigation of the effect of MP on motor deficits, was performed in rats unilaterally lesioned with 6-hydroxydopamine (6-OHDA). Moreover, MP effects were evaluated on tacrine-induced jaw movement, a test reproducing parkinsonian tremor and in the place-preference test to study the reinforcing potential. Finally, MP was administred in association with a subchronic MPTP protocol to assessed its neuroprotective potential.

Results: The results obtained reveal how acute administration of MP (16 mg/kg containing 2 mg/kg of L-DOPA) consistently antagonized the deficit in latency of step initiation and adjusting step induced by 6-OHDA, whereas L-DOPA was equally effective only at doses of 6 mg/kg. MP (16 mg/kg) significantly improved placement of the forelimb in vibrissae-evoked forelimb placing. In the turning behavior test and in the induction of AIMs, MP (48 mg/kg containing 6 mg/kg of L-DOPA) acutely induced a significantly higher contralateral turning behavior than L-DOPA (6 mg/kg). Subchronic MP (48 mg/kg) and L-DOPA (6 mg/kg) induced sensitization of contralateral turning behavior; however, L-DOPA alone induced a sensitization in AIMs. MP (48 mg/kg) was also effective in antagonizing tremulous jaw movements induced by tacrine. Furthermore, MP induced no compartment preference in the place preference test. Finally, MP did not prevent either MPTP-induced tyrosine hydroxylase decrease or astroglial or microglial activation supporting the absence of neuroprotective effects by MP.

Conclusions: Characterization of MP extract strongly support its antiparkinsonian activity, however, MP extract does not show neuroprotective properties in MPTP model of PD.

We-260

The effect of rotigotine transdermal patch on non motor symptoms of Parkinson'disease: A clinical observational study using the PD non motor symptoms scale

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Objective: To assess if use of continuous dopaminergic stimulation (CDS) using the non ergot rotigotine transdermal patch (RTG) in treated Parkinson's disease (PD) influenced improvement in aspects of non motor symptoms (NMS) as assessed by the internationally validated PD non motor symptoms scale (NMSS).

Background: Delivery of CDS with the RGT has shown to alleviate motor complications in PD and some studies have shown that it be effective to control some NMS in PD.

Methods: Treated PD patients were started on RTG based on clinical need and assessments including UPDRS, quality of life and NMSS were done as a routine practice. Assessments were repeated between a mean period of 8 months (2-24) while other treatment remained constant and RTG was titrated up to the maximum tolerated dose. Side effects and drop outs were noted.

Results: 40 treated but non-optimally controlled PD patients (mean age 65.4±9.5 (45-86), mean duration of PD 6.4±5.5 (1-20yrs)) were assessed at follow up (FU) after being able to tolerate RTG without any additional drug alterations. Most were in HY stages 1 (25%) or 2 (50%) and NMSS total score (NMSS-T, which includes non dopaminergic domains) improved from 40.3±35 (0-138) to 30.3±31.9 (0-134, p=0.04) with a relative change of 24.9%, effect size 0.28 and standardized response mean 0.34. Improvements were noted in sleep domain (p=0.002) and perception domain (p=0.03) while urinary and sexual function deteriorated. Within the domains which improved with rotigotine, daytime sleeping ((NMSS ques 3) (p=0.02)), sleeping difficulties ((NMSS ques 5) (p=0.0002)). Changes in NMSS correlated (p=0.02) with improvement in quality of life (QoL, PDQ-8) but not UPDRS-3. In particular changes in mood correlated with improvement of Qol (p=0.002). Improvement pattern was attenuated over time (changes in NMSS-T was -16.2 improvement at 6 months falling to -2.4 > 6 months).

Conclusions: This is the first demonstration of the effect of a strategy utilising CDS on NMS aspects of PD. Although observational and open label this study suggests that such strategy could improve NMS with beneficial effects on sleep and dopaminergic perception items and this positively influences QoL. The benefit however, decays with time, possibly linked to disease progression.

We-261

Intitation of apomorphine infusion in advanced Parkinson's disease and effect on non motor symptoms compared to non-invasive strategies

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Objective: As part of an observational audit data related to the PD non motor scale (NMSS) was used as the primary comparator between a group of advanced PD patients started on apomorphine infusion and a similar group using the rotigotine transdermal patch initially before considering apomorhine.

Background: Apomorphine is the most potent dopamine agonist used subcutaneously although in the UK, in fluctuating levodopa treated Parkinson's disease (PD) patients, many may choose to use transdermal rotigotine patch or long acting ropinirole first before apomorphine is considered. The effect of these strategies on the overall non motor symptoms (NMS) of PD is unknown.

Methods: Assessments were made as part of routine clinical practice in the clinic and those who had not made any other changes to concomitant treatment were included. 10 PD patients (age 62±14 (SD) yrs, HY stage 3-5) with dyskinesias were stabilised on apomorphine infusion (16-18hrs/day, 32-108mg/day) and UPDRS 3, quality of life (PDQ-8) and NMSS assessments were done before starting apomorphine and at 1 month following maximum tolerated dose. Assessments with NMSS were also undertaken in a group of 13 PD patients (mean age 57±10yrs, HY stage 3-4) who elected to use rotigotine transdermal patch initially. All were similar doses of levodopa (range 300-1200mg/day).

Results: Following apomorphine infusion, NMSS total score (NMSST, a sum of nine domains) was significantly reduced from74.5±43.4 to 40.7±22.4 (Wilcoxon signed-rank test, p =0.008) with significant improvements being noted in the sleep (p=0.006), mood (p=0.02), urinary (p=0.01) and miscellaneous (p=0.05) domains, the latter showing a marked improvement in dribbling of saliva. UPDRS 3 scores (32±10.5 to 12.5±7, p=0.01) and PDQ-8 (42.5±21.6 to 26±11.6, p=0.03) also improved significantly. Patients on rotigotine patch failed to show significant changes in NMSS (50.6±32 to 43.7±20).

Conclusions: Allowing for the limitation of the small number of cases, this pilot study suggests that in advanced fluctuating PD cases, stronger and invasive therapeutic options such as apomorphine infusion may be preferable give its holistic beneficial effect on motor and NMS and consequently health related quality of life.

We-407

Memantine improves L-dopa induced dyskinesias

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Objective: To report on the effect of memantine on L-dopa induced dyskinesias (LID) in four patients with Parkinson's disease (PD).

Background: Memantine is a noncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, which regulate the glutamatergic function. Recent evidence suggests that chronic pulsatile stimulation of DA receptors may lead to post-synaptic upregulation of gluatamate receptors. This may then induce abnormal motor patterns, as LID. Glutamate antagonists as amantadine have been used to decrease LID intensity. Memantine as a more selective glutamate antagonist may be an effective treatment for LID.

Methods: case series

Results: Case 1: a 68 year-old woman with a 12 years PD history, complicated by 6 years of LID. After one year from the LID onset memantine 20 mg was started and LID stabilized for the following 5 years as mild and infrequent. When memantine was stopped she developed daily disabling LID for 3 months. The restoration of memantine 20 mg was followed by the almost complete suppression of the LID in one month. Case 2: a 52 year-old woman with a 10 years history of PD, complicated after 5 years by frequent and moderately disabling LID, unchanged over a 2 years period. When memantine was gradually increased up to 30 mg, LID progressively improved and for the following 3 years remained infrequent over the week and no more than mildly disabling. Case 3: a 75 year-old man with a 15 years history of PD, complicated after 10 years by daily and mild to moderate LID. After 3 years from the LID onset memantine 10 mg was included to his treatment with almost complete suppression of LID. When memantine was accidently stopped for 1 month, the patient again developed daily and moderately disabling LID. The restoration of memantine was followed in 2 weeks by the almost complete suppression of LID. Case 4: a 74 year-old man with a 16 years history of PD, complicated after 4 years by LID. When LID became particularly pronounced, 10 years later, memantine 10 mg was included to his regular treatment with significant improvement of LID which became infrequent during the day and not disabling for the following 2 years.

Conclusions: Our case series suggests that memantine may be efficacious in the treatment of LID, and offers additional preliminary evidence for double-blind placebo controlled studies to investigate the optimal role for memantine in the treatment of PD.

We-418

Non-steroidal anti-inflammatory drug use and the risk of Parkinson's disease: Systematic review and meta-analysis of observational studies

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Objective: To determine whether the use of non steroidal anti-inflammatory drugs (NSAIDs) modifies the risk of Parkinson's disease (PD).

Background: PD is a progressive neurodegenerative disease without a cure. Inflammation is one the proposed mechanisms in the etiopathogenesis of PD. A number of studies have suggested that NSAID use may reduce the risk of developing PD.

Methods: We searched MEDLINE (1966-November 2008), EMBASE (1980-November 2008), ACP Journal Club (1991 to November 2008), Database of Abstracts of Reviews of Effects (DARE, 1990-November 2008), and the Cochrane Collaboration Controlled Trials Register for studies published before November 2008. We searched for randomized controlled trials, cohort studies, or case-control studies that looked at the association between NSAID/aspirin use and PD. We used the random effects model to calculate a pooled relative risk and its corresponding 95% confidence interval (CI). Odds ratios were considered an approximation of relative risks. We only combined relative risks (from cohort studies) and odds ratios (from case control studies) if the test of heterogeneity was negative. Heterogeneity was assessed using the Q statistic. We used RevMan (Cochrane Collaboration, version-5) and Microsoft Excel to analyze the data.

Results: We found a total of 11 studies that looked at the association between NSAID use and PD: seven case-control studies and four cohort studies. The pooled relative risk for ever NSAID use was 0.95 (95%CI: 0.80-1.12). Among the case control studies the pooled relative risk of developing PD was 0.97 (95%CI: 0.78-1.20). Among the cohort studies, the pooled relative risk of developing PD was 0.91 (95%CI: 0.67-1.23). The pooled relative risk of developing PD with higher dose or longer duration NSAID use was 0.91 (95%CI: 0.78-1.05). Six studies looked at aspirin use alone. The pooled relative risk of PD for aspirin users was 1.08 (95%CI: 0.93-1.26). There were only two studies specifically looking at ibuprofen. The pooled relative risk of PD among ibuprofen users was 0.75 (95%CI: 0.61-0.94).

Conclusions: NSAIDs as a class do not seem to modify the risk of PD. However, ibuprofen may have a protective effect in lowering the risk of PD. Future prospective studies are needed to address this question.

Th-251

Decreased cholesterol in olfactory mucosa-derived cells from Parkinson's disease patients with leucine-rich repeat kinase 2 mutations

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Objective: To investigate the changes in (1) the cholesterol level and (2) the activity and amount of the rate-limiting cholesterol biosynthetic enzyme, 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG CoA-R), in olfactory mucosal cells biopsied from idiopathic Parkinson's disease (iPD) patients and Parkison's disease (PD) patients with leucine-rich repeat kinase 2 (LRRK2) mutations.

Background: We have previously reported that neuromelanin-associated cholesterol is reduced in the substantia nigra in PD. Further, cholesterol biosynthesis is reported to be reduced in fibroblasts from patients with PD. Together these data suggest a change in cholesterol homeostasis in PD.

Methods: Olfactory mucosal cells were biopsied and cultured from six cases of iPD patients, four PD patients with LRRK2 mutations (two: A1442P and two G2019S mutations) and ten normal controls. Cellular cholesterol levels were measured by reverse phase high performance liquid chromatography and the activity and amount of HMG CoA-R were measured by metabolic radiolabelling and Western blotting, respectively.

Results: Cells from PD patients with LRRK2 mutations demonstrated significantly lower cholesterol levels compared with both iPD (37% reduction, $p=0.02$) and controls (38% reduction, $p=0.005$). HMG CoA-R activity and protein were, however, unchanged in these cells. No difference was found in cholesterol levels in cells from iPD cases compared with controls, nor did there appear to be any effect of LRRK2 mutation type on cholesterol levels.

Conclusions: Our findings suggest that LRRK2 might play a role in cholesterol-associated pathways.

Th-252

17-AAG protects against rotenone-induced apoptosis in SH-SY5Y cells via HSP70 induction

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Objective: To examine the protective effects of 17-AAG on rotenone-induced apoptosis in SH-SY5Y cells.

Background: Heat shock proteins (HSPs), such as HSP70, represent an important cellular protective mechanism against neuronal cell death in various models of neurological disorders. 17-allylamino-17-demethoxygeldanamycin (17-AAG) is an HSP70 inducer acting via Hsp90 inhibition. Recent studies have suggested that 17-AAG may have a therapeutic role in non-oncological diseases as neuroprotective agent. Here, we investigated the possible role of 17-AAG in rotenone (a potent complex I inhibitor)-induced apoptosis in SH-SY5Y cells, an *in vitro* model relevant to PD.

Methods: Cells were exposed to rotenone with or without 17-AAG pretreatment. The apoptosis were determined by Hoechst 33342 staining and immunoblotting assay. The changes in mitochondrial membrane potential were determined using Mitotracker Red CMXRos staining. The protein levels of HSP70 and P53, a major protein of apoptotic signaling pathway, and the release of cytochrome *c* were determined by immunobloting assay. The cells were treated with KNK437, a novel Hsp inhibitor, or transfected with *HSP70* siRNA, followed by addition of rotenone with or without 17-AAG pretreatment. Then the apoptosis of cells was evaluated by measuring the protein levels of cleaved PARP.

Results: 17-AAG treatment caused a time- and dose-dependent increase of HSP70 and decrease of P53. Pretreatment with 17-AAG alleviated rotenone-induced apoptosis, decreased cytochrome *c* release, and reduced the loss of mitochondria membrane potential caused by rotenone. The protective effect of 17-AAG was related to HSP70 induction and P53 inhibition, and was partially blocked by KNK437, or by *HSP70* siRNA transfection, in which the *HSP70* gene was suppressed. The attenuated accumulation of high molecular weight ubiquitin bands observed in rotenone-treated cells further support the neuroprotective effect of 17-AAG.

Conclusions: The protective effects of 17-AAG against rotenone-induced apoptosis through HSP70 induction may lead to a novel approach to neurodegenerative disorders involving mitochondrial dysfunction. Further studies are needed to examine the effect of 17-AAG in PD related animal models *in vivo* and other mechanisms involved in the neuroprotection will also be further investigated.

Th-253

A Phase II, double-blind, placebo-controlled, randomized, crossover pilot study of the safety and efficacy of multiple doses of intra-oral tropicamide films for the short-term relief of sialorrhea symptoms in Parkinson's disease patients: An interim-analysis

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Objective: To explore the anti-sialorrhea effect of single doses of tropicamide administered in a slow dissolving, muco-adhesive, intra-oral thin film. An interim analysis was performed using a subjective assessment of tropicamide thin film activity to determine the time of

maximum activity for objective quantitative saliva measurements in a subsequent larger patient sample.

Background: Sialorrhea in Parkinson's disease (PD) is a common non-motor symptom resulting mainly from dysphagia, dysautonomia and stooped posture. Short-acting anticholinergic agents, such as tropicamide with a plasma half-life of 30 min, have the potential to reduce saliva secretion without inducing the side effects associated with long-acting cholinergic blockers.

Methods: 12 non-demented, non-dysautonomic idiopathic PD patients who complained of sialorrhea were recruited. Each patient received 3 doses (0.3, 1, 3 mg) of tropicamide and placebo delivered in a muco-adhesive film, in random order, separated by at least 7 days. A 10-cm visual analog scale (VAS) was used to measure the patient's subjective assessment of saliva levels. VAS was assessed at baseline and at 15, 30, 45, 90 and 120 min after treatment administration. Differences between post and pretreatment VAS (mean ± standard error) were determined. Vital signs were monitored and ECGs were performed 120 minutes post-treatment.

Results: Ten of the patients were male., Mean age was 65±13 years and median disease duration was 9.5 years (range: 5.7-11.7 y). VAS levels prior to treatment administration did not show any differences ($p=0.5$). The maximal VAS differences between tropicamide and placebo were observed at 60 and 90 min post-dose, with a consistent dose-response trend. Between-treatment differences in VAS did not reach significance ($p=0.3$) in this small sample size. No adverse events were detected in any of the treatment sequences.

Conclusions: Treatment effects using an objective buccal saliva measurement at 60-90 minutes will be added to the design of a study in a larger group of PD patients.

Th-254

Should we concern about the cost of medical treatment for Parkinson's disease? A case study from developing country

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Objective: Measuring the direct medical cost of PD treatment. Analyze the affordability of medicines for PD.

Background: Medical interventions improve the quality of life of Parkinson's disease (PD) patients. The main treatment for managing PD in Indonesia is medical treatment. Surgical treatment is a very rare option. There is a very few research about PD from Indonesia.

Methods: Review of the prescribing for PD from 48 PD patients. The monthly cost of the treatment was calculated. The secondary data about the gross national income was obtained from the national statistic bureau.

Results: Indonesia is one of the most populated countries in the world. Indonesians have a low annual gross national income (GNI; US$ 1420). The national data showed that only a few (less than 10%) have health insurance. We review consecutive prescribing for PD patients. The data about the health insurance coverage and money spent for treatment were collected. The annual income of nearly half the patients was less than US$ 3.000,00. Patients in this study spend nearly 8% to 22% of the average monthly income for the medicines. The only available drug in primary health centre is THP (Trihexyphenidyl). The most expensive drug is entacapone. The cost of the medical treatment subjectively is too expensive for about two a third of patients.

Conclusions: The cost of medical treatment is very expensive in those who living in developing countries. Patients spend about 20% of their income for the cost of medications.

Th-255

Easy switching from immediate- to extended-release pramipexole in early Parkinson's disease at the same daily dosage

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Objective: To assess the dosage ratio for switching patients with early Parkinson's disease (PD) from immediate-release (IR) to extended-release (ER) pramipexole.

Background: Pramipexole IR is efficacious to treat early PD. An ER formulation will simplify the treatment regimen (once daily vs tid) and increase convenience.

Methods: Patients with early stable PD (n=156, mean age: 64±9 years, mean PD duration: 3±2 years) receiving pramipexole IR (mean daily dose: 2.7±0.9 mg/d) for 1.5±1.6 years, with concomitant levodopa (56% of patients) or without were included. Patients were switched overnight to ER (n=104) or IR (n=52) at unchanged daily dosage in a randomized (2:1) double-blind manner. At weeks 4 and 5, those with a UPDRS score II+III >15% worse than baseline were allowed a 1-dose step increase. Those with dopaminergic adverse events (AEs) were allowed a decrease. Dosage then remained stable for the last 4 weeks of the trial. The primary endpoint was defined as the proportion of patients successfully switched (no worsening of UPDRS II+III >15% from baseline and no drug-related AE leading to withdrawal) at week 9. Difference in successful switches between groups was tested with 1-sided noninferiority statistical analysis at the 5% level of significance and a noninferiority margin of 15%.

Results: Four patients switched from IR to ER withdrew prematurely from the study and 3 of those remained on IR. A large majority of patients (87/103, 84.5%) successfully switched to ER, although noninferiority could not be formally demonstrated vs IR (94.2%, between group difference -9.76%, 95% CI [-18.81, 1.66]). Of the 87 patients successfully switched to ER, 72 (82.8%) did not require dose adjustment. Mean ER dosage was only marginally increased by 0.12 mg/d (from 2.63 to 2.75), for a ratio of 1:1.05. For IR, the increase was 0.09 (from 2.74 to 2.83), for a ratio of 1:1.03. Incidence of AEs was low and comparable in both groups (ER: 36.5%, IR: 30.8%). Two patients (1 per group) dropped-out due to AE.

Conclusions: More than 80% of patients on pramipexole IR with early stable PD (with or without concomitant levodopa) can be switched easily overnight to ER at the same daily dose.

Th-256

Effect of zonisamide on apoptosis in a SH-SY5Y cell line

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Objective: To confirm the mechanism of neuroprotective effect of zonisamide (ZNS) in cultured cells.

Background: Although effects of ZNS in Parkinson's disease on parkinsonian features, especially wearing-off have been reported, the protective mechanism is still unclear.

Methods: SH-SY5Y and HeLa cell lines were used for this study. After treatment with retinoic adic and neurotoxins (staurosporine, dopamine or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine: MPTP) followed by ZNS administration, the cell death ratio and mitochondrial viability were assessed by TUNEL staining and an MTT assay, respectively. Also, apoptotic cascades and autophagic activity were examined with Western blotting.

Results: The cell death ratio with or without ZNS was 18.9% or 49.7%, respectively. The addition of ZNS increased cell viability against dopamine or MPTP up to about 150% or 200% compared with controls, respectively. Cleaved caspase 3 and 9 were decreased by ZNS administration. Likewise, phosphorylation of PI3K and Akt were increased, whilst LC3-II/actin ratios were not changed by the ZNS treatment.

Conclusions: ZNS protects the SH-SY5Y cells from toxic insults via activation of PI3K/Akt pathway, not autophagy-lysosome pathway. In the future, *in vivo* studies should be perfomed.

Th-258

Adenosine A_{2A} receptor inactivation in neuronal elements is neuroprotective in a model of Parkinson's disease

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Objective: To investigate the cellular basis of adenosine A_{2A} receptors ($A_{2A}R$) neuroprotection, complementary pharmacologic and

genetic approaches were used to inactivate A_{2A} receptors in a subchronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease (PD).

Background: Antagonism of $A_{2A}R$ displays neuroprotective effects in animal models of PD. The mechanisms by which these neuroprotective effects are elicited are not known at present, however, given the cellular distribution of $A_{2A}R$ in different cell types, neuroprotection through $A_{2A}R$ blockade can be either achieved by acting on adenosine receptors located on neuronal or glial cells.

Methods: MPTP·HCl was administered repeatedly (20 mg/kg ip daily for 4 days) in mice pretreated with the A_{2A} antagonist SCH58261, or in conditional knockout mice lacking A_{2A} receptors postnatally on forebrain neurons (fbnA_{2A} KO mice) or on astrocytes (astroA_{2A}KO mice).

Results: In control mice, MPTP induced partial loss of dopaminergic neurons in substantia nigra pars-compacta (SNc) and intense gliosis, characterized by increased astroglial and microglial immunoreactivity in SNc and striatum (Str). Reactive astroglia was similarly increased one, three and seven days after MPTP administration, whereas maximal microglial reactivity was detected on day one and returned to basal levels seven days after MPTP. SCH58261 fully counteracted the dopaminergic neuronal cell loss and reactive gliosis in SNc, and partially inhibited the latter in Str. Similarly, selective depletion of A_{2A}Rs in fbnA_{2A}KO but not astroA_{2A}KO mice, completely prevented MPTP-induced dopamine neuron degeneration and gliosis in SNc, and partially counteracted gliosis in Str.

Conclusions: The results provide the first evidence of a primary role played by neuronal A_{2A}Rs in the neuroprotective effects of $A_{2A}R$ antagonists in a model of PD. With the symptomatic antiparkinsonian potential of several $A_{2A}R$ antagonists currently being pursued in clinical trials, the present study adds to the rationale for broader clinical benefit and use of these drugs early in the treatment of PD.

Th-259

Parkinson's disease tremor is diminished with relaxation guided imagery

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Objective: To determine whether PD tremor would improve with relaxation guided imagery (RGI) and relaxing music.

Background: Parkinson's disease (PD) patients may have pronounced tremor. PD tremor exacerbates during stress and ameliorates with relaxation.

Methods: Twenty PD patients with moderate to severe tremor participated in sessions where relaxation techniques were implemented. Each session consisted of a baseline period, a period with relaxing music, a period of self relaxation and a period of relaxation guided imagery. Tremor was objectively monitored using an accelerometer.

Results: RGI dramatically decreased tremor in all 20 patients (baseline 270.38 $\pm$ 85.82 vs. RGI 35.57 $\pm$ 43.90 movements per minute $p<0.0001$). In 15 patients RGI completely abolished tremor for periods of 1-13 minutes. Average tremor activity remained significantly bellow baseline both 15 minutes ($p<0.0001$) and 30 minutes after RGI was discontinued ($p=0.0004$). Moreover, patients reported improvement lasting for 2-14 hours (mean 6.8 $\pm$ 3.8). Relaxing music significantly reduced tremor but to a lesser degree (220.04 $\pm$106.53 movements per minute $p=0.01$). Reduction in kinetic tremor was also observed after RGI. Self-relaxation had no effect on tremor.

Conclusions: RGI and music reduced tremor in PD patients on best medical treatment. RGI can supplement conventional medical treatments.

Th-260

Report on rasagiline – Antidepressant interactions in routine clinical practice, long-term follow up and issues of compliance

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Objective: Report incidence, severity and follow up of adverse events and obstacles to compliance in a cohort of patients with Parkinson's disease (PD) who were prescribed rasagiline concomitantly with antidepressants.

Background: Rasagiline is a selective MAO-B inhibitor approved for the treatment of early and advanced PD. The package insert warns about its potential serious interactions with selective serotonin reuptake inhibitors (SSRIs). Recent reports lack information on long-term follow up and compliance [1-2].

Methods: Retrospective chart review of 69 PD patients seen at the Movement Disorders Clinic by one of our neurologists (CS) between 2005-2008. Our criteria required patients who were prescribed Rasagiline and who were on antidepressants at any point of the treatment. Any adverse event reported by the patient after starting concomitant use of both medications was described.

Results: 69 patients with PD (M:F ratio, mean age: 65.15 +/- 9.8) were offered rasagiline between 2005-2008. Four of them declined due to fear of potential drug-drug interaction, two due to affordability/availability reasons, and three for unclear reasons. Of 60 patients on rasagiline with follow up information (mean 29 months), 6 patients (M:F ratio 5:1, mean age 58.5+/- 12.38) were on concomitant antidepressants. The mean duration for the appearance of adverse events was 13.75 months (range 3-37 months). Adverse events identified in four patients consisted of weight gain (duloxetine), tiredness (mirtazapine) and anxiety (2 patients on SSRI and/or bupropion). Three patients continued on rasagiline.

Conclusions: We did not identify any serious adverse events in our patients on antidepressants and rasagiline. These events could not be distinguished from the side effect profile of the antidepressants alone or from the underlying disease. Patient and pharmacist education efforts may be required in order to improve compliance. 1. Panisset M, S.S., Ondo W, Fitzer-Attas C, Chen JJ, 340. Safety of concomitant therapy rasagiline and antidepressants in Parkinson's disease. Movement Disorders, 2007. 22(Suppl 16): p. s104-s105. 2. Schwid, S.R.a.t.P.S.G.R., NY, 286. Safety of Rasagiline in Combination with Serotonine Reuptake Inhibitors. Annals of Neurology, 2005. 58 (suppl 9): p. S56.

Th-261

In vivo assessment of degeneration of the nigrostriatal dopaminergic tract in MPTP-treated monkeys with 18F-FECNT positron emission tomography

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Objective: To validate 18F-FECNT as a positron emission tomography (PET) ligand to quantify region-specific changes in the dopamine transporter (DAT) density in the nigrostriatal system.

Background: PET imaging of DAT ligands is a useful non-invasive method to assess the degree of striatal dopamine denervation in patients with Parkinson's disease, but has not been validated against an ex-vivo standard.

Methods: We used six rhesus monkeys, divided into two groups. Group 1: Three monkeys receiving once weekly injections of MPTP (0.2-0.5 mg/kg) for 21 weeks. We carried out 18F-FECNT PET at baseline (twice; four weeks apart) and at week 21. Postmortem stereological cell counts of dopaminergic (DA) neurons in the ventral midbrain and intensity measurements of DAT and Tyrosine hydroxylase (TH) immunoreactivity in the striatum were performed and correlated with PET data. Group 2: Three untreated monkeys, used to generate control data for the anatomical cell counting, DAT and TH immunoreactivity measurements.

Results: The 18F-FECNT test-retest variability was 4.3%. The sensorimotor putamen, caudate nucleus, nucleus accumbens and substantia nigra-to cerebellum ratios were reduced to 12%, 16%, 56% and 51% of the mean control values, respectively. The region of interest–to-cerebellum ratios of 18F-FECNT uptake was correlated with postmortem stereological cell counts of nigral dopaminergic neurons, and striatal DAT and TH immunoreactivity.

Conclusions: 18F-FECNT is a reliable PET imaging ligand to quantify absolute changes in DAT levels in the nigrostriatal system in primates.

Th-262

Potential neuroprotective effects of metabotropic glutamate receptor type 5 (mGluR5) antagonist in MPTP-treated monkeys

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Objective: To assess the neuroprotective effect of the mGluR5 antagonist, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced toxicity of nigrostriatal dopaminergic neurons in monkeys.

Background: Previous studies indicate that the effects of the dopaminergic (DA) neurotoxin MPTP are reduced in mGluR5 knock out mice, and that the mGluR5 antagonist MPEP protects against the effects of MPTP in normal mice. The effects of mGluR5 blockade in primates are not known.

Methods: Ten rhesus monkeys were divided into 2 groups. Group 1 consisted of seven monkeys treated with either MTEP (10 mg/kg; n=4) or vehicle (n=3) for a total of 31 weeks. Between weeks 5 and 26, these animals received weekly injections of MPTP (0.2-0.5 mg/kg), followed by a 2 week washout period. The animals were observed weekly for changes in motor behavior, and received 5 PET scans with the dopamine transporter (DAT) ligand 18F-FECNT to determine the density of DA terminals at fixed time points. Postmortem stereological cell counts of DA neurons in the ventral midbrain and intensity measurement of DAT and tyrosine hydroxylase (TH) immunoreactivity in the striatum were generated. Group 2 consisted of 3 untreated monkeys used as controls for the postmortem studies.

Results: After the 26 weeks treatment period, animals in the MPTP/vehicle group showed more severe parkinsonism than animals treated with the MPTP/MTEP combination. These behavioral changes were correlated with a more significant decrease of 18F-FECNT uptake in the striatum and the ventral midbrain of MPTP/vehicle-treated monkeys than in the MPTP/MTEP-treated group. The postmortem immunohistochemical analysis showed a significant difference in the degree of DA cell loss and reduction of striatal DAT and TH immunoreactivity between the 2 groups.

Conclusions: The mGluR5 antagonist, MTEP, protects monkeys against MPTP-induced nigrostriatal dopamine depletion. MGluR5 receptor antagonists may have neuroprotective properties if administered during the pre-clinical period in patients with Parkinson's disease.

Th-263

L-dopa effects on dysphagia in Parkinson's disease: A videofluoroscopic analysis

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Objective: To assess with videofluoroscopy the L-dopa effects on dysphagia in parkinsonian patients.

Background: In clinical practice, the videofluoroscopic examination (VFE) is the reference method for evaluating swallowing disorders (Troche et al, Dysphagia, 2008;23:26-32); these are common in Parkinson's disease (46%, according to Bird et al, Age Ageing, 1994; 23:251-254).

Methods: 10 parkinsonian patients were studied: mean age 69 y (range 60-80), mean disease duration 11 y (range 8-15) and mean L-dopa dosage 1370 mg (range 700-1900). 6 had symptomatic dysphagia (>1 year) and 4 were asymptomatics. The OFF state was assessed after overnight withdrawal of antiparkinsonian medications (>12 h) and the ON state after a mean L-dopa intake of 200 mg (range 50-400). The assessment was made of UPDRS motor score and VFE with a modified barium swallow using cinefluoroscopy and different food consistencies. The mean total time of X-ray exposure was 5.9 min (range 3.4-8.3). VFE images were recorded by a digital movie camera (25 frames/sec) and further analysed frame by frame in order to calculate a dysphagia score on 14 items (severity range: 0-2) for the swallowing events. Statistical analysis was made by comparing OFF and ON values with paired Wilcoxon test, significance level at 0.05.

Results: The mean UPDRS scores were 42 (range 19-71) in OFF and 14 (range 7-23) in ON. The VFE analysis showed a significant improvement by L-dopa for the following items (in decreasing order of the significance levels): tongue retropulsion initiation, tongue and velum containment, epiglottis tilting, residue in pyriform sinuses, delay in pharyngeal transport phase triggerring, oral stagnation of the bolus. The sum of item scores of the 3 phases of swallowing (oral preparatory, oral and pharyngeal transports) and the total scores for the 3 food consistencies (liquid, semi-liquid, solid) were significantly improved in ON state.

Conclusions: This study of L-dopa effects on swallowing disorders in Parkinson's disease confirms the improvement due to dopaminergic stimulation. Future research is needed for new methods of swallowing assessment by repeated measures more suitable for detection of the risk of laryngeal penetration, namely the acoustic and physiologic devices that have to be compared with the VFE.

Th-264

Vitamin D deficiency in a cohort of patients with Parkinson's disease

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Objective: To identify frequency of 25- Hydroxy vitamin D deficiency in patients with known PD and its possible relation ship with activity level and medication use.

Background: The role of vitamin D deficiency in Parkinson's disease has been recently described. Few studies have reported higher prevalence of vitamin D Deficiency in PD patients as compared to control. It is unclear that this deficiency is related to patients activity level, exposure to sunlight or medications use.

Methods: Vitamin D levels were checked in consecutive patients with established PD. The levels were defined as mild Vitamin D Deficiency; 15-20 ng/ml, moderate Vitamin D Deficiency; 10-14 ng/ml and severe Vitamin D Deficiency; less than 10 ng/ml. Activity level was described as normal, assisted ambulation and bed ridden or wheel chair bound.

Results: We analyzed 35 patients. Age range was 41-76 years (mean 55 years). There were 16 women. Mean duration of PD was 6 years (range 4-13 years). 22 patients were active as normal, eight patients were ambulatory with assistance and five patients were wheel chair bound or bed ridden. Only 3 patients were taking Dopamine agonist monotherapy, 16 patients Levadopa monotherapy and 16 patients were taking combination therapy. Vitamin D levels were normal in 7 (20%) patients, mild deficiency 12 (35%), moderately deficient in 10 (30%) and severe deficiency in 6 (17%) patients. There was no statistically significant correlation between activity level and vitamin deficiency states, duration of PD and number of medications. The lack of significance was most likely due to small sample size.

Conclusions: Vitamin D deficiency was highly prevalent in our patient population. There was no statistically significant correlation between activity level and vitamin deficiency states, duration of PD and number of medications. Large prospective studies are needed to analyze this correlation.

Th-411

Amantadine for refractory "dyskinetic storm" in emergency room

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Objective: To emphasize the opportunity to use amantadine for hyperacute and out of control dyskinesias secondary to levodopa (LD) treatment in emergency room.

Background: Amantadine not only provides an antidyskinetic effect, but an antiparkinsonian benefit in cases it is necessary to stop LD or dopaminergic drugs.

Methods: A 74 year old patient treated with LD for Parkinson's disease (PD) since he was 44; with low tolerance to multiple other dopaminergic drugs (he took only 150mg/day of LD). He developed a "dyskinetic storm" and had to be sedated to control it. He tolerated sedation withdrawal only after an amantadine infusion. We will attach a supplementary video to illustrate this case.

Results: "Dyskinetic storm" was controlled and dopaminergic treatment was adjusted to 100 mg LD per day. We discuss some possible genetic and physiopathological mechanisms for "dyskinetic storm" development and for hypersensitivity to dopaminergic therapy in this and similar patients.

Conclusions: Definitely, we will not only remark on the wide variability and sensitivity in the response to dopaminergic therapy and development of adverse events, but the well known benefit of amantadine for the management of secondary dyskinesias.

PARKINSON'S DISEASE: QUALITY OF LIFE/CAREGIVER BURDEN

Mo-261

Quality of life in patients with Parkinson's disease: Importance of gait disorders and rehabilitation using the method of tempo-rhythmic correction

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Objective: Determine gait disorders effect on patient's quality of life (QoL) and ways to increase it with traditional and tempo-rhythmic correction of gait (TRCG) methods.

Background: Many motor and non-motor reasons are decrease QoL in Parkinson's disease (PD) patients. One of most important reasons – gait disorders. We numerously presented fragments of our research concerning gait restoration, using tempoTRCG method, which improved gait parameters.

Methods: Experience group (EG): 60 patients (65,1±6,1years) stage 3,0 PD. Patients received medications and TRCG. Control group(CG): 30 patients (63,9±7,3 years) stage 3,0 PD, receiving medications only. Patients scored by Gait and Balance Scale (GABS), items 2, 3, 15, 16, 17, and PD Questioner-39 (PDQ-39), questions 4-8. Questions were chosen, because they connected with gait disorders mostly. Questioning was held initially, after 3 weeks, after 6month since research began. Medication dose was corrected during first 3 weeks in both groups, later therapy remained constant. Average group L-DOPHA dose was comparable in both groups (521,62±184,22 mg and 571,66±127,76 mg).

Results: Initially, QoL scores similar in both groups (GABS 7,42±3,09; PDQ-39–9,44±3,36 in EG, GABS 7,33±2,72; PDQ-39–8,30±3,52 in CG). After 3weeks results already seen, EG improving more significantly (GABS 5,55±2,52; PDQ-39 - 6,32±3,22 in EG, GABS 6,60±2,63; PDQ-39–7,17±3,41 in CG). Same improvement pattern after 6 month (GABS 4,43±3,00; PDQ-39–4,10±2,91 in EG, GABS 6,67±2,75; PDQ-39–8,83±2,97 in CG). Therefore, EG patients had significantly better results than CG. QoL results were decrease after 6 month, compared to 3 weeks- due to progressive disease nature. TRCG effect on QoL may be explained in 2 ways: more significant gait improvement; subjective feeling of "care".

Conclusions: We consider TRCG method reasonable for patients with stage 3 PD to increase QoL.

Mo-262

Parkinsonian dysarthria Uruguayan experience in a multidisciplinary team (open trial)

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Objective: The patients with Parkinson's disease present in their majority dysfunctions of the voice that alter their communication and determine a bad quality of life. This study will show the alterations of the voice and the values in the Scale of Quality of Life (PDQ 39) in the patients that receive attention in a multidisciplinary program dedicated to non pharmacological treatment comparatively to a group of patients that do not receive rehabilitation and a healthy control group.

Methods: A prospective study of three groups above mentioned was carried out. Twenty patients with idiopathic Parkinson's disease(PD) were selected to receive an interdisciplinary boarding in the Program of Education and Rehabilitation in the Parkinson's disease for patients, relatives and caregivers (PRENPAR). The three groups were paired by age and sex. Demographic data, years of treatment, plus quality of life was evaluated with PDQ-39. UPDRS scale were used. Controlled parameters of the voice and the speech were applied in three opportunities, the evolution of the speech is analyzed before and after having carried out an interdisciplinary therapy as well as the scales.

Results: The initial values of the parameters of the voice are similar in the patients although they are inferior to the group of healthy controls, at the end of the treatment an improvement of these is observed in the patients of PRENPAR, not existing improvement in the patients that don't receive the multidisciplinary treatment neither in the healthy controls. It is hoped to find a significant difference in the PDQ-39 among those patients that present the non pharmacological interdisciplinary treatment in group and the maintenance of the parameters of the speech after three months compared to the control group.

Conclusions: This study allows to determine that the voice is a fundamental element of the communication that should be approached in group to improve quickly and to maintain the achieved changes, which will redound to the welfare of the patient.

Mo-263

Hyperhidrosis and quality of life in Parkinson's disease

P.J. Browne, D. O'Donovan, T. Counihan (Galway, Ireland)

Objective: The objectives were to examine the prevalence, nosology and impact on quality of life of hyperhidrosis in patients with Parkinson's disease.

Background: Sweating (hyperhidrosis) is a common non-motor symptom in Parkinson's disease (PD), estimated to occur in 18% to 35% of patients. Little is known about the effects of hyperhidrosis on PD patients' quality of life (QoL), and the clinical contexts in which it occurs.

Methods: A validated questionnaire on hyperhidrosis was completed by participants from a PD patient database at a tertiary referral movement disorder clinic. Data was obtained on eighty-nine patients. Correlation was investigated with motor and autonomic symptoms and with QoL measures. QoL was assessed using the PDQ-39 and generic EuroQoL (EQ)-5D rating scales.

Results: Hyperhidrosis was reported by 53% of respondents and was often regional or asymmetric. Significant correlations were found in several domains of QoL subscores: embarrassment ($p<.0005$), feeling down ($p<.0005$), avoidance of public situations ($p=.001$), limitation of recreational activities ($p=.033$), worry about others' reactions ($p=.005$), worry about the future ($p=.003$), and sleep disturbances ($p<.0005$). There was no correlation between the presence of hyperhidrosis and PD severity or duration. Hyperhidrosis was not associated with other autonomic symptoms. Hyperhidrosis restricted

to specific motor states was reported in a minority of patients: "off" periods 4% (n=5); "on" periods 10% (n=9) and with dyskinesias 5.6% (n=5). A serendipitous finding of marked improvement in sweating symptoms was noted by a patient coincidentally receiving gabapentin for neuropathic pain; a post-hoc review of treatment of 6 patients in the cohort who had been prescribed gabapentin for neuropathic pain, noted subjective improvement in all patients.

Conclusions: Hyperhidrosis significantly impairs QoL in PD patients, is not correlated with other autonomic symptoms, and occurs in all motor states. The observation of improvement in hyperhidrosis with gabapentin demands formal study.

Mo-264

Fear of falling has a greater influence than other aspects of gait disorders on quality of life in patients with Parkinson's disease

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Objective: To determine the influence of GD on the QOL in patients with PD.

Background: Gait disorders (GD) and postural instability are common symptoms in patients with Parkinson's disease (PD) and may affect the patients' activities of daily living (ADL). Especially, freezing of gait (FOG) as a common cause of falls and injuries can greatly influence the quality of life (QOL) of PD patients.

Methods: A mail survey including clinical information, the PDQ39 questionnaire and our original 8-item questionnaire of GD (GD8Q) was sent out to all 683 PD patients that were seen at the Prague Movement Disorders Center between 6/2006 and 2/2007. In GD8Q the patients estimated (Item 1) their gait at the worst stage; (2) the effect of their GD on ADL, and (3) compared the severity of GD with their other motor symptoms of PD. The remaining 5 items of GD8Q evaluated the occurrence of phenomena such as (4) FOG, (5) levodopa resistant FOG in the "on" state, (6) falls, (7) the degree to which the patients' activity is limited due to fear of falling and (8) the occurrence of injuries. After the exclusion of incomplete answers, responses from a total of 491 patients (290 m, 201 f) of mean age 66.7 (SD 9.4) and mean PD duration 10 (SD 6) yrs were evaluated.

Results: Patients were divided into three groups with respect to the severity of GD (N1 =105: no GD, N2 =136: moderate GD; N3 =250: severe GD). Statistically significant intergroup differences were found in the total score of PDQ39 (means 18.8, 31.2, and 44.2 respectively, $p<0.01$) as well as in all of its subdimensions. Linear multiple regression analysis showed that fear of falling had the highest impact on PDQ39 scores (standardized regression coefficient=0.259, $p<0.001$). The impact of "on" freezing was smaller, yet statistically significant (0.17, $p=0.048$). The rest of parameters measured by GD8Q yielded statistically nonsignificant relationships.

Conclusions: Our results confirm that gait disorders have substantial influence upon the QOL in PD patients and suggest that some of their features, namely fear of falling and levodopa resistant "on" freezing, play a major role in QOL deterioration.

Mo-265

Three-dimensional gait patterns of Parkinson's disease patients who fall: A prospective study

M.H. Cole, G.K. Kerr, J.M. Wood, P.A. Silburn (Kelvin Grove, Queensland, Australia)

Objective: To establish the temporospatial and three-dimensional joint kinematic profiles of Parkinson's disease (PD) patients who prospectively reported falling during a 12-month follow-up period.

Background: PD is a common neurodegenerative condition, which was reported to affect between 53,000 and 72,000 Australians in 2005. Prospective research shows an increased incidence of falls in PD, with almost 50% of these falls occurring during locomotion. Clinical gait analyses show clear differences between PD patients and controls, but few studies have examined the gait profiles of PD patients who fall.

Methods: Forty-nine PD patients and thirty-four controls walked along a 12m walkway at a self-selected pace. Movement was captured using a 6-camera motion analysis system, which enabled the calculation of temporospatial and joint kinematic quantities. Monthly falls diaries were used to record any falls over the following year. These data permitted sub-division of the sample into fallers (32 PD, 17 controls) and non-fallers (17 PD, 17 controls). PD fallers had significantly longer disease duration, but were comparable with respect to disease state (Hoehn Yahr, UPDRS).

Results: PD fallers took shorter strides, walked slower and recorded poorer gait stability ratios (cadence/velocity) compared with all other groups. PD fallers spent a significantly increased time in stance and double support compared with the control fallers and non-fallers, but not compared to the PD non-fallers. These temporospatial differences were accompanied by a significant reduction in hip and knee range of motion in the sagittal plane for the PD fallers compared with the other groups, but when normalised to stride length, these differences diminished. No significant differences were found between control fallers and non-fallers for the examined variables or between PD non-fallers and the control groups.

Conclusions: PD fallers demonstrate significantly different temporospatial and joint kinematics, which may impair their ability to control their centre of mass under dynamic conditions. However, it remains unclear whether the reduced range of joint motion in these participants was related to the adoption of a more cautious gait pattern or differences in joint mobility. Nonetheless, an appreciation of these differences may help to identify PD patients at a higher risk of falling.

Mo-266

Delivering medication on time in Parkinson's disease

P. Cotton, H. Fleary, C. Kobylecki, K.R. McDonald, J.P. Dick, M.W. Kellett, M.A. Silverdale (Salford, United Kingdom)

Objective: To assess potential problems of medication delivery to patients with Parkinson's disease (PD), in hospital. Our aim was to develop a robust educational programme for hospital staff, to ensure appropriate management of patients with PD.

Background: Limited knowledge of antiparkinsonian medications, among health care professionals, can lead to undesirable outcomes for patients with PD when admitted to UK hospitals (Barber et al., 2001). Despite national UK guidelines and a recent campaign by the PD Society UK, we have identified problems with drug administration in multiple admissions of patients with PD in a retrospective case-note review. This could potentially lead to the worsening of parkinsonism, neuroleptic malignant syndrome and possible mortality.

Methods: 125 questionnaires were given to staff on our general wards (both medical and surgical) that care for people with PD, including elective or emergency admissions. Questionnaires were designed to identify multiple factors that could influence the timely delivery of medications to patients with PD.

Results: Preliminary results indicate a lack of insight and understanding of the need for patients with PD to receive their medications on time. These findings concur with reports from other UK institutions (Barber et al., 2001) and could potentially contribute to the adverse outcomes previously described.

Conclusions: Our data suggest traditional teaching methods may not meet the need for timely administration of antiparkinsonian medications. We are currently designing and implementing a teaching tool with the aim of highlighting areas where positive changes in practice can be made. This teaching method aims to reach all healthcare professionals regardless of grade and shift patterns of staff.

Mo-267

An audit of practice against National Institute of Clinical Excellence (NICE) guidelines for the diagnosis and management of Parkinson's disease (PD)

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Objective: To audit current practice in the Movement Disorder clinic at University Hospital Coventry and Warwickshire (UHCW) against NICE guidelines.

Background: NICE guidelines for diagnosis and management of PD (published June 2006) are the gold standard in England. Priorities for implementation are highlighted, including referral of possible PD patients untreated, specialist review within 6 weeks and access to a PD Clinical Nurse Specialist (CNS). Referral should be made to physiotherapy (PT), occupational (OT) and speech therapy (SALT) where needed.

Methods: We performed a retrospective audit of all patients referred to the Movement Disorders clinic with possible PD between October 2007 and October 2008. 96 patients were identified and 84 records examined. The referral letter, clinical notes and clinic letter were used.

Results: 76% new referrals were from family doctors, the remainder originating from hospital teams. 26% patients had previously been diagnosed with PD. 77% patients without previous specialist diagnosis were referred untreated. 59% patients on whom referral data were available were seen within 6 weeks. For the remainder, the additional wait was 1-15 weeks (mean 4.7 weeks). 48% patients were diagnosed with PD. Of these, 80% had documented assessment of Activities of Daily Living. Of the 30 patients likely to benefit from therapy input, 26% were offered referral to PT and 20% to OT. 6% were referred to SALT (1 patient already known to them). 72% eligible patients were given the contact details of the PD CNS. 11 (27%) patients were documented as not driving, and of the 30 remaining, 47% had documented advice regarding this.

Conclusions: This audit highlights the significant delay in seeing up to 41% of patients, encouraging non-specialists to consider starting treatment. Only 48% patients referred with a putative diagnosis are diagnosed with PD at the first visit, hence the importance of not treating prior to specialist assessment. A surprising number of opportunities for early therapy assessment are missed, probably due to limited resources. Documentation of advice regarding driving should be improved. Access to the PD CNS is limited, but where available, patients were referred. Reference: NICE guidelines for the diagnosis and management of PD in Primary and Secondary Care: June 2006

Mo-268

Validating the ADCS-ADL against performance-based measures of ADL in PD/PDD

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Objective: To validate the use of the Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL) in patients with Parkinson's disease (PD) and Parkinson's Disease with Dementia (PDD).

Background: The ADCS-ADL has been validated against the MMSE, but it is not clear whether it specifically reflects functional abilities, or is actually measuring cognitive impairment. Therefore, this study sought to validate the ADCS-ADL against objective performance-based measures of Activities of Daily Living (ADL).

Methods: Twenty-nine participants (17 PD, 12 PDD) over the age of 60 were administered the Naturalistic Action Test (NAT) and the Direct Assessment of Functional Status (DAFS). The NAT and DAFS do not penalize participants for motor imprecision/slowing. DAFS performance was scored for steps accurately accomplished (DAFS). The NAT was scored for the number of Total Errors. NAT error patterns also were analyzed, including the proportion of errors that were commissions (i.e., inaccurate execution of a step) versus omissions (i.e., failure to execute a step). Caregivers completed the ADCS-ADL.

Results: After controlling for MMSE, the ADCS-ADL significantly correlated with the DAFS ($rp = .48$, $p < .01$) and NAT Total Errors ($rp = -.74$, $p < .01$). This relation held for NAT omissions ($rp = -.64$, $p < .01$), but not commission errors ($rp = -.26$, $p > .05$). This pattern of correlations was observed for both simple ADL (ADCS-ADL items 1 – 6) as well as more complex IADL (Items 7 – 23).

Conclusions: The ADCS-ADL related to two objective performance-based measures of ADL function, and the relation could not be attributed to dementia severity. This suggests that the ADCS-ADL is a valid measure of ADL and is useful for PD/PDD participants. The link between the ADCS-ADL and objective performance was driven by omission errors, suggesting these errors are either especially problematic for patients or particularly salient to caregivers.

Mo-269

Effectiveness of an inpatient movement disorders program for patients with Parkinson's disease and predictors of rehabilitation outcome

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Objective: To investigate the effectiveness of an inpatient movement disorders program for patients with a primary diagnosis of Parkinson's disease, to determine whether gains made were clinically meaningful, and to identify predictors of rehabilitation outcome.

Background: In the outpatient setting, it becomes increasingly difficult to manage the complex medical and rehabilitation needs of persons with PD as the disease progresses. A movement disorders program in an inpatient rehabilitation setting may be a viable alternative.

Methods: One hundred and forty-six patients with a diagnosis of idiopathic PD were admitted from January 2004 to August 2008 to an inpatient rehabilitation hospital with a multidisciplinary movement disorders program. Patients participated in a rehabilitation program consisting of a combination of physical, occupational, and/or speech therapy for a total of 3 hours per day, 5 to 7 days per week and pharmacologic adjustments based on objective data collected daily. The differences between admission and discharge scores were analyzed for the Functional Independence Measure (FIM), Timed Up and Go Test (TUG), Two-Minute Walk Test (TMW), Berg Balance Scale (BBS) and Finger Tapping Test (FT). A regression analysis was conducted to determine predictors of rehabilitation outcome.

Results: Significant improvements were observed from admission to discharge for the Total FIM, Motor FIM, Cognitive FIM, TUG, TMW, BBS and Left and Right FT. Clinically significant improvements in Total FIM score were evident in 71.2% of the patients. The Left FT score on admission accounted for 21.4% of the variance in the Total FIM change score. The results were similar for fifteen patients whose medications were not adjusted during their stay (rehabilitation only).

Conclusions: Patients with a primary diagnosis of PD benefit from an inpatient multidisciplinary movement disorders program to improve functional status. Baseline finger tapping score may be a useful predictor of rehabilitation outcome.

Mo-270

The prevalence, associated factors, and impact of drooling in Parkinson's disease

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Objective: To determine the prevalence, associated factors, and impact of drooling in PD.

Background: Drooling is a frequent symptom of PD that is estimated to occur in three-quarters of all patients. This symptom can have a strong impact on the patients' QOL. There has been little research investigating the factors most commonly associated with drooling and its impact.

Methods: We administered a seven question survey on drooling to PD patients and age-matched non-PD controls. Each patient and control was assigned a drooling severity score and categorized as drooler or non-drooler. The age, disease duration, UPDRS scores, PDQ39

(QOL), and levodopa equivalent daily dosage (LEDD) were compared between PD droolers vs. PD non-droolers using t-tests for initial comparison followed by regression analyses.

Results: 58 PD patients and 51 age-matched controls participated. The mean age of the patient cohort was 69.27 years (SD 6.85) and the control cohort was 66.45 years (SD 9.17). In our patient cohort, the mean: disease duration was 10.96 years (SD 8.66); UPDRS on motor score was 30.76 (SD 10.57); and LEDD was 692.47mg (SD 544.03). The drooling severity score was significantly different between patients vs. controls (3.41 vs. 0.58; $p<.01$). 14% of controls vs. 59% of patients were droolers ($p<.01$). PD droolers scored worse on the ADL subscale of the PDQ 39 ($p=0.031$). Furthermore, PD droolers had significant difficulty speaking, eating, and socially interacting compared to PD non-droolers ($p<.01$). Interestingly, PD droolers scored worse on the mentation, hallucination and apathy items of the UPDRS Part I. On regression analyses, the UPDRS Part I had significant linear effect on drooling severity. As the UPDRS part I score increased by 1, the drooling severity score increased by 0.81. None of the other variables have significant effect, including age, disease duration, LEDD, motor severity and overall QOL.

Conclusions: There is a high prevalence of drooling in the PD population as compared to controls. PD droolers had worse QOL on the ADL subset. They had more difficulty speaking, eating and socially interacting compared to PD non-droolers. Further investigation is needed to clarify the association between drooling and mentation, hallucinations and apathy.

Mo-271

Impact of STN-DBS on health-related quality of life in patients with Parkinson's disease

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Objective: To determine the effect of subthalamic nucleus (STN) deep brain stimulation (DBS) on Health-Related Quality of Life (HRQoL) in patients with Parkinson's disease (PD).

Background: In order to better assess the adequacy of current PD treatments, health care providers have increasingly utilized various patient-based outcome measures, such as Perceived Health Status (PHS) and HRQoL. PHS questionnaires quantify the impact that disease has on one's ability to perform various life activities, while HRQoL instruments measure a patient's satisfaction with life conditions, i.e. to what extent functional limitations actually disturb the individual. Previous studies have aimed to evaluate the effect of DBS on HRQoL yet have employed questionnaires that assess PHS rather than HRQoL. Accordingly, there is a paucity of literature regarding the impact of DBS on HRQoL as it is defined by the World Health Organization Quality of Life Group (Den Oudsten et al. Mov Disord 2007;22:1528-37).

Methods: We prospectively analyzed HRQoL using a recently validated modular questionnaire (QLS^M) specifically designed for the DBS population (Kuehler et al. J Neurol Neurosurg Psychiatry 2003;74:1023-30). Twenty-three consecutive patients (13 men, mean age 61.9+/-8.4 years) with PD who met CAPSIT criteria for DBS were studied prior to surgery and postoperatively at 6 and 12 months.

Results: Following STN DBS, patients experienced an improvement in HRQoL, as measured by various items of the Movement Disorders and Health modules of the QLS^M (Table). Results from the Neurostimulation module of the QLS^M showed high satisfaction with DBS.

Conclusions: Prior work in patients with PD has shown improvements in function and PHS following DBS. This study adds to the existing literature by demonstrating that these functional improvements translate into higher patient satisfaction and improved HRQoL. Additional data describing the predictors and durability of HRQoL following DBS will be presented.

Table(Mo-271). Change in Various Health-Related Quality of Life Parameters of the QLS-M following STN-DBS

		Weighted Quality of Life Score				
		Baseline	6 Month		12 month	
QLS-M Module	Item Descriptor (number)	Mean (SD)	Mean (SD)	P-value*	Mean (SD)	P-value*
Health	Enjoyment of Life (3)	-1.45 (±7.0)	5.24 (±8.6)	0.01	5.58 (±12.5)	0.03
	Not Needing Help/Care (8)	-0.86 (±8.8)	5.65 (±7.0)	0.02	1.63 (±9.1)	0.4
Movement Disorders	Fluidity of Movement (1)	-2.05 (±9.1)	6.19 (±7.1)	<0.01	4.11 (±7.15)	0.02
	Steadiness when Walking (2)	-2.43 (±9.4)	7.44 (±10.3)	<0.01	2.11 (±9.71)	0.1
	Hand Dexterity (3)	-3.38 (±9.4)	6.69 (±8.4)	0.02	2.05 (±10.6)	0.1
	Absence of False Sensations (6)	2.00 (±8.5)	9.5 (±6.5)	<0.01	7.89 (±5.9)	0.01
	Independence from Help (11)	2.04 (±10.3)	9.4 (±5.6)	<0.01	4.10 (±9.4)	0.5
	Inconspicuousness of Illness (12)	-2.95 (±7.7)	5.25 (±5.1)	<0.01	5.32 (±7.3)	<0.01

*P-values versus baseline determined by paired T-test.

Mo-420

Impact of a support program in spouses of parkinsonian patients evaluated with the Zarit Caregiver Burden Inventory: A randomized study

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Objective: Parkinson's disease (PD) is a chronic illness occurring at a mean age of 60-65 years old. Spouses of PD patients are directly involved in the taking care of the disease which is time-consuming, stressing and leading to a feeling of powerless and anxiety. The main objective of this study is to evaluate, with the Zarit Caregiver Burden Inventory (ZCBI), the impact of a support program using principles of cognitive-behavioral therapy in spouses of advanced PD patients.

Methods: From 2005 to 2007, 75 couples, from 4 French references centers for PD, were randomized in an "educated" group (N=53) and in a control group (N=22). No differences were observed for ages of patients or spouses, mean duration of the disease or handicap in both groups. All patients were non-demented and fluctuating. ZCBI and MADRS scales were completed by the spouses at the onset of the study (M0) and 8 months later (M8). PDQ8 and MADRS scales were completed by the patients at M0 and M8. "Educated" spouses participated in 6 educative support groups using principles of cognitive-behavioral therapy. Medical information on PD and its treatments was given at the end of each session. From M0 to M8, no specific care was administrated to control spouses.

Results: Out of the 56 couples with complete data, M0-M8 difference of ZCBI score was not statistically different for the "educated" group (1.48) and for the control group (3.43). From M0 to M8, no differences were observed for scores of anxiety and depression, evaluated with MADRS, in spouses or PD patients or quality of life, evaluated with PDQ8 in PD patients.

Conclusions: In spite of a feeling of usefulness of cognitive-behavioral therapy and an improvement of items of SF36 scale in a previous study, this randomized study failed to demonstrate any improvement on ZCBI score in spouses of PD patients. This underlines the difficulty to evaluate this type of technique with existing scales. It was remarkable that the scores of ZCBI at M0 were under 40 reflecting a "low burden" while the stress of the spouses seemed important.

Tu-265

The impact of subtype and disease duration on quality of life in Parkinson's disease

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Objective: To evaluate the significance of disease duration and Parkinson's disease (PD) subtype in determining quality of life in PD patients.

Background: PD is a progressive disease that has a heterogeneous phenotype. Patients of the akinetic-rigid (AR) subtype are known to have a worse prognosis than those who are tremor-dominant (TD). The relationship of PD subtype and quality of life is not well-established.

Methods: This cross-sectional study analyzes patients (32 males and 17 females, age 63±10 years, disease duration 9.6±4 years, Hoehn & Yahr 3.1±0.8) consecutively selected as potential candidates for deep brain stimulation from 11/2000 to 12/2008. As part of their pre-operative screening, they completed the UPDRS and Parkinson's Disease Questionnaire (PDQ-39). Patients were categorized into TD (n=16), AR (n=24), and mixed (MX) (n=9) subtypes according to the tremor/rigidity ratio from the UPDRS in the OFF state (Schiess et al, *parkinsonism & Related Disord;*6,2000). 8 dimension scores (Mobility, Activities of Daily Living, Emotional Well-Being, Stigma, Social Support, Cognition, Communication, Bodily Discomfort) and 1 total score were calculated from the PDQ-39, each ranging from 0 (best) to 100 (worst). A linear regression model was used to observe the effect of disease duration and PD subtype on PDQ-39 dimension and total scores.

Results: Disease duration significantly influenced only Emotional Well-Being (regression coefficient [R1]=-1.65, 95% CI -3.08 to -0.22) and Bodily Discomfort (R1=-1.63, 95% CI -3.19 to -0.06). PD subtype influenced only Stigma, with Stigma scores of TD patients significantly higher than those of both AR (R2=-17.79, 95% CI -32.61 to -2.98) and MX (R2=-22.27, 95% CI -41.43 to -3.12) patients.

Conclusions: Emotional Well-Being and Bodily Discomfort were unexpectedly better for patients with a longer course of PD. Proper identification and treatment of problems within these dimensions, such as depression, and improved patient coping skills may play a role. TD patients appear more stigmatized by their symptoms in public than the AR and MX patients, perhaps due to the more visible nature of tremor.

Tu-266

Costs of illness in a Russian cohort of patients with Parkinson's disease

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Objective: The aim of the study was to evaluate the direct and indirect costs in a cohort of Russian PD patients over a 6-month period.

Background: The economic burden of PD on national health care systems and patients' families is substantial. During recent years, interest in the economic impact of PD in developed countries has increased. Data for Eastern Europe are still lacking.

Methods: We recruited 100 patients with idiopathic PD who visited the outpatient division of the Neurology Department of the Russian Medical State University in Moscow between October 2004 and December 2005. The Unified Parkinson's Disease Rating Scale was used to evaluate clinical status. Economic data were collected in a "bottom-up" approach and evaluated from the societal perspective. Indirect costs were estimated using a human capital approach. Russian currency was converted into 2005 Euros (EUR) using the purchasing power parity. Independent cost predictors were identified by means of multivariate regression analyses.

Results: From the societal perspective, total costs over six months amounted to EUR2620 (95%CI:2050-3200) with direct costs accounting for 67% and indirect costs for 33% of the total. Patients' expenditures accounted for 43% of their private income. The primary burden on patients was due to informal care and drugs. Only 10% of home care was provided by the formal service sector. Costs for the nation are estimated at 1.1 billion Euros.

Conclusions: The economic burden of PD in Russia is considerable, especially when taking into account low private incomes. Further development of a formal care system and better reimbursement systems for drugs are necessary.

Tu-267

Activities of daily living and health-related quality of life in persons with newly diagnosed Parkinson's disease, according to subtype of disease

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Objective: To describe activities of daily living (ADL) and health-related quality of life (HRQoL) at first visit to specialised care, in patients subsequently diagnosed with Parkinsons disease (PD), according to sub-type of disease.

Background: When a person who eventually will be diagnosed with PD first seeks medical advise, the complaint may be related to diffuse symptoms and to difficulties in cores of daily life such as handwriting, brushing teeth or turning in bed. The profile of disability at first visit in patients with subsequently diagnosed PD, according to different subtypes of PD, is yet inadequately described. In order to contribute from start with suitable rehabilitation strategies and support to patients, families, and carers, it is important to better understand the patients' initial activity profile and quality of life according to subtype of PD.

Methods: 125 consecutive patients with parkinsonian symptoms were referred to a movement disorders unit and the 99 patients (45 females) with subsequently confirmed PD at one year, were included. Patients were classified into 3 clinical groups according to predominant symptoms: 50 Postural instability and Gait difficulty (PIGD), 37 tremor dominant (TD) and 12 indeterminate (IND) patients. Baseline evaluation tools included Hoehn and Yahr staging, Unified Parkinson's Disease Rating Scale, Schwab and England ADL scale, mini-mental state examination (MMSE), the Montgomery-Asberg depression scale (MADRS), the ADL taxonomy, and the Parkinson's disease questionnaire (PDQ39).

Results: There were no differences between the various groups with respect to age at onset of symptoms, age at first visit, or in MMSE scores. The PIGD group exhibited significantly worse scores than the IND and the TD groups on all evaluation tools, except for MADRS where both PIGD and TD groups scored similar. On the ADL taxonomy, the PIGD and IND groups scored worse than the TD group on 20 out of 47 listed activities. On the PDQ39 the PIGD group exhibited worse scores compared with the TD group in mobility, ADL, communication, and bodily discomfort.

Conclusions: At first visit to a movement disorder center, and despite similar age and duration of symptoms, PD patients with PIGD subtype showed a strikingly worse status on almost all evaluation parameters than TD patients.

Tu-268

Outpatient assessment program visit reduces hospitalizations in patients with Parkinson's disease

L. Miller, B.P. Hersh (Boston, Massachusetts)

Objective: To retrospectively evaluate the number of emergency room (ER) visits and hospitalizations in patients with moderate to advanced Parkinson's disease (PD) before and after attending a single outpatient assessment program.

Background: Ambulatory day programs are used to evaluate motor fluctuations and adjust medications in PD patients. Five

patients were selected for 3 programs during October and November 2008, 4 of whom had motor fluctuations, and 2 with symptomatic postural hypotension. During each 5-6 hour session, patients were monitored for motor fluctuations, medication responses, side-effects and vital signs. Patients were accompanied by caregivers and received individualized teaching. Sessions were conducted by a trained PD nurse, and patients were assessed by the treating neurologist both at the start and end of the visit and a new care plan was delineated.

Methods: Using our electronic medical record, we retrospectively analyzed the frequency of ER visits or hospitalizations in 4 of the 5 patients who completed an ambulatory day program during this session, examining the 4 month period prior to and 2-3 month period following each patient's day program visit. The 5th patient was excluded from analysis as he did not have motor fluctuations.

Results: Of the 4 patients seen in the ambulatory day program with motor fluctuations, 3 were seen in an ER or hospitalized a total of 5 times in the 4 months preceding this program. Reasons for hospital visits included syncope, pelvic discomfort with bladder mass, dizziness, lumbar contusion after a fall, panic attack with hyperventilation. Syncope was the reason for admission in 2 of the 4 patients. Falls were associated with 2 of 5 visits to the hospital emergency room. In the 2-3 month period following each patient's day program visit (to date of this report), none of these 4 patients required a hospital visit.

Conclusions: An ambulatory day program with an emphasis on teaching, monitoring and adjusting medications can have significant short term benefit for patient's with moderate to advanced Parkinson's disease, motor fluctuations and/or postural hypotension. Although our patient number is small, our data indicates that hospital visits due to syncope, falls and anxiety in this population may be avoided if medications are carefully adjusted and patients are given clear guidance regarding symptom management at home.

Tu-269

Special aspects of Parkinsons disease. Disturbing factors of the natural course of the disease

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Objective: To investigate the main reasons why PD patients are administered to our emergency unit.

Background: Parkinson's disease is a chronic neurodegenerative disease characterized by tremor, muscle rigidity, bradykinesia and gait instability. In early disease, Parkinson's disease is well managed by replacement of dopamine. The gold standard for therapy is levodopa. However, as the disease progresses, a variety of syndromes may result in emergency department visits. Troublesome motor and non-motor complications arise in the advance stages of disease and may be triggered by medical illness such as infection. Patient in the early stages generally do well and do not require emergency treatment.

Methods: All emergency admissions of patients with Parkinson's disease were identified over a 31- month period. The patients were identified from the computer patient administration system. We analyzed the reasons for emergency admission. In addition we analyzed the patient's clinical records, laboratory findings, medical illness and current therapy. The total number of patients with Parkinson's disease was 84. While 30 patients (36%) were discharged from the emergency room, 54 patients (64%) needed to be treated in hospital. The most common reasons for admission were as follows: motor complications (n=19, 23%), falls (n= 5, 6%), psychosis (n=3, 4%), depression (n=1, 1%), dementia (n=6, 7%), impairment of speech (n= 2, 2%), worsening of swallowing (n= 4, 5%), confusion/ disorientation (n=3, 4%), motor fluctuations and dyskinesia (n=8, 9%), patients, whose impairment is not enumerate (n=43, 51%), urinary infection (n=14, 17%), infective disease (n=33, 39%). The most customary medication is levodopa combined with a peripheral dopadecarboxylase inhibitor (n=49, 58%). Other medications include dopamine agonists (n=23, 27%), Others (n=15, 18%) and neuroleptics (n=13, 15%).

Conclusions: From a search of available literature on this topic, we identified that there is little known about the reasons for emergency admission in Parkinson's disease. In the advanced stages of Parkinson's disease motor and non motor symptoms like cognitive dysfunction, dementia, depression, psychosis, autonomic disturbances and medical illness increase, which leads to emergency room visits.

Tu-270

Video assisted swallowing therapy for patients with Parkinson's disease

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Objective: Swallowing disturbances (SD) in Parkinson's disease (PD) are usually treated by traditional swallowing therapy (TST).

Background: Swallowing disturbances (SD) in Parkinson's disease (PD) are usually treated by traditional swallowing therapy (TST).

Methods: 42 PD patients were divided randomly into TST and VAST groups, filled an SD questionnaire (SDQ) and underwent 2 swallowing assessments: Bed side evaluation (BSE) and fiberoptic endoscopic evaluation of swallowing (FEES). TST and VAST consisted of 5 sessions in 2 weeks, practicing compensatory techniques. During the first FEES, two episodes were recorded: the patients' swallowing process (1) in a natural pathological way and (2) with the appropriate compensatory strategy. The video, used during all VAST sessions, provided the patient with visual feedback on the effectiveness of the swallowing compensatory strategy. SDQ and BSE were performed at pre, post and 4 weeks follow-up;FEES was performed pre and post therapy. Evaluators were blinded to the patients' therapy approach. The patients were unaware of the two therapy approaches.

Results: 42 (24 M) non-demented PD patients with SD were diagnosed by FEES (mean age 67.6±8.26 y, disease duration 7.43±4.66 y, Hoen&Yahr 2.21±0.79**,** and SDQ 14.65±5.81). A significant improvement was observed in swallowing functions in both groups from pre to post therapy ($p<0.001$): FEES ($p<0.05$), BSE ($p<0.001$) and SDQ ($p<0.005$). FEES demonstrated a significant greater reduction in pharynx food residues in the VAST group compared to the TST group ($p< 0.01$). According to BSE, VAST group patients were able to overcome 2 swallowing pathologies significantly better than patients from the TST group: Mouth residues ($p<0.001$), swallowing reflex ($p<0.001$). A significant difference was also observed in SDQ in the VAST group between post treatment and follow up measurements ($p<0.05$).

Conclusions: VAST was found to be a more effective therapy program than TST for treating PDP with SD.

Tu-271

Appropriate timing of introducing feeding gastrostomy for Parkinson's disease patients with dysphagia

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Objective: To evaluate the appropriate timing of introducing Percuteneous endoscopic gastrostomy (PEG) for higher quality of life in advanced Parkinson's disease (PD) patients with dysphagia.

Background: Dysphagia occurs in up to 40% of PD, mainly in advanced patients. Off-period dysphagia disturbs appropriate medication, which leads to the deterioration of symptoms and forms the vicious circle. Dysphagia can cause aspiration pneumonia and long term bed-ridden status due to pneumonia severely deteriorates patients' ADL. To prevent such miserable outcome, neurologist should be cautious in evaluating early signals of dysphagia and should introduce an appropriate management such as gastrostomic feeding.

Methods: Medical records of all PD patients admitted to our hospital from January 1999 through December 2008 were retrospectively

evaluated. The prognosis of patients with dysphagia was followed up until December 2008.

Results: Among 85 patients (mean age 65.6±10.9 y.o.), dysphagia was present on admission in 27 patients (70.5±6.8 y.o.). 58 patients (63.3±11.6y.o.) were without dysphagia. Age of onset was 56.4 and 53.2 y.o., disease duration was 14.2 and 10.1 years, Hoehn and Yahr stage was 4.3 and 2.9, on average, respectively. Serum albumin on admission (normal range: 3.7-4.9 g/dl) was decreased to 3.4 g/dl in patients with dysphagia, whereas it was normal (4.0 g/dl) in those without dysphagia. In those with dysphagia, 8 had PEG placement, 2 had nasogastric tube feeding, and oral intake was continued in other 17 patients. Two patients with off-period dysphagia were introduced with PEG as a reliable route for medication. They were followed up to 36 and 15 months, without any episodes of pneumonia. They were able to take food orally on on-period until the last follow-up, with normal albumin level. Other 8 patients were introduced PEG/nasogastric tubes after the first or recurrent pneumonia. All of them had severe dysphagia and became completely dependent on tube nutrition. Most of them suffered from severe deterioration in ADL due to the longer hospitalization periods (113 days vs 75 days in former two patients) and were obliged to remain hospitalized.

Conclusions: Introducing PEG as a reliable route for medication and nutritional management at appropriate stages may improve the prognosis of patients with off-period dysphagia.

Tu-272

Parkinson's disease service improvement in accordance with National Institute for Health and Clinical Excellence (UK)

S. Mavinamne, A. Sugumaran, S. Abraham (Wrexham, United Kingdom)

Objective: To see whether Parkinson's disease (PD) management in Wrexham Maelor Hospital adhere to The National Institute for Health and Clinical Excellence (NICE)guidelines.

Background: The NICE guidelines(2006) for Parkinson's disease(PD) highlights the importance of diagnosis and benefit from interventions provided by a range of health disciplines. We attempted to improve the existing PD services through an audit cycle.

Methods: Identification of deficiencies by an initial retrospective audit of 62 cases of PD in 2007 led to recommendations for changes in service, which were implemented in 2008. We reaudited the outcome of recommendations using similar parameters in 25 cases. The parameters assessed were 'delays in seeing referrals', 'follow-ups', 'access to specialist nursing', 'physiotherapy' (PT), 'occupational therapy' (OT), 'speech and language therapy' (SALT) and 'palliative care'.

Results: Following the initial audit in 2007 the need for a PD specialist nurse and increased referrals to PT, OT and SALT was identified, so was the need to increase number of clinics to accommodate more patients. Some changes were made since then and the results of the intial audit and the re-audit are as given in the table below.

Table (Tu-272). Change effect

	2007 (n=62)	2008 (n=25)
Delay in seeing referrals	58% of total	8% of total
Delay in Mild PD	5.4 weeks	5 weeks
Delay in Severe PD	5 weeks	No delay
Access to specialist nurse	No	No
Referral to PT	50%	41.17%
Referral to OT	25.8%	35.3%
SALT referral	9.7%	0%
Palliative care	0%	0%
Followup	93.5%	100%

Conclusions: The initial audit in 2007 led to identification of defeciencies in the service provided locally leading to changes. The reaudit in 2008 showed improvements in seeing referrals and followup within the timeframe stipulated by NICE and increased referrals to OT. Access to PD specialist nurse remains unfulfilled and further efforts need to be made to fulfill this need in the service.

Tu-273

Neuropsychiatric symptoms in Parkinson's disease: A caregiver perspective

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Objective: To describe the prevalence of neuropsychiatric symptoms in a sample of patients diagnosed with Parkinson's disease (PD) in our socio-cultural context using self and caregiver report.

Background: Although neuropsychiatric symptoms are often described in demented patients with PD, they can also be seen in patients without cognitive decline. As many of these patients are supported by their families until the very late phases of the disease, it is important to consider the impact of these symptoms from a caregiver perspective.

Methods: A total of 24 PD patients, 10 women and 14 men, were evaluated using the Hoehn and Yahr stages and the following scales: the motor score on the Unified Parkinson's Disease Rating Scale (UPDRS-III), Schwab and England scale and mini-mental state examination (MMSE). Additional neuropsychiatric data concerning levels of depression were collected through the Beck depression inventory (BDI) and the caregiver's point of view was assessed using the Spanish Neuropsychiatric Inventory Questionnaire, a brief clinical form of the Neuropsychiatric Inventory.

Results: The mean age was 69'88 (TD 7.415) years and the mean disease duration was 6'92 (TD 3'74) years. Eighty per cent of them were married. The mean UPDRS-III score was 21.7 (TD 10.5) and no patient had a score lower than 23 in the MMSE. In our sample, 75% met the BDI criteria for any degree of depressive symptoms and even 8% scored as severely depressed. Moreover, 92% of the caregivers reported at least one psychiatric symptom. The most common of these symptoms was depression (16 patients) followed by anxiety (13 patients), irritability (11 patients) and apathy (10 patients). Finally, depression was also considered the most stressful psychiatric symptom in any degree for caregivers (71%), followed by anxiety (54%), apathy (37%), irritability (37%) and sleep disturbances (33%).

Conclusions: More than ninety percent of caregivers were concerned about at least one psychiatric symptom. Their perception of them as stressful and its likely relation to quality of life and family burden might contribute to an early rest home placement. Based on our data, it seems a need to take into account these aspects in the assessment of these patients, to accomplish an affordable and appropriate treatment of PD.

Tu-274

Non-motor symptoms: An important contributor to the quality of life in Parkinson's disease

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Objective: To assess the frequency of non-motor symptoms in Parkinson's disease (PD), their treatment and their consequences on the quality of life (QoL).

Background: The non-motor symptoms (autonomic, neuropsychiatric and senzorial) are very common in PD and relatively easy to treat, sometimes preceeding the motor symptoms which lead to the diagnosis and can have an important impact on the QoL.

Methods: A prospective study was performed on 20 patients (6 women, 14 men) aged 40-79 years, diagnosed with PD for more

than 2 years. The treatment for the motor symptoms was optimised in all patients. The non-motor symptoms were assessed using a questionnaire created for this purpose, corroborated with historical information and data obtained from the following rating scales: UPDRS I-IV, Hoehn & Yahr, Schwab & England, analogic pain scale, Epworth sleepiness scale, Mini Mental Status and Hamilton depression rating scale. Parkinson's Disease Summary Index (Parkinson's Disease Questionnaire–PDQ 39) was used to study the impact on QoL of the non-motor symptoms. All patients were re-assessed for QoL changes after 3 months of specific treatment for the non-motor symptoms.

Results: The most common non-motor symptoms were fatigability, constipation, hyposmia, sialorrhea, pain and seborrhea. All studied patients presented at least 1 non-motor symptom and 80% more than 5 non-motor symptoms, especially those with longer history of PD and in the age group 60-69 years. These symptoms had a negative influence on QoL, since they're usually overlooked, hence not treated. By treating these non-motor symptoms, including the neuropsychiatric symptoms, we observed a statistically significant increase in the QoL score after 3 months treatment in case of mobility ($T = +5{,}77$; $df = 19$, $p < 0{,}01$ one-tailed), daily activities ($T = +6{,}66$; $df = 19$, $p < 0{,}01$ one-tailed), emotional status ($T = +7{,}1$; $df = 19$, $p < 0{,}01$ one-tailed), general discomfort ($T = +7{,}1$; $df = 19$, $p < 0{,}01$ one-tailed), PDSI ($T = +7{,}94$; $df = 19$, $p < 0{,}01$ one-tailed).

Conclusions: The non-motor PD symptoms are frequently overlooked, not addressed by the treating physicians. Their treatment can result, in just a short while, in a significant increase of the QoL scores of these patients with PD, especially in case of general discomfort, daily activities, emotional status, mobility.

Tu-275

Validity and reliability of Hong Kong Chinese version Parkinson's disease Questionnaire-8

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Objective: To investigate reliability and validity of Parkinson's Disease Questionnaire-8 (PDQ-8) among Chinese patients with PD.

Background: Parkinson's disease (PD) is a chronic progressive illness that causes deterioration of quality of life of patients with PD. PDQ-8 is a brief disease specific quality of life instrument. Its Hong Kong Chinese version is available but reliability and validity hasn't been studied.

Methods: Patients diagnosed with idiopathic PD, aged 25 year-old or above, were recruited from a neurology clinic. The Hong Kong Chinese version PDQ-8 was given to patients to complete. Clinical rating scales such as Unified PD Rating Scale (UPDRS) and Hoehn & Yahr stage were performed. Test-retest was performed 14 days after the first one among 11 patients.

Results: One hundred and one patients with PD were recruited, of which 59 subjects (58.4%) were male, with mean age ($\pm$SD) 63 ($\pm$9) year-old. The mean total score ($\pm$SD) of PDQ-8 was 34 (20). Internal consistency of PDQ-8 was good (Cronbach's alpha 0.83). The PDQ-8 total score for Hoehn & Yahr stage I, II III IV and V were (mean $\pm$ SD) 28$\pm$23, 31$\pm$17, 41$\pm$16, 46$\pm$8, and 69$\pm$21, respectively ($p=0.01$ by Kruskal Wallis test). A moderate correlation was seen between UPDRS ADL total score and PDQ-8 total score ($r=0.60$, $p<0.01$), as well as between UPDRS total score and PDQ-8 total score ($r=0.57$, $p<0.01$). Test-retest was assessed by Wicoxon signed rank test, with the total score of PDQ-8 at first time point being 13.9, the second time point being 13.2 (p value >0.05). Statistically and significantly higher percentage of younger patients (<54 year-old) reported they experienced problems in emotion (69%), close relationships (69%) and embarrassment (88%), compared to those aged 54 year-old or above (40%, $p=0.034$; 31%, $p=0.004$; and 46%, $p=0.002$; by Chi-square test).

Conclusions: This study demonstrated that the Chinese version of PDQ-8 is reliable and valid when applied to our native Chinese patients.

Tu-417

The use of laser walking aids to improve gait in a patient with Parkinson's disease – A case report

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Objective: To evaluate the use of laser walking aids with a patient with Parkinson's disease (PD) and to assess the level of improvement in gait when using these aids.

Background: Freezing of Gait is a common motor problem for patients with PD, and many take an increased number of steps to turn 180degrees. Both these problems can lead to falls. Studies have shown that visual cues can aid initiation of gait and reduce freezing. Laser walking aids (Laser cane and USTEP walking frame) have been developed to provide a mobile visual cue which can enable improved mobility.

Methods: A patient with typical symptoms of PD was assessed using a physiotherapy-specific functional objective outcome measure (Lindop Parkinson's Assessment Scale–LPAS), the gait section of which comprises 6 tasks (sit to stand, a "timed up and go" walk (TUG), timed unsupported stand, 180degree turn to right and left and walking through a doorway) giving a possible total score of 18. The patient was assessed at approximately six-month intervals over a period of 4 years, initially using a normal walking stick but later progressing to a laser cane and also trying a USTEP when her mobility required more stability and assistance. The comparison assessments were made at the same treatment sessions, approximately 15 minutes apart.

Results: The patient showed marked deterioration in gait performance during the first two years of the study. She was then assessed comparing mobility with the stick and the laser cane. Her TUG time reduced from 56 seconds with the stick to 19 seconds, the number of steps for a left turn reduced from over 20 to 6 and freezing improved from 2 freezes in the doorway to only some festination. Two months later the results were more marked: TUG reduced from 123 seconds to 15, turning reduced from 30 steps to the right and 35 to the left to 6 each way. Freezing reduced from 1 episode to 0 (Table 1).

Table 1 (Tu-417). Comparison of walking stick and laser cane

Date	Walking aid used	TUG time (seconds)	Steps to turn to right	Steps to turn to left	Number of freezes	LPAS gait score
13/04/2007	Walking stick	56	6	over 20	2	10/18
	laser cane	19	6	6	some festination, no freeze	17/18
13/06/2007	Walking stick	123	30	35	1	7/18
	laser cane	15	6	6	0	18/18

On re-assessment 8 months later, the patient's scores had reduced so she tried the USTEP. Results showed improvement inTUG and turning with the USTEP (Table 2).

Table 2 (Tu-417). Comparison of laser cane and USTEP

Date	Walking aid used	TUG time (seconds)	Steps to turn to right	Steps to turn to left
29/02/2008	laser cane	126	9	18
	USTEP	106	7	16

Conclusions: Laser walking devices can provide effective visual cueing to improve mobility in people with PD. In this case, gait speed, the number of steps to turn and freezing all improved using these aids. Such improvement can contribute to a better quality of life and a reduced risk of falls. A full study is indicated with a larger number of patients.

We-262

Pain in patients with Parkinson's disease with or without motor fluctuation

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Objective: To evaluate the frequency of pain in patients with PD and the improvement of quality of life by treating this symptom.

Background: Patients with Parkinson's disease (PD) complain of pain more often than patients with other chronic diseases and this symptom cannot be fully appreciated by clinical rating scales.

Methods: We recruited 39 patients with PD; 27 with advanced PD and 12 with early PD. All patients were assessed using Unified Parkinson's Disease Rating Scale, Hoehn and Yahr staging, Visual Analogue Scale for Pain; the Parkinson's Disease Questionnaire (PDQ-39), Activities of daily living (ADL) and Epworth Sleeping Scale. All tests were repeated after 4 weeks.

Results: Quality of life deteriorated significantly with increasing disease severity, but also by the presence of pain. The study showed that chronic pain is a frequent but underreported symptom in PD. The patients complained of pain more often in advanced PD (especially in the presence of motor fluctuation: 11 patients), but the pain was present also in patients with early PD (3 patients, with akinetic rigid subtype of PD). All patients complaining of pain received treatment (drugs or/and physical treatment) for pain, associated with their standard Parkinson's disease medication and they were reevaluated after 4 weeks. Treatment approaches, including general lifestyle modifications (rest and exercise), physical therapy confirm the importance of pain treatment in increasing QoL.

Conclusions: Treatment of Parkinson's disease is primarily aimed at improving motor function. However, especially in advanced stages, Parkinson's disease is often complicated by additional problems such is pain. After 4 weeks of treatment the patients improved their activities of daily living, also by improving their night sleep. Our data shows poorer QoL to be associated with presence of pain and the benefit of organized and sustained physical treatment and the need of drugs in some cases. The QoL is a complex concept which many factors other than health contribute to. The complexity of the concept of QoL is the main limitation of this study, as many variables that potentially contribute to QoL, such as social support and individual coping strategies, were not directly accounted for. Occupational therapists must be involved in pain management programmes, as part of a multidisciplinary approach to the patients with PD.

We-263

Vitamin D and bone density assessments are rarely obtained in veterans with Parkinson's disease (PD)

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Objective: To evaluate the percentage of persons with PD, in the Pacific Northwest Veteran Affairs (VA) system, who have had bone density testing and vitamin D levels assessed.

Background: Persons with Parkinson's disease are at higher risk for falls and recent data suggest they are at a higher risk for vitamin D deficiency and osteoporosis then the general population. Only one study specifically looked at men. The National Osteoporosis Foundation and a number of other organizations recommend bone density testing in all women 65 and older and all men 70 and older in addition to earlier testing for specific populations. Optimal vitamin D levels are agreed to be at least 30ng/ml with research supporting higher levels for optimal bone and muscle health. Vitamin D supplementation has also reduced fall rates in several studies.

Methods: We conducted a database search examining the frequency of vitamin D and bone density testing over a 5 year period (from August 2003 to August 2008) of veterans in the Veterans Integrated Service Network (VISN) 20 carrying a diagnosis of Parkinson's disease. We also examined the percentage of persons with sufficient, insufficient, and deficient levels of vitamin D.

Results: Out of a total of 3,128 persons carrying a diagnosis of Parkinson's disease only 236 or 7.5% had a vitamin D level checked, during the five year period assessed. Even fewer, 129 or 4.1%, had bone density testing. This is in spite of the fact that over 3/4 of these patients were over the age of 70. The mean vitamin D level was 26.6 ng/ml (95% CI of 24.7-28.4); below the recommended levels of 30ng/ml. The percentage of PD patients with sufficient levels (≥30ng/ml) was 33%, insufficient (20-30ng/ml) was 26%, and deficient (≤20ng/ml) was 40%.

Conclusions: Our data show that osteoporosis and its risk factors in Parkinson's patients are vastly under assessed within the VA system, despite the increased risk of falls and fractures in this patient population. It may be appropriate for movement disorders specialist to consider their patients bone health and work to ensure proper assessments are taking place.

We-264

The relationship between quality of life and swallowing in Parkinson's disease: The effects of depression

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Objective: Evaluate swallow-specific quality of life (QOL) in Idiopathic Parkinson's disease (IPD) independent of the effects of depression.

Background: Impairment measures and impairment specific QOL measures are generally only modestly positively correlated, suggesting multiple influences on patient reported QOL. Because perceived QOL is one predictor of patient's satisfaction with treatment, understanding influences on it is of clinical importance. Our previous work demonstrates a link between depression, swallowing function and self-reported QOL. The purpose of this investigation was to extend these previous findings to a larger cohort of persons with IPD utilizing an instrumented rather than clinical evaluation of swallowing function.

Methods: Forty-six patients diagnosed with IPD underwent videofluoroscopic evaluation of swallowing function. A trained clinician, blinded to participant identity, evaluated all swallows using the Penetration-Aspiration Scale (Rosenbek et al., 1996), a validated 8-point likert scale used to quantify presence/absence of penetration and aspiration. In addition, patients completed assessments of swallow-related QOL and depression using the Swal-QOL (McHorney et al., 2000) and Beck Depression Inventory (BDI). Analysis of Covariance (ANCOVA) was performed with depression scores (BDI) as the covariate. Additionally, we again assessed the relationship between swallow-related QOL and IPD disease severity, this time accounting for the depression using partial correlations.

Results: Overall swallow-specific QOL was mildly reduced in this population with mean scores across Swal-QOL domains ranging from 64-89. When accounting for depression, participants with dysphagia reported significant reductions in total Swal-QOL score ($p=0.00$); and seven of the ten domain scores when compared with the non-dysphagic group. After parcelating out the influence of depression, there were no significant relationships between swallow-related QOL and IPD disease severity.

Conclusions: These data add to our earlier findings linking swallowing function, QOL and depression and provide an impetus for continued investigation into quality of life in IPD as related to motor and non-motor systems; and the influence of these factors across systems and domains.

We-265

The relationship between quality of life and swallowing in Parkinson's disease: A preliminary Investigation

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Objective: 1) Evaluate swallow-specific quality of life (QOL) in Idiopathic Parkinson's disease (IPD); (2) Delineate potential relation-

ships between IPD duration and severity with swallow-specific QOL; (3) Investigate relationships between swallow-specific QOL and general health-related QOL; and 4) Investigate relationships between swallow-specific QOL and depression.

Background: A reported 90% of individuals with IPD develop dysphagia during the course of their disease with the leading cause of death being aspiration pneumonia (Sapir, et al., 2008). While the physiologic characteristics of swallowing have been well characterized in this patient population, no study has documented the impact of swallowing function on QOL in IPD.

Methods: Thirty-six patients diagnosed with IPD with and without dysphagia filled out validated assessments of (1) the Swal-QOL; (2) the Parkinson's Disease Questionnaire-39(PDQ-39); and (3) the Beck Depression Inventory (BDI). A series of Mann Whitney U tests were performed comparing dysphagic and non-dysphagic groups on the total Swal-QOL and individual domain scores. Correlation analyses were performed between the Swal-QOL and 1) PDQ-39; 2) Hoehn and Yahr stage; 3) PD disease duration; 4) UPDRS 'on medication' motor score; and 5) the BDI.

Results: Overall data for this group of IPD patients indicated that swallow-specific quality of life was mild to moderately reduced with scores across Swal-QOL domains ranging from 42-76. The dysphagia group reported significant reductions compared to the non-dysphagia group for the total Swal-QOL score ($p=0.02$), mental health domain score ($p=0.002$) and social domain score ($p=0.002$). No relationships were revealed between swallow-specific quality of life and disease duration or severity, however significant relationships were observed between swallow-specific quality of life and depression, as well as general health-related quality of life.

Conclusions: These exploratory data highlight the psychosocial sequelae that swallowing impairment can have in an IPD population and suggest a possible association between swallowing function and depression. Further analyses are needed to better identify the degree to which various factors influence swallowing related quality of life.

We-266

The effect of gym training on multiple outcomes in Parkinson's disease: A pilot randomised waiting-list controlled trial

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Objective: 1. To evaluate the effectiveness of a 10-week gym-training programme in improving reaction time, motor function and well being in Parkinson's disease (PD). 2. To assess the acceptability of the programme.

Background: Physiotherapy has been shown to provide benefits for patients with PD, but there is little evidence about the potential impact of group gym-training on PD.

Methods: Thirty-two adults with mild to moderate PD (Hoehn Yahr stage II-III; 11 women, mean age 65.2 years, mean illness duration 6.0 years) not currently in an exercise group, were recruited via clinics and advertisements in the local press. After stratification to match groups for illness severity, participants were randomised to either an immediate 20-week biweekly gym training programme at a local leisure complex, or a 10-week programme starting 10 weeks after baseline assessment. Assessments at baseline (T1), 10 weeks (T2) and 20 weeks (T3) included computerised measures of simple, choice and serial reaction time; videotaped motor performance, blind rated; PD-related quality of life (PDQ-39); and illness perceptions (BIPQ). Experiences of the programme were assessed via questionnaire items and via a focus group with six participants.

Results: Gym training was associated with significant improvements in reaction times in the immediate training group compared with the delayed group (T1-T2). The delayed group showed similar improvements after 10 weeks of gym training (T2-T3). The focus group showed that participants enjoyed the group and obtained social benefits. They gained in confidence, both in physical functioning and general life activities. In contrast, the questionnaire measures did not show significant improvements in subjective health ratings or illness perceptions, showing a trend in the opposite direction. Analysis of motor performance is proceeding.

Conclusions: Preliminary findings suggest that a 10-week gym training programme was beneficial for patients with PD, although this was not apparent in the questionnaire measures. Further research should assess the long-term benefits of such a programme, and explore the mechanisms by which improvements occur.

We-267

Effects of parkinsonism on quality of life in welding exposed shipyard workers

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Objective: To determine whether parkinsonism in shipyard workers exposed to welding fume is associated with reduced quality of life (QoL).

Background: Parkinsonian signs are often found in workers exposed to welding fumes. The PDQ39 is a widely used QoL measure that contains eight subscores [mobility, activities of daily living (ADL), emotional well being, stigma, social support, cognition, communication, body discomfort] and a total score, where higher scores indicate poorer QoL. In PD, there is a strong relationship between Hoehn & Yahr stage and quality of life as measured by the PDQ39. The impact of parkinsonism on welding exposed workers is unknown.

Methods: Subjects for this study included 185 shipyard workers evaluated for parkinsonism in a worksite based epidemiology study. Movement disorders experts examined each subject using the Unified Parkinson Disease Rating Scale Motor subsection part 3 (UPDRS3). Subjects were assigned a clinical diagnosis of parkinsonism based upon rigorous quantitative criteria requiring at least two cardinal signs. An alternate case definition of parkinsonism was UPDRS3$>$15. Normal was defined as UPDRS3$<$5. All subjects completed a PDQ39 and PD symptom questionnaire. All results are reported as odds ratios (OR) of outcomes among workers with parkinsonism compared to normal workers, adjusting for age at exam.

Results: Parkinsonism was diagnosed in 8% of subjects; 20% had UPDRS3 scores $>$15. The total PDQ score and all subscores were greater in subjects with parkinsonism as compared to normals, regardless of the clinical criteria used. Using the UPDRS3$>$15 as the case definition of parkinsonism, this diagnosis predicted increases in total PDQ39 score (OR 6.4; 1.6-26.2), mobility (OR 9.6; 2.0-46.8), and emotional well-being (OR 9.6; 1.7-55.0). The clinical criteria-based case definition of parkinsonism predicted increases in the same subscale tests as well as increases in ADL (OR 4.5; 1.1-19.0) and communication (OR 6.8; 1.8-26.1). Symptoms from the PD questionnaire best predicting diagnosis of parkinsonism were shuffling gait (OR 18.02; 2.2-147.0) and difficulty arising from a chair (OR 5.28; 1.4-20.3).

Conclusions: Parkinsonism in welding exposed shipyard workers is associated with reductions in quality of life affecting a broad range of categories.

We-268

Is Parkinson's disease a motor or non motor disorder?

A.Q. Rana (Toronto, Canada)

Objective: To discuss the importance of the non motor symptoms of Parkinson's disease, addressing of which improves the quality of life of patients.

Background: Traditionally Parkinson's disease have been known as a motor disorder. There is much less awareness of non motor symptoms of Parkinson's disease as compared to motor symptoms. The non motor symptoms cause significant disability, poor health related quality of life and caregiver's stress. The list of non motor symptoms of Parkinson's disease rapidly is growing with time. Due

to lack of awareness of non motor symptoms patients may not bring non motor symptoms in to discussion in the outpatient follow up visits. Hence screening of non motor sympotms by the neurologist is very important. Addressing non motor symptoms improves the quality of life of patients significantly.

Methods: We reviewed the medline, pubmed and other resources such as text book chapters to make a comprehensive list of non motor symptoms of Parkinson's disease.

Results: We were able to collect a huge number of non motor symptoms of Parkinsons's disease reported in the literature such as depression, hyposmia, cognitive dysfunction, visual hallucinations, anxiety, confusion, memory problems, frozen shoulder, internal tremor, episodic sweating, facial masking, drooling, hypometric saccades, conspitation, urniary bladder problems, sexual dysfuntion, swallowing problems, pain, sensory symptoms, loss of taste, weight loss, micrographia, diplopia, dry eyes, speech problems, balance problems, freezing, turning difficulty, falls, apathy, difficulty with dexterity among many other sympotms.

Conclusions: The exhaustive list of non motor symptoms underscores the importance of screening the patients for these symptoms and raises an interesting question whether Parkinson's disease should be regarded a motor or a non motor disorder.

We-269

Characterisation of Restless Legs like syndrome in Parkinson's disease

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Objective: To look into the variation of restless legs syndrome (RLS) in Parkinson's disease (PD) patients.

Background: RLS is thought to occur in 20% of Parkinson's disease cases. We describe variation in the presentation of RLS in PD based on data collected using the PD non motor symptoms scale (NMSS).

Methods: Patients having RLS symptoms on the NMSS were classified into mild (1-4), moderate (5-8) and severe (9-12) based on NMSS scores. Correlations with other assessments and response to dopaminergic agents were recorded.

Results: 57 patients (29.8% akinesia dominant, 12.2% tremor dominant, *58% mixed type)* had RLS based on NMSS and the IRLSSG criteria. Daytime sleepiness was seen in 16% most marked in severe RLS. High fatigue scores were recorded in 83% of severe and 50% of moderate RLS while insomnia was troublesome in 66% of severe and 50% of moderate RLS and pain was dominant in 55% of moderate and 33% of severe RLS. Severe and moderate RLS cases were all on varying dopaminergic (DA) therapy with motor fluctuations and in some symptoms responded to alteration of therapy with longer acting agents such as rotigotine patch and ropinirole XL while others required non-DA therapies.

Conclusions: RLS occurs in PD in several forms. Typical RLS is uncommon while a RLS like syndrome is common. The latter may be either non DA responsive or result from nocturnal motor fluctuations which respond to longer duration DA.

We-270

Comparison of depression, anxiety and quality of life in PSP and MSA

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Objective: To compare subjective health status and its correlates in progressive supranuclear palsy (PSP) and multiple system atrophy (MSA).

Background: MSA and PSP are two common types of atypical parkinsonism, clinical management of which is difficult and needs to be aimed at the most important clinical aspects that have an impact on patients' psychological well-being and quality of life. Few studies have assessed the impact of PSP and MSA on psychological well-being and quality of life and no direct comparison of health status between these disorders has been undertaken.

Methods: 188 PSP and 286 MSA patients completed the EQ-5D and the Hospital Depression and Anxiety Scale (HADS).

Results: On the EQ-5D, impact on mobility, usual activities and self-care was similarly high in both groups after similar duration. 56% of PSP and 43% of MSA had probable depression, and 37% of both groups had probable anxiety on the HADS. PSP patients had significantly higher depression scores, but groups did not differ in anxiety scores. MSA patients had significantly greater pain/discomfort than PSP patients. The most important association with subjective health status was with depression, which accounted for 38% and 29% of EQ-5D variance in PSP and MSA patients respectively, followed by disease severity and anxiety scores.

Conclusions: Depressive symptoms were common in both disorders, but more severe in PSP. Anxiety symptoms affected 37% of patients in both groups and contributed to impaired subjective health status. Pain was more problematic in MSA than PSP.

We-408

Sleep disturbances and sleep benefit in Parkinson's disease outpatients: An interview study

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Objective: To clarify the characteristic of sleep disturbance and sleep benefit in PD outpatients.

Background: It is well known that patients with Parkinson's disease (PD) exhibit various type of sleep disturbances. On the other hand, many patients are believed to benefit from sleep and awake on or become on after taking a nap (sleep benefit).

Methods: We studied 104 consecutive patients with clinical diagnosis of PD (age: 66 $\pm$ 8.7 years, 44 men, 60 women, age at onset :58.1 $\pm$ 10.4 years, HY stage at diagnosis: 1.9 $\pm$ 0.8, duration of the disease: 8.6 $\pm$7.3 years) who were attending PD clinic at the university hospital. We performed direct detailed interview to the individual patients (and family) asking the nature of their sleep disturbances, i.e. insominia, possible RBD (REM sleep behavior disorder) and sleep benefit if any.

Results: In our cohorts, forty seven percent had insomnia. Of these, twenty seven percent had difficulties initiating sleep, sixty three percent had difficulties in maintaining sleep and forty one percent had early morning awakenings. Nineteen percent of the total patients had possible REM sleep behavior disorder (RBD) and seven percent had violent possible RBD. Twenty eight percent had the modified ESS score of more than 10 points. Sleep benefit was found in sixty four percent of our patients. Of these patients with sleep benefit, forty eight percent awake "on" only in the morning and forty one percent awake "on" in the morning and after a nap. There was no significant difference in the current age or in the duration of the disease with or without sleep benefit.

Conclusions: In our cohorts, a large portion of PD patients suffer from various type of sleep disturbances, but even a larger proportion of patients claim that they benefit from good sleep. It is thought that it is essential to improve the quality of sleep and thereby improve motor impairments in PD.

Th-265

Advanced stage of Parkinson's disease and non-motor fluctuations

I. Smolentseva, E. Sozinova (Moscow, Russian Federation)

Objective: To investigate the frequency and profile of non-motor fluctuations in the advanced stages of Parkinson's disease (PD).

Background: Levodopa therapy is considered to be the most effective treatment of Parkinson's disease (PD). It is well known that long term dopaminergic therapy is associated with appearance of motor fluctuations and dyskinesias. In the advanced stages of PD motor fluctuations become more severe and difficult. Moreover, they are accompanied by non-motor symptoms, that changes the hole clinical picture of parkinsonism. Non-motor fluctuations can be divided into 3 main groups: vegetative, psychical and sensor dysfunctions.

Methods: 42 patients with PD (mean age 62,4±7,3, disease duration 9,5±5,3, levodopa therapy duration 7,8±8,3, Hoehn-Yahr stage 3,4±2,1) took part in our investigation. We used NMS and patient's questionnaire for recognition of non-motor symptoms (Stacy et. al., 2005).

Results: 99.8% of our patients had vegetative fluctuations, 90.0%–psychical and 76.4%–fluctuations in the sensor functions. The appearance of the main non-motor fluctuations depended on levodopa dose ($r=0,69$, $p<0.001$), Hoehn-Yahr stage ($r=0,36$, $p<0,05$) and onset of the severe motor fluctuations: "on-off" phenomenon ($r=0,48$, $p<0,01$) and freezing ($r=0,38$, $p<0,05$). In the "on" period vegetative and sensor dysfunctions were more frequent, whereas in the "off" period–psychical.

Conclusions: Unexpectedly high percent and variety of detected non-motor fluctuations, which caused patient's anxiety even more than motor fluctuations, point the importance of their detection. Non-motor symptoms are primarily connected with the "off" period, but they can also take place in the "on" period, "on" and "off" phases and during the peak-dose dyskinesia. Notable, that the majority of our patients used to associate their bad state of health with the appearance of non-motor fluctuations, especially vegetative and sensor dysfunctions.

Th-266

Health-related quality of life in Australians with Parkinson's disease

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Objective: To quantify dimensions of health-related quality of life (HRQOL) in an Australian sample of people with Parkinson's disease (PD) as a basis for understanding the burden of disease.

Background: Most studies of HRQOL in people with PD have used European and American samples. There are no published data on the HRQOL of Australians with PD. Findings from overseas studies cannot be generalised to the Australian population because HRQOL is specific to cultural norms and value systems. This study examines how an Australian sample of people with PD rate the mobility, emotional and social functioning dimensions of their HRQOL.

Methods: 154 participants were recruited from a wide variety of sources and sites in Victoria, Australia as part of an ongoing clinical trial. Health-related QOL was quantified using the Parkinson's Disease Questionnaire-39 (PDQ-39). The PDQ-39 is a highly reliable disease-specific measure of HRQOL and has been validated in different cultural populations. Scores from the eight dimensions of HRQOL assessed by the PDQ-39, range from 0 to 100, with higher scores indicating poorer HRQOL.

Results: Australians with PD (106 males, 48 females) had a mean age of 69 years (range 46 to 90), disease duration of 6.3 years (range 0.5 to 30) and a mean Hoehn and Yahr stage of 2.5 (range 1 to 4). The mean overall HRQOL as measured by the PDQ-39 summary index was 21.5 (SD 12.7; 95%CI 19.5, 23.5). Participants rated the PDQ-39 dimensions of bodily discomfort (mean 28.8; SD 21.2; 95%CI 25.5, 32.2), mobility (mean 27.0; SD 24.0; 95%CI 23.2, 30.8), activities of daily living (mean 25.1; SD 21.3; 95%CI 21.7, 28.5), cognition (mean 24.0; SD 18.5; 95%CI 21.1, 26.9), communication (mean 21.5; SD 22.1; 95%CI 18.0, 25.0) and emotion (mean 20.8; SD 16.9; 95%CI 18.1, 23.5) to be most affected by PD. Stigma (mean 14.5; SD 16.5; 95%CI 11.9, 17.1) and social support (mean 10.5; SD 16.3; 95%CI 7.9, 13.1) were less affected by the disease.

Conclusions: Participants in this sample considered PD to most influence bodily discomfort, mobility, activities of daily living, cognition, communication and emotion. A better understanding of the inter-relationships between the different dimensions of HRQOL and their determinants may assist clinicians assess accurately the full spectrum of disability domains associated with PD.

Th-267

Rate of disease progression among patients with Parkinson's disease in Singapore

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Objective: This study was carried out to investigate the time taken to transit between the various Hoehn & Yahr (H&Y) stages among patients with PD in Singapore.

Background: There is scant data available on the time taken for PD patients to transit through the various H&Y stages. Previous studies have shown that younger-onset patients took longer time to progress from one stage to another.

Methods: In this domain-specific review board approved study, patients were recruited from a tertiary neuroscience clinic in Singapore. Clinical and demographic information was obtained from the PD and movement disorders database which was established in 2002. H&Y stage was evaluated at each clinic visit. Time-to-transition was estimated using Kaplan-Meier analysis. Cox regression analysis was performed to examine the influence of gender, race, duration of PD and age-at-diagnosis on time-to-transition.

Results: A total of 695 patients (mean age: 65.3 years, male: 58%) were analyzed. Using Kaplan-Meier analysis, the mean time-to-transition from H&Y stage 1 to 2 was 22.3 months; from stage 2 to 2.5 was 52.9 months; from stage 2.5 to 3 was 30.3 months; from stage 3 to 4 was 27.4 months; and from stage 4 to 5 was 30.0 months. In Cox regression analysis, younger-onset (age at diagnosis=55 years) and shorter PD duration (4.9 years) predicted longer time-to-transition from stage 2 to 2.5 (Hazard Ratio (HR) (95% CI): 0.156 (0.042 to 0.580), $p=0.006$ and 0.163 (0.055 to 0.488), $p=0.001$, respectively). Shorter PD duration (duration of PD=3.0, 7.7, 12.7 years) similarly predicted longer time-to-transition from stage 4 to 5 (HR (95% CI): 0.195 (0.44 to 0.869), $p=0.032$, 0.123 (0.031 to 0.489), $p=0.003$, 0.175 (0.043 to 0.715), $p=0.015$ respectively). Gender and race did not affect time-to-transition between H&Y stages.

Conclusions: To the best of our knowledge, this is the first study to report on disease progression using time-to-transition between the various H&Y stages. PD patients with younger-onset and shorter disease duration took longer time to progress through some H&Y stages. These findings will be useful for clinicians to better understand disease progression and management in PD.

Th-268

Cost-effectiveness of rasagiline versus ropinirole extended release in delaying levodopa in the treatment of early Parkinson's disease in the United States

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Objective: This model examines whether rasagiline, a once-daily irreversible monoamine oxidase type-B inhibitor for treatment of early Parkinson's disease (PD), offers a cost-effective treatment strategy and delays the initiation of levodopa when compared with ropinirole extended release (ropinirole), a once-daily dopamine agonist.

Background: PD affects approximately 1 million people in the United States. A common PD treatment is levodopa; however, motor fluctuations and dyskinesias are common side effects.

Methods: A 5-year Markov model was utilized to examine the cost-effectiveness of initiating early treatment of PD with rasagiline versus ropinirole from a managed care perspective. Strategies

included initial therapy with rasagiline, followed by either ropinirole or levodopa, versus initiating therapy with ropinirole, followed by levodopa. Patients could transition therapy every 6 months; patients on levodopa could develop dyskinesias. Rasagiline transition probabilities obtained from the TVP-1012 in Early Monotherapy for Parkinson's disease Outpatients (TEMPO) trial. Medical costs and utility weights were from published literature. Drug costs were from Red Book. Model outcomes included time to levodopa treatment, time to levodopa-induced dyskinesias, life-years, quality-adjusted life-years (QALY), and incremental cost per QALY. One-way and probabilistic sensitivity analyses were performed.

Results: Compared to initiating treatment with ropinirole, treatment initiation with rasagiline was associated with a delay in the time to treatment with levodopa (4.45 months) and subsequently the time to levodopa-induced dyskinesia (1.00 month). Rasagiline initiation was also associated with lower costs (–$1,660) and higher expected QALYs (+0.0608) over 5 years, which is dominant. The model was most sensitive to clinical efficacy and drug costs.

Conclusions: Initiating treatment with rasagiline was found to delay treatment with levodopa and subsequent dyskinesias, compared to initiating treatment with ropinirole, and appears to be a cost-saving and clinically-effective treatment strategy.

Th-269

Disease burden and treatment patterns of Parkinson's disease in a long term care setting

S. Narayanan, M.L. Tarrants, J. Castelli-Haley (Kansas City, Missouri)

Objective: To examine the patient (pt) characteristics, treatment (tx) patterns and cost of care among residents with Parkinson's disease (PD) in a long term care setting (LTC), specifically, skilled nursing facilities (SNFs) in the United States (US).

Background: PD is a progressive neurodegenerative disorder that produces considerable morbidity. PD is estimated to affect more than 3% of the population older than 65 years and both the prevalence and incidence of PD increase with age.

Methods: Retrospective analysis of PD pts receiving care in one of 347 SNFs in the US from June 2004-2008. Using a large provider database, we identified 7885 pts with a PD diagnosis. Pt demographics, comorbidities, tx patterns and costs were assessed using administrative and clinical databases at baseline (BL) and at one year (1y).

Results: 4150 PD pts with both BL & 1y data constituted the analysis cohort, with a mean age of 82 years, 46% were male and 57% were admitted from an acute care hospital. At BL, 43% had a fall in the past 30 days, only 5% reported steady balance; 94% reported help with bathing; 24% & 38% were bladder & bowel continent; 71% & 44% suffered short and long-term memory loss. On average, PD pts received speech, occupational and physical therapy for 68, 153 and 157 minutes per week. The average pt had six comorbid conditions of which hypertension (64%), depression (46%), dementia (43%) and diabetes (31%) were the most common. Furthermore, 83% of pts were diagnosed with PD before or at SNF admission. At BL, 79% were not on PD medication (med); 49% remained PD med-free during the 1y period. At BL, pts were on a mean of 11 meds. Concomitant (con) med use of analgesics, antihypertensives and antidepressants were the most common at 1y. The average direct LTC medical costs per pt per month was $5355 at BL, $7841 at 6 months and $6097 at 1y.

Conclusions: At BL 79% of PD pts in this LTC setting were not on PD meds. PD pts have physical and cognitive impairment, combined with debilitating comorbidities. Falls, incontinence, memory loss, hypertension, depression, dementia and diabetes complicate the tx of PD in LTC. The burden of con meds may further complicate PD tx in LTC. Ongoing examination into the tx needs of PD pts and any barriers to PD med use is needed to alleviate the burden of PD in LTC.

Th-270

Driving ability in Parkinson's disease patients: What is your method of assessment?

S.W.K. Atherton, A.M. Thomson (Salford, Greater Manchester, United Kingdom)

Objective: The aim of this study was to investigate the current practices and attitudes of healthcare professionals in their assessment of driving competencies.

Background: A variety of motor and neuropsychiatric manifestations of Parkinson's disease (PD) are recognised to affect driving ability. Difficulties in movement planning, sequencing and undertaking simultaneous manoeuvres have been identified as particularly problematic. Healthcare professionals should be adopting a consistent approach in making assessments of driving ability.

Methods: A semi-structured questionnaire was sent to 54 PD specialists (neurologists, geriatricians and PD specialist nurses) in the North-West of England. A combination of direct questions, Likert items and open questions with free text responses was used. Anonymity was assured.

Results: 23 (43%) questionnaires were returned. Only 14 respondents (60%) asked patients about their overall driving capabilities 'very frequently' or 'quite frequently'. The frequency with which respondents enquired into individual factors which could affect driving ability are summarised.

Table 1 (Th-270). Frequency of enquiry into individual aspects affecting driving ability

	% of respondents enquiring
Sudden onset of sleep	100
Daytime sleepiness	95
Motor ability	95
Cognitive ability	90
Concentration	80
On/Off symptoms	80
Eyesight	70
Hallucinations	70
Problems with movement planning	50
Problems with movement sequencing	40
Problems with simultaneous movements	30

20 respondents (87%) thought there was inadequate guidance available to support them in making such assessments.

Conclusions: There is a variation in both opinion and practice concerning the assessment of driving ability in PD patients by specialists. Assessments of simultaneous movements and of movement planning and sequencing are undertaken less frequently than other domains. This heterogeneity creates inequity of care. There are also serious implications for road safety. Improved guidelines and frameworks are required to support healthcare staff and patients.

Th-271

Efficacy of self-management rehabilitation on quality of life outcomes in Parkinson's disease

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Objective: To investigate the effect of self-management rehabilitation on quality of life outcomes in Parkinson's disease, beyond medical treatment effects. We hypothesized that increasing hours of self-management rehabilitation would have increasing quality of life benefits.

Background: There is a lack of rigorous research investigating the effects of rehabilitation on the quality of life of persons with PD over the short and long-term. The impact of increasing doses of self-management rehabilitation is unknown.

Methods: Participants were randomized to one of three conditions for a six-week intervention: (I) medication only; (II) medication plus 18 hours of self-management rehabilitation in group clinic sessions plus 9 hours of attention control social sessions; and (III) medication plus 27 hours of self-management rehabilitation-- 18 hours in group clinic sessions plus 9 hours of home and community self-management rehabilitation. Quality of life was measured with the Parkinson's disease Questionnaire-39 at six weeks, two months, and six months.

Results: At six weeks there was a significant linear beneficial effect of increasing hours of self-management rehabilitation on quality of life changes (r=.29, p= .005). The linear effect persisted to a smaller degree at follow-up (r=.16, p=.124 at 2 mo.; r=.19, p=.075 at 6 mo.). The findings were not significantly different between the two rehabilitation conditions. Rehabilitation (II or III) was significantly more beneficial than medication alone at 6 weeks (ABI=.24, CI=.06-.41; NNT=4, CI=2-17; % increased benefit 47%), with smaller effects at 2 and 6 months.

Conclusions: Rehabilitation adds benefit to medication outcomes. Descriptive patterns suggest physical function quality of life domains were most responsive to rehabilitation that included home and community sessions (III) while psycho-social domains were most responsive to rehabilitation that included social sessions (II).

Th-272

Type and intensity of daily energy expenditures among Parkinson's disease patients based upon their body weight

M. Trail, N.J. Petersen, N. Nelson, E.C. Lai (Houston, Texas)

Objective: To describe daily energy expenditures (DEE) of PD patients by type and intensity of activity and to assess whether DEE differs by body mass index (BMI).

Background: PD can have significant effects on physical and cognitive functioning, but movement disorder specialists know little about the activities PD patients regularly engage in and if BMI effects activities.

Methods: Ninety-eight PD patients answered a questionnaire measuring their daily activities and clinical characteristics. We obtained PD severity from patients' charts. We categorized activities into 5 domains and 3 intensity levels. Nonparametric statistics were used for analysis.

Results: Mean age was 72.8. Mean disease duration was 8 years. 58.2% were overweight or obese. The 2 weight groups did not differ on most demographic or clinical characteristics. Overweight/obese patients were more likely than underweight/normal weight patients to take medications for depression (43.6% versus 24.4%), but had fewer falls than patients of lower BMI. There were no differences in the amount of pain, fatigue, memory problems, need for general assistance, or in self-reported quality of life. Overall, PD patients reported average energy expenditures of 1,956.9 kCal per day. Underweight/normal weight patients expended significantly fewer kCal (1,665.1) than did overweight/obese patients (2,166.8). Patients spent almost half their DEE on physical activities (47.3%), 14.9% on intellectual activities, 14.9% on ADLs, 12.5% on social activities, and 10.4% watching TV. The 2 weight groups differed significantly only on social activities, with higher percentages in the heaviest group (13.7% versus 10.3%). Overweight/obese patients were less likely to engage in moderate activities (86.0%) compared to underweight/normal patients (92.7%). Only 14% of all patients engaged in vigorous activities.

Conclusions: PD patients remain highly involved in at least some physical activities. Although overweight/obese patients did not differ significantly on most clinical features from underweight/normal weight patients, they should be encouraged to engage more in moderate intensity activities.

Th-273

How do patients with Parkinson's disease reach their diagnosis? In relation to their initial symptoms and the medical institutions/clinic they first visited

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Objective: To clarify how and where PD patients initially visit before they reach the correct diagnosis and how their initial symptom(s) affect their decision as to which medical institution/clinic they initially visit.

Background: The clinical diagnosis of PD is often difficult by non-experts, particularly early in the disease and patients may often be mistaken as having other disease causing stiffness or disabilities of limb(s). In Japan, every one is basically on medical insurance and has free access to any medical institutions/clinic, and could be examined even by neurologist without referral.

Methods: One hundred consecutive patients with clinical diagnosis of PD (age: 66 ± 8.7 years, 46 men, 54 women, age at onset: 58.1 ± 10.4 years) attending PD clinic at the university hospital were directly interviewed in detail asking what their initial PD symptom were, which medical institution/clinic they firstly visited and how they reached the final diagnosis of PD.

Results: In our cohorts, PD started mostly in tremor of the hand/arm (43%) and dragging of the foot (24%), followed by leg/foot tremor (16%), clumsiness of the hand (8%). HY staging at the diagnosis of PD was 1.4 ± 0.7, the time consumed before the diagnosis of PD was reached after their initial medical visit was 24.4 months on average (maximum 204 months) and number of medical institutions/clinic they visited before they reached the diagnosis of PD was 2.7 on average (maximum 9). Although nearly thirty percent of those with hand/arm tremor onset saw neurologist first, as for those with foot dragging onset, nearly half of them visited orthopedics first and only few saw neurologist. About 10% of the total patients firstly visited acupuncture/chiropractics etc. Only 16 % of total patients were diagnosed as PD at the first medical visit and only 8% were diagnosed by non-neurologist.

Conclusions: In our district, clinical diagnosis of PD by non-expert medical fractioned may be problematic, with high false-negative rates, and long delays in the diagnosis. Education to non-expert medical professionals as well as to general public may be needed to facilitate earlier correct diagnosis of PD, leading to proper treatment, and thereby improve quality of life in PD patients.

Th-274

Assessment of medical care for patients with Parkinson's disease during hospitalization

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Objective: In this study, we report on the medication schedule compliance and the incidence and nature of medication errors in hospitalized patients with Parkinson's disease (PD).

Background: In PD patients, dosing and timing of all Parkinson's medications should be individualized. Particular attention should be focused on maintaining a strict medication schedule. Failure to administer medications on time may have undesirable impact on these patients and decrease the quality of patient care. In addition, there are many contraindicated medications that should not be prescribed to PD patients or combined with Parkinson's medications.

Methods: The electronic medical records of 100 patients with parkinsonism and hospitalized at the Michael E. DeBakey VA medical Center from fiscal years 2002 to 2004 were reviewed. Patients with uncertain diagnosis or with admission duration shorter than 48 hours were excluded from the study.

Results: A total of 89 patients were qualified to be analyzed in this study. 86 (96.6 %) were man and 3 (3.4 %) were women. The mean age was 76.17 ± 7.6years. The mean admission duration was

8.21± 5.40 days. The most frequent cause of admission was infection (24%). Among a total of 3873 prescribed medication doses, 675 (17.4%) errors were found. 322 of them were missing doses that accounted for 47.7 % of the total medication errors. 300 (44.4 %) errors were for giving medications late by more than 30 minutes. 53 (7.9 %) errors were for giving medications too early. 19 (21.3 %) patients were prescribed with contraindicated medications. The most frequently prescribed contraindicated medication was haloperidol. Neurological consultation was ordered in 29 (32.6 %) admission. The incidence (6.1 %) of missing doses in patients with neurological consultation was significantly lower compared to patients without neurological consultation (14.8%; $p<0.05$).

Conclusions: The frequency of medication errors was high in hospitalized PD patients (17.4%). 21.3% patients were prescribed with contraindicated medications. The incidence of the incorrect medication administration was significantly lower in patients who had neurological consultations. Our report should draw the attention of health care providers to avoid medication errors in the care of hospitalized PD patients.

Th-275

Supporting caregivers in PD: A Survey

D. Breslow, C. Zadikoff, S. Dunlop, T. Kuhta, L. Marsh, K. Nichols, A. Videnovic, A. Martel, K. Williams, T. Simuni (Chicago, Illinois)

Objective: 1) Learn more about factors influencing caregiver strain 2) Determine if support groups and caregiver education augment the caregiver experience.

Background: PD patients' family members provide the majority of care. Caregiving can create considerable stress. Many factors contribute to this stress but research is lacking about these variables and interventions that might help.

Methods: 100 caregivers attending PD support groups and symposia or accompanying the patient to clinic at Johns Hopkins and Northwestern PD centers completed anonymous surveys which included demographics and 2 standard caregiver surveys- Caregiver Strain Index(CSI), with an established cut off (≥7) suggesting high caregiver strain, and Caregiving Distress Scale (CDS)-as well as questions about possible rewards associated with caregiving. **Analysis**: Demographics of subjects with CSI≥7 vs those with CSI<7 were compared. The prevalence of high strain in support group and caregiver training participants was assessed. Logistic regression evaluated the effect of support groups on CSI.

Results: 95 caregivers, 21% male, mean (SD) age 61.15 (+/-13.2) yrs, mean disease duration 7.37yrs (range 0-30) completed the survey. 52 caregivers participated in ≥1 support group in the last year. Younger age, higher education, and longer disease duration were risk factors for strain. No significant differences were seen in gender, race, relation of caregiver to patient, living location, or financial or employment status of the caregiver with high vs low strain. After adjusting for these factors, there was no difference in CSI of support group participants (38% ≥7) vs non participants (44% ≥7)(p=0.516). CSI was no different in those receiving caregiver training vs not. Despite this, 65% of caregivers found rewards, 40% of whom had a CSI≥7.

Conclusions: Younger age, higher education, and longer disease duration were risk factors for strain. Participation in support groups did not influence caregiver strain. Majority of caregivers had not received formal training; making this an area for future studies. Most caregivers, even those with CSI≥7, acknowledged rewards, suggesting that caregiving is a multidimensional experience. Professionals and caregivers may benefit by understanding the rewards and their effect on the caregiver experience.

Th-412

Is levodopa sparing strategy optimaly practiced in young onset Parkinson's disease?

A.Q. Rana (Toronto, Canada)

Objective: To review the use of levodopa sparing strategy in young onset Parkinson's disease.

Background: Young PD patients are particularly sensitive to levodopa induced motor fluctuations and dyskinesias. In spite of evidence of increased emergence of motor complications, levodopa is still used as first line drug in young patients by general neurologists and many patients develop motor complications soon after the drug is started.

Methods: We studied the first drug of choice started by non movement disorder neurologists in young onset Parkinson's disease. Our inclusion criteria was idiopathic Parkinson's disease, age 20-39, seen by non movement disorder neurologist. Four of our patients met this criteria who were initially seen by a general neurologists and later referred to a movement disorder clinic.

Results: First patient Mr. K.K., a 35 year old male, was started initially on mirapex by a neurologist but a second neurologist stopped low dose mirapex because of lack of significant response and initiated levodopa. Patient developed severe uncontrollable motor fluctuations within few days of introduction of levodopa. The second Patient Mrs. A.S., a 39 year old female was started on levodopa as first line treatment. Patient seeked a second opinion from a movement disorder neurologist and levodopa was changed to mirapex. Patient did not develop any motor fluctuations. Third patient Mr.K.M., a 35 year old male, was also started on levodopa as first line drug and also developed motor fluctuations. The Fourth patient Mrs. A. R., a 38 year old female seen by a non movement disorder neurologist in a teaching hospital and was started on mirapex as first line drug.

Conclusions: The levodopa sparing strategy is not optimally applied by community neurologists. This causes increased prevalence of early motor fluctuations and dyskinesias and resulting in poor qulity of life of patients. Hence there is increased need of education among community neurologists about levodopa sparing strategy in young patients.

PARKINSON'S DISEASE: RATING SCALES

Mo-272

Prevalence of wearing-off symptoms among Czech Parkinson's disease patients treated with L-dopa – Pilot analysis of the E.W.O study

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Objective: The primary objective of this study was to estimate the prevalence of wearing-off symptoms among Czech Parkinson's disease (PD) patients who have been treated with L-DOPA for more than 30 days (maximum 10 years).

Background: The prevalence of wearing-off symptoms was based on the WOQ-9 questionnaire and the assessment by clinicians.

Methods: E.W.O (Epidemiology of Wearing-Off symptoms among the population of PD patients on L-DOPA in the Czech Republic) was a multicentric, non-interventional, epidemiological and exploratory trial. From September 30, 2007 to June 30, 2008 altogether 563 valid records of PD patients were collected. Median age at diagnosis was 64 years with range 30– 89 years.

Results: When considering onset of the disease, 62.8 % patients were diagnosed during the first year after the occurrence of the first symptoms. Actual status of the disease showed most patients were in Hoehn and Yahr Stages 2, 2.5 and 3 (69.3 % in total). This corresponds with the overall length of treatment of PD patients which was 4.9 years (median, range 0.1 – 19.7 years) with the majority of patients treated for 2–8 years. For comparison, the median length of treatment with levodopa was 3.9 years (range 0.1–10.0 years). Wearing-off symptoms were observed according to clinicians' assessment in 372 patients (66.7 %, 95% CI: 62.8 %–70.6 %). On the other hand, according to patients' subjective evaluation of the WOQ-9 questionnaire, wearing-off symptoms were observed in 508 patients

(90.6 %, 95% CI: 88.1 %–93.0 %). The biggest discrepancy between clinicians' assessment and WOQ-9 evaluation was found in patients treated with levodopa for 0-2 years (35.2 %, 95% CI 26.8 %–43.7 % and 82.8 %, 95 % CI: 76.1 %–89.5 %, respectively).

Conclusions: Wearing-off symptoms were observed in 66.7 % of patients according to clinicians' assessment and in 90.6 % of patients according to WOQ-9 questionnaire ($p<0.001$), with the biggest discrepancy between clinicians' assessment and WOQ-9 evaluation in patients treated with levodopa for 0–2 years. The type and number of wearing-off symptoms occurrence is analyzed in detail and more careful explanation of the instructions to the patients about the WOQ-9 is discussed.

Mo-273

The motor UPDRS assessed via telemedicine is reliable and valid

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Objective: Assess the feasibility, reliability, and validity of the motor Unified Parkinson Disease Rating Scale (UPDRS) via a web-based telemedicine program.

Background: Clinical trials for Parkinson's disease (PD) are limited by the ability to recruit individuals who are unable to participate because of distance from research centers, travel difficulties or clinical condition. Using telemedicine to complete web-based assessments of motor function may allow the recruitment and assessment of these individuals.

Methods: In the context of a randomized trial of telemedicine for PD, we assessed the feasibility, reliability and validity of the motor UPDRS scored via telemedicine. Ten participants assigned to telemedicine received an in-person evaluation at baseline, followed by telemedicine visits at 1, 3, 6, and 6.5 months. A nurse trained to perform the motor UPDRS was present and completed rigidity and retropulsion items. Feasibility was determined by the ability to score all motor UPDRS items at each telemedicine visit. Test-retest reliability was evaluated by comparing the month 6 and 6.5 total motor scores. Validity was assessed by comparing the motor UPDRS and individual motor items completed in-person and at 1 month via telemedicine. Intraclass correlation coefficients (ICC) were calculated for total motor scores and Cohen's kappa coefficients ($C\kappa$) for individual motor items. A secondary analysis excluded fluctuators.

Results: The telemedicine participants had a mean age of 72 years, a mean Hoehn and Yahr of 2.7 and a mean motor UPDRS of 34.7. Three participants had motor fluctuations. All items of the motor UPDRS were able to be completed at each telemedicine visit. Test-retest reliability of the motor UPDRS via telemedicine was excellent ($ICC=0.82$). Comparison of the motor UPDRS to the gold standard in-person assessment was also excellent ($ICC=0.78$). All motor items had fair or better agreement ($C\kappa>0.20$) between telemedicine and in-person with the exception of rigidity ($C\kappa=-0.09$) and leg agility ($C\kappa=-0.30$). When fluctuators were excluded, there were no substantial changes, except agreement for rigidity ($C\kappa=0.18$) and leg agility ($C\kappa=0.25$) improved.

Conclusions: The motor UPDRS can be completed reliably via telemedicine and is valid when compared with the gold standard in-person assessment.

Mo-274

Detecting asymmetries in balance control in Parkinson's disease patients with system identification techniques

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Objective: To test the hypothesis that balance control in Parkinson's disease (PD) is asymmetrically affected using system identification techniques.

Background: PD is an asymmetrical disease. It is unknown whether axial symptoms, such as impaired balance, also show asymmetry. Clinical scales used to assess disease severity do not explicitly evaluate asymmetries in axial symptoms. Evaluation of asymmetrical balance control might improve our understanding and treatment of axial symptoms.

Methods: Eight patients with idiopathic PD were asked to maintain their balance during continuous random translational platform movements. Body sway angle and reactive forces of each foot were recorded. These yielded the Frequency Response Function (FRF) of the stabilizing mechanisms, which expresses the amount and timing of the generated corrective torque in response to sway at the specified frequencies. The FRFs were used to calculate the relative contribution of each ankle to the total amount of generated corrective torque to resist the perturbations. In addition, the amount of weight bearing of each leg was calculated. Furthermore, the motor part of the UPDRS and the Hoehn & Yahr disease stage were also evaluated.

Results: Results showed that six out of eight patients responded asymmetrically to the induced platform perturbations as shown by corrective ankle torques. Hence, one leg contributed significantly more to balance control than the other and there was no clear relationship between the contribution to weight bearing and to balance control.

Conclusions: Balance control in PD patients proved asymmetrical for some patients. This asymmetry of axial symptoms can be reliably identified with system identification techniques in the frequency domain. In this way, the effects of different treatments can be identified for each leg separately.

Mo-275

Predictors of patient- and physician-reported satisfaction/ease-of-use ratings with rasagiline in Parkinson's disease

P.O. Buck, J. Castelli-Haley, J.B. Conner (Kansas City, Missouri)

Objective: A post-hoc examination of whether improvement in Parkinson's disease (PD) symptoms and disabilities predicted subsequent ratings of patient- and physician-reported PD treatment Satisfaction/Ease-of-Use (SEU) with rasagiline.

Background: Several available treatments are effective in controlling symptoms of PD; however, relatively little research has examined patient- and physician-reported PD treatment SEU ratings. This is an important topic because the relative success of treatment may be judged in part through patients' and physicians' perceptions of the treatment experience.

Methods: The LEGATO trial was an open-label study of 0.5 mg and 1.0 mg once daily rasagiline, a selective irreversible monoamine oxidase type-B inhibitor, in PD patients at 38 community-based centers in the United States. Baseline treatment determined patients' stratification to mono- or adjunct therapy. Outcome variables were patient- and physician-reported treatment SEU ratings at weeks 4 and 12. Predictors included change from baseline in the bradykinesia subscale of the Unified Parkinson's Disease Rating Scale, change from baseline in patient- and physician-reported Activities of Daily Living (ADL), and patient- and physician-reported Clinical Global Impression (CGI). Data were analyzed using linear regression.

Results: SEU ratings with rasagiline were positive at all visits. Complete data were available for 109 monotherapy and 131 adjunct therapy patients at week 12. Patient- and physician-reported CGI were positively related to SEU ratings reported by the same individual at the same visit ($p<0.05$); patient-reported CGI was positively related to physician-reported SEU ratings at week 4 ($p<0.05$). Bradykinesia improvement from baseline predicted physician-reported SEU ratings at week 4 for monotherapy ($p<0.01$). Patient-reported ADL improvement from baseline predicted patient-reported SEU ratings at week 12 for adjunct therapy ($p<0.01$).

Conclusions: Patient- and physician-reported CGI were consistently related to patient- and physician-reported SEU ratings with rasagiline. Furthermore, improvement in bradykinesia symptoms and patient-reported ADL predicted subsequent ratings of treatment SEU

in some cases. Additional research on patient- and physician-reported treatment SEU scales in PD populations is needed to refine this important endpoint.

Mo-276

NMSQuest, NMSS and SCOPA-AUT metric properties in Mexican Parkinson's disease population

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Objective: To evaluate the metric properties of three clinimetric indexes of non-motor dysfunction (NMSQuest, NMSS, SCOPA-AUT) in Mexican PD patients.

Background: Non-motor dysfunction has become one of the main centers of attention in PD. Clinimetric indexes had been developed for assessing non-motor features; NMSQuest is a 30-item questionnaire with a yes or no input, NMSS is a 30-item scale which grades non-motor symptoms by frequency and severity and SCOPA-AUT is a 28-item questionnaire which evaluates dysautonomic symptoms in PD. Those indexes had been properly validated and translated to Spanish (Spain) but their clinimetric properties have not been evaluated in Mexican PD patients.

Methods: Due to differences in language use a linguistic validation was performed in a pilot study, then indexes were applied to 100 consecutive "on" mexican PD patients along with demographical data. Internal consistency was assesed by Cronbach's alpha. Inter-item and item-total Spearman's correlation was also calculated. Inter-rater reliability was assessed in a random subsample with intras-class correlation coefficient, agreement percentage and weighted kappa. Statistical significance was set at $p<0.05$.

Results: Sample data is shown on table I. NMSQuest mean score was 10.6 ± 5.5, test time was 6.7 ± 1.8 minutes, internal consistency (KR20) was 0.82. NMSQuest mean score was 69.7 ± 56.9, test time was 7.9 ± 2.1 minutes and Cronbach's alpha was 0.88. SCOPA-AUT mean score was 18.41 ± 11.53, test time was 7.78 ± 1.30 minutes and Cronbach's alpha was 0.80. For NMSS and SCOPA-AUT inter-rater reliability agreement was 85%, weighted-kappa was 0.79 and intra-class correlation coefficient was 0.78. Missing data was less than 5% for the NMSQuest (sexual items). Mean item-domain total correlation ranged from 0.52 to 0.85 for NMSQuest, 0.26 to 0.86 for NMSS and 0.46 to 0.77 for SCOPA-AUT excluding sexual items for females ($r=0.23$). Equivalent domain correlations ranged from 0.43 (miscellanous) to 0.76 (gastrointestinal).

Table (Mo-276). Demographic data

Female-Male Ratio	0.9:1
Mean Age (years)	64.5 ± 10.9
Mean Age at Diagnosis (years)	57.8 ± 11.3
Mean PD time (years)	6.6 ± 4.8
Mean Hoehn-Yahr	2.5
L-Dopa treatment	78%

Conclusions: Face and content validity were considered adequate for the indexes objectives. Inter-rater reliability was acceptable. Data quality was excellent, internal consistency was acceptable. Inter-item and item-total correlations were similar to published data.

Mo-277

Dynamic posturography in evaluation of balance in patients of Parkinson's disease with normal pull test

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Objective: To detect subclinical balance impairment in patients of Parkinson's disease (PD) with normal pull test, using dynamic posturography.

Background: Pull test in the assessment of balance in PD has subjective bias and it is unknown whether those with normal pull test have subtle instability which can be detected by dynamic posturography.

Methods: Twenty patients with PD (F:M=8:12, age=58.3±8.7 yrs, duration=3.6±2 yrs) with Hoen & Yahr stage II and 20 age and gender matched healthy controls (CTRL) participitated in this study. The patients were on stable doses of dopaminomimetics and were evaluated in the best ON state, using UPDRS and Dynamic posturography (Biodex, USA). The latter included (a) ability to control balance in all directions (overall balance index, OBI), front to back (anterior-posterior index, API) and side-to-side (medio-lateral index, MLI), and (b) the limits of stability (LOS) in 8 directions: forward (FW), backward (BW), right (RT), left (LT), forward-right (FW-RT), forward-left (FW-LT), backward-right (BW-RT) and backward-left (BW-LT).

Results: There was no significant difference of OBI, API and MLI between PD and CTRL. The total LOS score also did not differ significantly, but the time taken to complete the test was significantly higher in PD than in CTRL (PD=204±42.4 secs, CTRL=141.2±26.1 secs, $p<0.001$). Moreover, direction-wise analysis of LOS showed that PD patients had significantly lower scores (suggesting impaired balance) compared to CTRL only in FW-RT (PD=21.2±13.8, CTRL=34.5±17.5, $p=0.01$) and BW-LT (PD=20.8±9.8, CTRL=31.8±15.1, $p=0.01$) directions. In LOS test, CTRL had a better stability in FW than BW directions ($p<0.001$) and on RT than LT directions ($p<0.001$), which was also reflected in the diagonal directions (FW-RT > FW-LT, BW-RT >BW-LT, FW-RT>BW-RT, and FW-LT >BW-LT). Though the PD patients maintained the greater stability in the FW direction like the CTRL, they lost the advantage in the other directions, irrespective of the asymmetry of motor signs.

Conclusions: The pattern of normal balance maintenance seen in healthy subjects was lost in PD even with normal pull test. The impairment was more apparent in a diagonal direction consisting of forward right and backward left. This information may be useful in modification of the standard pull test for detection of early balance impairment in PD.

Mo-278

Teaching program for the Unified Dyskinesia Rating Scale

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Objective: To enhance a uniform application of the Unified Dyskinesia Rating Scale (UDysRS), we developed a DVD-based training program with instructions, patient examples, and a certification exercise.

Background: The UDysRS has been introduced as a comprehensive rating tool for the evaluation of dyskinesias in Parkinson's disease (PD). The four-part scale covers patient perceptions of ON and OFF dyskinesias (Parts 1 and 2) and objectively rates severity (impairment) and disability (Parts 3 and 4).

Methods: Instructions and examples of patient interview techniques were developed for training of Parts 1 and 2. For training on the objective assessment of dyskinesia (Parts 3 and 4), (none to severe), 70 PD patients spanning the gamut of dyskinesias were evaluated by 20 international movement disorder specialists using the UDysRS. For the teaching program, an example of each severity level for each of 7 body parts was selected based on the criterion that they received a uniform rating (±1 point) by at least 75% of the raters. For the certification exercise, four cases were selected to represent the four quartiles of overall objective UDysRS scores to reflect slight, mild, moderate, and severe dyskinesia based, all with a minimum kappa or intra-class correlation coefficient = 0.6.

Results: The teaching program lasts approximately 45 minutes, and the certification exercise requires approximately 15 minutes. Forty-five patient examples were selected for presentation; 25 segments for Part III (Impairment) and 20 segments for Part IV (Dis-

ability). In the four complete examinations selected for the program certification exercise, intraclass correlation coefficients (ICC) and 95th CI (rounded to the nearest whole number) were acceptable for the four examinations (patient 1 ICC = 0.88, 95th CI ± 1; patient 2 ICC = 0.78, 95th CI ± 2; patient 3 ICC = 0.91, 95th CI ± 2; patient 3 ICC = 0.84, 95th CI ± 3).

Conclusions: This training program, based on visual examples of dyskinesia and anchored in scores generated by movement disorder experts is aimed at increasing homogeneity of ratings among and within raters and centers. Large scale multicenter randomized clinical trials of dyskinesia treatment are strengthened by a uniform standard of scale application. This teaching tape is owned by the MDS. Contact the MDS for access details.

Mo-279

Applying the nonmotor symptoms questionnaire to a Singaporean population

L.J. Jaffe, L. Tan, W.-L. Au, P.N. Lau (San Diego, California)

Objective: To evaluate potential differences in nonmotor symptoms in a Singaporean PD population using the NMS Questionnaire.

Background: The importance of assessing PD patients' nonmotor symptoms has become clear as it's been found that these symptoms may affect quality of life even more than motor deficits(1). In 2006 the 30-question NMS Questionnaire was developed and obtained validity after administration in US and European centers (2). No centers from Asia were included in that study and thus it is unknown if there might be significant differences in responses across different population/cultural groups.

Methods: While on sabbatical at the Parkinson's Disease and Movement Disorders Center of the National Neuroscience Institute, Singapore over summer 2008, I administered the NMSQ to 30 PD patients using the same methods used in the International Multicenter Pilot Study (2). The responses from these 30 patients are shown in Table 1. Those from the original 2006 study population are shown in Table 2 in percentages of respondents who answered positively to the question.

Table(Mo-279). PD NMS Questionnaire – Singapore 2008

1. Dribbling of saliva during the daytime	Yes 33%
2. Loss or change in your ability to taste or smell	Yes 26%
3. Difficulty swallowing food or drink or problems with choking	Yes 40%
4. Vomiting or feelings of sickness (nausea)	Yes 13%
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool	Yes 70%
6. Bowel (fecal) incontinence	Yes 16%
7. Feeling that your bowel emptying is incomplete after having been to the toilet	Yes 56%
8. A sense of urgency to pass urine makes you rush to the toilet	Yes 46%
9. Getting up regularly at night to pass urine	Yes 73%
10. Unexplained pains (not due to known conditions such as arthritis)	Yes 56%
11. Unexplained change in weight (not due to change in diet)	Yes 33%
12. Problems remembering things that have happened recently or forgetting to do things	Yes 66%
13. Loss of interest in what is happening around you or doing things	Yes 56%
14. Seeing or hearing things that you know or are told are not there	Yes 20%
15. Difficulty concentrating or staying focussed	Yes 53%
16. Feeling sad, 'low' or 'blue'	Yes 46%
17. Feeling anxious, frightened or panicky	Yes 43%
18. Feeling less interested in sex or more interested in sex	Yes 23%
19. Finding it difficult to have sex when you try	Yes 20%
20. Feeling light headed, dizzy or weak standing from sitting or lying	Yes 33%
21. Falling	Yes 50%
22. Finding it difficult to stay awake during activities such as working, driving or eating	Yes 46%
23. Difficulty getting to sleep at night or staying asleep at night	Yes 43%
24. Intense, vivid dreams or frightening dreams	Yes 43%
25. Talking or moving about in your sleep as if you are 'acting' out a dream	Yes 26%
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	Yes 40%
27. Swelling of your legs	Yes 20%
28. Excessive sweating	Yes 26%
29. Double vision	Yes 26%
30. Believing things are happening to you that other people say are not true	Yes 6%

Results: The range of responses in our study was 2–23 with the range in the 2006 study being 0–27. The median score in our study was 11.6 whereas the median score in the index study was 9. This reflects no statisticallly significant difference overall in positive responses to the NMS questions. However, there were some differences noted when examining the individual questions which could be informative. A higher percentage complaints of dysphagia, constipation, unexplained pain, dysmemory and falls were reported in the Singaporean population study.

Table (Mo-279). PD NMS Questionnaire – 2006

1. Dribbling of saliva during the daytime	Yes 35%
2. Loss or change in your ability to taste or smell	Yes 26%
3. Difficulty swallowing food or drink or problems with choking	Yes 24%
4. Vomiting or feelings of sickness (nausea)	Yes 8%
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool	Yes 46%
6. Bowel (fecal) incontinence	Yes 5%
7. Feeling that your bowel emptying is incomplete after havinig been to the toilet	Yes 27%
8. A sense of urgency to pass urine makes you rush to the toilet	Yes 61%
9. Getting up regularly at night to pass urine	Yes 66%
10. Unexplained pains (not due to known conditions such as arthritis)	Yes 27%
11. Unexplained change in weight (not due to change in diet)	Yes 22%
12. Problems remembering things that have happened recently or forgetting to do things	Yes 44%
13. Loss of interest in what is happening around you or doing things	Yes 29%
14. Seeing or hearing things that you know or are told are not there	Yes 20%
15. Difficulty concentrating or staying focussed	Yes 37%
16. Feeling sad, 'low' or 'blue'	Yes 45%
17. Feeling anxious, frightened or panicky	Yes 40%
18. Feeling less interested in sex or more interested in sex	Yes 29%
19. Finding it difficult to have sex when you try	Yes 24%
20. Feeling light headed, dizzy or weak standing from sitting or lying	Yes 39%
21. Falling	Yes 31%
22. Finding it difficult to stay awake during activities such as working, driving or eating	Yes 28%
23. Difficulty getting to sleep at night or staying asleep at night	Yes 40%
24. Intense, vivid dreams or frightening dreams	Yes 31%
25. Talking or moving about in your sleep as if you are 'acting' out a dream	Yes 32%
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	Yes 37%
27. Swelling of your legs	Yes 31%
28. Excessive sweating	Yes 25%
29. Double vision	Yes 22%
30. Believing things are happening to you that other people say are not true	Yes 12%

Conclusions: There was not a statistically significant difference in responses to the NMS Questionnaire in Singaporean respondents versus respondents from US and European centers. The NMS-Q seems to remain valid across different populations/cultural groups. However, some of the differences in responses to the individual questions may have further value in understanding differences in various populations.

Mo-280

UPDRS rater training: Assessing raters' ratings

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Objective: This study examines an approach to rater training and certification on the motor section of the UPDRS focusing on assessing inter-rater agreement with the Gold Consensus Ratings (GCRs) arrived by Parkinson's disease (PD) experts.

Background: UPDRS is widely used for the clinical evaluation of PD. Training and evaluation of investigators, particularly on the motor section, is critical before clinical trial initiation to make certain that rating scale measures are accurately and consistently administered. Rater performance was assessed using early and advanced stage PD patient videos.

Methods: 229 raters from 34 countries participated in the rater training and certification program. A combination of online and face to face training at the investigators' meeting (IM) was used. The IM included an intensive review of rating conventions, discussion of difficult to rate items, and a certification session using early and advanced patient videos with individual ratings being compared to the GCRs. Inter rater agreement was assessed for the total motor score using Kappa statistics. Ratings between the raters and the GCRs for the individual items were assessed using McNemar Test for paired binomial proportions.

Results: Inter-rater agreement for the total UPDRS motor score between raters was substantial (kappa = .89, $p < .001$) for early PD, and moderate (Kappa = .64, $p < .001$) for advanced PD patient. For the individual items the McNemar Test for paired binomial proportions showed agreement for 15/27 items for early PD and 17/27 items for advanced PD patient. Based on these results speech, facial expression, leg agility and tremor at rest were found to be difficult to rate for both the patients. These items were targeted for additional training before trial initiation. Previous UPDRS experience did not significantly affect scoring of early and advanced PD patients.

Conclusions: Overall acceptable inter-rater agreement was achieved for both patients, difference in agreement level, substantial for early PD and moderate for advanced PD suggest that raters have differential difficulties rating PD patients at different stages of the disease. This finding suggests that it is critical for raters to undergo

intensive rater training on UPDRS with emphasis on different patient vignettes. Further, additional training may be warranted as difficult to rate items are identified.

Tu-276

Can falls be accurately predicted in people with Parkinson's disease?

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Objective: To develop a clinical model to predict falls in people with Parkinson's disease (PD).

Background: Falls are a major health and injury problem for people with PD. Accurate prediction of falls risk in individual PD patients could lead to improvements in quality of life, reduced burden of care, and targeted therapy.

Methods: This project assessed 101 people with PD (age 66.5 yrs; disease duration 6.3 yrs; UPDRS 33; Hoehn & Yahr 2.1) on six clinical tests commonly used to assess falls risk. These were the Tinetti, Berg, Timed Up and Go (TUG), Functional Reach and the Physiological Profile Assessment (PPA). The PPA includes tests of visual function, proprioception, leg strength, cutaneous sensitivity, reaction time, and postural sway. Participants also completed the Mini Mental State Exam, Freezing of Gait (FOG) questionnaire and the Schwab and England (S&E) activities of daily living scale. A measure of postural instability and gait disability (PIGD) was derived from the UPDRS scores. Falls were prospectively recorded by each participant over six months using a monthly falls diary.

Results: 48% of participants reported a fall and 24% of participants were recurrent fallers. Fallers had longer disease duration and disease severity based on the UPDRS and the PIGD scores. Fallers scored lower on the S&E activities of daily living scale and had higher scores on the FOG questionnaire. Dyskinesia was more often present in fallers than non-fallers. Fallers also had a greater incidence of symptomatic orthostasis and sleep disturbance than non-fallers. Fallers performed worse on the Tinetti, Berg, and TUG tests, had significantly poorer peripheral sensation, knee extension strength and had greater anterior-posterior postural sway when standing on a firm surface. The multivariate model of falls prediction that produced the best sensitivity (78%)and specificity (84%) included UPDRS total score, total FOG score, occurrence of symptomatic postural orthostasis, Tinetti total score and extent of postural sway on a firm surface with eyes open.

Conclusions: It is important to include disease-specific clinical as well as physiological measures of sensory, motor and postural stability function to reliably determine falls risk in PD patients.

Tu-277

Non-motor symptoms in de novo Parkinson's disease before and after dopaminergic treatment

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Objective: The aim of this study was to evaluate the burden of non-motor symptoms (NMS) in untreated de novo Parkinson's disease (PD) patients, both quantitatively and qualitatively, and to compare the results with those in control subjects. In addition, we examined the effect of dopaminergic treatment on NMS.

Background: NMS are common in PD patients, and they could be more disabling than motor symptoms. While some NMS increase with age and advanced motor symptoms, other NMS can antedate the onset of motor symptoms by many years. Therefore, a considerable proportion of PD patients may already have NMS by the time they are first diagnosed with PD. To date, the burden of the full range of NMS has not been well studied in de novo PD patients.

Methods: NMS were evaluated in 23 patients with untreated de novo PD (mean disease duration 9.8±9.9 months) and 23 controls. In the PD patients, motor UPDRS (mUPDRS) and HY stage were also checked. The number of NMS and the NMSS scores of the PD patients were compared with those of the controls. Three months after the start of dopaminergic medications, 16 PD patients were reevaluated with respect to NMSS, mUPDRS, and HY stage.

Results: The number of NMS and the NMSS scores were significantly higher in the PD patients than in the controls. The 3 most prevalent NMS in PD patients were 'nocturia,' 'forget things or events,' and 'restless legs.' In PD patients, the number of NMS was correlated with the HY stage but not with age, disease duration, or mUPDRS score. Follow-up of 16 patients at 3 months showed no changes in the number of NMS nor the NMSS score, despite improvement in motor symptoms.

Conclusions: Untreated de novo PD patients have more non-motor problems than controls, and these NMS are not ameliorated with dopaminergic medications.

Tu-278

Development of a non-motor fluctuation assessment instrument (NoMoFA) for Parkinson's disease

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Objective: Develop a comprehensive, comprehensible, patient-based instrument that accurately assesses the presence of non-motor fluctuations (NMFs) in individuals with Parkinson's disease (PD).

Background: NMFs include sleep, mood, cognition, autonomic and sensory symptoms that impact on quality of life in patients with PD. In contrast to other non-motor symptoms that may be mediated by non-dopaminergic neurotransmitter pathways, NMFs vary according to plasma dopaminergic tone in a manner similar to motor fluctuations. While it is likely that NMFs are amenable to medical and surgical interventions, there has been no instrument available to assess the presence of NMFs, and this has limited the assessment of symptomatic burden as well as efforts to quantify the impact of interventions.

Methods: PD patients who were cognitively intact and endorsed symptoms of NMFs participated in development of the questionnaire. Three Nominal Group Technique (NGT) sessions were carried out. A final composite list including items generated from each session was compiled and incorporated into a questionnaire format. A scoring system was created using a 4 point scale (none, mild, moderate, severe) for each item to assess severity of symptoms, with a higher score reflecting a greater burden of symptoms. Clinicians with expertise in PD critiqued the questionnaire for content, language, comprehensiveness and redundancy, leading to creation of an initial questionnaire. Two patient/caregiver focus groups critiqued the questionnaire further. A revised questionnaire was distributed to both clinician experts and methodological experts in questionnaire development for further review, and this semi-final version of the questionnaire was administered to patients to provide further feedback using cognitive debriefing methods.

Results: The final revised questionnaire consists of 29 items pertaining to domains of mood, cognition, sensory and autonomic symptoms, allowing quantitative assessment of the presence and severity of NMFs.

Conclusions: This study has identified the key symptoms experienced as NMFs in PD. Strengths of this questionnaire include extensive expert and patient input to ensure face and content validity. Assessment of the reliability and validity of the questionnaire will soon be underway.

Tu-279

Multidisciplinary team management in Parkinson's disease: The role of occupational therapy

M. Makoutonina, R. Iansek, B. Kirkwood (Melbourne, Victoria, Australia)

Objective: To define the role of occupational therapy (OT) in multidisciplinary team (MDT) management in Parkinson's disease (PD).

Background: PD is a complex illness, requiring continuous comprehensive care which is best delivered by a MDT. However no guidelines exist to define the scope of practice for each discipline. Rehabilitative guidelines[1] exist for improvement of motor function and activities of daily living (ADL) but not for non-motor symptoms. We now report on specific guidelines for OT intervention based on assessments performed with ADL (UPDRS), quality of life (PDQ39) and fatigue (PDFS16) scales.

Methods: Following initial assessment, interventions were developed and applied to patients admitted (average 14 days) for comprehensive care to a private geriatric hospital. MDT care included medication optimisation and strategy training[1] (ST). Specific OT interventions included ST for ADL, education, energy conservation, stress and fatigue management, environmental modifications, functional medication management, care giver supports and participation advice. Measures, which reflected these interventions (UPDRS I & II (OFF medication), PDQ39 and PDFS16), were administered on admission to, and on discharge from hospital. Comparisons utilised paired T tests and correlation analysis.

Results: The records of 177 patients (males = 100) were reviewed. The mean age was 71.6 (9.9 sd) years, with mean disease duration of 7.2 (5.9 sd) years. Significant changes ($P < 0.0001$) occurred for all parameters following intervention. It was also found that the improvements in the PDFS 16 were not reflected in the changes for the UPDRS and PDQ 39.

Conclusions: This proof of concept study suggests that the OT interventions, defined in the study, have the capacity to improve outcomes for PD patients when applied to inpatient management. However, randomised controlled trials with long-term follow up are necessary to confirm these interventions. 1. Morris, M. et.al. 2009 Movement Disorders. Effects of hospital based rehabilitation in Parkinson's disease. (In press)

Tu-280

Impact of rate of motor progression on patient-rated outcomes in Parkinson's disease (PD)

T.M. Mangin, A. Siderowf (Portland, Oregon)

Objective: To ascertain whether rate of clinical motor progression is a predictor of various patient-rated health outcome measures in Parkinson's disease.

Background: The symptomatic nature of PD treatment has led to an increasing emphasis being placed on patient-oriented outcome measures. These outcome measures evaluate related but distinct concepts of health, health-related quality of life (HRQL), and quality of life (QoL). It is unknown how the rate of motor progression impacts these outcomes.

Methods: A group of 43 subjects with PD were followed over a one year period. Data on demographic and clinical factors, motor symptoms, cognitive function, and depression were collected at baseline and at 12 months. Subjects' HRQL and QoL were assessed with the Medical Outcome Study Short Form (SF-12), a visual analogue rating scale of health (RS Health), and a visual analogue rating scale of quality of life (RS QoL). Multiple linear regression analyses were conducted to identify determinants of health outcome measures.

Results: The scores obtained on the three outcome measures at the final visit were associated with different clinical variables. Rate of clinical motor progression predicted only the RS Health scores and only for the most rapidly progressing patients. Current levels of depression, but not motor progression, was a predictor of the SF-12 and RS QoL.

Conclusions: Rate of clinical motor progression influences perceived health status of rapidly worsening patients, but does not contribute to patient-rated quality of life or health-related quality of life. This study emphasizes the distinction between these outcome measures and the important impact of depression on all patient-oriented outcomes in PD.

Tu-281

Depression in Parkinson's disease and essential tremor

C.-J. Mao, J.-P. Chen, W.-D. Hu, J.-F. Liu, D.-Q. Chen, C.-F. Liu (Suzhou, Jiangsu, China)

Objective: To study the incidence and associated factors of depression in Parkinson's disease and essential tremor.

Background: Parkinson's disease (PD) and essential tremor(ET) are the most common diseases among movement disorders. Depression is one frequent non-motor symptoms in PD. As depression in PD has been studied extensively, depression in ET has relatively fewer reported. Those researches simultaneously on the depression of PD and ET is even fewer.

Methods: Unified Parkinson's Disease Rating Scale (UPDRS) - motor examination (UPDRS-III) and Hoehn and Yahr scale were used in 121 PD patients to evaluate the severity of the disease. Tremor Rating Scale for Tremor-motor examination (items 1–15 of the rating scale) was perrformed in ET patients. Hamilton Depression Rating Scale(24 items) was tested in all participants to measure the depression.

Results: 56.2% of PD patients and 53.2%% of ET patients were found to be depressed. There were no differences on the incidence of depression, mild depression, moderate depression and severe depression between the two groups. Anxiety/somatization, lose weight, changes day and night, block and sleep disorders were different between PD group and ET group. Score of HAMD was positively correlated with the score of UPDRS -IIIin PD patients($r=0.511$, $P<0.01$), as well as in ET patients, it was positively correlated with score of Tremor Rating Scale for Tremor-motor subscale($r=0.828$, $P<0.01$P).

Conclusions: The incidence of depression is higher in PD and ET patients. The severity of depression was similar between the two groups. The mainly manifestations of depression were anxiety/somatization, dysthymia, anhedonia, retardation and insomnia. Depression was positivly correlated with motor disturbance.

Tu-282

International validation of the non-motor symptoms scale: Comparison with the pilot study

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Objective: To compare the results of the pilot and the validation study of the Non-Motor Symptoms Scale (NMSS).

Background: NMSS is a specific tool for assessment of non-motor symptoms in Parkinson's disease (PD). A pilot study has been published (Mov Disord 2007; 22: 1901-1911) and an international validation study has been carried out.

Methods: International, multicentre, cross-sectional studies. In the pilot study, the NMSS, Hoehn and Yahr staging (HY), UPDRS Parts 3 and 4, Cumulative Illness Rating Scale-Geriatrics, Frontal Assessment Battery, Parkinson's Disease Questionnaire-8 items (PDQ-8), Fatigue Visual Analogue Scale, Hospital Anxiety and Depression Scale, and the NMS Questionnaire (NMSQuest), were included. In the validation study, the NMSS, HY, Clinical Impression of Severity Index for PD, Scales for Outcomes in PD-Motor, SCOPA-Psychiatric Complications (SCOPA-PC), SCOPA-Cognition, SCOPA-Autonomic (SCOPA-AUT), PD Sleep Scale (PDSS), EQ-5D, and PDQ-39, were applied. NMSS acceptability, reliability, validity and precision were evaluated.

Results: Pilot study recruited 242 PD patients (57.3% men; mean age, 67.2±11 y.; mean disease duration, 6.4±6 years). In the validation study, the figures were: 411 patients (61.3% men); age 64.5±9.9 y.; and disease duration, 8.1±5.7 y. NMSS total score was 56.5±40.7 (range: 0-243) for the pilot, and 57.1±44.0 (range: 0-233)

for the validation study. In both studies no floor or ceiling effect was detected, and skewness was 1.2. For domains, Cronbach's alpha range was 0.37-0.85 (pilot study) and 0.44-0.85 (validation study). The intra-class correlation coefficient was 0.97 (pilot study) and 0.89 (validation study). NMSS correlated highly with health-related quality of life scales, NMSQuest, and SCOPA-AUT, PDSS, and SCOPA-PC. NMSS significantly discriminated among HY severity levels in both studies ($p<0.0001$). SEM was 7.04 (pilot) and 14.6 (validation study).

Conclusions: The psychometric properties of the NMSS explored in the pilot study were confirmed and expanded in the validation study.

Tu-283

Convergent validity of the non-motor symptoms scale (NMSS) in Parkinson's disease

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Objective: To assess the convergent validity of the Non-Motor Symptoms Scale (NMSS) with specific Parkinson's disease-related measures.

Background: The NMSS, a specific instrument for comprehensive assessment of non-motor symptoms (NMS) in Parkinson's disease (PD), has been recently validated, with good psychometric properties.

Methods: International, multicentre, cross-sectional study. In addition to the NMSS, the Hoehn and Yahr staging (HY), Scales for Outcomes in PD-Cognition (SCOPA-COG), SCOPA-Psychiatric Complications (SCOPA-PC), SCOPA-Autonomic (SCOPA-AUT), PD Sleep Scale (PDSS), EQ-5D and PD Questionnaire-39 items (PDQ-39), were applied. Spearman's rank correlation coefficients (r_s) were calculated for convergent validity of NMSS total score and domains with the rest of scales. Coefficient values ≥ 0.50 were considered high and <0.30 low.

Results: The sample was composed by 411 PD patients (61.3% men, with mean age of 64.5 ± 9.9 years, and mean duration of disease 8.1 ± 5.7 years). NMSS total score was 57.1 ± 44.0 (range: 0-233). NMSS total score highest correlations were with PDQ-39 (0.70), and SCOPA-AUT (0.67). Correlation coefficients >0.50 were reached with EQ-5D, SCOPA-PC, and PDSS ($r_s=0.51$-0.57). NMSS domains correlated with instruments evaluating related constructs: Sleep/fatigue, with the PDSS (-0.56); Perceptual problems/hallucinations, with SCOPA-PC (0.53); Attention/Memory with CISI-PD Cognition ($r_s=0.51$). Correlation values between NMSS domains and the corresponding SCOPA-AUT subscales were as follows: Cardiovascular, $r_s= 0.62$; Gastrointestinal, $r_s= 0.65$; Urinary, $r_s= 0.65$; and Sexual function, $r_s= 0.51$. Some NMSS domains showed high correlations with the PDQ-39: Sleep/fatigue, 0.58, and Mood/Apathy, 0.57. Furthermore, six out of the eight PDQ-39 domains correlated 0.51-0.71 with NMSS total score (all mentioned values, $p<0.0001$).

Conclusions: Convergent validity of the NMSS with other PD related scales and, in particular, health-related quality of life measures was robust and satisfactory.

We-271

Non- motor staging of Parkinson's disease (PD) and early longitudinal follow up results from an international study

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Objective: To provide baseline data on 163 patients with NMS staging and follow up assessment (up to 24 mnths) on 18 patients on otherwise stable medications.

Background: While motor staging of PD is well established the concept of " non motor staging" of PD is relatively new and we have suggested a novel non motor staging of PD based on non motor questionnaire (NMSQuest) scores (0-5 = no (stage 1), 6-12 = mild (stage 2), 13-20 = moderate (stage 3) and $>$ 20= severe (stage 4).

Methods: Patients completing the NMSQuest were staged as above. Baseline motor, quality of life, demographic details and drug history were collected. The longitudinal study aims to collect yearly FU data on these patients for 5 years and follow up data on 18 are presented.

Results: 163 PD (68.9 ± 10yrs, disease duration 6.08 ± 5.4yrs, Hoehn and Yahr stages 1-5) have been staged and baseline NMS staging of PD discriminated among the PD groups significantly with UPDRS Sections III and IV, PDQ-8, and HADS scores ($p=0.0001$ for all). At follow up (17.9 ± 8.1 months (range: 6-26)) NMSS worsened (8.94 ± 13.88 points; range: -8 to 47, $p=0.02$) with worsening in all domains except sleep but only urinary domain was significantly worsened ($p=0.002$). Quality of life (PDQ-8) also worsened (Wilcoxon test, $p=0.02$) while changes in UPDRS were non significant. The changes were unrelated to age, sex and HY stage.

Conclusions: NMSQuest allows a new NMS staging in PD. When judged by NMS scale, in a small number of patients over a period of 6-26 months, there is worsening of NMS alongside PDQ-8 although changes in UPDRS scores are not significant suggesting that non motor progression may be independent of motor progression and influences quality of life.

We-272

Achieving excellent inter-rater reliability on the SAPS in a psychosis in Parkinson's disease study using raters with limited SAPS experience

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Objective: It has been repeatedly shown that low inter-rater reliability (IRR) negatively impacts the outcome of clinical trials, especially those employing subjective outcome measures. A method for establishing IRR is examined.

Background: Psychosis in Parkinson's disease (PPD) is a serious condition that significantly affects the patient's subjective wellbeing and the caregiver's burden. Despite enormous effort the treatment of this condition remains unsatisfactory and new drug development is needed. As PPD clinical trials rely on subjective efficacy assessments, achieving a high level of IRR is paramount.

Methods: As part of a multi-national industry sponsored study of PPD, 168 raters were trained on the primary endpoint, the Scale for the Assessment of Positive Symptoms (SAPS). Training consisted of a) didactic presentations on SAPS administration and scoring guidelines; b) practice scoring of a videotaped SAPS interview, with immediate feedback, and c) interview skills training. After training, raters were divided into language-specific breakouts, which were led by Clinical Trainers fluent in their native language. Assessments consisted of 1) viewing and scoring a videotaped SAPS interview subtitled in their native language, and 2) interviewing standardized actors portraying patients and their caregivers. Raters needed to demonstrate competence both in scoring the video and administering the SAPS in order to be selected for study participation.

Results: Out of 168 potential raters, 100 (60%) lacked prior experience with the primary rating instrument. Additionally, 19 (11%) had $\leq$1 year of experience with the SAPS. 108 raters (64%) were non mental health professionals (i.e. neurologists, internal medicine doctors, research nurses, etc.). The overall level of inter-rater agreement was excellent (**kappa = .872**), with levels of inter-rater agreement of each individual rater relative to all other raters ranging from .543 to .921. Of the 168 potential raters, 139 (83%) achieved inter-rater agreement **> 0.8. Analysis:** IRR was assessed on the video scores using the kappa statistics modified for multiple raters assessing a single subject.

Conclusions: This study shows that comprehensive training on the SAPS can achieve high levels of agreement between a large number of raters, many of whom never previously used the scale.

We-273

A validation study of the Chinese wearing off Questionnaire 9-symptom for Parkinson's disease

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Objective: We aimed to validate a Chinese version WOQ-9 (CWOQ-9) among Chinese patients with PD.

Background: An English version "wearing off questionnaire 9-symptom" (WOQ-9) has been proposed for detection of wearing off (WO) among Parkinson's disease (PD) patients.

Methods: The original English version of the questionnaire was translated into Chinese by a group of movement disorder specialists. We recruited literate Chinese PD patients among 4 different neurology or movement disorder clinics in Hong Kong to participate in this study by completing the CWOQ-9. Clinical judgment by the specialists was considered the gold standard for diagnosing WO. We determined the sensitivity, specificity, and positive and negative predictive values of the CWOQ-9.

Results: One hundred and one patients participated in the study. The mean age (±SD) of the patients was 61 (±9) years and 35 (34.7%) of them were female. The disease duration was 7.4 (±5.4) years and 69 (68.3%) of them were diagnosed clinically to have WO by the specialists. The sensitivity and specificity of the CWOQ-9 for detection of WO were 87% and 69% respectively. The positive and negative predictive values were 86% and 71% respectively.

Conclusions: The CWOQ-9 is a simple and valid tool for the detection of WO among Chinese PD patients.

We-274

Non declaration of non motor symptoms (NMS) of PD: An international study using the NMSQuest

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Objective: Use of the NMSQuest, validated for Parkinson's disease (PD) to identify currently prevalent non motor symptoms (NMS) and what proportion is reported to healthcare professionals (HCP).

Background: Non motor symptoms of PD are a key determinant of quality of life (QoL) yet studies have suggested that issues related to NMS are often not discussed in clinical consultations. It is likely therefore that many potentially treatable NMS are either not disclosed and as a result not treated with a possible long term consequence on patient or caregivers' QoL.

Methods: NMSQuest was administered across 5 international centres (Germany, Spain, UK, US, Italy). Patients were then asked if the items declared positive were previously discussed with any HCP. Correlation with the other parameters and demographics were analysed.

Results: Data from 242 patients: mean age 68 ± 10 (SD) years [range 34 – 91 years], disease duration 7.9 ± 5.7 years [range 0 – 28 years] were collected. 42.8% of the total routine NMS assessed (mean 10.8 ± 5.6) were undeclared to HCP prior to the use of the NMSQuest. Delusion, intense, vivid dreams, daytime sleepiness and dizziness were least declared while bowel incontinence and sweating were most declared. The percentage of non declared NMS was significantly lower with p= 0.0001 in Spain while significantly less NMS were declared in patients who were less than 75 years old. The percentage of patients not declaring NMS was significantly related to all 9 domains of the NMSQuest (p= 0.0001 for all of them). Non declaration appeared to be related to either patients not being aware of link of symptoms with PD, embarrassment about discussing symptoms (sexual problems) and relevant questions not being asked by the HCP.

Conclusions: This study confirms the widely held view that NMS of PD are often not discussed in clinic consultations unless specific tools for flagging these symptoms such as the NMSQuest is used. The problem appears uniform across all the international centres. Patients with lower age group appear to have higher numbers of non-declared NMS while the proportion of non- declared NMS was lowest in Spain when compared to the other centres.

We-275

Impact of an exercise program on patients with Parkinson's disease and on their physiotherapists practice

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Objective: To assess the effect of an individual rehabilitation program based on the patients' prevalent symptoms in Parkinson's disease (PD) on quality of life and on the satisfaction of the patients and their physiotherapists.

Background: In PD there are only few guidelines graded about physiotherapy according to scientific evidence. Physiotherapy is often prescribed in PD in combination with medical treatment but there is uncertainty about the nature of the therapy given by physiotherapists to patients with PD and also about the satisfaction of the patient with physiotherapy.

Methods: In association with expert physiotherapists for PD, medicine and rehabilitation physicians, we elaborated a physical therapy program based on the core areas for physical therapy in PD: (i) transfers, (ii) posture, (iii) balance and falls, and (iv) physical capacity and inactivity. For each patient, according to their motor impairment, we selected physiotherapy exercises and we proposed this program to their local physiotherapist for 3 months. Quality of life (PDQ-39) was evaluated at baseline and after 3 months of physical therapy program. We built a satisfactory questionnaire for the patient and the physiotherapists which were anonymous and fulfilled at the end of the program.

Results: 1O3 PD patients Hoehn et Yahr stage (percentage of patients): ≤2(43.6%);]2-3] (49.5%); =4 (6,8%) were included. Significant improvement of quality of life was found for the emotional well being, bodily discomfort and stigma domain $p \leq 0.05$. No significant improvement was found for the other PDQ 39 domains. For the patients, the mean global satisfaction note for this program was 5.98 ± 2.4. For the physiotherapist, the mean global satisfaction note for this program was 7.2 ± 2.1.

Conclusions: Our study finds evidence of the potential benefits of physiotherapy for patients with PD. If specific physiotherapy may be effective to limit physical mobility impairment, our results point out that physiotherapy may be also efficient to confine the negative impact of social isolation, pain and emotional reactions. Such a program should be associated with therapeutic education intervention such as encouraging patients to realize alone physical therapy.

We-276

Development of a QOL-oriented severity scale for Parkinson's disease (A novel QOL-oriented severity scale for Parkinson's disease)

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Objective: The purpose of the present study as firstly to establish a new method for calculation of the relative weight of the observed variables in a patient with PD utilizing conjoint analysis, and secondly to develop a novel, weighted, QOL-oriented scale for measuring the severity of PD, a quantitative severity scale for PD (QSSPD).

Background: Attempts have been made to quantify the severity of Parkinson's disease (PD). However, due to the lack of information as to the relative weights of the observed variables which is essential for the integration of the severity, none of them are universally accepted as the gold-standard of quantitative scale for measuring the severity of PD.

Methods: The study was conducted in 6 Japanese medical universities that had been rigorously evaluated for neurological expertise and quality of neurological management. The scale consists of 4 variables which were most closely related to the prediction of outcome weighted on QOL of PD. The variables were as follows; (1) mentation, behavior and mood, (2) performance of activities of daily living (ADL), (3) motor aspects, (4) non-motor aspects of disease.

Results: As a result of conjoint analysis, the relative importance of the each variables against the QOL of the patients were 16.5, 39.0, 20.5 and 24.0%, respectively, indicating that performance of ADL was the most important factor for determining the severity among PD patients. We have validated QSSPD by assessing 40 patients with multiple raters of 6 medical universities. Using the 39-item Parkinson's Disease Questionnaire (PDQ-39) as an independent variable, this study found a significant correlation ($r = 0.62$) between the QSSPD and the PDQ-39.

Conclusions: The present study utilizing conjoint analysis revealed the potentiality of our scoring system to be an universally accepted and reliable standardized system with higher consistency, reliable validity and superior quantification.

We-277

Development of a new olfactory function scale for Parkinson's disease patients

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Objective: To develop and validate a self-administered scale for the evaluation of olfactory dysfunction in PD patients.

Background: Olfactory dysfunction is common in Parkinson's disease (PD) and has been shown to precede the motor symptoms of the disease.

Methods: A consecutive serie of PD patients recruited from a tertiary out-patient movement disorder clinic were polled about their perceptions regarding their olfactory function (normal or abnormal). Then a 20 Likert-type items self administered questionnaire was presented to them. Fifteen items were related to the frequency at which the patient perceived different odors (1-not at all, to 4- always spontaneously) and five items to patient's ability to discriminate between smells (1-not at all, to 4-clearly). Perception of common smells such as coffee, baked-bread, flowers, cigarette, grass, butane-gas, burning-goods, ambient fresheners, garbage, combustion of gasoline, perfume, bleach, transpiration, food and paint were evaluated. Total score was expressed as the percentage of the maximal score possible. Another group of 16 Parkinson's disease patients and 11 healthy controls were recruited for the evaluation of the scale's clarity, response range, internal consistency (by Chronbach's alfa) and its ability to differentiate healthy controls from PD patients complaining about olfactory problems or not.

Results: All items were easily understood by controls and patients. One patient failed to respond one item. Two patients (12%) displayed ceiling effect. Chronbach's alfa was > 0.90. Six patients complained about olfactory dysfunction (37%). Olfactory scores in controls, non-complaining or complaining PD patients were $95.2 \pm 1.1\%$, $94.5 \pm 1.7\%$ and $57.3 \pm 9.7\%$ respectively ($p = 0.006$, Brown-Forsythe ANOVA). In the latter, the total score ranged from 31-90%.

Conclusions: The scale was easy to understand and complete, with little ceiling effect. It showed adequate internal consistency and good ability to differentiate controls and non-complaining PD patients from those complaining from olfactory problems. Future studies should evaluate the scale reproducibility and validity.

We-278

Wearable sensor system for monitoring motor function in Parkinson patients

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Objective: The development of a wearable sensor system (3-4 sensors) that automatically and continuously monitors: a) the presence and severity of motor signs of PD (matching the UPDRS motor scales), b) the status of "On-Off-On w/Dyskinesia" motor fluctuation in response to anti-Parkinson's medication, and c) the mobility status of the patient.

Background: Current reliance on self-report instruments to capture changes, often unpredictable, in PD motor complications is problematic. Such instruments offer limited temporal resolution, are time-consuming, interfere with daily activities, rely on patient memory, and may be subjectively biased. Wearable activity monitors offer inherent advantages (portability, high temporal resolution, and automatic operator-independent measurements); however current devices have not progressed to the level of useable "real-world" technology.

Methods: We are developing a system of 8 wireless sensors that combines electromyographic (EMG) and accelerometer (ACC) data acquisition and software that incorporates Artificial Intelligence tools organized and enhanced for decision support using a custom architecture. These technologies were used to acquire and analyze data from $n = 18$ subjects in a laboratory-based "apartment". Videotaped data are annotated and scored by clinicians to serve as the gold-standard for algorithm assessment.

Results: Algorithms have been implemented using a blackboard-based signal processing architecture coupled with feature extraction procedures and time-dependent neural networks. Training from a sub-set of the data (ACC signals from 2 sensors) provided greater than 90% accuracy for classifying sitting, standing, walking, and lying down. Of the four specific motor signs being annotated (*Tremor, Dyskinesia, Bradykinesia, and Freezing*), user-dependent training of the algorithms from a sub-set of the data (ACC signals from 8 sensors) has resulted in greater than 95% accurate detection of Tremor and Dyskinesia.

Conclusions: Preliminary results support the likelihood of achieving the objectives using the technologies under development. This work was supported in part by grant # EB007163 from the NIH/NIBIB. Our thanks to the patients and staff of the BU Parkinson's Disease and Movement Disorder Center.

Th-276

Investigating the relationship between UPDRS symptom assessment and an objective movement outcome assessment of Parkinson's disease

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Objective: The current study aimed to determine whether objective outcome measures might accurately represent the symptoms (measured by UPDRS) of Parkinson's disease (PD).

Background: An important limitation of many therapeutic intervention studies is the over reliance on clinical measures, with little agreement on other objective and quantitative outcome measures.

Methods: One hundred and eleven PD participants ($F = 42$, $M = 69$, age $= 67.1 \pm 9.1$) were assessed as part of a large exercise rehabilitation trial at the Movement Disorders Research and Rehabilitation Centre, WLU, Canada. Symptomatic assessment utilized the Unified Parkinson's Disease Rating Scale (UPDRS), while objective outcome measures included the Timed-Up-and-Go (TUG), place and remove phase of the grooved pegboard (GP) on both the PD affected and non-affected sides, and spatiotemporal aspects of self-paced gait. Participants were assessed before commencing exercise (pre-test) and immediately following the end of the twelve week program (post-test).

Results: A backward elimination linear regression was performed using all outcome measures to predict PD symptom severity (UPDRS). The GP place phase on the non-affected side was found to be the most predictive of PD symptom severity, accounting for 26.9% of the variability in UPDRS score. More relevant for outcome measures to be used in therapeutic intervention trials, a correlation analysis was conducted to determine the relationship between the objective measures (TUG and GP) and subsets of the UPDRS that represent the specific symptoms assessed by the TUG and GP. Percent change was used to standardize the measures, and control for pre-test differences. No significant relationships between the UPDRS subsets and corresponding outcome measures were identified.

Conclusions: None of the outcome measures identified were able to reflect changes in PD symptom severity. Thus, the current approach to evaluate success of therapeutic interventions (e.g. exercise rehabilitation) should involve both symptomatic assessment and objective measures to ensure that the therapy results in improvements in the most relevant manner, symptom severity. Additionally, the GP and new measures should be carefully investigated for their ability to reflect symptomatic assessment to ensure that future interventions are effectively evaluated.

Th-277

Validation of the WHO-5 wellbeing index as a screening tool for Parkinson's disease depression

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Objective: To validate the WHO-5 wellbeing index as a screening tool for depression in Parkinson's disease (PD).

Background: Depression has a high prevalence in PD patients. However it often remains undetected. Currently, the Beck Depression Inventory (BDI-1) is the gold standard screening tool for PD depression, but as a result of its length and complexity it is of limited suitability as a quick and easy screening device. The WHO-5 wellbeing questionnaire is a short screening instrument for the detection of depression in the general population, but not validated in PD.

Methods: We assessed 225 Patients with PD (mean [SD] age: 68±8.8 years) at Hoehn&Yahr stages I-V (mean [SD]: 2.5±0.4) in a multicenter study using the 5 item self-report WHO-5 wellbeing index and BDI-1. ICD-10 diagnoses were made using the structured Mini International Neuropsychiatric Interview (M.I.N.I). External validity for detection of depression was evaluated by ROC analysis.

Results: 223 patients completed the WHO-5 and 218 the BDI-1. ROC analysis showed that both questionnaires adequately detected depression without differences in the validity indices (AUC 0.858 [95%CI: 0.791-0.926], $P<0.001$, for WHO-5; AUC 0.929 [95%CI: 0.895-0.963], $P<0.001$ for BDI-1). The cut-off values for detection of depression (at least 80% sensitivity and specificity) were 12 points for WHO-5 and 15 points for BDI-1.

Conclusions: The WHO-5 showed a good external validity for screening for depression in PD with similar validity compared to BDI-1. The WHO-5 is thus an useful instrument for identifying PD subjects with depression.

Th-278

A probabilisitc approach for patient classification in Parkinson's disease

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Objective: To (1) apply a novel, probabilistic approach for identifying patient subgroups in Parkinson's disease (PD) based on symptom profiles and (2) characterise the resulting subgroups with respect to a number of demographic and clinical factors.

Background: The classification of patients into clinical subtypes plays a critical role in understanding the population structure of complex disease. PD methods of classification like Hoehn and Yahr (HY) staging and Tremor/PIGD dominance are based on deterministic criteria. These systems consider few symptoms and may not account for the variability observed in PD symptom profiles. Current advances in statistics provide a basis to better understand population structure by exploring the influence of more symptoms and their laterality on patient subgroup identification.

Methods: We used a finite mixture model to identify patient subgroups based on data collected on the Unified Parkinson's Disease Rating Scale (UPDRS). These include laterality of tremor and rigidity, the presence of postural instability (PI), speech impairment and drug-induced offs. Given these subgroups, we describe and compare them with respect to number a demographic (duration of diagnosis, early onset PD, gender, dominant side of onset) plus clinical covariates such as HY stage and Tremor/PIGD dominance. Analysis was performed on a cohort of 351 subjects with idiopathic PD and no previous surgical treatment. Data was collected as part of the Queensland Parkinson's Project.

Results: The model generated three subgroups. Class 1 was defined by unilateral tremor and rigidity. Class 2 had strong chances of speech impairment and bilateral motor symptoms. Class 3 was characterised by bilateral symptoms and high probabilities of PI, speech impairment and offs. The demographic profile of these groups revealed that average duration was greatest in Class 3. The model's comparion with HY stage and Tremor/PIGD dominance suggested that whilst some features of each were captured by the model, each group was a mixture of classifications.

Conclusions: This model validates the progressive nature of PD and suggests the influence of new symptoms on subgroup identification. Given comparison with deterministic methods, this model offers an alternative to patient classification that accounts for more variation in symptom profiles.

Th-279

Validity of a Brazilian version of the Zung self-rating depression scale for screening of depression in patients with Parkinson's disease

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Objective: To study the validity of a Brazilian version of the Zung Self-rating Depression Scale (SDS) for diagnosis of depression in patients with PD.

Background: SDS is a depression scale that must be interesting to be used in patients with PD.

Methods: We evaluated 78 consecutive patients with diagnosis of PD at a specialized clinic, with schooling higher than 3 years, older than 40 years and without dementia. They self-completed the SDS and the Geriatric Depression Scale with 15 items (GDS-15). The diagnosis of depression was made after a structured clinical interview based on criteria of the DSM-IV for diagnosis of major depression (SCID-IV).

Results: The prevalence of current major depression was 23.1%. The Cronbach's alpha was 0.73 and the area under the ROC curve was 0.93 for the SDS. The score index of 55 had a sensibility of 88.9% and a specificity of 83.3% for diagnosis of depression. The total scores of the SDS and GDS-15 were highly correlated (0.652, $p<0.0001$) and correlated weakly with the scores of motor scale, however, the SDS had stronger correlation with motor scores than the GDS-15.

Conclusions: SDS is a valid tool for screening depression in patients with PD, and should probably be interpreted above a specific SDS index designed for this group of patients.

Th-280

Can an accelerometer enhance Timed-Up & Go test sensitivity among patients with Parkinson's disease?

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Objective: To test the hypothesis that insight into gait and mobility among patients with Parkinson's disease (PD) could be further achieved if subjects wear an accelerometer as they carry out the Timed Up and Go test (TUG).

Background: The TUG is a widely used measure of mobility and fall risk in older adults and in PD patients. Performance on the TUG is typically quantified by measuring the time required to complete the test.

Methods: 18 patients with PD (Hoehn & Yahr: 2-4; mean age: 65.6±5.0.yrs) and 15 age-matched healthy controls (CO) wore a 3-D accelerometer on the lower back. The sit-to-stand and stand-to-sit components of the TUG were analyzed. Measures included the sit-to-stand, stand-to-sit range of the anterior-posterior (AP) accelerations (Rap_start, Rap_end, respectively), and the min, max, median, standard deviation, CV, main harmonic of acceleration in all 3 axes, the high and low frequency content of the signal (low band= 0.5-3 Hz, high band=3-8 Hz) and their ratio.

Results: The TUG duration was higher in the PD (9.88±2.71 sec) compared to CO (8.73 ±2.00 sec), but not significantly ($p>0.1$). The low AP frequency power in the locomotion band was significantly lower ($p<0.007$) in the PD (4.5±2.5) vs. CO (6.7±1.9 1000*power/rad/sample). Rap_start was significantly lower ($p<0.02$) in PD (0.9±0.3g), compared to CO (1.4±0.6g). In contrast, Rap_end was not different in the two groups. The median AP acceleration value was significantly higher ($p<0.01$) for the PD compared to the CO (0.2±0.2g vs. 0.0±0.2g). The median accelerations in the other two dimensions were not different between groups.

Conclusions: Accelerometer-derived measures were more sensitive to group differences than TUG duration. Patients with PD have a lower starting momentum when rising from a chair and higher AP acceleration values while performing this task. Together, these results demonstrate the potential of using an accelerometer that measures TUG activity to detect and quantify subtle differences in mobility and function, to identify early markers and response to therapeutic interventions.

Th-281

Defining a test score for status assessment during motor fluctuations in Parkinson's disease

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Objective: To define and evaluate a computer method for assessing drawing impairment in spiral drawings. To define an overall score, summarizing self-assessments and motor test data from a test battery for patients with advanced Parkinson's disease (PD).

Background: A test battery, consisting of self-assessments (modified PDQ-8) and motor tests (tapping and spiral drawing) was developed for a hand computer with touch screen in a telemedicine setting. Assessments and tests were carried out four times per day in a group of 65 patients with advanced PD (Duodopa® treated or candidates) during 1-6 weekly test periods each. For most test periods, UPDRS ratings were available.

Methods: In a web interface, a PD specialist assessed drawing impairment in 505 selected spiral drawings, representing all categories on the Bain & Findley 10-category scale (example in figure a.). A computer method, using wavelet transforms and principal component analysis, processed the same spirals to generate a 'spiral score'. According to the PD specialist and co-author Dr Nyholm, the information content of a test period with the test battery could be descibed by six dimensions, 'off', 'dyskinesia', 'walking', 'satisfaction', 'spiral', and 'tapping' (illustration in figure b.). Each dimension was defined as the first principal component of the level (mean) and fluctuation (standard deviation) for the questions or tests that this dimension is based on. Tapping dimension was based on both speed and accuracy. To obtain weights for an overall score, linear regression of the dimensions *vs.* simultaneous UPDRS ratings was performed. To assess the internal consistency of the test battery, Cronbach's Alpha for the six dimensions was calculated.

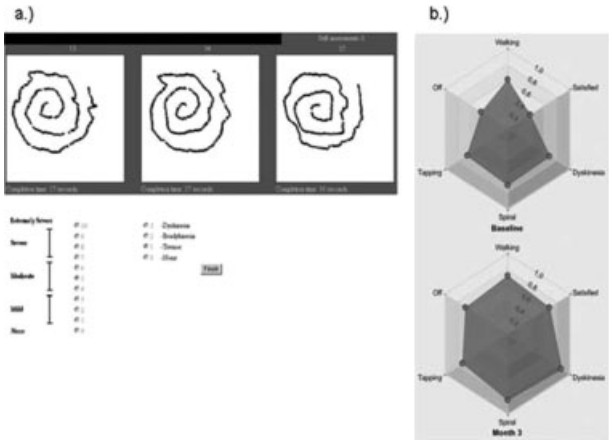

FIG. 1 (Th-281). (a) Example of three spirals of category 5 impairment, from the web application. (b) Illustrates the test battery dimensions for one patient at two different test periods. Zero is worst and one is best.

Results: Pearson correlation between spiral score and clinical rating of drawing impairment was 0.87. Weights in overall test score were (%): spirals, 41, tapping, 24, satisfied, 19, dyskinetic, 10, walking, 5.4 and off, 0.1. Internal consistency for the dimensions was 0.81.

Conclusions: The computer generated spiral score was strongly correlated to clinical assessment of drawing impairment. Spirals were assigned highest weight in overall score, reflecting the high weight of motor function in total UPDRS. Internal consistency was strong, implying all dimensions represent aspects of a common characteristic.

Th-282

Validation of a home environment test battery for status assessment in patients with advanced Parkinson's disease

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Objective: To validate a test battery for assessing motor status in Parkinson's disease (PD). To assess usability, patient compliance, test-retest reliability, correlations to other assessment methods and ability to detect differences between patient groups at different disease stages.

Background: A test battery, consisting of self-assessments (modified PDQ-8) and motor tests (tapping and spiral drawing) was developed for a hand computer with touch screen in a telemedicine setting (figure). Assessments and tests were carried out four times per day during one week test period. We summarised test results in an 'overall score', designed to provide comparable information content as total UPDRS.

Methods: We recruited 35 patients, both in stable (UPDRS IV items 32-39 all=0) and fluctuating (>2 hrs/day, off or dyskinetic) conditions. The dataset analysed consisted of 15 age and gender matched pairs. Clinical features of the two groups are shown in the table.

Table (Th-282).

	Stable group	Fluctuating group	Combined group
Patients (n, gender)	15 (13m; 2f)	15 (13m; 2f)	30 (26m; 4f)
Age	64.6 ± 7.0 ys	64.7 ± 6.9 ys	64.7 ± 6.8 ys
Age at onset	56.5 ± 9.2 ys	54.0 ± 8.7 ys	55.2 ± 8.9 ys
Duration of disease	8.1 ± 5.7 ys	10,7 ± 4.4 ys	9.4 ± 5.2 ys
L-Dopa equivalent daily dosage	618 ± 416 mg/day	1024 ± 419 mg/day	814 ± 458 mg/day
Hoehn & Yahr on	1.8 ± 0.4	2.2 ± 0.4	2.0 ± 0.4
Hoehn & Yahr off		2.8 ± 0.9	

Clinical features (mean ± sd) at baseline.

FIG. 1 (Th-282).

Patients used the test battery for one week, and were assessed with UPDRS and PDQ-39 at the end of the test period. This procedure was repeated one week later without allowing treatment changes. Patients responded anonymously to the 'IBM after-scenario' usability questionnaire. Compliance was assessed as percentage completed occasions per test period. Reliability and validity were assessed by Spearman rank correlations. The Mann-Whitney statistical test was used to test if the overall score's median was different between stable and fluctuating groups.

Results: Responses to the IBM questionnaire were generally very positive. Median compliance was 93%. The test-retest reliability of the overall score was 0.71 in the stable group and 0.84 in the fluctuating group. The correlation (combined group) to UPDRS was -0.60 and to PDQ-39, -0.66. Median overall score differed 18% between the two groups ($p<0.0001$).

Conclusions: Usability, compliance and reliability of the test battery were good overall, with better reliability in fluctuating patients. Correlations to UPDRS and PDQ-39 were adequate and difference in test score between stable and fluctuating patient groups was detected. We believe this system can be used in the selection and monitoring of PD patients undergoing complex treatments such as infusion therapies.

Th-283

Parkinson's disease. 10-year follow up

R.M. Zaidan (Riyadh, Saudi Arabia)

Objective: To assess to the clinical features of Saudi parkinsonian patients 10 years, at least, after onset on medical treatment To assess the response to antiparkinsonian treatment 10 yeras or more after starting it.

Background: response to antiparkinsonin treatments decline with the time. Little informations existes about progression of Parkinson's disease in saudi patients and their respones to treatment 10 years or more after starting it.

Methods: We studied 74 Parkinson's disease Saudi patients in KK University Hospital or by KKUH services. All of them have been followed up in neurology OPD clinic. Unified Parkinson's Disease Rating Scale has been used in the clinical assessement SSPS program has been used in the statistical analysis.

Results: Decline of reponse to treatment has been seen in all patients 10 years after starting it. More than 50% of them became dependent of an other person in their daily needs. The most important motor dysfunction was the akinesia the rigity while tremor was not a major problem of handicap. On/off phenomenon was observed in less than 20% of cases. Autonomic dysfunction symptoms have been seen in their majority however sympatthetic skin responses (SSR) are preserved for long time. The results show that L-DOPA is the most effective regarding akinesia and rigidity.

Conclusions: This study show clearly the decline of response to medical treatment in saudi parkinson's patient 10 years after onset as in many other old and recent studies. The discovery of etiological factors behind this disease is very important to find more effective treatment.

PARKINSON'S DISEASE: SLEEP DISORDERS

Mo-281

Clinical profile of Parkinson's disease patients with subjective sleep disturbances

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Objective: The aim of our study was to establish the clinical features of patients with moderate stage of idiopathic Parkinson's disease (PD) with subjective sleep complaints.

Background: Sleep disturbances are the most important non-motor symptoms of PD and may affect 60%–98% of PD patients. The results of previously published studies do not indicate decisively how various clinical features affect sleep in PD.

Methods: 102 PD patients (by the UKPDSBB Criteria) of Movement Disorders Outpatient Clinics in Katowice, Poland, with moderate stage of the disease (by the Hoehn&Yahr staging: 2-3 stage, UPDRS part III–15-65 points) and without dementia (by the MMSE >23) were included into the study. Patients were included into two groups based on a positive (Group I) or negative (Group II) answer to the question: "Do you have sleep problems?". Group I consisted of 51 patients (27 men and 24 women) with subjective sleep disturbances and Group II consisted of 51 patients (37 men and 14 women) without sleep problems. A very detailed clinical history, neurological and psychological examination was performed and statistically analyzed. P values of <0.05 were considered statistically significant.

Results: Patients in Group I were younger (61.6 vs 33.3 years, $p=0.0076$) and more depressed (BDI-18.5 vs 11.1 points, $p<0.001$). The presence of motor fluctuations and posture instability was much more common in Group I: 43.1% vs 23.5% ($p=0.0356$) and 52.9% vs 31.4% ($p=0.0443$), respectively. Genito-urinary disorders were more common in Group II (7.8% vs 25.5%, $p=0.0335$). There were no differences in the duration, the onset, type of the disease and the type of dopaminergic therapy. The average L-dopa dose in Group I was significantly higher than in Group II (811.5 vs 512.2 mg/d, $p<0.001$). There were no statistically significant differences in the total daily dose of other antiparkinsonian medications.

Conclusions: The most important reasons of sleep disturbances in PD are: depression, motor fluctuations and posture instability. The type of dopaminergic therapy does not influence sleep disorders. Only the high dose of L-dopa has a significant negative impact on the sleep problems.

Mo-282

Midbrain hyperechogenicity and impaired olfactory function in patients with idiopathic REM sleep behavior disorder

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Objective: The aim of the study was to investigate whether there is an association between hyperechogenicity and olfactory function in patients with iRBD.

Background: Recent studies have reported an increased risk to develop Parkinson's disease (PD) in patients with idiopathic REM sleep behavior disorder (iRBD). Midbrain hyperechogenicity is a common transcranial sonography (TCS) finding in PD and has been suggested as a PD risk-marker in nonparkinsonian subjects. Further, in several studies olfactory dysfunction has shown to be a potential non-motor antecedents of PD.

Methods: 31 patients from the sleep centers of the Medical University of Innsbruck, Austria (n=21), and the Hospital Clinic de Barcelona, Spain (n=10), with a diagnosis of iRBD were included in this study. All patients underwent a TCS investigation from both sides using the temporal approach to display the butterfly-shaped mesencephalon and the echogenic signal in the area of the substantia nigra. Olfactory testing was performed using the Sniffin sticks battery including testing of odour identification, discrimination and threshold.

Results: 66% (n=18) of the iRBD patients showed an impaired olfactory function and 39% (n=11) were found to have midbrain hyperechogenicity. There was no significant difference in the results of the Sniffin stick test between patients with midbrain hyperechogenicity and those without. Statistical analysis did not reveal any significant association between midbrain hyperechogenicity and olfactory dysfunction.

Conclusions: In this study there is no association between midbrain hyperechogenicity and impaired olfactory function in patients with iRBD. Due to the small population of patients, a beta-error cannot definitely be excluded. Further studies in larger iRBD samples are needed to determine if hyposmia and midbrain hyperechogenicity are independent risk markers for developing PD in patients with iRBD.

Mo-283

REM behavior sleep disorder is associated with non frontal cognitive dysfunction in early stage Parkinson's disease

P. Bugalho, J. Alves da Silva, B. Neto (Lisboa, Portugal)

Objective: We aimed to study the association between REM sleep behaviour disorder (RBD) and cognitive dysfunction in the early stages of Parkinson's disease (PD).

Background: Studies in non selected PD populations have suggested a relation between REM sleep behaviour disorder (RBD) and cognitive dysfunction, although this still remains controversial. There are no studies performed on the early stages of disease, where the influence of other variables on cognition could have lesser weight.

Methods: 43 early stage PD patients (disease duration less than five years, Hoehn and Yahr stage bellow 2.5) were classified as RBD or non-RBD patients, according to a validated RBD questionnaire. RBD and non RBD patients were compared in terms of age, age of disease onset, disease duration, Hoehn and Yahr and dopaminergic treatment (t-tests). These two groups and a control group of 44 healthy volunteers were compared on the performance of simple cognitive tests; the Mini Mental Sate Examination (MMSE) and the Frontal Assessment Battery (FAB). Motor function was assessed with the Unified Parkinson Disease Rating Scale part III. We tested differences in FAB and MMSE total, memory and visuo-spatial function scores (ANOVA).

Results: 29 patients (66%) were classified has having possible RBD. There were no significant differences between the two patients groups on any variable. RBD and non RBD patients differed significantly from the control group on FAB performance ($p<0.05$). RBD patients also scored signficantly lower than controls on MMSE total and recall scores ($p<0.005$).

Conclusions: Our results suggest that RBD is a common phenomenon in the early stages of PD. RBD was associated with a specific cognitive dysfunction pattern, in which cortical type deficits were added to a background of executive frontal lobe related dysfunction. This could be due to earlier degeneration of brainstem nucleus responsible for cortical activation, and could explain a higher risk of dementia in this sub-group of patients.

Mo-284

Dreaming and cognition in the early stages of Parkinson's disease

P. Bugalho, T. Paiva (Lisboa, Portugal)

Objective: To characterize the dreams of early stage Parkinson's disease (PD) patients and to study the relation between dream features, cognitive function, motor stage and dopaminergic treatment.

Background: Vivid dreaming is a common feature in PD. Some authors have suggested that dream alteration could be associated to cognitive deterioration in these patients. However, few studies have directly investigated the relation between dream features and cognition in PD.

Methods: 19 male, early stage (Hoehn and Yhar < 2.5) PD patients and 21 matched control subjects were asked to keep a dream diary for a fifteen day peŕiod. These dreams were classified according to Hall and van de Castle system. Cognitive function was assessed with Frontal Assessment Battery and the Mini-Mental State Examination memory and visuo-constructive sub-tests; motor stage was assessed with the Hoehn and Yahr scale. Patients were subdivided taking into consideration the frontal and memory functions, motor stage and dopaminergic treatment. H statistics was used to compare dream content between patients and controls and between PD patients groups.

Results: Patients' dreams (n=114) contained significantly more aggression, animal and negative emotion related features than those of healthy controls (n=158). Patients with frontal dysfunction, more advanced motor stages and higher dopaminergic treatment showed more aggressive features in their dreams than the corresponding patient groups without those features. There were no significant differences between the groups in terms of age, education, number and dream length, motor stage, disease duration and memory and visuconstructive dysfunction.

Conclusions: This suggests that dreams are significantly more aggressive in the early stages of Parkinson's' disease, possibly related to frontal dysfunction, higher dopaminergic treatment and motor stage progression. Defective interplay between limbic and prefrontal structures could be in the basis of these findings. A follow-up study should be important to confirm if dream agressiveness could be a predictor of cognitive deterioration in PD.

Mo-285

Sleep-disordered breathing in patients with idiopathic Parkinson's disease

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Objective: To evaluate sleep-disordered breathing (SDB) in patients with idiopathic Parkinson's disease (PD) who had nocturnal sleep apnea, poor sleep quality, daytime sleepiness and impaired concentration.

Background: Sleep disorders including REM sleep related behavioral disorders, and excessive daytime sleep are important non-motor and antecedent symptoms in patients with PD. Especially, SDB in patients with PD is not fully understood.

Methods: 102 patients with PD (44 men and 58 women, mean age; 72.4 years) were screened by simple polysomnography, and di-

vided according to their apnea/hypopnea index (AHI) of which normal is <5. Patients with an AHI of 5 or >5 were considered to have sleep apnea syndrome (SAS), which was classified as mild (AHI, 5-14), moderate (15-29) or severe (>30). Each PD patient was also evaluated for body mass index (BMI), and their disease severity classified according to Yahr's criteria.

Results: Mean AHI of patients with PD was 13.0 without gender difference. Based on the AHI, the frequency of mild, moderate and severe SAS were 47.1, 20.6 and 9.8% respectively. All the patients had obstructive type SAS without any correlation with their BMIs. Furthermore, there was no significant correlation between AHI and Yahr's classification of disease severity.

Conclusions: Our data indicate that the frequency of SAS in PD patients is significantly high as compared with previous reports of normal elderly subjects. SAS is commonly accepted to be a significant risk factor for developing cerebrovascular and cardiovascular diseases in the elderly. Further studies are necessary including the elucidation of why SAS in PD is exclusively of the obstructive type. However, we believe that SAS is also a possible risk factor for the development of PD.

Mo-286

Pathological correlates of sleep disturbances in Parkinson's disease

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Objective: To examine the anatomical and pathological basis of disordered sleep in Parkinson's disease (PD).

Background: Sleep disturbances represent one of the most common non-motor complications of PD and occur in up to 98% of patients. These include, REM Behaviour Disorder, Periodic Limb Movements of Sleep, restless legs syndrome, vivid dreams and nightmares as well as hallucinations and confusional states, along with nocturia, pain and discomfort resulting in non-restorative sleep and day-time hypersomnnolence with sudden sleep attacks. Several of these disorders may pre-date overt parkinsonism by many years. Although several causative factors have been implicated, including cognitive decline, motor and autonomic deficits and side-effects of medication, disturbed sleep may relate to pathological change and/or dysregulation in specific neuroanatomical loci involved in sleep physiology.

Methods: Thirty two cases were included in this study comprising 23 PD cases with sleep disturbances and 9 PD cases without. Semi-quantitative assessment (0-3+; absent to severe) of αSyn immunostaining in the locus coeruleus, raphe nuclei, pontine reticular formation, substantia nigra, red nucleus, hippocampal formation, entorhinal cortex, amygdala as well as the thalamic nuclei including lateral geniculate body and dorsomedial nucleus was carried out blind to clinical diagnosis. Differences between diagnostic subgroups were analyzed with the non-parametric Mann-Whitney U-test.

Results: Compared to PD cases without sleep disturbances, PD cases with sleep complications and without dementia demonstrated a significantly greater αSyn burden in the locus coeruleus ($p=0.03$), raphe nuclei ($p=0.02$), amygdala ($p=0.03$) and dorsomedial nucleus of the thalamus ($p=0.01$).

Conclusions: Our study provides evidence that disturbed sleep in PD relates at least in part to specific pathological changes in brain regions functionally involved in sleep physiology as well as cognition and other neurobehavioural functions.

Mo-421

A small scale study of sleep disturbances in Parkinson's disease

E.M. Morgan, M. Oliver, LLandough Day Hospital Team (Cardiff, Wales, United Kingdom)

Objective: To assess the frequency of sleep problems in an elderly population of parkinsons disease[PD] patients using the parkinsons disease sleep scale[PDSS] To analyze the impact of age sex and cognition using the mini-mental status examination [MMSE]on this group.

Background: The non motor symptoms of PD are now recognised as important. Excessive sleepiness and cognitive impairment are just two aspects. Various methods exist to evaluate sleep in PD. The PDSS is a comprehensive assessment of sleep problems that has undergone validation. Ref Chaudhuri R. 2008 Sleep dysfunction in Parkinson's disease. Parkinson's disease in the older patient Arnold publisher 2008 **9** 193:217 This scale assesses the clinical aspects of sleep disabilities of PD and was felt to be appropriate for our audit purpose. The MMSE is the most widely used test of cognition in clinical and research settings. Ref Ridha B Rosser M 2005 The mini mental state examination Practical Neurology **5** 298:303. This validated tool provides useful screening information, and was deemed suitable by all involved.

Methods: Forty nine patients who attend a rehabilitation day hospital were recruited for this audit. Thirty six men and thirteen women Data was collected by the multi disciplinary team in October 2008. Eligibility criteria were that the patients had a clinical diagnosis of PD. Information on age and sex were also recorded. All patients were asked the two questionnaires consecutively. The maximum cumulative score for the PDSS is 150 with a score of below 90 indicating significant sleep problems. The maximum cumulative score for the MMSE is 30 while a score of below 24 is also indicative of a degree of cognitive impairment.

Results: Age range Male 62-93 mean 78.6 yrs Female 57-90 mean 74.3yrs Sleep score Male 37-119 mean 92.2 Female 42-130 mean 87.4 MMSE range Male 16-30 mean 25.2 Female 16-30 mean 25.8.

Conclusions: Reults of this audit indicate that sleep problems are common and a majority of male patients had an mean PDSS score in excess of 90. This was not replicated in the female sample who had an mean score of 87 The results of the MMSE were surprising in that all patients had a higher than 24 score. The hope is that the findings from this study will encourage further research, bring greater awareness of sleep and cognitive problems of PD patients and improve management and quality of life for PD patients.

Mo-422

Paroxysmal nocturnal behaviours in parkinsonian syndrome extrapyramidal diseases: Not only RBD

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Objective: Videopolysomnographic (videoPSG) evaluation of paroxysmal sleep disruptive nocturnal behaviours (PSDNB) in subjects with parkinsonian syndrome.

Background: PSDNB are frequently reported in subjects affected by extrapyramidal diseases, REM sleep behaviour disorder episodes (RBD) being reportedly the most frequent ones. Less is known about the occurrence and features of NREM arousal-related paroxysmal episodes (NREM-PA) in these disorders.

Methods: We studied 95 subjects with parkinsonism with and without anamnestic report of PSDNB. A full night video-PSG caught PSDNB in 52 patients, with a pattern of RBD (45 cases), NREM-PA (9 cases), alone or in overlapping. The 52 patients with PSDNB were compared to a subgroup of patients with PSG and clinical history negative for any PSDNB, with respect to demographics and clinical features, MMSE score, BECK depression inventory, Epworth Sleepiness Scale score and sleep comorbidities (Sleep disordered breathing, Periodic Limb Movements).

Results: The patients with PSDNB were characterized by higher frequency of cognitive decline (MMSE score below 24, 25.5% vs none, $p<.05$), overrepresentation of men (67.3% vs 33.3%, $p<.05$), higher prevalence of sleep disordered breathing (25.0% vs 6.7%). The prevalence of NREM-PA in patients with SDB was three times as high as in patients without SDB (30.7% vs 12.8%). Four of the

nine patients (44.4%) with NREM-PA, the episodes occurred upon arousals at the end of apneic events.

Conclusions: RBDs represent the most commonly encountered nocturnal motor-behavioural paroxysmal episodes in extrapyramidal diaseases. However the occurrence of NREM arousal related motor behavioural paroxysmal episodes, alone or in overlapping with RBD, is not negligible and should be taken into account. The profile of patients at risk of nocturnal paroxysmal episodes seems to be one of male subjects with cognitive decline and co-morbid sleep pathologies, namely SBD which seems to trigger, in a proportion of cases, NREM-PA.

Tu-284

Is insomnia related to motor disability or affective symptoms in Armenian Parkinson's disease patients?

S.G. Khachatryan, Z.D. Tavadyan (Yerevan, Armenia)

Objective: To find relations of insomnia to motor disability, depression and anxiety in Armenian Parkinson's disease (PD) patients.

Background: Sleep disorders and especially insomnia are common in PD, explained primarily by motor and behavioral abnormalities. Depression and anxiety are well-known contributors to insomnia in PD with bidirectional relationship.

Methods: Fifty-nine non-demented PD patients aged 43-80 (Mean age=66.4 years, F=47.5%) were enrolled in the study. PD was diagnosed according to UK PDS Brain Bank criteria. Patients passed evaluation through all UPDRS domains, Hoehn&Yahr (H&Y) staging and Schwab and England Activities of Daily Living (ADL) Scale. Sleep history and sleep diary were used to detect presence and clinical types of insomnia. Patients were divided into 3 groups: 1) no insomnia, 2) mild-to-moderate insomnia (sleep-onset OR sleep-maintenance), 3) moderate-to-severe insomnia (mixed). Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) were used for assessment of depression and anxiety. Proportional analysis, ANOVA and Spearman correlation tests were used for statistics.

Results: Enrolled PD patients had H&Y stages 1-4 and ADL scores 40-100%. Forty-nine patients (83%) had insomnia complaints: mild-to-moderate – 23 patients (39%) and moderate-to-severe – 26 patients (44%). We found significant positive correlations between insomnia and mood assessing UPDRS domain 1 ($r=0.366$, $p=0.004$), and HAMD ($r=0.474$, $p<0.01$) and HAMA ($r=0.302$, $p=0.02$) scores. No correlations with other UPDRS domains, including domain 3 (motor examination) and total score, H&Y stages and ADL were found. HAMD scores of moderate-to-severe insomniacs, but not HAMA, were significantly higher than in mild-to-moderate and no insomnia groups ($p<0.05$). On the other hand in depressed PD patients (independent of severity) insomnia was more severe than in the non-depressed ($p<0.05$).

Conclusions: We found high rates of insomnia among patients with PD in Armenia. Interestingly, according to our results insomnia is not dependent on motor disability, disease stage or ADL but depends on affective symptoms, mostly depression. We revealed bidirectional relationship between insomnia and depression in agreement with existing literature.

Tu-285

Sleep-related problems in patients with Parkinson's disease

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Objective: To evaluate the associations between disease severity and sleep-related problems in 50 PD patients.

Background: Sleep-related problems are a frequent finding in patients with parkinson syndrome. It is estimated that 67–98% of the patients are affected, with increasing prevalence in more severe stages of Parkinson's disease (PD). Although sleep-related problems are a frequent finding in patients with PD, the etiology is still unknown.

Methods: We reviewed the clinical data and sleep questionnaire results in 50 patients with PD at our movement disorder clinic. Demographic data were obtained via structured interview and medical record review. Self-reported measures included Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality index (PSQI), Insomnia Severity Index (ISI), Berlin Questionnaire (BQ), and Beck Depression Inventory (BDI). ESS is self-administered scale used to measure an individual's general level of daytime sleepiness. PSQI is measure of sleep quality and disturbances during the previous month and yields a global scale score. ISI is brief questionnaire to quantify perceived insomnia. BQ is brief questionnaire developed to identify patients with sleep apnea and assesses risk factors for sleep apnea including snoring behavior, wake time sleepiness or fatigue, and the presence of obesity or hypertension. All patients underwent the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr classification.

Results: All 50 PD patients (64.0± 10.5 years; 31 females, 19 males) completed of sleep questionnaire. 47.4% of the patients with PD showed excessive daytime sleepiness, 86.7% impaired sleep quality, 34.7% pathological insomnia, 66.2% depressive mood and 10.4% obstructive sleep apnea. The disease severity was significantly associated with excessive daytime sleepiness, impaired sleep quality, insomnia and depressive mood.

Conclusions: In summary, our study confirmed the high prevalence of sleep disturbances in PD patients. We were able to address sleep-related problems in detail and found that the UPDRS motor score are related to different aspects of sleep disturbances. We conclude that sleep disturbance is common in patients with PD and the severity of motor symptoms of PD contributes to sleep disturbance.

Tu-286

Factors related to clinically probable REM sleep behavior disorder in Parkinson's disease

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Objective: To investigate factors associated with presence of REM sleep behavior disorder (RBD) in PD patients.

Results: REM sleep behavior disorder (RBD) is commonly accompanied in Parkinson's disease (PD), but the mechanism of RBD in PD is still unclear. To investigate factors associated with presence of RBD in PD patients, we interviewed and examined 447 consecutive patients with PD. Using the minimal diagnostic criteria for the parasomnias provided in the International Classification of Sleep Disorders Revised (ICSD-R), 164 patients (36.5%) were diagnosed with clinically probable RBD. PD patients with RBD had an older age, a longer duration of PD, more severe PD disability, a longer duration of antiparkinson therapy, and a lower proportion of their Unified Parkinson Disease Rating Scale (UPDRS) score accounted for by tremor than those without RBD. Multivariate logistic regression analysis revealed that the proportion of tremor score and patients' age were significant factors associated with the presence of RBD in PD patients.

Conclusions: The present results support a previous observation that PD with RBD may have a different underlying pattern of neurodegeneration than PD without RBD.

Tu-287

Sleep disorders in Parkinson's disease in Singapore

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Objective: To describe the prevalence of sleep disorders in Singapore PD patients.

Background: Sleep problems are reported to occur frequently in PD, but are not well studied in Asian patients.

Methods: PD patients and healthy controls prospectively recruited from a tertiary hospital were evaluated, including using questionnaires: Epworth Sleepiness Scale (ESS), Insomnia Severity Index (ISI), Pittsburg Sleep Quality Index (PSQI). All patients underwent polysomnography (PSG).

Results: 50 PD patients (30 male, 21 female; Mean age 65.0 years; 88.2% Chinese, 7.8% Indian, 2.0% Malay, 2% Other Race), and 64 Healthy Controls (35 male, 29 female; Mean age 58.7 years; 90.6% Chinese, 6.3% Indian, 1.6% Malay, 1.6% Other Race) were recruited over 1 year. Most PD patients had mild disease, 72.5% Stage 1 Hoehn & Yahr. PD patients had a mean ESS score of 8.98 $\pm$ 5.81, significantly higher than that of controls (5.75 $\pm$ 4.84) ($p < 0.05$). Difference in PSQI scores for PD and controls was also significant, with poorer sleep quality in PD ($p < 0.05$). *Obstructive sleep apnea* (OSA) was found on PSG in 46.9% PD patients (mean AHI = 11.65 $\pm$ 15.15)(14.3% mild, 20.4% moderate, 10.2% severe) vs 71.9% controls (mean AHI = 10.76 $\pm$ 8.72) (40.6%, 17.2% moderate, 7.8% severe) ($p = 0.007$). *restless legs syndrome (RLS)* was found in 7.8% PD patients and 3.1% *controls* ($p = 0.24$). *Insomnia* was reported *in* 33.3% PD vs 3.1% *controls* ($p < 0.05$). However mean ISI score in PD patients was 8.78 $\pm$ 7.382, not significantly different from controls ($p = 0.65$). *Dream enactment behavior* was reported in 23.5% PD patients suggestive of REM behavior disorder (RBD), but none of the controls. *Sleep talking* was reported in 47.1% PD patients, vs 4.7% controls ($p < 0.05$). Poorer sleep efficiency (mean sleep efficiency 59.70% $\pm$ 21.93 in PD vs 76.79% $\pm$ 18.68 in controls, $p = 0.027$) was found in PD. However percentages of light and deep sleep, PLMI and mean AHI were not significantly different in PD vs controls.

Conclusions: PD patients report more insomnia and parasomnias than controls, and had poorer sleep efficiency on PSG. However RLS, PLMs and OSA were not found more frequently in PD patients. Unusually high prevalence of OSA (majority mild to moderate) on PSG was found in our controls. Besides reported insomnia and parasomnias, primary sleep disorders were not more common in PD when compared to gender and age-matched controls.

Tu-418

State space dynamics of sleep and wakefulness in healthy controls and Parkinson patients

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Objective: For a better description of sleep-wake dynamics, we have adapted state space analysis (SSA) to analyze sleep in healthy controls and patients with Parkinson's disease (PD).

Background: Sleep is commonly scored in stages, but the succession of behavioural states is only poorly understood.

Methods: We obtained polysomnographic recordings from 7 PD patients and 7 age-matched healthy controls. 30-s epochs were scored visually. EEG data were Fourier-transformed to obtain the power spectral density for each epoch. Thereafter, we calculated 3 ratios of frequency bands. While these ratios aim at capturing specific spectral features, their final nature is heuristic. After data processing via principal component analysis, smoothed time series were plotted as clusters and trajectories in a three-dimensional state space. The congruence between visual scoring and the classification based on EEG spectra was quantified with discriminant analysis (DA). We assessed ratios with best cluster discrimination (optimized for maximal surface of the triangle spanned between the centroids of the DA) and congruence.

Results: Power spectra revealed only small differences between PD patients and controls. Optimal power ratios focus on alpha peaks and spindle frequency ranges. Congruent scoring was obtained for a median of 90% of epochs in PD patients, and 93% in controls. The median surface of the triangle between centroids was 49 for PD patients and 180 for controls. In all subjects, trajectory velocity within clusters was low for NREM4 and REM sleep, indicating that EEG spectra of subsequent epochs in these sleep states show low variability. Highest velocities were found for NREM1 and wakefulness. The same pattern of velocities appeared for epochs adjacent to state transitions.

Conclusions: State space analysis can be applied to sleep EEG recordings of both healthy controls and PD patients. Embedding of more polysomnographic parameters may improve discriminatory power further.

We-279

REM sleep behavior disorder in patients with Parkinson's disease and atypical parkinsonism

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Objective: To analyze the frequency of REM sleep behavior disorder (RBD) in patients with parkinsonian syndromes, including Parkinson's disease (PD) and atypical parkinsonism (AP).

Background: RBD is caracterized by excessive motor activity during sleep with loss of normal atonia during REM sleep. RBD may be idiopathic or occur associated with several neurological disorders such as the synocleinopathies that include PD, multiple system atrophy (MSA) and Lewy body dementia (LBD). Its occurrence in other forms of AP is considered less significant.

Methods: We assessed 653 consecutive patients with either PD or AP using a standardized protocol including demographic and clinical data. The diagnosis of RBD was established using historical information. Diagnostic criteria were based on established parameters.

Results: Among the 653 patients assessed 82,3% had a diagnosis of PD (n=538), 5,9% MSA (n=39), 5,0% LBD (n=33) and 6,5% PSP (n=43). Mean ages were 67 years for PD, 75 for LBD, 63 for MSA and 71 for PSP. In the whole sample, 51,4% had a RBD. The included 50% of those with PD, 74.3% of those with LBD, 66,6% of MSA patients and 37.2% of PSP cases. Frequency of RBD in LBD was significantly higher in comparison with those with PSP (p=0,02), the same been valid for the comparison of MSA and PSP cases (p=0,0017). On the other hand, the comparison of RBD in PD and PSP, as well as the comparison of PD and the other synucleinopathies, did not show significant difference (p>0,05 for all).

Conclusions: Our results show, as already described in the literature, a higher frequency of RBD in MSA and LBD in comparison with PSP. However, we did not confirm the value of the occurence of this complication for the differentiation of PD and PSP.

We-280

Association between REM sleep behavior disorders and ^{123}I-meta-iodobenzylguanidine MIBG scintinogrphic findings in patients with Parkinson's disease

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Objective: We investigated association among polysomnographic (PSG) findings, and RBD related symptoms, and MIBG scintinographies in patients with PD.

Background: Patients with Parkinson's disease (PD) frequently complicate REM sleep behavior disorder (RBD). Cardiac uptake of meta-iodobenzylguanidine (^{123}I-MIBG) scintinographies is reduced in patients with PD. Also, patients with REM sleep behavior disorder (RBD) have been known to show decreased intake of MIBG scintinographies similar to those with Parkinson's disease (PD). Reduced MIBG scintinographies and RBD might be risk factors of hallucination in patients with PD.

Methods: We conducted clinical interviews about RBD related symptoms on 55 patients with PD (mean age 69.7 $\pm$ 10.7 years old, 21 male and 34 female). We made all patients PSG. We estimated their proportion of REM sleep without atonia (RWA) to REM sleep on PSG. Moreover, we evaluated their heart-to-mediastinum (H/M) ratio MIBG scintigraphic findings. We compared H/M ratio of MIBG among the existence of RWA and the existence of RBD related symptoms.

Results: The patients with REM sleep without atonia (RWA) (n=32) had decreased intake of scintinographies than those without RWA (n=23). There was significant correlation between amount of RWA and that of MIBG scintinographies. Also, patients with RBD related symptoms had more reduced MIBG uptake than those without RBD related symptoms and those without RWA.

Conclusions: RBD related symptoms seemed to reflect on cardiac sympathetic function in patients with PD. They might have wilder pathological change.

We-281

Impulse control disorders in Parkinson's disease are associated with increased sleep disturbance

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Objective: To investigate the quality of sleep in patients with Parkinson's disease (PD) compared to healthy controls. We compare patients with PD according to the presence or absence of Impulse Control Disorders (ICDs).

Background: Altered sleep is an important symptom in PD, with insomnia and REM sleep behaviour disorders (RBDs) occurring frequently. Although sleep problems can precede the motor symptoms and therapy of PD, RBDs have been associated with increased amounts of dopamine replacement therapy (DRT). Recent awareness of ICDs in PD has highlighted other potentially detrimental effects due to DRT-related psychomotor activation. There are currently no published data investigating the associations between ICDs and altered sleep in PD.

Methods: Patients with PD were recruited from a specialised PD clinic, and ICDs were identified through an interview with the patient and family members. Healthy controls were recruited from friends or family members of the PD patients. Participants completed questionnaires including the PD Sleep Scale (Chaudhuri et al, 2002), the Typical Dreams Questionnaire, the Mood Disorder Questionnaire and The Hospital Anxiety and Depression Scale (HADS).

Results: 146 participants were included. Patients with PD and ICDs (PD +ICD) had a younger age of onset of PD, and were taking a higher total amount of DRT per day than the PD patients without ICDs (PD – ICDs).

Table (We-281). Participant details

	Total PD group	PD + ICD group	Non-ICD PD	Healthy Controls	p-value
Number	98	30	68	48	
Male : Female	73:25	24:6	49:19	39:9	NS
Age when completing questionnaire	64.8 ± 9.9*	59.0 ± 8.5†	67.2 ± 9.5†	57.9 ± 10.6*	*<0.0005, †<0.0005
Age PD onset	52.2 ± 12.7	46.2 ± 10.1*	56.6 ± 12.7*	N/A	* <0.0005
Duration of PD at time of questionnaire (yrs)	10.6 ± 6.7	11.5 ± 5.9	9.9 ± 7.2	N/A	NS
H + Y off medications at time of questionnaire	2.4 ± 0.6	2.8 ± 0.5*	2.2 ± 0.5*	N/A	* 0.035
Current L-dopa dose/day (mg)	609 ± 452	701 ± 508	549 ± 405	N/A	NS
Current DA LEU dose/day (mg)	191 ± 354	280 ± 515	135 ± 181	N/A	NS
Combined L-dopa + DA LEU/day (mg)	787 ± 549	981 ± 651*	665 ± 439*	N/A	* 0.026

DA LEU = Dopamine agonist L-dopa equivalent units. Comparisons made using t-tests.

PD patients had worse sleep scores than healthy controls, and the PD + ICD group scoring worse than the PD–ICDs. Patients with PD had more frequent nightmares than healthy controls, with a trend to increased frequency of vivid dreams and nightmares comparing the PD + ICD group to the PD–ICDs. Anxiety, depression and mania measures were higher in PD + ICD than the PD–ICDs. Using hierarchical multiple regression analyses, age (p=0.015) and the presence of an ICD (p=0.006) were associated with a worse sleep score in PD, independent of factors including gender and total DRT.

Conclusions: We show that PD + ICDs have worse sleeping scores, and higher levels of anxiety, depression and hypomanic symptoms than PD – ICDs. Increased nightmares and vivid dreams in the PD + ICD group may be a factor in their reduced quality of sleep, and suggests a link between this form of psychomotor activation and impulsivity related to DRT.

Table (We-281). Sleep, dreams and psychological data

	Total PD group	PD + ICD group	Non-ICD PD	Healthy controls	P value
Dreams/ month	2.8 ± 5.8	4.4 ± 7.8*	2.2 ± 4.7*	3.0 ± 5.2	NS * (0.15)
Nightmares/month	0.8 ± 2.0†	1.3 ± 2.8*	0.5 ± 1.5	0.3 ± 0.7†*	† = 0.038, *0.064
Total Sleep score	91.7 ± 30.8*	79.4 ± 30.7†	97.0 ± 29.5†	104.6 ± 44.7*	*<0.0005 (MWU); †0.006 (MWU)
HADS total score	8.2 ± 3.7†	10.2 ± 3.9*	7.3 ± 3.2*	6.6 ± 4.0†	*0.001; †0.02
HADS anxiety score	8.2 ± 3.7†	10.2 ± 3.9*	7.3 ± 3.2*	6.6 ± 4.0†	* 0.001; †0.02
HADS depression score	6.2 ± 2.9†	7.5 ± 3.4*	5.7 ± 2.7*	2.9 ± 2.7†	*0.014; †<0.0005
Mood disorder score of hypomanic symptoms	3.9 ± 3.3	5.4 ± 3.4*	3.3 ± 3.1*	2.9 ± 3.1	*0.004

Comparisons made using t-tests, except MWU (Mann-Whitney U).

We-409

Sleep-related falling out of bed in Parkinson's disease

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Objective: To describe 6 cases of patients with diagnosis of Parkinson's disease (PD) who fell out of bed while sleeping.

Background: Falling out of bed is one of the causes of sleep-related injury in PD. There is limited information as to what extent falling out of bed can be attributed to REM behavior disorder (RBD). Other causes of self-harm during sleep include REM-related obstructive sleep apnea, NREM parasomnias or seizures [1, 2].

Methods: We performed a retrospective review of our experience with six PD patients with history of falling out of bed, seen at the Movement Disorders Clinic by one of our neurologists (CS). We investigated demographics and histories consistent with dream enactment.

Results: Six patients with PD reported having fallen out of bed. All patients were male with a mean age of 66 (+/- 12.1 range 48-78 SD) . The average duration of PD was 5.2 years (+/- 4.4) and the average Hoehn and Yahr stage was 2.3. All six patients had increased motor activity during sleep (IMAS) or vivid dreaming (VD) before the episode of falling out of bed. Two patients had increase in motor activity during sleep with associated phonatory activity in one. Four patients described vivid dreaming, with one of them reporting throwing punches and kicks, One patient had associated phonatory activity. The average time between the initial symptoms of PD and the appearance of IMAS or VD was 7 years (+/- 4.2 range 3-14) and the average time of appearance of falling out of bed was 8 years (+/- 5.6 range 2-14). None of the patients had sleep studies. All patients reported a single episode of falling out of bed with one of them sustaining injuries. The frequency of these episodes could not be determined.

Conclusions: IMAS and VD may be premonitory symptoms for sleep-related falling out of bed episodes in PD. A specific screening questionnaire addressed to the patient and the bed partner may identify those patients at higher risk for falling out of bed. Such patients should be encouraged to undergo sleep studies and should be counseled on treatment strategies. 1. Comella, C.L., et al., Sleep-related violence, injury, and REM sleep behavior disorder in Parkinson's disease. Neurology, 1998. 51(2): p. 526-9. 2. Larsen, J.P., Sleep disorders in Parkinson's disease. Adv Neurol, 2003. 91: p. 329-34.

Th-284

REM sleep behavior disorder severity scale: A video classification of RBD in Parkinson's disease

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Objective: To develop a polysomnographic rating scale for severity of rapid eye movement (REM) behavior disorder (RBD), test its

reliability and determine RBD severity in 20 patients with Parkinson's disease (PD).

Background: RBD is recognized as a preclinical marker as well as a general hallmark of neurodegenerative disease presenting with Parkinson syndromes. Recent studies suggest, that RBD is associated with cognitive impairment and an akinetic subtype of PD. Comparative and longitudinal studies are needed to further clarify the role of RBD in these phenotypes.

Methods: 20 PD patients identified with RBD were investigated with video-supported polysomnography (PSG). 73 motor behavior events during REM sleep were visually and polysomnographically graded on an event-to-event basis according to categorial location of movements: "0.-" = no visible movement; "1.-" = movements only in distal extremities; "2.-" = movements involve proximal extremities; "3.-" = axial involvement. Vocalizations are rated as "-.1" for present or "-.0" for absent. Ratings were performed by 2 blinded raters. Reliability was calculated with Cohen's kappa. Final RBD severity diagnosis was determined by the highest score given.

Results: Interrater reliability of the scale was 0.8 for movement data and 0.89 for vocalization data. RBD severity was determined at 3.1 for 7 patients, 3.0 for 3 patients, 2.1 for 3 patients, 2.0 for 5 patients, 1.0 for 1 patient and 0.1 for 1 patient. All patients showed severely disturbed sleep with reduced sleep efficiency (66 +/- 17 %), loss of slow wave sleep, sleep fragmentation and increased index of periodic limb movements (PLM).

Conclusions: The RBD severity scale (RBDSS) is a reliable, easy-to-use tool for assessing motor events during REM sleep with PSG. 10 of 20 PD patients (50%) showed axial involvement, calling for treatment to prevent nocturnal bed falls.

Th-121

The clinical characteristics of periodic limb movements in REM sleep behavior disorder

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Objective: To elucidate the clinical characteristics of periodic limb movement disorders during sleep (PLMS) comorbid with REM sleep behavior disorder (RBD).

Background: RBD is diagnosed by the existence of both dream enactment behaviors and REM sleep without atonia (RWA) on polysomnogram (PSG). PLMS has been known to be often comorbid with this disorder.

Methods: Consecutive 27 patients with PLMS comorbid with RBD (RBD-PLMS, age; 67.5±7.3, M:F=15:12) and 31 patients with idiopathic PLMD (age; 63.5±5.8, M:F=21:10) were enrolled in this study. Variables on nocturnal PSG such as PLM index, isolated leg movement (LM) index, PLM arousal index, and mean values of both PLM duration and inter-PLM interval were calculated in REM sleep and NREM sleep, respectively. These PSG variables and Epworth Sleepiness Scale (ESS) scores were compared between the two patients groups. In RBD-PLMS group, these variables were compared between in REM sleep with atonia (atonic REM) and in RWA. Additionally, these variables in RWA were compared between the period with phasic REM sleep and those with tonic REM sleep.

Results: RBD-PLMS group showed a significantly higher REM sleep/total sleep time ratio of PLM index, a lower PLM arousal index, and a lower score of ESS than PLMD group. Especially in REM sleep, RBD-PLMS group showed significantly higher index of both PLM and isolated LM and longer duration of them, as well as a shorter inter-PLM interval than PLMD group. In this group, the PLM index was significantly higher in the period with RWA than in that with atonic REM, however, any other variables showed no differences between these periods. No significant differences in any of these variables were seen between in phasic REM sleep and in tonic REM sleep.

Conclusions: Our results suggested that the lower daytime sleepiness in RBD-PLMS group could be explained by the lower arousal response to PLM. In this patients group, the higher index, the longer duration, and the shorter interval of PLM or LM in REM sleep might indicate that the activity of anterior tibialis muscle was increased in this period. PLM occurred more frequently in the period with RWA, however, this rhythmic activity of anterior tibialis muscle could not be explained only by the phasic activity of the submentalis muscle, indicating the existence of any other factors contributing to the rhythm formation process of PLM in this patients group.

Th-285

A screening tool for REM behavior disorder in Parkinson's disease

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Objective: To examine the utility of a recently developed REM sleep behavior disorder (RBD)screening questionnaire (RBDSQ) as a screening tool for RBD in patients with PD.

Background: RBD may be an early marker of a neurodegeneration and precede PD by decades. Sensitivity of clinical interviews for the diagnosis of RBD relative to polysomnography (PSG) findings remains low in the PD population. Development of screening instruments that will lead to early diagnosis of RBD is therefore becoming increasingly important. The recently developed RBDSQ has excellent sensitivity for diagnosing RBD (0.96) and has been validated relative to PSG (Stiasny-Kolster, 2007). The RBDSQ has not been studied in the PD population.

Methods: PD patients from a subspecialty movement disorders practice completed a 10-item RBDSQ (max score =13). The primary outcome measure was the total score on the RBDSQ. A score ≥5 was used as a cut-off suggestive of RBD. Demographics, disease duration, medication regimen, other sleep co-morbidities and available PSG data were also ascertained.

Results: 84 PD subjects (52M/32F), age (mean±SD) 66±10.5 yrs, disease duration 5.6±4 yrs completed the RBDSQ. Forty subjects (48%) had the RBDSQ score ≥5, and 44 (52%) scored <5. 29M/11F subjects with disease duration 6±4.5 yrs scored ≥5. 23M/21F subjects with disease duration 5±4 yrs scored <5. Gender ratio and disease duration were not statistically different among two groups (p=0.93; p=0.26). Among 13 subjects who had PSG, 3 subjects were diagnosed with RBD. Additional 8 subjects had clinical diagnosis of RBD. Among these 11 subjects with RBD, 10 had RBDSQ score ≥5, and 6 were actively treated for RBD. Obstructive sleep apnea (OSA) and restless legs syndrome (RLS) were diagnosed in 8 and 7 subjects, respectively. Six subjects with OSA and 4 subjects with RLS scored ≥5 on the RBDSQ. Five subjects (45%) with diagnosis of RBD and 14 subjects (35%) with the RBDSQ score ≥5 were on antidepressants. Antidepressant use was not statistically different among two groups (RBDSQ score <5 vs. ≥5) (p=0.59).

Conclusions: Forty eight percent of our cohort screened positive for RBD, using the RBDSQ cut-off score ≥5. The RBDSQ may be a sensitive screening tool for RBD in patients with PD, but has to be validated against PSG in this population.

Th-286

Study of non-motor symptoms in patients with Park2: RBD, olfactory functions, and cardiac sympathetic nervous system

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Objective: We examined REM sleep behavior disorder (RBD), olfactory dysfunctions, and cardiac sympathetic nervous dysfunctions in patients with parkin gene mutation (park 2) like as non-motor symptoms accompanied in early stage of Parkinson's disease (PD).

Background: In synucleinopathy before the onset of disease, they had RBD, also patients with RBD have dysfunction of cardiac sympathetic nerve. In PD patients, olfactory dysfunction was an early symptom, and affected up to 90% of PD patients. so these symptoms could be an indicator of synucleopathy. We examined whether this same hypothesis could be formed in Park2.

Methods: The patients with park2 were 46.0±15.3 (range 28-71) years old, three men and three women. RBD was examined by polysomnography, with Alice 1 or 5, olfactory functions; threshold, discrimination, identification by sniffin stick test. And myocardial scintigraphy with 123I-MIBG (111 MBq) was performed and calculated the counts of heart to mediastinum (H/M) ratio.

Results: Three patients had the twitching of the anterior tibialis muscles. RBD was not detected. Threshold score of sniffin stick test was 6.13±1.53, discrimination score was 10.00±2.45, and identification score was 10.17±4.79, which were higher than patients with PD ($p<0.005$). Also, except threshold test, there were no differences from the results of our control. The decrease of H/M ratio of MIBG scintigraphy in Parkinson's disease was not detected in park2. In addition, for them the treatment of the constipation did not have.

Conclusions: Non-motor symptoms; RBD, olfactory dysfunction, disturbance of cardiac sympathetic nervous were not detected. Different from PD, in park2 patients these non-motor symptoms were not early stage symptoms, but also not accompanied symptoms.

Th-413

Effect of controlled-release levodopa/carbidopa on the microstructure of sleep in Parkinson's disease (PD)

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Objective: To evaluate the impact of controlled released levodopa/carbidopa on the microstructure of sleep in PD.

Background: Sleep disorders may occur early in the course of PD and even precede motor symptoms. The etiology is multifactorial. Dopamine itself plays a crucial role regulating sleep and the sleep/wake cycle. Changes in the microstructure of sleep have been confirmed by polysomnography in PD patients, but little is known about the effect of dopamine replacement therapy. Here we address the question, whether controlled-release levodopa/carbidopa, which is frequently prescribed to treat nighttime akinesia, has a direct impact on the microstructure of sleep in PD.

Methods: 34 patients (mean age 62 years, mean disease duration 6 years) with dopamine responsive, akinetic-rigid PD, not taking neuroleptic medication or suffering from dementia were randomised into two groups. Both groups had to withhold their usual dopaminergic medication after noon. At bedtime one group received 200mg controlled-release levodopa/carbidopa while the other group spent the night in the "off"-state. Polysomnographic recordings during the whole night, adapted to the habitual bedtime of the participants, were performed in all patients and 14 age-matched, healthy controls.

Results: Compared to healthy controls PD patients suffered from a significantly decreased total sleep duration, REM sleep and deep sleep duration, while waking time was increased. The administration of levodopa/carbidopa CR had no impact on any of these variables.

Conclusions: Levodopa/carbidopa CR has previously been shown to be effective for treating nighttime akinesia, but according to this study it has no impact on the altered microstructure of sleep in PD. Hence, the impaired sleep pattern with increased arousals and decreased REM and SWS phases, may rather result from an extranigral degeneration of brainstem nuclei than from a dopaminergic deficiency.

PARKINSONISM (SECONDARY AND PARKINSONISM-PLUS)

Mo-287

Camptocormia in Parkinson's disease

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Objective: In this epidemiological and clinical study we investigated the prevalence of camptocormia in PD, the relationship of camptocormia with the clinical, especially non-motor features of PD and the presence of possible risk factors for developing camptocormia.

Background: Abnormalities of posture represent one of the main features of Parkinson's disease (PD). Among them, camptocormia has been considered as rare in PD. We investigated camptocormia in PD patients. Having more information on camptocormia in PD would help to improve these patients' quality of life (QOL).

Methods: Outpatient population of 153 PD patients(mean 68.5±10.7 years old, duration 5.1±3.6 years)were recruited. The diagnosis of PD was made according to the UK Brain Bank Criteria. The diagnosis of camptocormia was made if the patients exhibited marked (>45°) flexion of their thoracolumbar spine that increased during walking and markedly abated or disappeared in the recumbent position. 27 PD patients(mean 65.8±12.1years old, duration 5.2±2.7years)have camptocormia. There are no significant differences between patients with and without camptocormia concerning age, duration, severity, drugs, and drug doses. For further evaluation, we recruited age- and sex- matched 27 PD patients without camptocormia (11 men and 16 women; mean age ± SD, 61.1 ± 9.4 years). We rated on the Unified PD Rating Scale, mini-mental state examination (MMSE). In addition, patients completed the following self-assessments: the frontal assessment battery (FAB), Parkinson's Disease Questionnaires-8(PDQ8), the hospital anxiety and depression scale (HADS), the fatigue scale questionnaire (FSQ), a fatigue visual analogue scale, the non-motor symptom questionnaire (NMSQuest) scale. Also we evaluated patients with camptocormia by MRI, spine roentgen, and RI and no findings that denied diagnosis of PD.

Results: There are no significant differences between patients with and without camptocormia but FAB, PDQ8 and NMSQuest scale.

Conclusions: There are controversies concerning pathogenesis of camptocormia. Some reports described that camptocormia might be a rare type of dystonia. However, in our study, camptocormias in some patients are not clarified the definition. We believe that camptocormia in PD patients may include heterogeneous pathogenetic factors, but in our study, higher brain disfunction may be related to developing of camptocormia.

Mo-288

Vascular parkinsonism: New classification proposal

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Objective: Identifying the signs and symptoms that suggest vascular parkinsonism (VP). Correlating the clinical findings with the MRI. Proposing a new classification for VP.

Background: The concept of VP is highly controversial, not well defined and its clinical and imaging correlates not well established.

Methods: We reviewed the records of 356 patients with parkinsonism, and they were broken down into three groups. In the first, we included patients with sudden onset post-stroke parkinsonism (SPP), in the second, patients with incomplete parkinsonism with insidious onset and atypical signs (PIAS), and in the third, patients with Parkinson's disease (PD). Patients with parkinsonism secondary to other causes and with parkinsonism-plus syndromes were excluded. We compared the clinical and magnetic resonance imaging (MRI) findings of the three groups. All the patients had MRIs and were assessed using Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn & Yard (H&Y) scale.

Results: Twenty-nine patients had SPP, 38 PIAS, and 289 PD. In the first assessment, in PD the age of onset was lower ($p<0.01$). In the patients with SPP and PIAS, the hypertension was highly prevalent, as well as other vascular risk factors ($p<0.001$). Patients with SPP and PIAS showed bilateral and a more severe compromise in the lower half of the body ($p<0.001$). Patients with SPP had less compromise in the H&Y scale ($p<0.01$). The response to levodopa was good in the patients with PIAS ($p<0.001$). The MRI showed ischemic lesions in the basal ganglia and in other deep brain areas in

PPS patients ($p < 0.001$) and hyperintense lesions in the white subcortical matter in the PIAS patients ($p<0.001$).

Conclusions: The clinical and imaging characteristics of the three groups suggest a different pathogenesis. Our results show that it is possible to differentiate two types of vascular parkinsonism. The SPP was characterized by bilateral affection with unilateral dominance of abrupt onset, with MRI evidence of lacunar infarcts in the basal ganglia, brain stem and exceptionally in the cortex. The PIAS presented insidious bilateral parkinsonism with dominance of the lower limbs, and in the MRI, hyperintense lesions and small lacunar infarcts in the white subcortical matter, basal ganglia and brain stem.

Mo-289

Neurological presentation of chronic heroin encephalopathy

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Objective: The aim of this study was to find out the features of the main clinical syndromes that take place in chronic heroin encephalopathy.

Background: Cumulative incidence of heroin drug addiction may be up to 90%. It was considered, that opiate don't cause severe neurological disturbances, excluding cases, when posthypoxic encephalopathy is developed as a result of overdose. Diffuse neurological disturbances appears during acute heroin abstinence or in the early postabstinent period. However cases of chronic heroin encephalopathy with extrapyramidal disturbances, pseudobulbar syndrome, gait and balance disturbances were described last years.

Methods: We investigated 16 patients with chronic heroin encephalopathy (age 22-32, disease duration 3,6±2,4 years) without acute heroin abstinence in the anamnesis and haven't been taking drugs during 1 year and more. We used UPDRS (Fahn S., Elton R.L., 1987), Dystonia Assessment Scale (Fahn S., Marsden C.D., Burke R.E. 1985), Tinetti Assessment Tool (M. Tinetti et al., 1986), Axial Movement Disorders Assessment Scale (Levin et al, 1997), Pseudobulbar Syndrome Assessment Scale (Levin, 1995) and MRI 0.5 Tesla in Ti and T2.

Results: Mean results of the Tinetti scale–17,0±3,2 points. We found more or less severe pseudobulbar syndrome, characterized by dysphonia, dysarthria, axial reflexes and motor and affective disinhibition in all cases. All patients had postural tremor: 37.5% severe, 37.5% moderate and 25% mild. Parkinsonism as a hypokinesia and rigidity was found at 44% patients (mean of the II part 28,5±4,8). Our patients didn't have the rest tremor. 17.% of the patients had horeoathetosis. 1 patient had cervical dystonia. All patients had gait and balance disturbances. Clinical investigation showed decreased step length, shuffling, difficulties of the gait initiation and during turns. Postural disturbances caused frequent falls. MRI data showed posthypoxic changes in subcortical structures and expansion of encephalocoel system and cortical sulcuses. In 25% of cases we found prevalence of atrophy in the frontal lobe. These patients had much more severe movement disorders.

Conclusions: Thus, chronic heroin encephalopathy can be characterized as a combination of extrapyramidal disturbances, gait regulation disturbances and pseudobulbar syndrome, that indicate the diffuse damage of subcortical structures in patients without posthypoxic changes.

Mo-290

Medically intractable diaphragmatic myoclonus complicating corticobasal degeneration

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Objective: To describe an unusual case of CBD presenting with persistent repetitive diaphragmatic myoclonus.

Background: CBD is charaterized by parkinsonism, dystonia, myoclonus, oculomotor and gait disturbances and dementia, Diaphragmatic myoclonus is an uncommon disorder and may be associated with central or peripheral nervous system lesions. It has rarely been described in CBD.

Methods: Case report.

Results: 74-year-old right-handed diabetic man presented with imbalance and involuntary movements of eight-month duration. At onset the right arm was stiff, unable to follow commands. Once, while driving he held the steering wheel with the affected arm pulling the car to the opposite lane, noticing both hands fighting each other. Later the right leg stiffened, affecting walking. Contrast enhanced brain MRI was normal saved for left asymmetric cortical and subcortical atrophy. A brain technetium SPECT scan showed decreased uptake left parietal region. Neuropsychological testing revealed marked left frontal involvement with alterations in confrontational naming, and verbal fluency. EMG/NCS confirmed a sensorimotor axonal peripheral neuropathy. On exam we noticed he would held a water bottle cap tightly in his hands and was unable to release it, marked difficulties with rapid alternating movements, constructional apraxia, motor perseveration, difficulties with shifting tasks (Luria's) and right hand mirror movements while toe tapping were present. No spontaneous grabbing or groping noted. He needed assistance getting out of the chair, demonstrating gait ignition failure and disequilibrium, with slow cadence, short stride and stooping turning en-bloc. Bradykinesia and increased tone in his upper extremities was present. A year later he was unable to walk without assistance, as he would have fallen to the ground and became wheelchair bound. He developed frequent, regular diaphragmatic myoclonus occurring at a frequency of approximately 3 to 10 attacks occurring every 45 to 60 minutes. These became quite uncomfortable and painful. Rotigotine, ropinirole and levodopa were tried for symptom control, but no significant relief was found.

Conclusions: Diaphragmatic myoclonus is an unusual presentation of CBD. Myoclonus may be the presenting or accompanying feature of CBD. Its origin is unknown but likely represent brainstem involvement.

Mo-291

Can vascular parkinsonism be differentiated from idiopathic Parkinson's disease? A systematic review

S. Kalra, D.G. Grosset, H.T.S. Benamer (Wolverhampton, United Kingdom)

Objective: We performed a systematic review to compare the clinical and neuro-imaging features that could distinguish VP from idiopathic Parkinson's disease (PD).

Background: Vascular parkinsonism (VP) remains ill-defined, combining clinical movement disorder features with cerebrovascular damage.

Methods: Medline, Embase, Cinahl, and PsycINFO were searched by appropriate key words. Reports were included if the study population contained a comparison of clinical and/or neuroimaging findings between VP and PD.

Results: Nine papers fulfilled the selections criteria. VP patients were older, with a shorter duration of illness, presented with symmetrical gait difficulties, were less responsive to levodopa, and more prone to postural instability, falls, and dementia. Pyramidal signs, pseudobulbar palsy, and incontinence were more common in VP. Tremor was not a main feature of VP. More significant abnormal structural neuroimaging was found in VP (90-100%) than PD (12-43%). However, there was no specific abnormal vascular pattern for VP. One study of pre-synaptic striatal dopamine transporters using SPECT found a significantly lower mean asymmetry index in VP than PD. Another two reports showed a significant reduction in striatal uptake ratios in PD but not VP.

Conclusions: The diverse diagnostic criteria used in these studies makes it difficult to reach a firm conclusion. The present review could serve as a platform for developing diagnostic criteria for VP, which would greatly enhance our understanding of this condition.

Mo-292

Secondary parkinsonism in the pediatric population: A case of radiation-induced parkinsonism

G. Bernard, S. Chouinard (Montreal, Quebec, Canada)

Objective: We wish to report a case of parkinsonism due to radiation therapy.

Background: Various well known causes of secondary parkinsonism have been described: medications (e.g. neuroleptics), lesional (e.g. stroke), etc. Secondary parkinsonism is much less common in the pediatric population.

Methods: We performed a chart review of one pediatric case of radiation-induced parkinsonism.

Results: The patient was diagnosed at the age of 16 years with a thalamic and midbrain dysgerminoma. The tumor was partially resected and the patient received chemotherapy (VP-16, Cisplatin, Vincristine, Cyclophosphamide) followed by radiation therapy (23,4 Gy craniospinal and 7,2 Gy at the tumor site). The patient improved during chemotherapy. Approximately 2 months after the initiation of the radiation therapy, without any evidence of tumor progression on imaging, the patient developed a severe parkinsonian syndrome, including severe bradykinesia, facial hypomimetism, hypophonia, bradypsychia, rigidity, hypersalivation, dysphagia and tremor. Initially, this parkinsonian syndrome was accompanied by an encephalopathy that required intensive care unit admission. He was treated with levodopa-carbidopa at doses up to 550mg per day, benztropine, dantrium and clonazepam. His level of consciousness gradually improved but did not return to baseline and he was able to be discharged from the intensive care unit. His parkinsonian syndrome improved as well but remained severe, even with aggressive pharmacological treatment. Ten months after the onset, without any significant modification of his medication, his neurological status improved significantly; his bradykinesia and tremor were mild on medication, his bradypsychia had almost disappeared and he was able to follow and participate actively in discussions.

Conclusions: Radiation-induced parkinsonism has been described on rare occasions in both the pediatric and adult populations. Our patient is an example of an atypical form of delayed radiation induced encephalopathy. The evolution of his neurological status is somewhat surprising; after 10 months of static post radiation encephalopathy, we would not have expected such good neurological improvement.

Mo-293

High prevalence of chronic primary intracerebral hemorrhage in vascular parkinsonism

Y.-Y. Chang, J.-S. Liu, Y.-F. Chen, C.-S. Su, Y.-L. Tseng, M.-Y. Lan (Kaohsiung, Taiwan)

Objective: To investigate the prevalence and clinical relevance of chronic primary intracranial hemorrhage (ICH) in patients with vascular parkinsonism (VP).

Background: VP, also known as arteriosclerotic parkinsonism, is commonly related with multiple lacunar infarctions, leukoaraiosis, and Binswanger's disease. While ICH accounts for about 10∼15% of all stroke, the prevalence and clinical relevance of ICH in VP have not been evaluated.

Methods: To study the impact of chronic ICH on VP, 62 consecutive patients with VP were examined by cerebral MRI including T2*-weighted gradient-echo sequence. Bivariate or multivariate analysis was used to evaluate the contribution of several demographic and clinical variables, including motor and cognitive function, to the presence of ICH.

Results: Chronic primary ICH were found in 40.3% (25/62) of VP patients (70.2 ± 9.2 years old, 66% male). Among VP patients with ICH lesions, 14 (56%) were asymptomatic. Younger age, the presence of cerebral microbleeds (CMB), the numbers of CMB, and homocystein level were significantly associated with the presence of chronic ICH ($p<0.05$). There were no significant relationships between ICH and gender, hypertension, diabetes, cholesterol, triglyceride, smoking status, or anti-platelet use in this cohort. In terms of chronic ICH and neurologic deficit, the presence of chronic ICH was not a predictor for cognitive, behavioral, mood, activities of daily living or motor dysfunction in VP. Otherwise, it was an independent factor increasing the risk of future ICH.

Conclusions: In conclusion, using MRI T2*-weighted sequences, there is a high prevalence of chronic ICH in VP patients, which denotes the presence of microangiopathy and a future risk of ICH. This study emphasizes the prevalent hemorrhagic-prone microangiopathic lesions in VP patients, which should be considered in adopting a therapeutic strategy.

Mo-294

Objective quantification of the pattern of habitual physical activity in advanced Parkinson's disease

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Objective: To quantify the pattern of physical activity and sedentary behaviour in people with advanced PD.

Background: Physical activity reflects human behaviour and functional ability in daily life. Accelerometers allow objective long term monitoring of habitual physical activity. Daily activities can be classified into sedentary, upright or walking activities which constitute the building blocks of physical activity profiles.

Methods: The activity profiles of 17 PD (mean age = 54.06 years; UPDRS III 29.1+5.5; disease duration 12.5+6.4) and 17 age and gender matched healthy control participants (mean age = 54.4 years) were compared. Each participant wore an activity monitor (activPAL^{TM}) continually for 3-7 days, which recorded the sequence and period of time of individual bouts of sedentary, upright or walking activity. Individual bouts of each activity were classified according to their length of time from which their distribution was determined. We applied a generic statistical methodology to quantify the distribution of activity bouts based on power law statistics. This method enabled patterns of physical behaviour to be quantified.

Results: Bouts of sedentary activities followed a power law relationship $p(t) \sim t^{-n}$ allowing their distribution to be described statistically using the exponent n of the power law and indicates the proportion of long to short sedentary bouts. A smaller n indicates greater proportion of longer sedentary bouts contribute to the total sedentary time. n was significantly different ($p=0.02$) between the PD and control groups ($n_{control} = 1.93$; $n_{Parkinson}=1.33$). No significant difference ($p= 0.64$) was found between the groups total daily percentage of the day spent sedentary (PD 76.6 +/- 11.6 %, Control 71.5 +/- 9.4). The results therefore suggest that PD subjects adopted different sedentary behaviour tending to prefer longer bouts of sedentary activity compared to controls whilst demonstrating the same total amount of activity during the day.

Conclusions: Patterns of habitual physical behaviour may provide a more sensitive method to quantify and differentiate the impact of PD rather than total amount of inactivity. This method has potential as a quantitative outcome measure of subtle changes in physical behaviour as a result of PD.

Mo-295

The relationship of cerebral white matter lesions and clinical severity in patients with vascular parkinsonism

Y.-F. Chen, Y.-Y. Chang, M.-Y. Lan, C.-S. Su, J.-S. Liu (Kaohsiung County, Taiwan)

Objective: The aim of the study was to assess the impact of white matter lesions (WML) on cognitive and motor functions in patients with vascular parkinsonism (VP).

Background: VP is referred to secondary parkinsonism most commonly related with multiple lacunar state or subcortical WML in

brain. VP is also associated with vascular risk factors and the clinical features of VP are different from Parkinson's disease such as lower-body involvement with earlier gait disorder, pseudobulbar palsy and cognitive impairment.

Methods: Sixty-two consecutive patients (70.2 ± 9.2 years) with VP were included. The clinical severity was evaluated in all patients using the Unified Parkinson's disease Rating Scale (UPDRS). WML load was assessed with the scoring system based on the fluid-attenuated inversion recovery T2-weighted MR images. Association between WML score and the UPDRS score was examined.

Results: There were no association between WML score and demographics and vascular risk factors. WML score was positively correlated with the UPDRS part I score (correlation coefficient = 0.311, p= 0.022, Spearman's r test) but not that of the total, part II and part III UPDRS scores. The association remained after adjusted for age, gender, stroke history and use of levodopa (b-estimate = 0.101, p= 0.02).

Conclusions: The severity of WML is associated with cognition, behavior, and mood, but not with activities of daily living or motor function, in VP patients.

Mo-296

Acquired hepatocerebral degeneration and Wilson's disease: Differential diagnosis

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Objective: Compare clinical and imagiological characteristics of Wilson's disease (WD) and acquired chronic hepatocerebral degeneration (ACHD) patients, in order to identify characteristics that distinguish these entities.

Background: Two forms of chronic hepatocerebral degeneration (CHD) have been described, familial or Wilson's disease and acquired non-Wilsonian (ACHD). Both entities share clinical, neuroradiological and neuropathological characteristics.

Methods: Fourteen patients (8 WD and 6 ACHD) refereed to neurologic evaluation with chronic liver failure, persistent neurological symptoms, basal ganglia (BG) T1 hyperintensity on magnetic resonance imaging (MRI) were selected for study.

Results: Mean age at neurological symptoms onset was 22,2±7,0 yrs for WD versus 52,3±10,4 yrs for ACHD. The most common cause of chronic liver failure in ACHD group was alcoholic cirrhosis (5 of 6). In this group, hepatic symptoms always preceded neurological symptomatology. In contrast, in all WD patients, hepatic involvement was asymptomatic and identified during neurological investigation. Parkinsonism with variable severity was present in all patients, frequently associated with chorea, dystonia, dysarthria, dysphagia and gait disorders in WD group and with mental, memory and behavior disorders in ACHD group. Neurological symptoms onset was insidious in all WD, while precipitating factors were identified in one ACHD. Basal ganglia T2 hyperintensity was systematically present in WD group, associated with typical BG T1 hyperintensity of liver failure; while in ACHD group the others MRI findings were variable and not always present.

Conclusions: We selected only patients with basal ganglia T1 hyperintensity on MRI, recognizing, like others, this as a biomarker of brain manganese accumulation and the substrate of symptoms like parkinsonism, shared by all our patients. We believe that, age at onset of neurological disease, precocity of neurological symptoms, clinical symptoms besides parkinsonism and MRI findings other than GB T1 hyperintensity, may be the useful characteristics to distinguish WD from ACHD.

Mo-297

Acquired olfactory impairment in a transgenic rat expressing the human mutated alpha-synuclein

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Objective: We have recently generated a transgenic rat expressing the human double mutated alpha-synuclein (A30P and A53T) under the control of the rat tyrosine hydroxylase promoter.

Background: Parkinson's disease is characterized by a progressive and massive loss of dopaminergic neurons in the substantia nigra pars compacta which leads to several clinical motor symptoms such as akinesia, rigidity and resting tremor. Many patients also present others symptoms such as olfactory dysfunction which often appears before motor deficits.

Methods: The localization of the human alpha-synuclein was analysed by immunohistochemistry in different anatomical regions in transgenic and wild type rats. Several behavioral tests were used to evaluate olfactory and motor functions in 5 transgenic and 5 wild type rats from birth to the age of 25 month. To test olfactory function in neonates, we performed a test based on the discrimination of clean saw dust versus home saw dust. For young adult and adult rats, we performed a test based on the perception of an attractive odor (coconut milk). In the transgenic rats, the human alpha-synuclein immunostaining was observed in the olfactory bulb, the substantia nigra and the locus coeruleus.

Results: There was no marked motor behavioral change in 25-month-old transgenic rats as compared to wild type controls. At birth, neither wild-type nor transgenic rat had an olfactory dysfunction. From 6 month, transgenic rats developed olfactory deficits evidenced by a reduction of the time spent in the immediate surroundings of the attractive odor.

Conclusions: Although no marked motor impairment was observed, the development of olfactory impairments in our transgenic rat suggests that a transgenic rat expressing the human double mutated alpha-synuclein (A30P and A53T) is a good model of an early stage of Parkinson's disease.

Mo-298

Levodopa (L-dopa) responsive parkinsonism in a 16 year-old male with brainstem infiltrating astrocytoma

C.K. Sagert, K. Dashtipour (Loma Linda, California)

Objective: To report a case of dopamine responsive parkinsonism due to brainstem tumor and shunt placement.

Background: The effectiveness of levodopa (L-dopa) on the symptoms of idiopathic Parkinson's disease (PD) is well documented. However, the use of dopaminergic medications on patients who have developed parkinsonism secondary to brainstem tumors or after neurosurgical procedures is described in only a handful of case reports.

Methods: We describe a 16 year-old male who presented to the university neurology clinic with masked facies, right upper extremity resting and kinetic tremor, and decreased arm swing during ambulation after undergoing stereotactic biopsy of a brainstem infiltrating astrocytoma and placement of an Ommaya reservoir ventriculoperitoneal shunt.

Results: Brain MRI showed a well circumscribed focal lesion, bright on T2 and isointense on T1, measuring 2.7 x 1.7 x 3.1 cm in the left side of the brainstem extending from the midbrain/left cerebral peduncle to the inferior aspect of the pons at the time of admission. The patient was started on a trial of levodopa (L-dopa) which was then titrated up to effectiveness. He had significant improvement with improved facial expression, decreased tremor, improved gait pattern and increased independence with activities of daily living.

Conclusions: Dopamine responsive parkinsonism is not specific for PD and can be seen in other forms of parkinsonism such as atypical syndromes, vascular parkinsonism and parkinsonism due to medications. Our case responded significantly to dopaminergic therapy. The etiology of his parkinsonism could be from the expansion of the tumor within the brainstem or due to the shunt placement. Our case supports a trial of dopaminergic treatment in those patients who demonstrate parkinsonism with brain tumor or following neurosurgical procedures.

Mo-299

Natural history and predictors of survival in a cohort of southern Italy PSP patients

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Objective: to measure survivorship and identify predictors of survival in a cohort of italian PSP patients.

Background: Progressive Supranuclear Palsy (PSP) is the more frequent form of degenerative parkinsonism after Idiopatic Parkinson's disease (PD) and is associated with higher degree of disability and shorter survival than PD.

Methods: natural history of disease of consecutive PSP patients referring to our center from 1988 to 2008 was analized in a retrospective study. A group of age at onset/sex matched PD patients was used as control. PSP diagnosis was based on NINDS criteria. Clinical and demographic informations were abstracted from medical records and caregivers interview. The presence of clinical milestones of disability was determined. Length of survival was ascertained from death certificates or by contacting relatives.

Results: 43 PSP patients (23 [male]/20[female]) and 86 PD patients (46 [male]/40[female]) were enrolled. Mean age at onset was 62,8 ±6,7 years in the PSP group. PSP patients were diagnosed later (40,5±23,6 months vs 11,4 ±10,1), had a shorter mean follow-up duration (46,4±33,6 months vs 96,4±52; p<0,001) and a lower number of outpatients visit (5,2±6 vs 17,8±16; p<0,001) then PD patients. At the end of the follow up the 60,5% of PSP patients and the 26,7% of PD patients were died (p<0,001), whith a median survival of 7 years(2,2-18) for PSP patients and 10,2 years for PD patients (p=0,004). PSP patients reached disability milestones more frequently (80% vs 22,7%; OR 13,6, 95%CI 5-36,7) and earlier then PD patients (63±36,3 months vs122,4±57,3; P=0,0002). The more frequent milestone reached in both groups was the inability to walk unassisted. Survival rate at ten years was 40% for PSP and 83% for PD. Older age at onset, shorter interval from disease onset to reaching the first clinical milestoneand and early cognitive changes were independent predictors of shorter survival.

Conclusions: Conclusion: older age at onset and the presence of early cognitive impairment are indicators of poor prognosis in clinically diagnosed PSP patients. The time to the first clinical milestone could be an useful prognostic predictor for survival. Eventual therapeutic intervention should be performed before than the reachment of clinical milestones.

Mo-300

The EMSA natural history study: Data from the final analysis

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Objective: MSA is a sporadic neurodegenerative disorder characterised by parkinsonism or cerebellar ataxia in combination with autonomic failure. Disease progression is rapid steadily leading to death.

Background: We have studied the natural history in a large series of MSA patients and prospectively assessed disease progression using validated clinical scales.

Methods: A total of 144 patients were included at 15 EMSA-SG centres. Patients were followed up for two years with a complete neurological investigation every six months. Disease progression was assessed using the Unified MSA Rating Scale (UMSARS). For survival analysis, vital status was assessed again 24 and 36 months after study end to reduce the number of censored investigations.

Results: During the study period, clinical diagnosis was revised to a related disease in 12 cases, 27 patients died and 52 were lost to follow-up. All patients fulfilled the consensus criteria (58.6% MSA-P, 41.4% MSA-C; male 57.8%, female 42.2%). Mean age at disease onset was 56.5 ± 8.4 years, mean disease duration at baseline 5.7 ± 3.3 years. UMSARS motor scores progressed compared to baseline by 49% in the first year and by 74% during the 2 year follow-up, activities of daily living scores progressed by 32% and 49% respectively. During an extended follow-up period of 36 months, additional 29 patients had died. Median survival as determined by Kaplan-Meier analysis was 9.8 years (95% CI: 8.4 – 11.3). Survival was significantly less in MSA-P compared to MSA-C patients (8.5 vs. 11.5 years; p=0.025).

Conclusions: This analysis for the first time provides 2-year UMSARS rates of decline in a large series of MSA patients. In line with previous work, predominant parkinsonism was associated with more rapid progression than ataxia. Our data will be useful for the planning of therapeutic and neuroprotective studies.

Mo-301

Movement disorders in paraneoplastic limbic encephalitis-Ma 2, NMDA R. Comparatives with Whipple's disease diagnoses

S.G. Echebarria (Las Arenas, Spain)

Objective: Ma 1 + Ma 2 and Ma 2 antigens, extrapyramidal signs and pseudo–Whipple's disease may be related in a sizing–grouping case sample descriptors–position.

Background: Recent case samples and extended series in Antibodies-mediated neurological syndromes in paraneoplasttic conditions, may deserve a reappraisal of case-sizing and antibodies spectrum in such descriptions. Ma and Ta antibodies (Ma 1 + Ma 2 and Ma2 antibodies, respectively) may be observed in up to 6-8 % of extrapyramidal signs in paraneoplastic cases. As it is known, main groups in neoplastic antibodies diseases are divided according to membrane or intracellular antigens samples. Novel new membrane Antigens (Ma 1, Ma 2) have been associated to extrapyramidal signs in up to 41 %.

Methods: Case samples, unique-case observations (x=1), longitudinal series in paarneoplastic limbic encephalitis + movement disorders. 1ry-2ry Whipple's disease extended series. -Variance-covariance in limbic encephalitis and/or cerebellar syndrome associated to Ma 2, ta 2 NMDA antibodies findings. -Oromandibular /lingual movement disorders in intracellular/extracellular antibodies syndromes. Rank correlation with OMM, OFM in Whipple's disease. -Rank correlation between extrapyramidal signs/level of consciousness/hypoventilation. -Tumour-type associated movement disorders and r derived from WD-mimicking casuistics.

Results: General Whipple's disease with brain manifestations + gammopathy and Ma 2 paraneoplastic limbic encephalitis show a rank correlation (r) = 0.74 The rank correlation between paarneoplastic new membrane antigens with decreased level of consciousness (59 %) and WD with brain manifestations, is r= 0.29 The r between 1ry WD with sleep obstructive apnea and cMAg paraneoplastic limbic encephalitis is r=0.03 Craniomandibular movement disorders in 1ry WD and Ma 2–NMDA paarneoplastic encephalitis is r=0.40.

Conclusions: Significant relationship may be obtained between WD-mimicking cases and Ma2 paraneoplastic limbic encephalitis, considering serologic variants and extrapyramidal signs.

Mo-302

Acquired hepatocerebral degeneration

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Objective: To determine the prevalence of acquired hepatocerebral degeneration (AHD), its clinical picture, risk factors and response to treatments.

Background: AHD is a chronic encephalopathy with predominant motor signs in the context of severe liver disease. Although recognized for more than 4 decades, its clinical picture is not well defined, and its prevalence and risk factors are not well known.

Methods: Review of a database of 1000 cirrhotic patients to identify cases already diagnosed of ADH and patients with tremor, dysarthria, gait abnormalities or other motor disorders. Clinical and neu-

roimaging data, follow-up and response to treatments, including liver transplantation, were recorded.

Results: Eight AHD were identified: prevalence of 0,8 % of cirrhotic patients. The main risk factor for AHD was the presence of porto-systemic shunts. The etiology of cirrhosis was variable and previous acute hepatic encephalopathy was recorded in 62 % of AHD cases. Movement disorders, especially a combination of parkinsonism and cerebellar signs were observed in all patients. All AHD showed on MRI T1-weighted images hyperintensities in the globus pallidus and 75% of them had extrapallidal involvement as well. The more severe basal ganglia and brainstem involvement was seen in the more clinically affected cases. B-blockers and antiparkinsonian drugs were not effective. Three patients who underwent liver transplantation did not experience neurological improvement. Persistence of porto-systemic shunts was demonstrated in two cases.

Conclusions: AHD is a chronic encephalopathy which occurs in ~1% of patients with liver cirrhosis, and seems related to porto-systemic shunts. It is clinically characterized mainly by a combination of parkinsonism and cerebellar signs. MRI pallidal and extrapallidal lesions are seen in most patients (probably reflecting intracerebral deposits of manganese). AHD is an irreversible disorder. Liver transplant did not improve the neurological signs in our patients, perhaps due to the persistence of porto-systemic shunts.

Mo-303

Differentiation of guadeloupean parkinsonism and progressive supranuclear palsy by multimodal magnetic resonance imaging

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Objective: The aim of the present study was to determine the structural and metabolic profiles of guadeloupean parkinsonism (GD-PSP) compared to progressive supranuclear palsy (PSP) patients and controls using combined structural, diffusion, and metabolic MRI.

Background: In the Caribbean island of Guadeloupe, two thirds of patients with parkinsonism present with an atypical form (1), most likely related to the consumption of annonacin, an inhibitor of complex I of the mitochondrial respiratory chain (2). Clinically, these patients present either PSP-like syndrome or Parkinson-dementia complex. It remains unknown to which extent areas of neurodegeneration differ between GD-PSP and PSP. (1) Lannuzel A. et al. Brain. 2008;131:2701-9, (2) Lannuzel A. et al. Neuroscience. 2003;121:287-96.

Methods: We included 10 PSP, 7 GD-PSP and 9 age-matched controls. Extensive neurological, psychological and psychiatric examination was performed. Images were acquired at 1.5T and included 3D T1, diffusion tensor imaging (DTI), and FLAIR images. Image analysis included voxel-based (VB) morphometry and VB-DTI, brainstem volume measurements, and diffusion measurements in the mesencephalon and putamen. Single voxel spectroscopy was performed in the lenticular nucleus.

Results: In PSP, atrophy was observed in the mesencephalon, bilateral medial thalamus and insula. In GD-PSP, atrophy affected large cortical and limbic areas as well as the cerebellum and the mesencephalon was relatively preserved. Decreased mesencephalic and pons volumes were observed in PSP only. Frontal, insular and brainstem diffusion changes were observed in PSP and temporo-limbic and cerebellar changes in GD-PSP. ADC increased in the mesencephalon of PSP patients only and in the basal ganglia of both PSP and GD-PSP patients. The NAA/Cr ratio was decreased as compared to controls in PSP patients but not in GD-PSP subjects.

Conclusions: The pattern of structural and diffusion abnormalities differed between PSP and GD-PSP patients. Widespread cortical atrophy was observed in GD-PSP patients who present marked cognitive changes. Midbrain (PSP) or cortical (GD-PSP) atrophy were distinctive neuroradiological features for differential diagnosis.

Mo-304

Paleoneurological reappraisal of movement disorders, parkinsonism, neurodegenerative and age-related diseases

J.A. Ghika (Sion, Switzerland)

Objective: To reappraise neurodegenerative diseases from a darwinian perspective from prehuman primates.

Background: Neurodegenerative diseases selectively involve brain areas recently developed by homo sapiens, perhaps due to their plasticity and therefore sensitivity to environement and genetic deficits. Movement disorders reproduce prehuman motor behaviors inhibited by new human cortico-subcortical areas to allow new motor control: bipedal standing and gait, fine motility of hand and face for speech, tools, written language and executive choices.

Methods: Compared anatomy of humans and apes allows to understand the 20 syndromic presentations of neurodegenerative diseases.

Results: Parkinsonism is a restricted (dopasensitive) or extended (atypical dopa-resistent parkinsonism) summary of retrograding from human skill bipedal locomotion and fine motility of hand and larynx towards prehuman stooped bipedal posture and gait ("simian posture, gait and hand"), loss of rapid motility of hand and larynx, disihnibition of grooming scratching behavior (tremor), loss of supranuclear vertical gaze and autonomic control for upright locomotion and executive context-oriented control. Similarly, hyperkinetic movement disorders result from intrusions of older tonic tree- or mother -oriented prehension postures (palmar prehension in hand dystonia, foot inversion and neck dystonia, arm levitation, Babinski and triple retraction, decortication rigidity...), even older ones (retrocollis, decerebration rigidity, fetal posture...), or primate hyperkinesia (choreo-ballism), or more primitive motor schemes such as seen in focal tremor and myoclonus (branchial myoclonus, wing beating mesencephalic tremor...). This adds variably to cognitive deficits, mood and behavior control resulting from new human brain regions.

Conclusions: Understanding movement disorders and neurodegenerative diseases from a darwininan perspective allows to understand their focal, multisystemic or asymmetrical presentations. A new chapter in neurology, paleoneurology, should reapprise clinical signs and presentations as regression towards the best equilibrium available with residual brain regions, such as a in a russian puppet model. This should prompt basic science to move towards understanding of the molecular biology mechanisms that underly function- or cell-specific age-sensitivity of brain areas developed by homo sapiens.

Mo-305

Clinical and pathologic findings in a parkinsonism family

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Objective: To study the clinical and pathologic features in a family where a neurodegenerative disease appears to run as an autosomal dominant trait.

Background: We have been studying a French Canadian family that spans five generations and consists of more than 95 individuals where a parkinsonism has been the primary feature.

Methods: Clinical information was collected and a blood sample drawn from all participants. 6 individuals have now undergone pathologic study using standard procedures including immunostaining for ubiquitin, tau, synuclein and TDP-43.

Results: 14 individuals have now been identified with a parkinsonism (average age of onset 58 yrs old–range 39-70). All individuals that have been treated with levodopa have responded. 4 PD-affected individuals had a postural and kinetic tremor before the development of their parkinsonism and 2 more had marked postural and kinetic tremors but no parkinsonism. One individual presented with a dementia but no evidence of parkinsonism and was diagnosed clinically as having Alzheimer's disease (AD). 5 of the 6 individuals with autopsies were felt clinically to have a levodopa responsive parkin-

sonism. 4 autopsies showed neuronal loss and gliosis of the substantia nigra (SN). Of these 3 had ubiquitin positive inclusions but only 2 showed typical synuclein positive Lewy bodies (LB). In one, the LB were limited to brainstem nuclei and the other had in addition diffuse cortical LB. One case with a parkinsonism had no neuronal loss seen within the SN nor LB found. Instead, there were tau-based neurofibrillary lesions in the SN with very rare cortical neurofibrillary tangles and scattered neuritic plaques. One individual clinically was felt to have AD without parkinsonism. On autopsy there were abundant cortical tau positive tangles and beta -amyloid plaques in keeping with this diagnosis. 5 of the autopsy cases had TDP-43-immunoreactive staining performed. 3 showed clear TDP-43 positive inclusions (one was the AD case).

Conclusions: This family suggests that a common mechanism exists that causes neuronal dysfunction that can lead to a wide range of clinical and pathologic findings. This family has many of the same characteristics of the LRRK2 mutation positive families yet sequencing for the common LRRK2 mutations has been negative.

Mo-306

Longitudinal monitoring of gait and mobility in Parkinson's disease (PD) using an instrumented timed up and go test (iTUG)

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Objective: To identify sensitive measures of longitudinal decline in gait and mobility in early PD using the iTUG.

Background: The Timed Up and Go Test (TUG) is commonly used to assess mobility and predict falls in PD and other balance disorders. In the present study, we instrumented the TUG test (iTUG) using wearable inertial sensors and monitored performance on the test over 18 months.

Methods: Twelve patients with early, untreated PD (UPDRS motor 20 +/- 9.4) and 15 age-matched controls performed an 6-meter iTUG test at baseline, and 6, 12, and 18 months. A Physilog portable data-logger with 7 inertial sensors attached on the trunk, upper and lower limbs recorded angular velocities and linear accelerations. Gait spatial-temporal parameters, sit-to-stand, stand-to-sit and 180-degree turns were quantified. A Linear Mixed Models analysis was used to compare groups and longitudinal effects.

Results: Arm swing amplitude and peak arm swing velocity of the more affected side showed a significant group effect ($F=5.6, p=0.023$; $F=18.9, p=0.001$) and an interaction effect ($F=4.4, p=0.045$; $F=9.6, p=0.004$), indicating a decline of amplitude and speed of arm swing for the PD, but not the control group, across the 18 months. Similarly, turning velocity showed a significant group effect ($F=5.0, p=0.03$) and interaction effect ($F=5.8, p=0.021$), with turn velocity slowing in the PD group across time. In contrast, sit-to-stand and stand-to-sit parameters were not different between groups or across time. Among lower body gait parameters, cadence was significantly different in the PD group ($F=8.7, p=0.05$) but did not decline across 18 months.

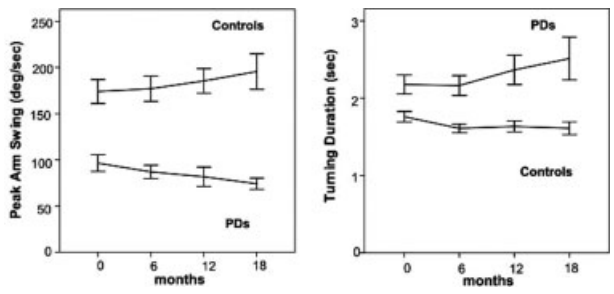

FIG. 1 (Mo-306).

Conclusions: The iTUG is a sensitive instrument to detect differences between early PD and healthy individuals, and also to detect longitudinal decline of mobility in PD. Arm swing and turning parameters were more promising than gait for monitoring longitudinal changes in early-to-moderate PD.

Mo-423

Neuropsychological tests versus FP-CIT SPECT to differentiate idiopathic Parkinson's disease (IPD) from multiple system atrophy (MSA). A study with follow-up

A. Delabie, S. Dethy, V. Donckels, A. Vervaet, A. Hambye (La Louviere, Belgium)

Objective: 1. Evaluate neuropsychological (NP) and scintigraphic (FP-CIT) tests to differentiate MSA from IPD compared to clinical evaluation (CE) and 2. Assess the tests evolution after 18 months.

Background: Distinction between MSA and IPD is clinically challenging but has major prognostic and therapeutic implications.

Methods: 15 IPD and 15 MSA pts were prospectively included. All underwent extensive neurological CE (motor UPDRS, Hoehn&Yahr [H&Y],..), complete NP testing (episodic+long-term memory, attention+ executive functions) and a semi-quantitative FP-CIT SPECT at baseline (T_0) and 18 m (T_{18}).

Results: The 2 groups were demographically similar. At T_0, CE and FP-CIT (global, caudatus, putamen uptake) were significantly different between MSA and IPD (Table), whereas NP testing was not. Despite lower FP-CIT uptake in MSA, values were too overlapped to accurately distinguish MSA from IPD. At T_{18}, clinical evolution confirmed the diagnosis in all pts. CE and FP-CIT remained significantly different between MSA and IPD (Table), and NP testing not. Between T_0 and T_{18}, deterioration was significant for UPDRS in IPD but not in MSA. Conversely, H&Y scale worsened significantly in MSA but not in IPD. Global and caudatus FP-CIT activity significantly decreased only in IPD. Putamen uptake did not change. NP testing remained rather stable in IPD. In MSA, work memory and attention capacity significantly worsened.

Table(Mo-423). Mean ± SD values for UPDRS, H&Y and left/right global striatal uptake at T0 and T18

	T0			T18		
	IPD	MSA	P value	IPD	MSA	P value
UPDRS	24,5±9,37	41.1±9,81	<0.0001	32.6±8.70	47.3±12,64	<0.0001
H&Y	2.7±0.46	3.2±0.41	0.017	2.9±0.46	3.9±0.46	<0.0001
Global L	1.87±0.717	1.05±0.415	0.001	1.59±0.758	0.97±0.561	0.017
Global R	1.92±0.720	1.09±0.394	0.001	1.55±0.730	1.02±0.564	0.034

Conclusions: NP is not significantly different between MSA and IPD at T_0, but work memory and attention capacity significantly deteriorates in MSA at T_{18}. FP-CIT uptake is significantly lower at T_0 in MSA than IPD but, due to the large overlap of values, not enough discriminative by itself. Associated to a careful clinical evaluation, FP-CIT SPECT might be helpful to orientate the diagnosis in the early phase of the disease.

Mo-424

Neurocysticercosis, cerebral blood flow velocity (CBFV) and CSF-related movement disorders

S.G. Echebarria (Las Arenas, Spain)

Objective: Neurocysticercosis diagnosis, categorical series and related movement disorders may be disclosed according to Cerebral Blood Flow Velocity (CBFV)–Venous/CSF Pressure indexes and associated movements.

Background: Typical descriptions in neurocysticercosis case series and casuistics with movement disorders generation have been termed around parenchymal and ventricular racemous presentations, with

nowadays consideration about diagnostic categories (probable, possible, definite) and cysticercous antigens diagnostic methods. On the other hand, CBFV and CSF dynamics correlation may be obtained in parenchymal hemodynamic movements, according to hyperkinetic shaky-form or stereotypic movements and CSF values. Associated to movement onset, has been suggested a CBFV-CSF/Venous Pressure correlation, which may be described in movement disorders sampling/sizing.

Methods: -Series and case–samples defining Diagnostic ascertainment in neurocysticercosis Probable neurocysticercosis :–1 major + 2 minor criteria–1 major + 2 minor criteria and epidemiological evidence -3 minor criteria and epidemiological evidence -Series with CT suggestive of neurocysticercosis and normal individuals -ABP/cerebral perfussion pressure, rank correlation with Cerebral Blood Flow velocity (CBFV) in normal cerebrovascular reactivity -ICP-Venous Pressure indexes -Variance and co-variance methods in Paroxysmal hemodynamic movements: CSF-dynamic related movements. CsF-dynamics -origined hyperkinetic movmeents -Diagnostic criteria in neurocysticercosis-Spearman r and CSF/CBFV -related movement disorders.

Results: Preliminary results in CBFV- Venous/CSF Pressure may describe r coefficients such 0.57-0.52 (CBFV 25 cm/s–43 cm/s).

Conclusions: Significant correlation may be obtained from CBFV * Venous Pressure and diagnostic criteria derived from 2/3 criteria established in neurocysticercosis diagnosis (antigenic ELiSA) 0.57 * 2 criteria = 0.39 * 3 * 2 issues ----> 0.6 to 0.9.

Mo-425

PSP-like syndrome developing after aortic aneurysm repair: Two case reports

E. Haberfeld, S. Frucht (New York, New York)

Objective: To report two cases of patients who developed PSP-like syndrome after aortic aneurysm repair.

Background: Reports of a PSP-like syndrome developing after aortic aneurysm repair surgery are rare. We report two additional cases, including the youngest ever reported, and the first that includes neuropsychiatric features. The etiology of this syndrome is debated. Vascular, hypoperfusion, and hypothermic hypotheses have been proposed.

Methods: Case report and relevant literature review.

Results: Pt 1 a 25yo m underwent AVR & aortic root replacement, followed 6 weeks later by hypotension, seizure and replacement of the infected valve and graft. Immediately after the second surgery, he noted loss of voluntary saccades. Exam showed absent saccades and fast-phases of OKN, with otherwise preserved VORs and smooth pursuit. He moved his eyes to a desired target by tracking his glowing, beeping cellular phone [video 1]. To turn, he turned his body, then tracked the phone to bring his eyes, head and neck into similar alignment. Dysarthria, dysphagia, eyelid apraxia, and forceful masseter clenching developed. The syndrome progressed for 3 months then stabilized. MRI showed 2 small anatomically unrelated lesions in the splenium of the CC and left frontal lobe. Vertebrobasilar system was tortuous. A sinemet trial was stopped after hallucinations; he subsequently developed depression and psychosis requiring hospitalization. Pt 2 a 53 yo m with emergency ascending aortic aneurysm repair complicated by post-operative TIAs and right occipital ischemic stroke, and a syndrome of dysarthria, dysphagia and gait imbalance. After a second surgery on the descending aorta, he developed supranuclear gaze palsy, anarthria and spastic gait requiring a walker.

Conclusions: We describe two additional cases of this uncommon syndrome. Both included radiographic findings anatomically distant from the usual structures involved in PSP-like phenomena. Prior authors have demonstrated microinfarction pathologically where none was visible on neuroimaging. We suspect a similar mechanism, affecting the brainstem, underlies these cases.

Mo-426

High neck tone in Parkinson's disease is associated with reduced mobility

F. Erika, P. Carlson, J. Nutt, V. Gurfinkel, F. Horak (Portland, Oregon)

Objective: To quantify axial rigidity in Parkinson's disease and to determine the relationship between axial rigidity and functional mobility.

Background: It has been suggested that rigidity may underlie many of the motor disabilities associated with Parkinson's disease (PD). We recently developed a new method for quantifying axial tone in the neck, trunk and hips during active stance. We hypothesized that axial rigidity affects functional performance of tasks involving balance, walking and turning.

Methods: The magnitude of axial postural tone in the neck, trunk and hip segments in 15 subjects with PD (both ON and OFF levodopa) and 15 control subjects were related to their performance of six functional tests (Figure of Eight, Timed Up & Go, Berg Balance Scale, Roll-over, Functional Reach and a 360 deg turn-in-place). Axial tone in the neck, trunk and hips was objectively quantified as the resistance to axial twisting while maintaining balance in standing. Our unique device for measuring axial tone twists the axial musculature by fixing the head, shoulders or pelvis against rotation while rotating the surface] 10 deg at 1deg/s .

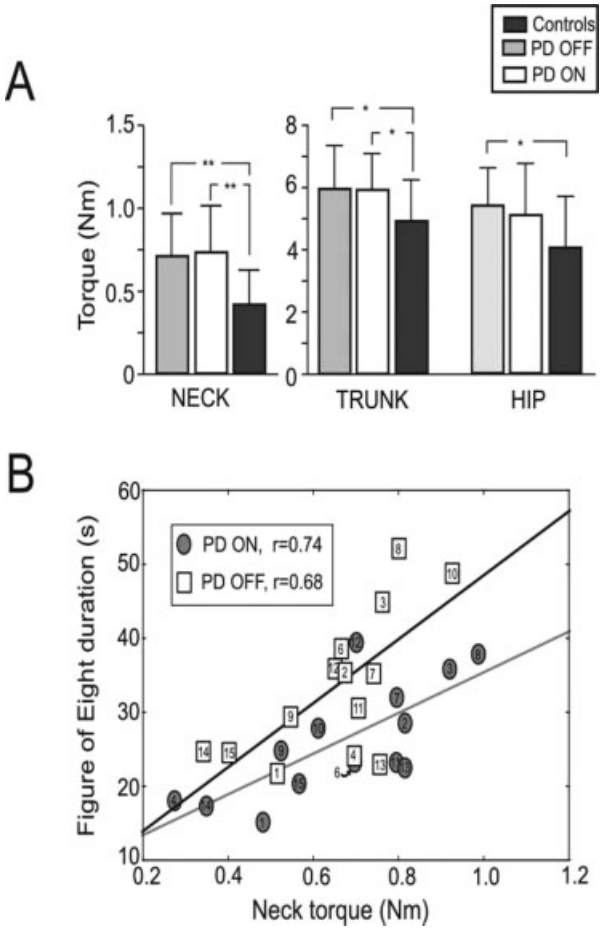

FIG. 1 (Mo-426).

Results: The subjects with PD had 3-5X larger axial tone than age-matched controls ($p=0.008$). The largest increase in tone compared to controls was at the neck. Neck tone was also most strongly related to the functional mobility tests. Neck tone accounted for an especially large portion of the variability in performance of the Figure of Eight walking test (rOFF=0.68 and rON=0.74, $p<0.05$) and the Rollover test (rOFF=0.67and rON=0.55, $p<0.05$).

Conclusions: The results suggest that control of neck tone has a significant role in functional mobility and that high axial postural tone may be an important contributor to balance and mobility disorders in individuals with PD.

Mo-427

Nicotinic receptor activation and imbalance in progressive supranuclear palsy: An open-label experience with varenicline

J.L. Juncos, K.L. Sullivan, T.A. Zesiewicz (Atlanta, Georgia)

Objective: We report on the open-label use of varenicline (Chantix®) in 5 patients with progressive supranuclear palsy (PSP).

Background: Nicotinic receptors are widely expressed in brain regions involved in balance control. Varenicline was recently shown to improve balance in experimental models of ataxia possibly related to its activation nicotinic receptor subtypes $\alpha4\beta2$ and/or $\alpha7$. In a case report, imbalance in Fragile X Tremor Ataxia Syndrome seemed to benefit from varenicline. (Zesiewicz et al. 2008).

Methods: Five patients with PSP and imbalance received varenicline 1 mg bid after failing antiparkinsonian medications. Patients were evaluated at baseline and for up to 12 months. Outcomes were the United Parkinson Disease Rating Scale adapted for use in PSP (UPDRSpsp) and the CGI-severity scale.

Results: Three patients who responded to varenicline have now used the drug for 6, 9 and 12 months respectively. Two non-responders stoppped the drug after 3 months due to lack of efficacy. Response consisted of a 1 point improvement in two key balance items of the UPDRSpsp: Part II, falling-unrelated to freezing; Part III, gait. Other items did not change. CGI scores improved 1 point in responders. Subjectively, patients reported a reduction in the feeling of "being pushed from within" that often leads to falls. Functionally, responders went from falling or 'near falling' 1-2 times/week [near fall =a 'fall' broken by holding on to something] and ambulating with difficulty, to $\leq$1 fall a month and ambulating with minimal assistance on varenicline. In responders, balance improvement was noted within a week and was lost within 3 weeks of stopping varenicline. Benefit persisted even with the expected gradual decline in motor function. One non-responder had severe arthritis and proximal muscle weakness. The other had severe frontal cognitive dysfunction and the lowest MMSE score in the group (24/30). Two patients had transient bad dreams but the drug was otherwise was well tolerated.

Conclusions: Varenicline, and presumably nicotinic receptor activation, may benefit balance in select patients with PSP. Although apparently well tolerated, the long term safety of varenicline remains unknown. Nicotinic receptors may offer benefit in the control of balance disorders like PSP for which there is no treatment.

Tu-288

Treatment with rivastigmin in progressive supranuclear palsy – First results of a phase II open label study

H. Huber, K. Srulijes, I. Liepelt, D. Berg (Tubingen, Germany)

Objective: To investigate the efficacy of cholinergic treatment on specific cognitive function, motor performance and the occurrence of side effects in PSP-related dementia.

Background: Dementia and personality changes, affecting up to 50% of patients with PSP, can have a major disabling effect. To date there is still a lack of effective treatment strategies for motor, behavioural and cognitive decline in PSP. As changes of cortical and subcortical neurotransmitter systems, particularly in the frontal lobe, are related to cholinergic dysfunction, cholinergic treatment may be helpful. However, results of previous studies using different cholinesterase inhibitors (ChEI) were controversial. Rivastigmine in contrast to other ChEI inhibits both the acetylcholinesterase and the butyrylcholinesterase. Patients with Parkinson's disease and dementia have shown positive effects of acetylcholine esterase inhibitors on cognitive function.

Methods: In this ongoing study a total of 20 patients with PSP and dementia will be included. At date of abstract submission data of the first four patients (median age 71.5 years range 62 to 78 years) is available. All patients have been treated with rivastigmin orally for a period of 6 months. Dose of medication was initiated with 1,5 mg/day and was weekly increased by 1,5 mg up to a well tolerated daily dose of 12 mg. Baseline and follow-up assessment includes a broad range of neuropsychological measurements, test of motor function (UPDRS-III) and behavioural scales (NPI).

Results: Our preliminary results show slight improvement of specific cognitive abilities e.g. memory and executive function in three of four patients. However, medication did not affect motor performance. Alterations in behaviour was also mildly positively affected in two patients. Medication was not tolerated by one patient who dropped out after 4 weeks of participation. Another patient suffered from nausea which lasted only for some days.

Conclusions: Rivastigmin may be an effective treatment option in patients with PSP and dementia, which needs to be verified by the data of additional patients in our and in further studies.

Tu-289

Glucocerebrosidase mutations p.L444P and p.N370S are not associated with multisystem atrophies in Polish patients – Preliminary report

Z. Jamrozik, A. Lugowska, J. Slawek, H. Kwiecinski (Warsaw, Poland)

Objective: To evaluate the presence of two most common mutations in the *GBA* gene in Polish patients with MSA.

Background: Recently, mutations in the *GBA* gene coding for lysosomal beta-glucocerebrosidase were proposed as a probable risk factor for Parkinson's disease (PD) and Lewy Body Dementia (DLB). The incidence of mutations in the *GBA* gene in PD patients is variable and related to population studied, methods of DNA testing (sequencing versus looking for most common mutations only) and control groups. PD and DLB are classified as synucleinopathies; the third most common group of synucleinopathies are multisystem atrophies (MSA) which may share with PD and DLB at least a part of pathogenesis.

Methods: To identify mutations in the *GBA* gene, genomic DNA was extracted from the white blood cells by standard techniques. A screening for mutations, p.L444P and p.N370S was performed in a group of 50 MSA patients (MSA-P = 31) and (MSA-C = 19). PCR-RFLP methods were used as described earlier. Results were compared to incidence in European population and PD/DLB patients published earlier.

Results: Neither of examined mutations in the *GBA* gene was found in the MSA patients.

Conclusions: Although a limited number of our patients with MSA-P cannot completely rule out the possibility of increased frequency of p.L444P and p.N370S mutations in the beta-glucocerebrosidase gene (*GBA*) it seems rather unlikely that the incidence of these particular *GBA* mutations in MSA is compatible to the incidence in PD or DLB as reported in literature.

Tu-290

Preserved cardiac ^{123}I-MIBG uptake and lack of severe autonomic dysfunction in a PARK9 patient

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Objective: To investigate whether autonomic dysfunction and Lewy body pathology are present in PARK9 using autonomic func-

tion tests and ^{123}I- metaiodobenzylguanidine (MIBG) myocardial scintigraphy.

Background: PARK9 is an autosomal recessive parkinsonism known as Kufor-Rakeb syndrome, which is characterized by juvenile-onset levodopa-responsive parkinsonism, pyramidal signs, dementia, and supranuclear gaze palsy. Recently, *ATP13A2* was identified as the causative gene for PARK9. However, pathologic findings in PARK9 and physiological roles of ATP13A2 are still unknown. Many studies have shown that decreased myocardial ^{123}I-MIBG uptake might be of potential diagnostic value to indicate the presence of Lewy body pathology in patients showing parkinsonism.

Methods: We performed ^{123}I-MIBG myocardial scintigraphy and autonomic function tests (70° head-up tilt test, the coefficient of variation of R-R interval on an electrocardiogram, plasma norepinephrine concentration, sympathetic sweat response and urodynamic variables) in a 43-year-old PARK9 woman with a homozygous *ATP13A2* missense mutation (F182L) who showed severe motor disturbance (Hoehn-Yahr rating scale: 5.0) and dementia.

Results: No severe autonomic dysfunction was detected despite the patient's 20-year history of the disease. The results of ^{123}I-MIBG myocardial scintigraphy in the patient revealed normal cardiac MIBG uptake in the early phase and mildly decreased uptake in the late phase, and were similar to those observed in PARK2 patients with long disease duration who lack Lewy body pathology in postmortem examination.

Conclusions: This study suggests that PARK9 patients can lack Lewy body pathology despite multisystemic neurodegeneration. Our results could provide important insights into the pathogenesis of PARK9.

Tu-291

Subacute dopa-responsive parkinsonism after successful surgical treatment of aqueductal stenosis

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Objective: To describe a patient who developed subacute levodopa responsive parkinsonism with proven presynaptic dopaminergic dysfunction, 3 months after placement of a ventriculoperitoneal shunt (VPS) and was then treated with neuroendoscopic third ventriculostomy (TV) with a full recovery.

Background: There are few reports of patients who developed dopa responsive parkinsonism following VPS placement for obstructive hydrocephalus despite the normalization of ventricular size. In this setting, parkinsonism can be isolated or associated with other signs of rostral midbrain dysfunction. The pathogenic mechanisms may be related to local CSF dynamic changes inducing physical constraints on the nigro-striatal pathway.

Methods: Neurological examination, neuropsychological testing, and 123I-FP-CIT (DaTSCAN) imaging before and after treatment with TV.

Results: A 49 year-old man developed a progressive symptomatic hydrocephalus due to idiopathic acqueductal stenosis (AS). Treatment with VPS completely relieved his symptoms. Three months later, he developed a subacute parkinsonism with intermittent diplopia and hypersomnolence. Neuropsychological examination found altered executive functions. Brain MRI showed no hydrocephalus. DaTSCAN showed a moderate, symmetrical, presynaptic dopaminergic denervation. On examination, he had bilateral akinetorigid syndrome, intermittent resting tremor of the left upper limb (UPDRS III=21) and Parinaud's syndrome. He had a dramatic improvement of the parkinsonism when treated with L-dopa. After one year, treatment withdrawal resulted in full reappearance of the parkinsonism. We thought that the condition of the patient was caused by the VPS related changes in CSF dynamics and decided to treat him with TV. He totally recovered from all symptoms. In keeping with the clinical findings, DaTSCAN returned to normal.

Conclusions: Dopa responsive parkinsonism is a possible side effect after VPS in obstructive hydrocephalus and may occur within few month after surgery due to physical constraints on the nigrostriatal projection fibers. Treatment of AS should be TV, to avoid VPS side effect and to reach a more physiological approach of the CSF circulation.

Tu-292

Dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD) share a common fingerprint in glucose and dopamine metabolism

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Objective: To study the similarities and differences of DLB, PDD and PD.

Background: DLB and PDD are classified as Parkinson plus syndromes. Clinically, these two entities are distinguished by their evolution, the former beginning with dementia and hallucinations before the advent of parkinsonian symptoms, the latter vice versa. DLB, PDD and idiopathic Parkinson's disease(PD) are all Lewy body diseases, but DLB and PDD are markedly distinct from PD in that they present with early cognitive dysfunction and severely reduced life expectancy. There is ongoing debate if these two are separate diseases, or if they are two different presentations of the same neurodegenerative process. In this study, we investigated glucose metabolism (CMRGlc) and dopaminergic transmission (DT) in groups of DLB, PDD and PD.

Methods: Patients diagnosed with PDD, DLB or PD (n=7,8,10) received FDG and FDOPA-PET to assess CMRGlc and loss of DT. We acquired two sets of normal controls (FDG:n=11,

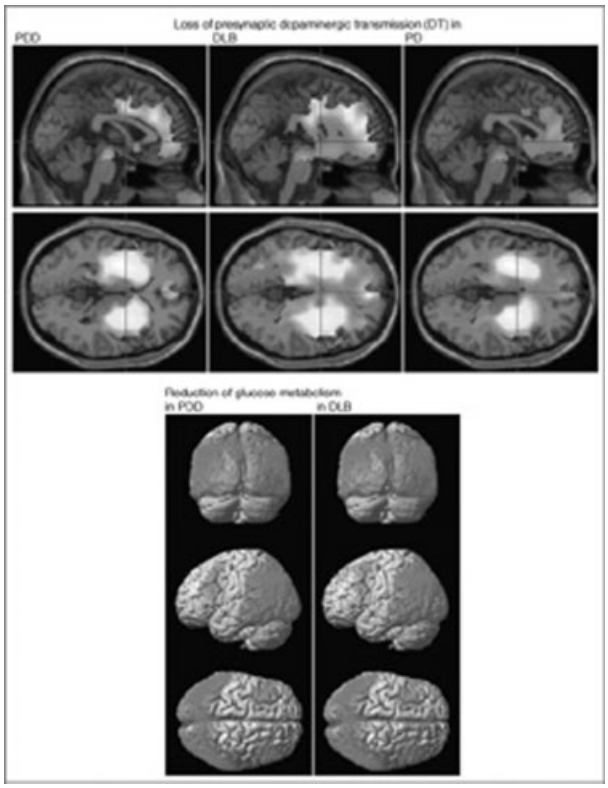

FIG. 1 (Tu-292).

FDOPA:n=9). FDOPA influx was quantified voxelwise with Patlak's model using a cerebellar reference ROI. Data were subjected to ANOVA in SPM5(FDR,$p<0.05$).

Results: Spatial patterns of DT loss in all three conditions were comparable in striate and cortical (limbic and orbitofrontal) grey. Glucose metabolism is unaffected in PD, while DLB and PDD present with occipital, parietal and frontolateral loss of CMRGlc. Patterns of impaired CMRGlc did not overlap with those of dopaminergic loss. We failed to detect difference between DLB and PDD in patterns of dopaminergic loss or CMRGlc.

Conclusions: Dopaminergic transmission is equally affected in DLB, PDD and PD. The exclusion of metabolic impairment from areas with reduced DT further supports the hypothesis that the pathology responsible for cognitive dysfunction in DLB and PDD is not related to DT. Also, we failed to detect significant difference between DLB and PDD in impairment of DT or glucose metabolism. These findings would suggest that DLB and PDD are closely related, perhaps even different presentations of the same disease. Other neurotransmitters must be responsible for cognitive impairment, and further studies into non-dopaminergic transmission are needed to establish the pathogenesis of these conditions.

Tu-293

HIV-associated parkinsonism with levodopa-induced dyskinesia and response to highly-active antiretroviral therapy

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Objective: To present a case of HIV-associated parkinsonism in whom levodopa-induced dyskinesia developed, and who responded well to highly-active antiretroviral therapy (HAART).

Background: Parkinsonism has been reported as a primary manifestation of HIV infection, as well as a consequence of opportunistic infection. Clinical features atypical for idiopathic Parkinson's disease (PD) are described in the literature, and the development of levodopa-induced dyskinesia has not been reported. One case report has previously described improvement following HAART.

Methods: A 40 year-old man presented with a history of left-sided upper limb tremor and problems with manual dexterity. Examination revealed left-sided parkinsonian signs and seborrhoeic dermatitis, and routine blood tests showed a polyclonal gammopathy. He was initially treated with dopamine receptor agonists with no benefit, and commenced levodopa after right-sided signs developed. Initial symptomatic improvement was complicated by motor fluctuations and dyskinesia that necessitated continuous apomorphine infusion.

Results: MRI brain showed confluent areas of high T2 signal in the deep white matter of both frontal lobes. Bilaterally reduced putaminal uptake was evident on [123I] FP-CIT SPECT. An HIV test was positive, with a CD4 count of 150. CSF examination was unremarkable. Following the introduction of HAART, his parkinsonism gradually improved, allowing a progressive reduction in his dopaminergic medications. Four years after starting HAART he was taking no antiparkinsonian medications; signs of parkinsonism and dyskinesia were absent.

Conclusions: The presence of features of HIV infection at the onset of motor symptoms, and lack of evidence of opportunistic infection, suggests parkinsonism was a primary manifestation of HIV infection. Dopaminergic dysfunction secondary to HIV is well-described, and his abnormal dopamine transporter SPECT could reflect this. Our patient presented in a similar manner to idiopathic PD and developed levodopa-induced motor complications in a manner not previously reported in HIV-associated parkinsonism. The therapeutic response to HAART described supports the potential reversibility of HIV-associated parkinsonism, even after several years.

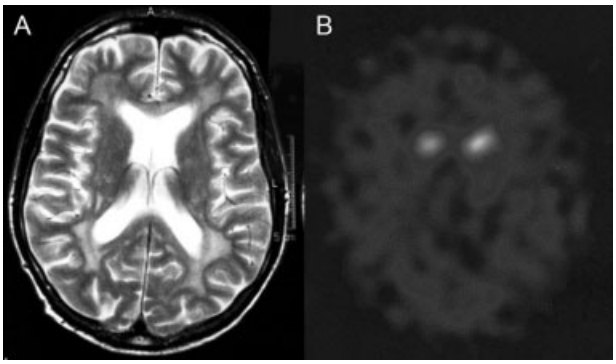

FIG. 1 (Tu-293).

Tu-294

PERFORM: A system for the continuous remote monitoring of patients with neurodegenerative diseases and the objective evaluation of patient status

S. Konitsiotis, K. Baga, D. Fotiadis, A. Tzallas, M. Diakou, S. Tsouli (Ioannina, Greece)

Objective: To detect and quantificate the symptoms of patients with neurodegenerative diseases, such as Parkinson's disease (PD), throughout all day, so as to schedule a more personalized treatment.

Background: The management of PD and other neurodegenerative diseases needs personalization, monitoring and quantitative and qualitative assessment. Previous systems/projects/products have partially addressed the issue, however many aspects remain to be clarified.

Methods: Twenty four patients with a diagnosis of idiopathic PD will be recruited for the study and they will be evaluated in two periods of recordings: short term and long term. The recordings will be obtained by the following sub-systems 1) **Light and small wearable device with body sensor network for the day monitoring:** The recorded signals are transmitted wirelessly to a small wearable device. 2) **Light and small wearable device and sensors for the night monitoring** 3) **Set of stand-alone test devices for the periodic patient test evaluation:** Devices such as reality gloves, video cameras and microphones are used to record the patient when he is performing the UPDRS part III tests at home. 4) **Home touchscreen and system for the recording of additional patient information and the communication with the treating clinician.** 5) **Hospital unit for the monitoring of multiple patient and the alerting of the treating physician**.

Results: With small sensors which are located at the patients body the system will record patient movement, detect and quantify patient symptoms. By processing the collected sensor signals, the system will be able to report the exact offset of the symptom and its severity according to the UPDRS scale. Data will be used to develop innovative decision support tools/algorithms and the exploitation of the vast pool of monitored parameters and the generated statistical data for the production of new diagnostic models and protocols.

Conclusions: Perform system will benefit PD patients as it allows health professionals to remotely monitor their patients, personalise their treatment and generate statistical data, so as to study and evaluate the efficacy of medication and drugs on various patient groups.

Tu-295

The characteristics of Parkinson's disease patients in Greece. A cross sectional hospital-based outpatient study

G. Mentenopoulos, S. Bostanzopoulou, Z. Katsarou, G. Tagaris, P. Stathis, S. Konitsiotis (, Greece)

Objective: To assess the clinical characteristics and current treatment of patients with PD followed in outpatient clinics based in hospitals of major cities in Greece.

Methods: This is a large-scale, nationwide, cross-sectional, epidemiological study of the clinical characteristics and current treatment in an unselected representative sample of PD patients from hospital-based outpatient clinics throughout Greece. The Greek Neurological Society is the patron of the study which is coordinated by a steering committee. 23 neurologists running outpatient PD clinics, distributed in 11 major cities throughout Greece agreed to participate in the study. Patients of all ages with the clinical diagnosis of idiopathic Parkinson's disease according to the UK Brain Bank criteria are eligible for the study, including familial cases as well. Face-to-face interview is used in data collection.

Results: So far data on 780 patients were collected. Up to the completion of the study approximately 2000 patients are estimated to be included. The patients are primarily male (57.5 %), and their mean age is 70.2 years. The average PD onset was 63.7years, with 6.6 years duration of disease. According to the HY scale, 5.8% of patients were stage I, 44.5% were stage II, 41% were stage III, and 8.8 % were past stage III. 18,9 % of patients describe "difficulty with movements" as severe or very severe, 23,6% severe or very severe gait difficulty, while only 9% report a severe or very severe tremor. Motor fluctuations are reported in 38.9%, drug-induced dyskinesia in 26.4% and dystonia in 14.4%. Depression is reported in 28,5 % and 15,3 % have dementia/psychotic features. 91 % of patients in our sample do not drink or smoke 93.7 %.

Conclusions: To our knowledge this is the first study of this kind in Greece, and the first of the Greek Parkinson's Study Group. It will provide useful information on the clinical characteristics and current treatment of PD patients in Greece, taken from a large unselected representative sample of PD outpatients in hospital-based settings. In addition such data are of interest for improved care, design of health care policy and a more adequate provision of treatment resources.

Tu-296

A patient with cerebrotendinous xanthomatosis and levodopa-responsive secondary parkinsonism

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Objective: To describe the case of a young male with genetically verified cerebrotendinous xanthomatosis (CTX) and levodopa responsive secondary parkinsonism who developed psychogenic movement disorders.

Background: CTX is an autosomal recessive lipid storage disease caused by a 27-hydroxylase enzyme deficiency, characterized by tendon xanthomas, premature cataracts, chronic diarrhea, progressive neurologic dysfunction and rarely parkinsonism.

Methods: Case study.

Results: The patient was born in 1974. At the age of 10 bilateral cataracts, chronic diarrhea was diagnosed. At 20-years-old, bilateral, asymmetrical tremor was observed at resting and postural conditions. Bilateral pyramidal signs, mild ataxia, bradykinesia and gait disturbances accompanied the rigorous muscle tone. Dopamin-agonists, later levodopa, dramatically improved the parkinsonian symptoms; whereas, chenodeoxycholic acid medication made better the biochemical parameters and the other neurological and gastrointestinal signs. In 2006, the patient met a primary dystonic girl treated with deep brain stimulation (DBS). Since then distractible tremor and unclassifiable gait problems developed. Electrophysiological tremor analysis and neuropsychological tests suggested psychogenic origin. MMPI, Szondi and Rorschach tests verified craving for DBS treatment in the background.

Conclusions: Psychogenic movement disorders can be evolved in patients with other types of movement disorders. The identification and the treatment of psychogenic problems are rather difficult.

Tu-297

Unsteadiness among patients with Parkinson's disease: A posturographic study

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Objective: The aim of this study is to determine whether the balance problems experienced by Parkinson's disease (PD) patients may in part be due to dysfunctional processing of vestibular information, and to search for factors that may help predict the risk of falls.

Background: It is suspected that the quantitative reduction of muscle strength in the spine, hip, and ankle, along with impaired proprioception, visual sense, and smaller base of support, were the main causes for postural instability in Parkinson's disease patients.

Methods: We evaluated the balance of 45 idiopathic PD patients and 40 healthy subjects by means of computerized dynamic posturography using sensory organization tests (SOT), and limits of stability (LOS) tests; and by the motor control test(MCT).

Results: PD patients had poorer scores in the SOT than controls for overall balance and vestibular and visual inputs. RESULTS: Between OFF state and controls, a significant difference was observed for SOT-2 ($P < 0.005$), SOT-6 ($P < 0.001$), and SOT-4 (eyes open with sway support, $P < 0.038$), and there was less use of ankle strategy in SOT-3 ($P < 0.04$). No significant difference was observed for vestibular function (SOT-5). Significant difference was also observed ($P < 0.001$) for all variables in limits of stability except for reaction time and for muscle strength of trunk, hip, and ankle ($P < 0.001$) between OFF state and controls. Hoehn-Yahr stage did not correlate with vestibular input.

Conclusions: Balance impairment in PD patients involves deteriorated processing of vestibular input, but this deterioration is independent of disease progression. The quantitative reduction of muscle strength in the spine, hip, and ankle, along with impaired proprioception, visual sense, and smaller base of support, were the main causes for postural instability in Parkinson's disease patients. Falls are related to PD patients' reduced limits of stability.

Tu-298

Direct modulation of striatal dopamine release by preterminal glutamate afferences on 6OHDA lesioned rats

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Objective: The objective was to evidence the role of glutamate in the striatal changes of extracellular DA induced by partial lesion of the substantia nigra. This experimental situation constitutes an animal model of the presymptomatic stage of Parkinson's disease.

Methods: Laterally restricted 6-OHDA lesions were realized in SN of rats that consequenced in a lateral denervation of the ipsilateral CPc leaving spared the both medial part of CPc and SN. Three set of experiments were realized. The first was devoted to a cartography of the extracellular DA in the striatum using in vivo votametry. In a second set of experiments, chronic treatment with Glutamate receptor antagonists were applied to counteract the changes observed in the extracellular DA concentration, using HPLC-ED. In a third set of experiments the effects of chronic treatment with GBR12909 a blocker of the DA transport was evaluated.

Results: In the first set of experiment, a slight increase of the extracellular dopamine (Daext.) and a decrease of the extracellular dihydroxyphenylacetic acid (DOPACext) were observed in the denervated part of the striatum. In contrast, DOPACext was unchanged and Daext greatly enhanced in the non denervated medial part of the striatum. Surprisingly an enhancement of Daext was also observed in the medial part of the controlateral CPc. Analysis with HPLC-ED showed an increase of the extracellular GLU (GLUext). Chronic treatment with GLU NMDA receptor antagonists including memantine (5 mg/kg/d), riluzol (5 mg/kg/d) and amantadine (30 mg/kg/d) between the lesion and the microdialysis test counteracted the

increased Daext. Concerning the effect of the DAT blockade, nigral lesion was observed to increase the GBR 12909 effect on spontaneous Daext.

Conclusions: This suggested that a bilateral activation of the both nigrostriatal DA path resulted from partial and unilateral DA-cells depopulation. This suggested also NMDA receptors located on DA terminals be involved in the tonic increase of DAext. The effects of GRB are in line with the hypothesis that the lesion induced compensatory DA release in the striatum is related with a GLU activated reverse transport of the amine at presynaptic level.

Tu-299

ATP13A2 mutation is rare in patients with early-onset or familial Parkinson's disease in Chinese population

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Objective: To assess the association of *ATP13A2* gene mutation among patients with early-onset Parkinson's disease (EOPD, onset <50 years) in ethnic Chinese population.

Background: *ATP13A2* mutation was recently reported contribute to early-onset Parkinson's disease (EOPD) without atypical features.

Methods: We analyzed *ATP13A2* gene in a cohort of 87 EOPD and familial PD patients and 70 matched controls in a Chinese population. Three of index patients were heterozygous *PINK1* mutation carriers and mutations in the *Parkin*,*DJ-1*,*SCA2* and *SCA3* gene were excluded. The entire *ATP13A2* coding region and intron-exon boundaries were sequenced. RT-PCR assay was used to examine the cDNA expression level in patients carrying *ATP13A2* mutation.

Results: We did not find any homozygous or compound heterozygous mutations. One novel missense mutation, Ala746Thr, in a single heterozygous state was identified in two patients, one is EOPD Y56 who is also a *PINK1 M371I carrier and the other one is familial late-onset PD. This variant is absent in additional independent 150 matched controls and 100 EOPD patients. The clinical phenotypes including* ^{18}F-dopa PET image are similar with idiopathic PD, albeit the earlier onset age and more deleterious disease course of Y56 suggesting an additive effect of digenic heterozygous mutations.

Conclusions: Our results suggest that *ATP13A2* mutation is not a major cause of EOPD in this population and other genetic and/or environmental factors remain to be identified.

Tu-300

Different phenotypes correlate to joint findings of dopaminergic transporter and receptor images in progressive supranuclear palsy

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Objective: To investigate the presynaptic transporter and postsynaptic receptor of dopaminergic system in patients with different phenotype of progressive supranuclear palsy(PSP).

Background: Two clinical phenotypes of PSP; Richardson's syndrome(RS) and progressive supranuclear palsy-parkinsonism(PSP-P) have been proposed recently. The tau pathology of two phenotypes is different and the disease duration of RS is shorter than that of PSP-P. Up to date, there was no imaging study of dopamine system to distinct these two phenotypes.

Methods: Ten PSP patients, 8 patients with Parkinson's disease (PD) and 5 normal volunteers were recruited in the pilot study. The diagnosis of PSP was based on the NINDS-SPSP criteria. Clinically 6 and 4 patients fitted with RS and PSP-P respectively according to their features. The patients with PD fulfilled with the UKPDS Brain Bank diagnostic criteria. [^{99m}Tc]TRODAT-1 SPECT for studying dopamine transporter was firstly performed in all participants, followed by [^{123}I]IBZM SPECT for studying receptor 4 to 12 days later. The uptake values of both tracers were measured with the volume of interest technique. In PSP-P and PD groups, the imaging opposite to the predominantly affected limb was defined as the contralateral side. In the RS and health groups, the left side was defined as the contralateral side. We analyzed the specific uptake ratio with Kruskal-Wallis and Mann-Whitney tests.

Results: Binding of TRODAT-1 and IBZM over bilateral striatum were significantly different among the four groups. The IBZM binding of bilateral striatum in PSP-P and PD were higher than that in RS. But no difference of IBZM binding was found among PSP-P, PD and health. The reduced TRODAT-1 binding of bilateral striatum in RS is significant lower than that in PD. In PSP-P, only TRODAT-1 binding of contralateral caudate is lower than that in PD.

Conclusions: The asymmetrical reduction of dopamine transport between PSP-P and PD are similar. The TRODAT-1 study indicates the presynaptic dopaminergic impairment in PSP-P involves caudate and putamen but the dopaminergic impairment in PD mainly involves the putamen. Combined studies of presynaptic transporter and postsynaptic receptor SPECT may be helpful to differentiate PSP-P from RS phenotypes in PSP.

Tu-301

Diagnostic accuracy in 18 cases of pathologically confirmed corticobasal degeneration

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Objective: To assess the diagnostic accuracy of CBD in hospital practice.

Background: The pathological findings of corticobasal degeneration (CBD) may be associated with several distinct clinical syndromes and it is also acknowledged that 'look alikes' exist (corticobasal syndrome).

Methods: We reviewed cases in the Queen Square Brain Bank (QSBB) between 1990 and 2008 with either a clinical or pathological diagnosis of CBD.

Results: Of 18 CBD cases, only 5 had been diagnosed correctly in life and 3 of these had received a different earlier diagnosis(sensitivity=27.8%). These cases had the classical clinical presentation: myoclonus(5), alien limb phenomena(2) and ideomotor apraxia(2). Moderate initial L-Dopa response was observed in 2 cases and transient L-Dopa-induced dyskinesias were noted in 1 case. The clinical diagnoses in the 13 false-negative cases included 9 progressive supranuclear palsy(PSP), 1 frontotemporal dementia(FTD), 1 progressive non-fluent aphasia(PNFA), 1 atypical Parkinson's disease(PD) and 1 undiagnosed. Common clinical features in the 9 cases diagnosed as PSP were falls in the first year(7), frontal lobe signs(4), pseudobulbar palsy(3) and apraxia of eyelid opening(3). Only 3 cases had slowing of vertical saccade or gaze palsy. One case had history of falls backwards. Symmetrical parkinsonism(5) was not uncommon in CBD cases diagnosed as PSP in life. Of 16 cases diagnosed with CBD in life, only 5 had CBD, with a positive predictive value(PPV) of 31.3%. Eleven false-positive cases had other pathological conditions(see table). Five out of 169 pathologically proven PSP cases had been diagnosed as CBD in life. In contrast to CBD, the sensitivities and PPV were 73.4%(124 out of 169) and 84.4%(124 out of 147) respectively for the 169 cases diagnosed as PSP in the QSBB. The PPV of a clinical diagnosis of multiple system atrophy(MSA) from a previous QSBB study was 85.7%(30 out of 35).

Table (Tu-301). Pathological Diagnoses of Cases Clinically Diagnosed as CBD

Pathological Diagnosis	Total Number of Cases
CBD	5
PSP	5
PD	3
Alzheimer's Disease	1
FTLD-TDP with MND	1
Dementia Lacking Distinct Histology	1

Conclusions: The diagnostic accuracy of CBD presenting to movement disorder specialists is much lower than for PSP and MSA. Errors of commission and omission occur in relation to the distinction between PSP and CBD. The scarcity of slowing of vertical saccade and gaze palsy in CBD even in terminal stages highlights that saccadic eye movements may prove to be particularly informative in the differential diagnosis between CBD and PSP.

Tu-302

Prospective differentiation of multiple system atrophy from Parkinson's disease

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Objective: The severity and distribution of autonomic failure appear to be different in multiple system atrophy (MSA) compared with Parkinson's disease (PD), but reports have been retrospective reviews and have tended to exclude PD with autonomic failure (PD_AF). We report preliminary results of a prospective ongoing study of MSA and PD, with a large subset of PD_AF (25%) to evaluate autonomic indices that distinguish MSA from PD.

Methods: We used Consensus criteria, detailed autonomic studies (composite autonomic symptom score (COMPASS), composite autonomic severity score (CASS), thermoregulatory sweat test percent anhidrosis (TST%), plasma catecholamines, and functional scales (United MSA rating scale (UMSARS) I-IV, Hoehn-Yahr grading) on a prospective, repeated and ongoing basis.

Results: We report the results of a study based on 52 patients with MSA (61.1 7.8 years; BMI 27.2 4.6; Hoehn-Yahr grade, 3.1 1.0; UMSARS_1 21.5 7.4; UMSARS_2, 22.7 9.0) and 29 patients with PD, including PD with autonomic failure (66.0 8.1 years; BMI 26.6 .5.5; Hoehn-Yahr grade, 2.2 0.8; UMSARS_1 10.4 6.1; UMSARS_2, 13.0 5.9). Autonomic indices were highly significantly more abnormal in MSA than PD ($P<0.001$) for each of: CASS (5.9 1.9 vs. 3.3 2.3), COMPASS (54.4 21.8 vs. 24.7 20.4), TST% (57.4 35.2 vs. 9.9 17.7). Progression of autonomic failure and functional status was analyzed in 25 MSA and 20 PD patients, who had completed follow-up evaluation at 12 month. Deterioration of autonomic function, assessed by COMPASS_change, was three-fold greater in MSA than PD patients (56.9 45.9 vs. 22.1 32.8). Progression of autonomic impairment is exemplified by progressive anhidrosis in MSA (TST%), not seen in PD. Motor impairment (UMSARS_2) continued to be 2 times greater in MSA than PD patients (24.3 6.6 vs. 11.5 6.8).

Conclusions: The severity, distribution and pattern of autonomic and functional deficits at entry will distinguish MSA from PD when quantitative validated instruments are used. These differences continue and increase with follow-up. Autonomic indices support the notion that the primary lesion in PD is ganglionic/postganglionic while MSA is preganglionic.

Tu-303

The potential red flags in early parkinsonism

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Objective: To test a population of early parkinsonian patients for the presence of signs and symptoms characteristics of multiple system atrophy (red flags).

Background: Parkinsonism is a syndrome characterized by resting tremor, bradykinesia, rigidity and postural reflex impairment. Parkinson's disease (PD) constitutes 75% of all causes of parkinsonism according to United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) Criteria. The diagnosis of Parkinson's disease continues to be challenging with misdiagnosis rates as high as 20-30% in early stages. This diagnostic inaccuracy is determinated by failure to recognize atypical parkinsonian disorders including multiple system atrophy (MSA), progressive supranuclear palsy (PSP), cortical basal degeneration (CBD) and dementia with Lewy bodies (DLB). Early diagnosis of atypical parkinsonism is important for prognostic and therapeutic aspects.

Methods: We recruited 100 consecutive patients with early parkinsonism (<2 years of history). A complete neurological examination, GH stimulation test with arginine, brain MRI and FDG-PET were performed. All patients were investigated for the presence of any feature tending to exclude PD according for the UKPDSBB Criteria and of any "red flags" reported to be specific for MSA vs PD by the European MSA Study Group (EMSA-SG).

Results: Emotional incontinence, which consist in inappropriate crying or laughing, was present in 28% of patients. Contractures of hand or feet (excluding Dupuytren's disease or contracture due to other known cause) was present in 17% as soon as early instability was present in 18%. The predictive value of these characteristics, together with neuroendocrinological and neuroimaging features, in the differential diagnosis of early parkinsonism will be investigated prospectively.

Conclusions: We described the frequency of these "red flags" in early parkinsonism.

Tu-304

Intrathecal baclofen therapy slows progressive disability in multiple system atrophy

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Objective: Evaluate the benefit of intrathecal baclofen (ITB) on function, quality of life and progression in patients with multiple system atrophy (MSA) before and after pump placement using the modified Ashworth scale (MAS),Hauser ambulation index (HAI), and expanded disability status scale (EDSS).

Background: Intrathecal baclofen,a GABA B receptor agonist, has long been used to improve abnormal hypertonicity and spasms. Taken orally its dose is limited by side effects before it reaches effectiveness and given intrathecally the severity and number of adverse effects is greatly reduced. ITB is an established effective treatment for spastic hypertonia and has been extensively applied and studied in cerebral palsy, traumatic brain injury, spinal cord injury, multiple sclerosis and to a lesser extent stroke. Its use in MSA has never been evaluated although the rigid tone greatly effects the level of disability, quality of life and the hypertonic state is the primary factor contributing to the immobilized bedridden stage.

Methods: A retrospective analysis comparing a small series of patients diagnosed with MSA from a movement disorders clinic divided into an ITB treated group and into a non-ITB treated group. MSA patients were staged using Watanabe et al. ADL milestones for disease progression. Tone was assessed using MAS, ambulation by HAI and disability by EDSS. Data points included before pump placement, at the time of entry, and 1 year. All evaluations and diagnoses were completed by a movement disorders specialist.

Results: The patients had the pumps placed at different points in their disease course (mean-4.6 years). The patients had different levels of tone, ambulation and disability. All had an improvement in the MAS and none had progression in their disability or ambulatory outcomes, in comparison to non-ITB treated patients in the same practice who had an increase in disability and ambulatory outcomes (without significant changes in tone).

Table (Tu-304). ITB treated patients versus non ITB treated patients

Patient	ITB versus Non ITB treated	Disease Length	Baseline (HAI/EDSS)	Expected* (HAI/EDSS)	1 year progression (HAI/EDSS)	Expected* 1 year progression (HAI/EDSS)
Patient 1	ITB treated	10 years	Bedridden (9/9.5)	Death (**/10)	No progression	Death (**/10)
Patient 2	ITB treated	6 years	Bedridden (9/9)	Wheelchair (7-8/7-8)	No progression	Death (**/10)
Patient 3	ITB treated	5 years	Walk unaided (3/3)	Wheelchair (7-8/7-8)	No progression	No progression
Patient 4	Non ITB treated	10 years	Wheelchair (8/8)	Death (**/10)	Bedridden (9/9)	No progression
Patient 5	Non ITB treated	5 years	Wheelchair (8/8.5)	Wheelchair (7-8/7-8)	Bedridden (9/9)	No progression
Patient 6	Non ITB treated	4 years	Aid Walking (6/6.5)	Aid Walking (6/6-6.5)	Wheelchair (8/8)	No progression

*Expected based on Watanabe et al. ADL milestone progression (Brain: Volume 125(5)May 2002pp 1070-1083)

**no equivalent value.

Conclusions: MSA is a rapidly progressive disorder. There are well established time frames to certain levels of disability and evolution of the disease (Watanabe et. al). Our results suggest that ITB can maintain (or improve function) and maintain quality of life in patients with MSA. ITB is currently not indicated for patients with MSA but should be studied further for the quality of life benefits and delay in disease progression it potentially provides.

Tu-305

Total tau and P-tau cerebrospinal fluid levels in distinct clinical phenotypes of progressive supranuclear palsy

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Objective: This study aimed to investigate whether the levels of the neurodegenerative cerebrospinal fluid (CSF) markers total tau and phospho-tau (P-tau 181P) differ between the PSP subgroups.

Background: According to the landmark paper of Williams and colleagues (Brain, 2005), progressive supranuclear palsy can be divided mainly in two distinct phenotypes: the Richardson's syndrome (RS) is characterized by the early onset of postural instability and falls, supranuclear vertical gaze palsy and cognitive dysfunction, and the PSP-parkinsonism (PSP-P) group is characterized by asymmetric onset, tremor, a moderate initial therapeutic response to levodopa. A small third group (here called RS/PSP-P) could not be separated according to these criteria. Between RS and PSP-P, the isoform composition of insoluble tangle-tau in the basal pons differed significantly.

Methods: Nineteen PSP subjects were included, from whom six could be classified clinically as RS and eight as PSP-P. Five patients were classified as RS/PSP-P. For clinical details, we refer to the poster of Srulijes and colleagues. CSF total tau and P-tau 181P levels were measured with commercial ELISA kits (Innogenetics, Ghent, Belgium).

Results: We found that the three PSP subgroups did not differ significantly concerning CSF total tau levels (RS, 153 pg ml, 86-256; median, range; RS/PSP-P, 145 pg/ml, 104-1300; PSP-P, 192 pg/ml, 147-793; p=.29). Also, P-tau 181P levels were comparable (RS, 29 pg ml, 21-53; RS/PSP-P, 28 pg/ml, 20-43; PSP-P, 36 pg/ml, 27-126; p=.31). There was no significant correlation between these levels and age at onset of disease, duration of the disease, and severity of the disease measured with the Palsy Rating scale and the MiniMental State Examination.

Conclusions: These findings indicate that CSF total tau and P-tau 181P levels are not useful markers to differentiate PSP subgroups according to the classification as proposed by Williams and colleagues.

Tu-306

Combination of clonidine growth hormone test and cardiac I123 MIBG SPECT to differentiate multiple system atrophy from idiopathic Parkinson's disease

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Objective: To compare clonidine growth hormone test (CGHT), cardiac I123 MIBG SPECT and combination of these two tests to differentiate multiple system atrophy (MSA) from idiopathic Parkinson's disease (IPD).

Background: Absence of growth hormone increase after intravenous injection of clonidine in MSA, and decreased myocardial MIBG uptake in IPD have been proposed to differentiate MSA and IPD which clinical presentation can be very closed.

Methods: CGHT and cardiac I123 MIBG SPECT were performed in 22 patients presenting MSA or IPD. Thirteen patients (9 men and 4 women), with a mean age of 61.4, had a probable MSA according to Gilmann et al. criteria. Nine patients (6 men and 3 women) with a mean age of 59.6 years had a probable IPD (Brain bank criteria). Mean disease durations were respectively of 4.5 and 6.3 years. None of the patients had a history of myocardial disease.

Results: For 9/13 patients with MSA and 5/9 patients with IPD, CGHT was consistent with clinical diagnosis (no increase of GH in MSA patients and normal elevation of GH in IPD patients). The sensibility and the specificity of CHGT were 69% and 55% respectively for MSA diagnosis. Cardiac I123 MIBG uptake was normal in 8 /13 patients with MSA, and decreased in 8/9 patients with IPD. The sensibility and the specificity of this test were respectively 61% and 89% for MSA diagnosis. For 5/9 patients with IPD and 5/13 patients with MSA, both tests were consistent with the clinical diagnosis. One patient with MSA and 1 with IPD had both tests discordant with the clinical diagnosis. In the other patients (3/9 IPD and 7/13 MSA), only 1 of the 2 tests was consistent with expected results. The combination of these 2 tests showed a sensibility and a specificity of 38% and 89% for MSA diagnosis. For IPD diagnosis, these characteristics were 55% and 92%.

Conclusions: Combination of CGHT and I123 MIBG SPECT doesn't increase sensitivity or specificity of each of these tests for the diagnosis of MSA. However, it seems to increase specificity for the diagnosis of IPD. Neither CGHT, nor I123 MIBG SPECT should be used alone for the differential diagnosis between MSA and IPD. The interest of the combination of theses two tests seems to exist and has to be confirmed.

Tu-419

Atypical Parkinsonism: A moving target the change of diagnosis over the course of disease based on clinical presentation, DAT and IBZM scan and CSF in 153 consecutive patients

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Objective: Evaluation of diagnosis of Atypical Parkinson patients followed in an out-patient clinic at first visit, after termination of standard investigation programme and after follow up.

Background: Atypical Parkinson syndromes (AP) as MSA, PSP and CBD are progressive neurodegenerative disorders. Some patients are difficult to classify using the existing diagnostic criteria due to overlap of symptoms with other conditions especially early in the course of the disease. Some patients with CBD and PSP have been reported to change phenotype over time. In this study we evaluated the clinical diagnosis in a highly specialized out-patient clinic for AP patients and evaluated the diagnosis for each patient over a time period.

Methods: 153 patients in our clinic for AP was evaluated by medical history and core features of atypical Parkinson syndromes e.g. bladder and erectile dysfunction, ortostatic hypotension, ataxia, dysarthria, dystonia, afasia, gaze palsy, levodopa response, apraksia, falls, visual hallucinations, fluctuations and dementia. All the patients have been examined with MRI, and patients with brain lesions explaining the condition (in part or completely) was excluded. All patients also had SPECT DAT and IBZM scans performed. Furthermore a neuropsychological examination and orthostatic blood pressure and an urodynamic examination have been made. CSF was obtained in some of the patients and send for analysis for cell count, total protein, amyloid-beta, tau and phospho-tau. From these data a tentative diagnosis of possible or probable MSA, PSP, CBD, LBD, IPD or another neuropsychiatric disorder has been evaluated according to the clinical criteria. Three diagnostic set point were made; 1: at first visit (Early diagnosis), 2: after termination of standard investigation programme (After investigation), and 3: after follow up (Late diagnosis). "Late diagnosis" was made at last visit in 2008 or at time of death.

Results: As cut off was end of 2008, all "Late diagnosis" are not available when this abstract was submitted. Results will be presented and analysed at the meeting.

Tu-420

Rasagiline and the improvement of motor scores and cognition in multiple system atrophy

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Objective: Rasagiline (Azilect) is a selective, irreversible MAO-B inhibitor that is used as either monotherapy or combination therapy for Parkinson's disease. The study demonstrated improved motor scores and cognition in multiple system atrophy (MSA) patients on rasagiline.

Background: Currently, no specific therapies have demonstrated promise in the management of MSA. Recent reports indicate rasagiline may be neuroprotective in the MSA transgenic mouse model. The N-Propargylamine structure up regulates anti-apoptotic genes and suppresses pro-apoptotic genes. Additionally, it increases the expression of free radical oxidizers such as superoxide dismutase and catalase.

Methods: This is a retrospective study done at Georgetown University Hospital, Movement Disorder Clinic involving patients with MSA who were on rasagiline. Patients had UPDRS motor scores done prior to starting rasagiline and at subsequent follow up visits. Patients also had a Montreal Cognitive Assessment (MoCA) done with at least one follow up while on rasagiline.

Results: The average age was 65.67 years old and all three patients were on 1mg of rasagiline. The mean UPDRS improvement was 10.5 points (range 1 to 19 points). The mean MoCA improvement was 1 point (range -1 to + 4 points). The mean follow up time was 13.3 months (range 8 to 26 months). The mean dose of levadopa was 533mg (range 500 to 600mg) and stayed constant for the duration of the follow up time.

Conclusions: This is the first study to examine the role of rasagiline in improving motor scores and cognition in MSA. Due to the small sample size, this study did not achieve statistical significance, but the results deserve closer examination. A study with a larger sample size and longer follow up time should be done to further evaluate the benefit of rasagiline in the MSA population.

Tu-421

Freezing of gait improved by venlafaxine

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Objective: To report two cases of isolated freezing of gait (FOG) which improved with venlafaxine therapy.

Background: Freezing of gait can occur in parkinsonian syndromes (progressive supranuclear palsy, advanced Parkinson's disease) and also in isolation (primary progressive freezing of gait). Treatment of FOG is notoriously unsatisfactory. Case reports of improvement of FOG with monoamine oxidase inhibitors, carbidopa/levodopa, and deep brain stimulation have been reported, but no definitive treatment for freezing currently exists.

Methods: Case reports.

Results: Case #1: A 69-year-old man first noted difficulty initiating gait. During the next 4 ½ years, he developed arrests in his gait when he turned, entered a crowded area, or passed through a doorway. He sustained a few falls due to his gait problems. He was often able to break the freezing episodes by throwing a crumpled tissue on the ground and stepping over it. Exam revealed freezing of gait and tachyphemia. Trials of levodopa, ropinirole, pramipexole, and selegiline were unsuccessful. Venlafaxine was started and on 75mg qd the patient experienced significant improvement in his gait and no longer required the use of his visual cue. Exam 3 months after initiating therapy revealed only occasional freezing on turns. The patient enjoys continued efficacy after 18 months. Case#2: An 84-year-old woman began to experience freezing when attempting to turn, and then when walking normally in her apartment. During the next year, she developed severe freezing on initiation of gait, at doorways, and when crossing the street. Visual cues and counting helped to break the episodes. She had no tremors, impaired eye movements, rigidity, or difficulty with manual dexterity. Levodopa, amantadine, pramipexole, and diazepam all failed to ameliorate her gait. Venlafaxine was started and gradually increased to 150mg daily. At this dose, she reported significantly fewer episodes of freezing, as well as decreased anxiety about her episodes.

Conclusions: Venlafaxine blocks reuptake of multiple neurotransmitters and effectively treats depression and anxiety. Here we report two cases of primary freezing of gait that improved after treatment with venlafaxine. Freezing of gait may thus involve multiple neurotransmitters and may respond to venlafaxine.

Tu-422

Novel throwing sign discriminates patients with progressive supranuclear palsy

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Objective: To evaluate the capacity of a ball-throwing test to differentiate between progressive supranuclear palsy (PSP) and other neurodegenerative diseases.

Background: Clinical observation of two patients who reported a selective difficulty in throwing objects and were subsequently diagnosed with PSP prompted us to examine this ability in a series of patients.

Methods: The ability to throw a tennis ball in an upwards and downwards direction using each hand was tested in 40 consecutive subjects: 10 diagnosed with PSP, 10 with Parkinson's disease, 10 with Alzheimer's disease, and 10 control subjects. The inability to perform this test with either hand or an abnormal performance disproportionate to motor impairment was designated "throwing sign". All participants also underwent the three-clap test ("applause sign"). We calculated the sensitivity (S) and specificity (E) of each test to diagnose PSP.

Results: Throwing sign was present in 8/10 PSP patients (S= 0.80; 95% CI= 0.50-0.94) and absent in the other groups (E=1.00; 95% CI= 0.89-1.00). The three-clap test showed lower sensitivity (S=0.70; 95% CI= 0.37-0.92) and specificity (S= 0.93; 95% CI= 0.79-0.98) in the present series. Throwing sign was not related to rigidity/bradykinesia or cognitive impairment but was related to limb-kinetic apraxia.

Conclusions: Throwing sign is a newly described and easily tested sign that likely reflects a specific type of limb-kinetic apraxia characteristic of tauopathies such as PSP. Further studies are warranted to fully characterize this striking phenomenon.

Tu-423

Phenotypes of dysarthria in progressive supranuclear palsy (PSP)

G. Mallien, G. Ebersbach (Beelitz-Heilstatten, Brandenburg, Germany)

Objective: Progressive Supranuclear Palsy (PSP) is an atypical parkinsonian syndrome characterized by gait ataxia, slowing or inability to generate vertical saccadic eye movements, axial rigidity, cognitive disorders and a progressive dysarthria. As the disease progresses, important functional components of speech including respiration, phonation, resonance, articulation and prosody are affected. The question is what kind of dysarthria do we find in PSP?

Background: Until now it remains unclear, if the dysarthric characteristics of PSP vary in way as described by Williams et al. (2005, 2007) who found clinically distinct symptom patterns of a parkinsonian form of PSP (parkinsonian Type) distinct from a classical form (Richardsons type) and a special third type of pure akinesia with gait freezing (PAGF).

Methods: In a multi center study, we analyzed the the speech impairments of patients suffering from PSP. The "Bogenhausener Dysarthrieskalen" (BoDys) was used as baseline dysarthria scale.

Furthermore, the intelligibility is a most important index of functional impairment in dysarthria. Therefore, the "Munich Intelligibility Profile (MVP)", a computer-based method for the assessment of the intelligibility of dysarthric patients, was used to describe the intelligibility of the patients.

Results: The results show that the patients with PSP generally suffer from severe and more progressive speech impairments beginning early after disease onset, whereas the PD group showed rather moderate symptoms over a long period of time. Moreover, the patterns of the PSP speech disturbances varied in terms of various dysarthric symptoms.

Conclusions: Further investigation is needed to define the special kind of dysarthria in PSP. The most challenging problem at the moment is to find a profile of dysarthria in PSP to further develop training strategies considering the different components of the speech impairment including the resources. The detailed description of the dysarthria in PSP could eventually be a "red flag" for differential diagnosis.

We-282

Successful liver transplantation in a patient presenting Wilson's disease with severe neurological impairment

W. Meissner, M. Neau-Cransac, J. Saric, J.-M. Trocello, F. Woimant, V. De-Ledinghen (Pessac, France)

Objective: To describe a Wilson's disease (WD) patient who presented severe neurological impairment with dramatic improvement after liver transplantation.

Background: WD is a rare autosomal-recessive disorder which is characterized by a deficient excretion of hepatic copper leading to progressive overload. Neurological symptoms are the presenting feature in 40-50% of WD patients and may aggravate despite proper medical treatment. Successful liver transplantation has been described in some of these patients.

Methods: Single case observation.

Results: Clinical findings at diagnosis were mild ataxia, mild dysarthria, discrete bilateral finger dystonia, asthenia with moderate weight loss and difficulties concentrating at school. Despite treatment with chelators (trientine, D-penicillamine) and zinc, neurological symptoms worsened in one year time. Liver enzymes were moderately increased, liver biopsy disclosed mild hepatic cirrhosis and gastroscopy did not show esophageal varices. The patient eventually received liver transplantation 15 months after symptom onset. At that time, he displayed anarthria, severe dysphagia requiring feeding via a gastrostomy, parkinsonism, painful dystonia of both upper limbs, disabling postural and action tremor of both upper limbs, marked ataxia and dysmetria, as well as myoclonus. The early postoperative phase was complicated by transient graft failure, difficulties in weaning from mechanical ventilation and critical illness neuropathy. Parkinsonism, dystonia, myoclonus and anarthria rapidly improved and the patient was able walking two months after transplantation. At last follow-up eight months after transplantation, liver function was normal, the patient had mild rigidity in both upper limbs, mild postural hand tremor, discrete bilateral finger dystonia, mild lower limb dysmetria and mild weakness of right foot dorsiflexion.

Conclusions: The present case report underlines the usefulness of liver transplantation in the treatment of WD with severe neurological impairment and only mild to moderate liver disease.

We-283

Dyspnea as red flag in "minimal change" multiple system atrophy

W. Meissner, A. Vital, D. Guehl, F. Tison (Pessac, France)

Objective: To describe a patient with "minimal change" multiple system atrophy (MSA) who showed unexplained and persisting dyspnea as the initial sign of autonomic failure.

Background: MSA may resemble Parkinson's disease (PD). The presence of so-called "red flag signs" and the results of paraclinical examinations may help distinguishing MSA from PD. Respiratory disturbances are considered to be a "red-flag" sign. Moreover, obstructive sleep apnea and exertional dyspnea may be the presenting symptom of MSA. Some MSA patients present a "minimal change" variant which may misleadingly appear as PD for many years. In these patients, dopaminergic treatment remains effective for a long time and signs of autonomic failure may be missing in early stages.

Methods: Single case observation.

Results: Left-sided levodopa responsive parkinsonism with resting tremor was first observed at age 55. Dyskinesia appeared within two years of dopaminergic treatment. The patient was explored for unexplained and persisting resting dyspnea seven years after symptom onset. Blood gas analysis, respiratory function tests, ECG, transthoracic echocardiography and chest x-ray were all unremarkable. She eventually received deep brain stimulation (DBS) of the subthalamic nucleus eight years after disease onset. At the time of surgery, she had a preserved levodopa response (45% reduction of UPDRS III scores), severely disabling dyskinesia up to 25% of waking day time, without significant cognitive impairment. During the first 16 months of DBS she gained 16 kg of weight. Urinary incontinence developed during the first year after surgery, while levodopa response was still 30%. Parkinsonism rapidly deteriorated and the patient became bedridden five years after DBS surgery. She finally died 15 years after symptom onset and the diagnosis of MSA was confirmed post mortem.

Conclusions: Dyspnea may be the first sign of autonomic failure in "minimal change" MSA and should cautiously be considered in PD patients who are scheduled for DBS.

We-284

Poor mobility, falls and fractures in patients with parkinsonism

A. Michael, P. Wallis, P. Crome (Dudley, West Midlands, United Kingdom)

Objective: The objective of this study was to investigate falls and fractures in patients with parkinsonism who were admitted to hospital.

Background: Patients with parkinsonism have different combinations of bradykinesi, rigidity and postural instability. They may have poor mobility, be liable to falls and may sustain fractures.

Methods: Prospective observational study. The study included 133 consecutive patients with parkinsonism who were admitted for any reason to an UK hospital. Patients who did not fulfill the diagnostic criteria and those on the psychiatric wards were excluded. Patients were reviewed, and clinical notes studied. Data were analysed using SPSS version 11 for Windows.

Results: The study included 107 patients, who were admitted 133 times. The mean age was 79.4 years (range 52 – 95). There were 84 male and 49 female. 103 patients (77 %) had idiopathic Parkinson's disease, whereas 24 patients (18 %) had secondary parkinsonism and 6 patients (5 %) had parkinsonism plus syndrome. 17 admissions (13%) admissions were due to fractures; 12 patients (9%) had fracture neck of femur, 3 patients (2%) had fracture femur, one (1%) had periprothetic fracture, and one (1%) had fracture humerus. 15 admissions (11%) were due to poor mobility and 12 admissions (9%) were due to falls. 25 % of the admitted patients had history of previous falls. Fractures, poor mobility and falls, were responsible for 33 % of admissions of patients with parkinsonism to hospital and were the most common reason for hospital admission in this study. The average duration of rehabilitation was 19.3 days, compared to an average length of 8.5 days for rehabilitation of hospitalised patients over 65 years.

Conclusions: • Fractures, poor mobility and falls constituted 33 % of the reasons for admission of patients with parkinsonism to hospital; the most common reasons for hospital admission in the study • Patients with parkinsonism, who were admitted due to fractures,

poor mobility or falls, needed longer rehabilitation period compared to other older patients. • Bone density measurement and treatment for osteoporosis should be considered for patients with parkinsonism who are at risk of falls and fractures.

We-285

Multiple systematrophy project: A multidisciplinary diagnostic approach

D. Monaco, F. Ciccocioppo, L. Marchionne, I. Borelli, F. Anzellotti, L. Bonanni, M. Onofrj, A. Thomas (Chieti, Italy)

Objective: Since MSA passed often misrecognized in early stages, the aim of this study is to sharpen early diagnostic accuracy using compound battery made by both traditional and routinal investigations selected on the basis of new trends on psychometric assessment of patients affected by MSA.

Background: Multiple system atrophy (MSA), an atypical parkinsonism, is characterized by the presence of parkinsonism and autonomic, cerebellar and pyramidal dysfunction in different combinations. Cognitive dysfunctions are also reported.

Methods: Thirty patients referring to our Centre for Movement Disorders and Dementia who meet the Consensus Criteria of the American Autonomic Society and the American Academy of Neurology for MSA, will be evaluated regularly for a period of 12 months with the following-tests: –Clinical specific assessment (UMSRAS)–Questionnaires administered to patients (COMPASS, SF-36, SS-3)–Neurovegetative assessment–Anatomical and functional imaging (volumetric-MRI, DATSCAN-SPECT, F-DOPA PET)–Ideomotor apraxia assessment–Assessment of apathy –Sleep investigations (especially regarding the presence of daytime sleepiness and REM sleep behaviour disorder)–Peripheral immunological assessment –Transcranial sonography (figure 1) and (figure 2).

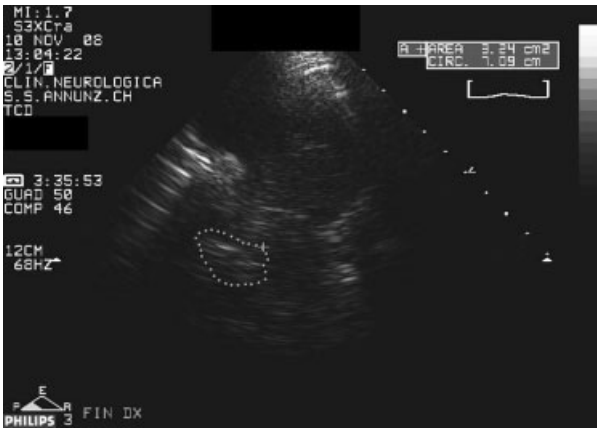

FIG. 1 (We-285).

Results: We aspect that the applicability of methodologies recently evidenced in literature, such as transcranial sonography, as first choice in differential diagnosis with Parkinson's disease and other atypical parkinsonisms as MSA and PSP, furthermore we are locking fot the confirmation of frontal dysfunctions in MSA and evaluate the severity in comparison with other Parkinson-Plus syndroms (PSP, CBS). We will describe the peculiar characteristics of apathy with purpose to differentiate it from depressive symptoms. Finally, the evaluation of possible new therapeutic approaches.

Conclusions: A multidisciplinary diagnostic approach might improve diagnostic tools to separate different Parkinson-Plus sindroms.

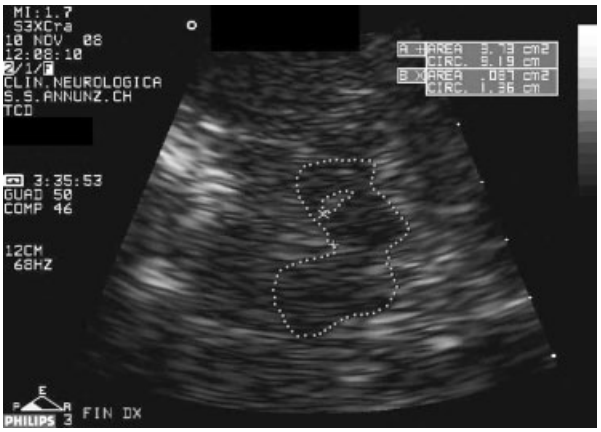

FIG. 2 (We-285).

We-286

Posterior alien hand phenomena as the first manifestation of HIV encephalopathy

R.P. Munhoz, H. Famelli, T.F. Lyra, H.A. Teive (Curitiba, PR, Brazil)

Objective: To report the case of posterior alien hand phenomena (AHP) caused by a parietal lesion secondary to HIV encephalopathy.

Background: AHP are complex movement abnormalities in which an upper limb (UL) performs complex motor activities with no volitional control. AHP are typically caused by focal lesions or degenerative disorders. Three main anatomical subtypes have been characterized: (i) a callosal form tends to give rise to "purposeful" actions in the non-dominant hand as well as intermanual conflict; (ii) a frontal form causes contralateral groping, grasping with inability to release (frontal lobe reflexes); (iii) a posterior form (parietal) leads to withdraw the palmar surface of the hand away from contact rather than reaching out to grasp onto objects.

Methods: Single case report.

Results: A 42 year old male presented progressive difficulties moving the left UL during the previous week, associated with gait ataxia and cognitive deficits (short term memory deficits, confusion, anomia and apathy). Symptoms were accompanied by moderate headache. Past medical history was remarkable for right UL fracture 12 years ago with blood transfusion. On examination, the patient was confused, MMSE was 18/30, speech was dysarthic. There was mild parkinsonism with left UL bradykinesia and left asymmetric bilateral rigidity. Left UL examination showed uncoordinated and coarsely ataxic movements, levitation backwards while distracted by contralateral movements. When the right hand was approached by an object, it tended to become extended and move away involuntarily. Ideomotor apraxia was present in the right UL. Sensation was normal. Gait was ataxic and wide based with postural instability. The left UL movements were significantly exacerbated while walking. Laboratory investigation revealed lymphopenia; cerebrospinal fluid analysis was normal, except for mildly elevated protein levels. HIV ELISA was positive. Brain MRI showed T2 weighted confluent hyperintensities involving the right basal ganglia, right parietal and left parietal areas, sparing subcortical U fibers. HAART was started and during the following weeks total improvement of AHP, significant improvement in parkinsonism and mild cognitive recovery were observed.

Conclusions: We report for the first time a case of acute HIV encephalopathy with parkinsonism, gait disorder and AHP.

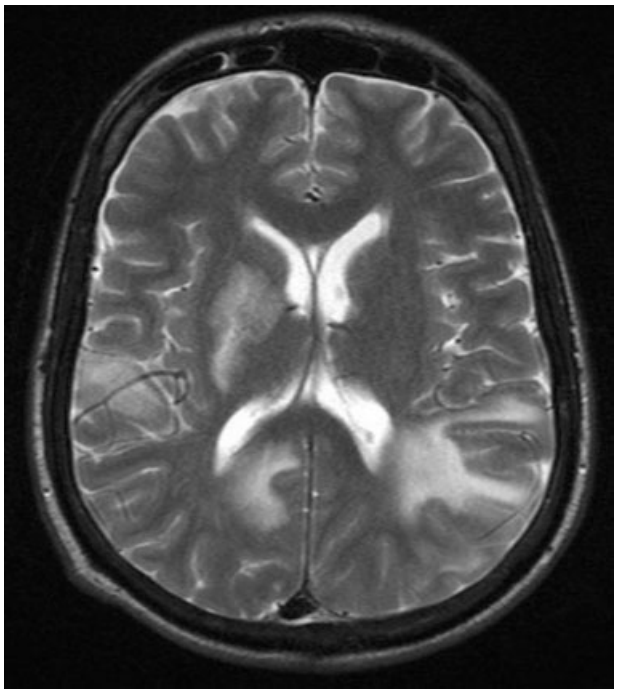

FIG. 1 (We-286).

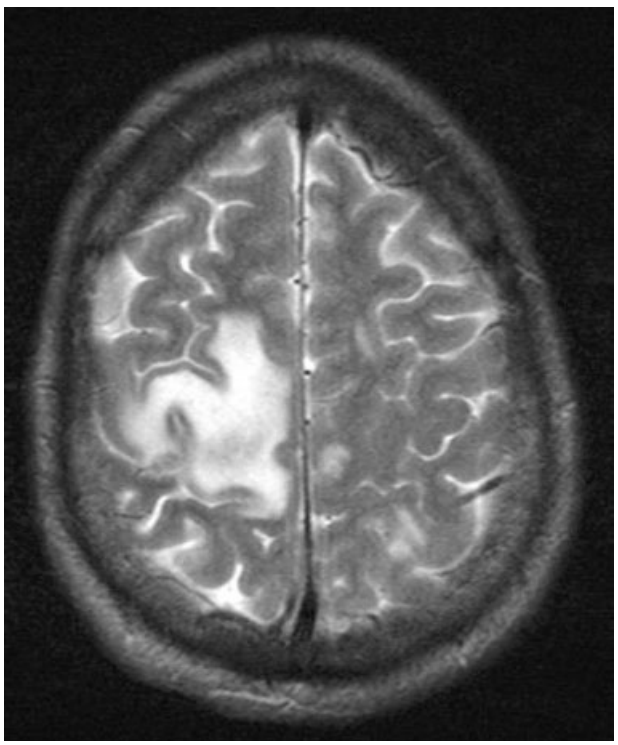

FIG. 2 (We-286).

We-287

Infectious causes of parkinsonism

R.P. Munhoz, H. Famelli, H.A. Teive, L.C. Werneck (Curitiba, PR, Brazil)

Objective: To report cases of parkinsonism caused by infectious agents (PI) in a large series of patients with a syndromic diagnosis of parkinsonism.

Background: Nowadays, infectious agents are regarded as rare causes of parkinsonism. PI most commonly occur as infectious or post-infectious parkinsonism. Seven categories of PI are accepted: (i) Von Economo's disease/encephalitis lethargica; (ii) Post-encephalitic parkinsonism of von Economo; (iii) Sporadic, postpandemic cases similar to (ii) and (iii); (iv) parkinsonism associated with known viral encephalitis; (v) parkinsonism associated with nonviral encephalitis; (vi) parkinsonism associated with non encephalitic infections; (vii) Post vaccinal parkinsonism.

Methods: We collected data from a total of 1529 patients with a syndromic diagnosis of parkinsonism systematically evaluated at the movement disorders outpatient clinic of the Federal University of Parana. Criteria for the diagnosis of PI included the presence of parkinsonism emerging during the acute or convalescent phase of an infectious process know to be a cause of PI. In all cases with a diagnosis of PI, serologic and neuroimaging studies were used to confirm the diagnosis.

Results: We found 8 (0.5%) cases with a final diagnosis of PI, including: 2 cases secondary to neurocysticercosis, 2 cases of following viral encephalitis, 2 cases related to HIV encephalopathy, 1 case secondary to neurosyphilis and 1 case related to toxoplasmosis. Six (75%) patients were male, mean age was 43.1 years, mean age of onset was 34,4 years. The only cases with a duration longer than 2 years were the two cases with post-encephalitic parkinsonism, which were follow for 23 and 42 years, with a relatively benign course. Most, (6, 75%) had a rigid akinetic presentation. Cognitive/behavioral symptoms were found in the cases of HIV encephalopathy, neurosyphilis and, one of the cases of post-encephalitis parkinsonism.

Conclusions: PI are rare causes of parkinsonism, corresponding to 0.5% of the cases followed at a tertiary hospital during a three years period.

We-288

A SPECT image analysis in patients with Parkinson's disease and Parkinson related disorders

Y.K. Nakao, A. Satoh, M. Seto, M. Ochi, M. Tsujihata (Nishisonogi-gun, Nagasaki, Japan)

Objective: Brain perfusion images were compared using an easy Z-score Imaging System(eZIS)(Kanetaka H et al. Eur J Nucl Med Mol Imaging 2004;31:975) and a Voxel Based Stereotactic Extraction Estimation(vbSEE) analysis (Mizumura S et al. Ann Nucl Med 2003;17:289) of 123I-IMP SPECT among patients with PD associated with dementia and/or hallucinations, and Parkinson related disorders [dementia with Lewy bodies(DLB), progressive supranuclear palsy(PSP), corticobasal degeneration(CBD) and a Parkinson-variant of multiple system atrophy(MSA-P)].

Background: The patterns of regional cerebral blood flow in PD and Parkinson related disorders remain inconsistent.

Methods: Forty-three patients with PD (8PD with visual hallucination, 9PD with dementia, 13PD with both hallucination and dementia, and 13 PD with neither of them), 5 with DLB, 9 with PSP, 9 with CBD, and 8 with MSA-P were recruited. In the vbSEE analysis, a greater than 20% of decrease/increase in the extent % in comparison to the control subjects was used to assess the hypoperfusion/hyperperfusion.

Results: PD patients showed a significant hypoperfusion in the medial and middle frontal gyrus (supplementary motor area), angular gyrus, inferior parietal lobule and middle temporal gyrus. Additional hypoperfusion was also seen in the visual associative cortex in PD

with hallucination and DLB. This study also showed the hyperperfusion in the striatum and cerebellum in PD. Thalamic hyperperfusion significantly increased in PD with hallucination and DLB. In PSP, a significant hypoperfusion was observed in the anterior cingulate gyrus, medial orbitofrontal cortices, medial frontal gyrus, extending to the middle frontal gyrus (prefrontal and orbitofrontal cortices), thalamus and midbrain. Hyperperfusion was also seen in the inferior parietal lobule. In CBD, hypoperfusion was observed in the precentral gyrus, medial and middle frontal gyrus, postcentral gyrus, inferior parietal lobule and thalamus. In MSA-P, hypoperfusion was found in the striatum, medial and middle frontal gyrus and cerebellum.

Conclusions: Our results conform with 18F-FDG PET studies reported previously. An eZIS and a vbSEE analysis of 123I-IMP SPECT shows detailed differences of PD and PD related disorders and may be a useful tool for a clinical examination making a differential diagnosis of parkinsonism in any hospital.

We-289

Neuropsychiatry complications after liver transplantation in a patient with Wilson's disease: A case report

E. Nikfekr, D. Nicholl (Birmingham, United Kingdom)

Objective: To report post liver transplantation psychiatric complications in Wilson's disease.

Background: Wilson's disease can be complicated with psychiatric symptoms including behaviours, mood swings, temper outbursts, depression and psychosis (1-2). However, These symptoms are rare post liver transplantation.

Methods: We report a case of Wilson's disease with neuropsychiatric complications post liver transplant.

Results: The case is a 34 year-old Caucasian woman, who was diagnosed with Wilson's disease at age 11 year old. Genetic testing later in her life confirmed that she was heterozygous for the G1266R mutation on exon 18 of ATP7B gene. Her condition remained stable for many years with only some liver impairmentan. Her liver dysfunction deteriorated further around age 26 and she developed features of extrapyramidal complications of Wilson's disease including an asymmetrical postural hand tremor which worsen with action and mild bradykinesia more obvious in the left side. There was reduced arm swing during gait. Her speech was dysarthric, but the rest of neurological examinations including cranial nerves were intact. Due to end stage liver failure and signs of mild encephalopathy she underwent a liver transplant. Her liver transplant was complicated with acute psychosis presented with behavioural changes, aggression, paranoid and grandeur delusions for which required prolonged admission and antipsychotic medications. It was thought that her acute psychosis was steroid induced and she initially improved, but did not return to her pre transplant psychological and cognitive state. In addition, she developed sever anxiety and depression which required multiple admissions to psychiatric units including admissions for self harm attempts. She was treated with neuroleptics, antidepressants and immunosuppressants. Over the last few years her mental and cognitive function have been fluctuating but mainly stable and she has been under regular neuro-psychiatric review. Her liver functions have normalised and repeat brain MRI suggested some improvement compared to pre-transplant images.

Conclusions: The current case illustrates the potential for the presentation of psychotic and depressive symptoms after liver transplant therapy. Physicians and their patients should be aware of the possibility of this complication post liver transplant in Wilson's disease.

We-290

Clinical syndromes and disease progression in progressive supranuclear palsy

D. Ottaviani, R. Elble, C. Colosimo, G. Fabbrini, A. Berardelli, D.R. Williams (Rome, Italy)

Objective: To measure the rate of change of disability in four different clinical phenotypes of PSP.

Background: Golbe's recently published PSP-rating scale is the first validated disease specific scale proposed for use in patients with PSP. Pathologicaly diagnosed PSP has been associated with four major clinical phenotypes: Richardson's syndrome/classic PSP (RS), PSP-parkinsonism (PSPP), pure akinesia with gait freezing (PAGF) and corticobasal syndrome. We sought to assess the different rates of clinical change in these groups using Golbe's rating scale (GRS).

Methods: Patients from the movements disorders clinic were selected who satisfied proposed criteria for: RS, PSPP, PAGF, or CBS. No patient satisfied the UKPDSBB criteria for the diagnosis of PD. Clinical assessments were performed at study entry and again within two years (12-24 months), and included GRS, UPDRS, MMSE, FAB and applause sign. The rate of change was compared between different clinical groups.

Results: 29 patients were initially assess assessed (RS=15, PSPP=4, PAGF=7, CBS=3) at entry. Patients with RS had significantly worse GRS scores (mean 54) than PSPP (mean 44), PAGF (mean 24) and CBS (mean 31). They also scored worse on UPDRS, FAB, MMSE and applause sign. Within two years 9 patients died (RS=8, PAGF=1, PSPP=1; 1 RS & 1 PAGF were pathologically confirmed as PSP). We report findings of 10 that have been re-examined to date. The GRS scores deteriorated by between 3 and 19 points/year. As a function of disease duration (0=disease onset), the greatest deterioration was seen in RS (10/year) and CBS (13/year). Differences at study entrey were maintained at follow-up on UPDRS, MMSE and FAB scores.

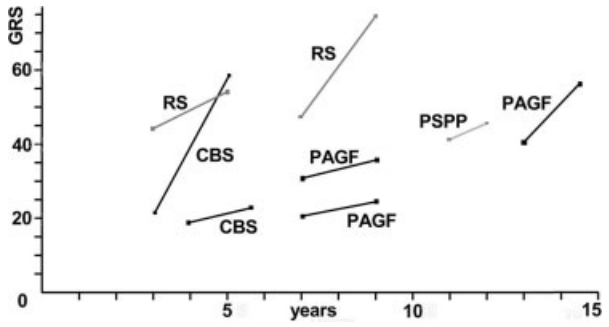

FIG. 1 (We-290).

Conclusions: RS, PSPP, PAGF and CBS have previously been differentiated clinically and pathologically. We now show that the evolution of symptoms in these syndromes occurs at different rates, having a substantial influence on disability. This documentation of dynamic differences in disease progression lends further support to the idea that pathological changes are more mild and less widely spread, and progress at a slower rate in PSPP and PAGF than in RS. Further evaluation of these changes are needed to fully inform clinicians about prognostic factors, and pathologists about pathological severity.

We-291

The spectrum of pathological involvement in Japanese patients with multiple system atrophy: A population-bound phenotype distribution

T. Ozawa, M. Tada, O. Onodera, A. Kakita, T. Shimohata, H. Takahashi, M. Nishizawa (Niigata, Japan)

Objective: To determine the spectrum of pathological involvement of the striatonigral (StrN) and olivopontocerebellar (OPC) systems in Japanese patients with multiple system atrophy (MSA).

Background: The determination of the spectrum of pathological involvement in English patients with MSA using semi-quantitative

pathological analysis (Ozawa et al. Brain 2004;127:2657–2671) has led to the hypothesis that genetic factors underlie the population-bound phenotype distribution of MSA. This perspective needs to be explored further by determining the phenotype spectrum of MSA in different ethnic groups.

Methods: A semi-quantitative pathological analysis was performed on 50 MSA patients whose brains were donated to the Brain Research Institute, Niigata University, Japan. All cases were assessed for neuronal and glial synuclein pathology according to the pathologic criteria for definite MSA. In 24 areas, chosen from both the StrN and OPC regions, the severity of neuronal cell loss was determined as previously described (Ozawa et al. Brain 2004;127:2657–2671). Clinical information was abstracted from the patients' medical records.

Results: 40% of the cases had OPC-predominant pathology, and 18% had StrN-predominant pathology, while the remainder (42%) had equivalent StrN and OPC (StrN=OPC) pathology. Cerebellar dysfunction was the initial symptom in 70% of cases with the OPC-predominant type and in 42% of cases with the StrN=OPC type. In the StrN-predominant type, parkinsonism was the initial symptom in 55%; however, 22% of this group had cerebellar dysfunction as the initial symptom.

Conclusions: This study demonstrated the spectrum of pathological involvement of the StrN and OPC systems in Japanese patients with definite MSA. In contrast to the previously reported results in English patients, the results of the present study in Japanese MSA patients showed more pathological involvement of the OPC system than of the StrN system. These results support the hypothesis that there is a population-bound phenotype distribution of MSA. Further investigation is needed to determine the genetic modifiers that account for the differences in the pathological involvements of the OPC and StrN systems in MSA.

We-292

Assessment of praxis function in patients with multiple system atrophy

S. Ozekmekci, H. Apaydin, S. Ertan, D. Uluduz, O. Erturk, G. Kenangil, E. Erginoz (Istanbul, Turkey)

Objective: To determine praxis function in patients with multiple system atrophy (MSA) by using a standardized test battery.

Background: Among Parkinson-plus syndromes, it is well-known that apraxia is one of the major manifestations of corticobasal degeneration. However, we noticed that some MSA patients exhibited apraxia on neurological examination.

Methods: 16 patients (age range 50-78 years, 68% men) with probable MSA meeting to Quinn criteria were recruited prospectively into the study. Age-matched 19 Parkinson's disease (PD) patients at Hoehn-Yahr Stage II or III and 22 healthy subjects were included as controls. Disease severity was evaluated by using Unified MSA Rating Scale (UMSARS) for MSA and Unified PD Rating Scale (UPDRS, Part I-III) for PD patients. Mayo Clinic Praxis Test Battery with a total score of 120 points was applied to all subjects. Pantomime tasks including oral/facial, trunk, upper and lower extremities for evaluation ideomotor apraxia, sequential tasks including Luria test for ideational apraxia, and use of real objects for transitive performances were tested. Additionally, Standardized Mini Mental Test (MMSE), Hamilton Depression (HAM-D) and Anxiety (HAM-A) Scales were performed in three groups. Kruskal-Wallis, Mann-Whitney-U and Chi-Square tests were used for statistical analysis.

Results: Mean ages were 68 years in MSA, 66 in PD and 63 in control groups. Mean of total UMSARS score was 39 and UPDRS was 21 in MSA and PD groups, respectively. Mean of total praxis scores were significantly differed between groups being the worst in MSA (93.5±2), followed by 112±4 in PD and 117±2 in controls (p=0.000). Comparison of mean values for MMSE, HAM-D and HAM-A test scores were also significantly differed between groups with the lowest scores in MSA group (p=0.000). As an additional finding, PD patients exhibited mild apraxia and cognitive impairment when compared to controls ($p<0.05$).

Conclusions: These results supported our observation that although not a major and a presenting symptom, apraxia may be a feature of MSA. Our results deserve further evaluation of this symptom in a blinded clinical design and among larger groups of MSA patients.

We-293

Secondary parkinsonism and intraventricular subepandimoma of the brain

N. Oztekin, F. Oztekin, S. Gencler (Ankara, Turkey)

Objective: We describe an unusual case of secondary parkinsonism who presented with parkinsonian features caused by an intraventricular epandimoma.

Background: Parkinson's disease has infrequently been described in association with intracranial tumors.Parkinsonism-like syndrome. Parkinsonism is produced more often by external masses impinging on the basal ganglia than by intrinsic infiltrating lesions.

Methods: A 61 year old male presented with symptoms of parkinsonism of one year duration in 2006. His initial symptoms wereintermittent right-hand tremor, followed by a righ foot tremor, mild bradikinesia. Neurologic examination revealed moderate rigidity in the neck, mild cogweel rigidity in both upper extremities, and both kinetic and postural tremor in the left. Cranial MRI revealed an contrast enhanced intraventricular lesion filling the corpus of of the left lateral ventricule. Subtotal excision of the lesion revealed subepandimoma. He was treated with radiotherapy which resulted compression af the lesion. But the patients complaints begin to worsen . In 2007 he was treated with pramipexole and the dose was titrated to the upper limit but there was no remarkable response. He was hospitalized in December 2008 . Neurologic examination revealed mild rigiditiy in both extremities, mild bradikinezia, postural and kinetic tremor prominent in the left. He had a mild shuffling gait and did not swing his arms. The pull test, Myerson and snout tests were all positive. Tendon reflexes were hyperactive with bilateral Babinski signs.

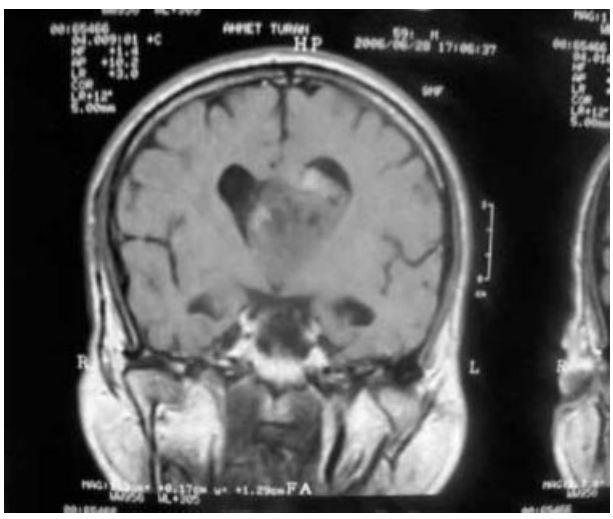

FIG. 1 (We-293).

Results: MRI scan of the brain revealed the same enhanced lesion filling the corpus of of the left lateral ventricule and extending to foremen Monro compressing the 3rd ventricule and resulting ventriculomegaly. Pramipexole is stopped and he was responsive to the test dpse of levodopa 375 mg. He was assigned to use levodopa 125 mg bid and was discharged.

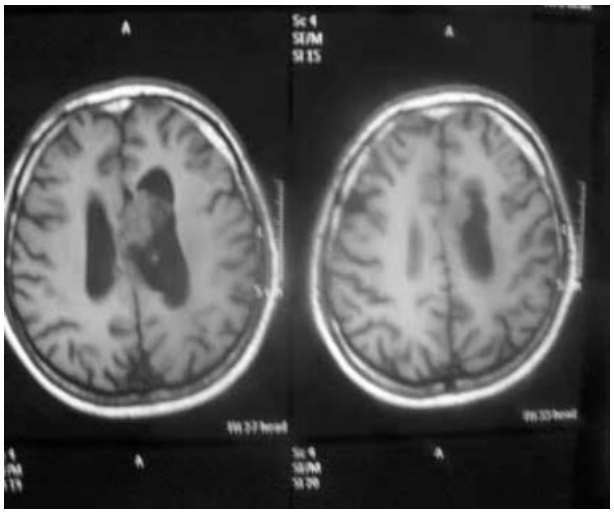

FIG. 2 (We-293).

Conclusions: The cause of this patient's parkinsonism is likely due to the direct mechanical compression of the substantia nigra and ascending nigrostriatral projections by this large mass lesion. The other proposed mechanism is midbrain compression from upward or downward transtentorial herniation.] Such herniation may result in the impairment of blood flow to the basal ganglia via the posterior cerebral artery, leading to ischemia of the subthalamic nuclei.

We-294

Juvenile parkinsonism: Clinical aspects of parkinsonism in children and adolescents

T. Pearson, M. Rotstein, R. Pons, S. Fahn (New York, New York)

Objective: To describe the clinical spectrum of parkinsonism in the pediatric and adolescent population.

Background: Juvenile parkinsonism is a rare clinical syndrome characterized by the onset of parkinsonian symptoms (rigidity, bradykinesia, postural instability or tremor) before the age of 21 years. These children and adolescents pose a formidable diagnostic and management challenge. Knowledge about the clinical manifestations, etiology, treatment options and outcome of this entity remains limited.

Methods: We conducted a retrospective review of the medical records of 40 patients with juvenile parkinsonism who were evaluated at a university-affiliated specialty movement disorders center between 1983 and 2008. Data regarding the patients' clinical features, diagnosis, response to treatment, and treatment complications were analysed.

Results: Age at symptom onset ranged from 5 months to 20 years (mean ± SD: 12.2 ± 5.8 years). The time from onset of symptoms to clinical diagnosis of parkinsonism was more than 2 years in half of the patients. A specific underlying diagnosis was identified in approximately one-third of patients. Diagnoses included mutation in the parkin gene (3), defects of neurotransmitter metabolism (3), mitochondrial disease (3), Wilson's disease (1), neuronal intranuclear hyaline inclusion disease (1), spinocerebellar ataxia type 3 (1), and pantothenate kinase-associated neurodegeneration (1). In many patients, an underlying diagnosis could not be confirmed despite extensive investigation. A notable subgroup of undiagnosed patients had parkinsonism as part of a complex neurodegenerative disease involving multiple systems. 22 of the 30 patients treated with levodopa showed a favorable response. Levodopa-induced dyskinesias and dystonia were common complications, and often occurred early in the course of treatment.

Conclusions: This retrospective study highlights the complexity of the clinical spectrum of juvenile parkinsonism. There is often a delay in the recognition of a parkinsonian syndrome since it is such an unusual clinical presentation in this age group. Additionally, in contrast to adult parkinsonism, most cases of juvenile parkinsonism are secondary to underlying diseases from an extensive list of potential causes. Medication-induced adverse effects are a significant problem.

We-295

Pregabalin-induced parkinsonism: A case report

S. Perez-Lloret, M. Amaya, M. Merello (Buenos Aires, Argentina)

Objective: We report the case of a 64-year old woman who developed full-blown parkinsonism after PGB administration.

Background: Pregabalin (PGB) is a GABA-analog which binds to the $\alpha 2$-δ subunit types 1 and 2 of the L-type voltage-dependent Ca-channel, inhibiting release of neurotransmitters such as glutamate, noradrenaline, acetylcholine and Substance P. It is useful for the treatment of neuropathy pain and some forms of seizures.

Methods: A female patient suffering from long-term diabetes treated with daily insulin injections since the age of 40, developed diabetic sensory-motor polyneuropathy and began treatment with Gabapentin 300 mg plus amytriptyline 25 mg in 1996 with acceptable pain control and without developing other neurological symptoms. In 2006, she consulted elsewhere and PGB 150 mg was added to her usual medication.

Results: Three months later she presented with monotone voice and slurred speech, slight but definitely abnormal loss of facial expression, chin tremor and moderate symmetric postural-holding and action tremor. Mild to moderate symmetric upper and lower limb rigidity, and mild symmetric slowing and reduction in finger-tapping and hand movement amplitude were also noticed. Gait was normal but slow, with evident slow and reduced arm swing. Unified Parkinson's Disease Rating Scale (UPDRS) motor score was 27/108 points. Clear link to PGB introduction as well as symmetric limb involvement and degree of affectation after two months of use, made us suspect drug-induced parkinsonism and PGB was withdrawn. Six months later the patient had almost completely recovered with a UPDRS motor score of 4/108, and three months after that, UPDRS motor score was 0.

Conclusions: Though some cases of tremor were reported in clinical trials on PGB, to our knowledge this is the first report of full-blown parkinsonism associated with PGB use. Vigilance of PGB-treated patients is recommended.

We-296

Cough and Parkinson's disease: Effects of expiratory muscle strength training (EMST)

T.E. Pitts, D. Bolser, K. Lewandowski, M. Troche, C. Sapienza (Gainesville, Florida)

Objective: To determine if EMST is a viable method for improving cough function in a Parkinson's disease population.

Background: Cough is a vital mechanism for upper and lower airway clearance, cough provides the necessary high expiratory airflows to aerosolize and remove material that cannot be moved by ciliary action. Cough is particularly important for clearing foreign material from the airway for those with dysphagia who are at risk for penetration/aspiration. Expiratory muscle strength training is a program designed to strength muscles that are necessary to produce an effective cough. Previous studies with smaller population sizes have demonstrated significant improvement in this "at-risk" population.

Methods: Sixty participants completed the study. 30 were randomly chosen to complete four weeks of an expiratory muscle strength training (EMST) and 30 were assigned to complete a similar

program with a sham trainer (which does not provide resistance on the expiratory muscles) to test the hypothesis that EMST would improve cough function. Participants cough function was tested before and after the training program. They were seated and asked to voluntarily cough into a pneumotachograph tube following three rest breaths. The task was completed three times. Measured parameters from the airflow waveform included: inspiratory phase duration (IPD), compression phase duration (CPD), expiratory phase peak flow (EPPF), expiratory phase rise time (EPRT), and cough volume acceleration (CVA) (EPPF/EPRT).

Results: A repeated measures analysis of variance was completed with a between subjects factor of group (EMST v. sham) and within subjects factor of time (pre v. post). A significant time by group interaction was found ($p=.018$) with post-hoc analyses revealing that although groups were similar in cough function at baseline, the EMST group significantly improved their cough performance over time, whereas the sham group did not.

Conclusions: EMST significantly affected voluntary cough function in a population of Parkinson's disease patients above the sham training.

We-297

Ocular movement studies yield early diagnosis in pathologically-proven atypical progressive supranuclear palsy (PSP)

A.M. Hardwick, J.C. Rucker, K. Gustaw, M.L. Cohen, R.J. Leigh, R.P. Friedland, D.E. Riley (Cleveland, Ohio).

Objective: To highlight the utility of careful analysis of ocular motility in diagnosis of atypical PSP.

Background: Diagnosis of atypical parkinsonism is often problematic. In PSP, characteristic eye movement findings may be subtle, and atypical features may lead clinicians to a false-negative diagnosis.

Methods: A 48-year-old man developed horizontal diplopia and then cognitive and handwriting impairment, behavioral changes, and uncontrolled laughter. He relinquished family finance duties. He had impaired balance but rarely fell. On exam, there was reduced facial expression, slow speech, a brisk jaw jerk, a left knee spastic catch, right hyperreflexia with clonus, 4-5 steps of retropulsion and no applause sign. Eye exam showed a 6-diopter esophoria, slow but accurate vertical saccades, and impaired vertical OKN. Later came cervical dystonia with marked bilateral shoulder elevation responding modestly to botulinum toxin. Subsequent clinical course included jaw-closing oromandibular dystonia and grunting/moaning on exhalation. MRI was normal. Tau and progranulin mutations were absent. He died of aspiration pneumonia 5 years after onset.

Results: Magnetic-search-coil eye movement recordings 18 months after onset showed slow but accurate vertical saccades, milder horizontal saccade slowing, square-wave jerks, mildly impaired vergence and pursuit, and a normal angular VOR. Repeat studies 2 years later showed slower but still accurate vertical and horizontal saccades, and impaired vergence and pursuit. Autopsy showed gross midbrain atrophy. Subcortical tau burden was very high (4 nigra, 3 caudate, 3 dentate). The midbrain riMLF (housing burst neurons for vertical saccades) also showed prominent tau accumulation. Immunohistochemical staining for progranulin and TDP-43 was negative.

Conclusions: The early age of onset, initial involvement of horizontal eye movement, jaw-closing OMD, corticospinal tract findings and accurate vertical saccades constitute an atypical presentation for PSP. Pathologic examination established a diagnosis of PSP, with prominent involvement of midbrain nuclei concerned with vertical saccades. Careful examination of the speed of vertical saccades in patients with atypical parkinsonian disorders remains the cornerstone for recognition of PSP.

We-298

Echogenicity of the substantia nigra in different types of parkinsonism-potential clinical utility. Preliminary results

K. Sadowski, M. Serafin-Król, A. Friedman (Warsaw, Poland)

Objective: To evaluate the potential clinical utility of transcanial sonography in differential diagnosis of idiopathic Parkinson's disease and atypical parkinsonism.

Background: The differential diagnosis of Parkinson's disease and atypical parkinsonian syndromes is based mainly on clinical examination. The results of initial studies indicate that midbrain abnormalities, as determined by transcranial sonography might be the useful diagnostic finding in uncertain cases. However, there is still limited amount of studies describing sonographic abnormalities in different populations and applying different ultrasound systems.

Methods: Transcranial sonography (TCS) was applied to 12 patients with idiopathic Parkinson's disease (according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria) and 8 patients with atypical parkinsonian syndrome (3 patients with multiple system atrophy according to MDS criteria and 5 patients with progressive supranuclear palsy according to NINDS-SPSP criteria respectively) to visualize the midbrain through temporal acoustic bone window and assess the echogenicity of the substantia nigra. The echogenicity of the substantia nigra was compared with adjacent brain tissue. The patients were examined using Esaote MyLab 70 XVision scanner equipped with a 2 MHz 90° sector scan. The clinical diagnosis was previously established by the experienced movement disorders specialist.

Results: 2 out of 12 iPD patients and 1 out of 8 atypical parkinsonian patients were excluded due to insufficient temporal acoustic bone windows. In 6 (60%) iPD patients and 1 (14,29%) patient with atypical parkinsonism TCS depicted hyperechogenic substantia nigra on at least one side. 1 iPD patient showed hyperechogenicity of the substantia nigra on both sides. In the remaining patients the substantia nigra was nondetectable by TCS.

Conclusions: TCS findings might be helpful for differential diagnosis of parkinsonian syndrome. TCS is a noninvasive and potentially useful additional diagnostic tool in movement disorders clinic. However, the low number of working groups employing this method and ultrasound systems being used as well as the limitations of the method itself (dependency on acoustic temporal bone windows and dependency on examiner's skills) determine the necessity for further research.

We-299

Role of vascular lesions load on neuropsychological profile of patients with parkinsonism

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Objective: To compare neuropsychological profile of patients affected by vascular lesions with and without degenerative Parkinson's disease (PD) to patients with PD alone, and to evaluate whether brain vascular lesion load is associated with neuropsychological variables.

Background: Clinically, VP is not always easy to distinguish from idiopathic Parkinson's disease (PD), although recent studies had identified some clinical aspects differentiating between VP and PD. Previous studies reported that dementia or cognitive impairment were significantly more common in patients with VP as compared to patients with PD alone. In these studies specific cognitive processes were not assessed by means of neuropsychological tasks. Therefore, neuropsychological profile in patients with VP was not fully elucidated.

Methods: Thirty-six non-demented patients with parkinsonism were divided into 3 groups according to clinical history and the presence of brain vascular lesions at a MRI scan and/or dopamine denervation as revealed by DaTSCAN. The first group included 12 patients with vascular lesions without PD (VP group); the second

group included 12 patients with vascular lesions and PD (VP+PD group); the third group included 12 patients without vascular lesions but with dopamine denervetion (PD group). All patients underwent neurological and neuropsychological assessments.

Results: The groups differed for disease duration, age at onset, and cerebrovascular risk factors. Covarying for disease duration and age at onset, VP and VP+PD groups performed worse than PD group on frontal/executive tasks. The correlation analysis showed a significant association between vascular load in hemispheric white matter and mnestic dysfunctions; a significant correlation between vascular load in both basal ganglia and in infratentorial regions and frontal dysfunctions.

Conclusions: Cerebrovascular lesions in patients with and without PD might have an important effect in determining early onset and severity of cognitive impairment.

We-300

Neuroimaging features in addicts with manganese-ephedrone exposure

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Objective: To specify neuroimaging features in manganese-ephedrone toxicity.

Background: A severe extrapyramidal syndrome developed in several young addicts in Estonia after long-term intravenous use of a home-made psychostimulant mixture consisting of ephedrone (methcathinone) with a high concentration of manganese as a toxic by-product of the synthesis.

Methods: MRI, ^{123}I Ioflupane SPECT and FDG PET of the brain were performed at Uppsala University Hospital in 2007 in four former ephedrone addicts with extrapyramidal symptoms. All patients had been drug free for at least four years.

Results: Visual evaluation of MRI did not reveal pathological signal intensities in any patient. All four patients were visually classified as having a normal pattern of ^{123}I Ioflupane uptake. Also, the striatal binding ratio and the ratio between putamen and caudate uptake were estimated as normal. All four patients showed a widespread, but not uniform, pathological pattern of FDG uptake with changes mainly located to the central part of the brain including the basal ganglia, thalami and the surrounding white matter. All but one of the pathological areas showed a decreased uptake of FDG. The only area of increased uptake was located in the white matter above the right ventricle. FDG PET in Patient 3. Decreased uptake in the left thalamus.

Conclusions: Presynaptic neurons in the nigrostriatal pathway are intact in manganese-induced parkinsonism after prolonged abstinence from ephedrone. The results of our PET study show a widespread non-uniform pathological subcortical affection of FDG uptake. Whether these brain metabolism changes are mainly manganese induced or partly related to long-term effect of ephedrone abuse is presently unknown.

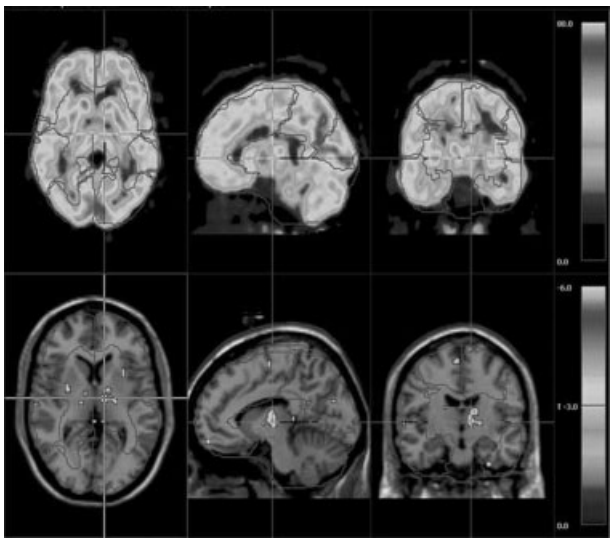

FIG. 1 (We-300).

We-301

Olfaction in progressive supranuclear palsy (PSP)

L. Silveira-Moriyama, G. Hughes, A. Church, H. Ayling, D.R. Williams, A. Petrie, J. Holton, T. Revesz, A. Kingsbury, H.R. Morris, D.J. Burn, A.J. Lees (London, United Kingdom)

Objective: To evaluate if smell identification tests can be used to differentiate patients with PSP from patients with Parkinson's disease (PD).

Background: Progressive supranuclear palsy (PSP) is frequently misdiagnosed as Parkinson's disease (PD). Previous studies have raised the possibility that testing olfaction might help to differentiate the two conditions.

Methods: We used the 40 item University of Pennsylvania Smell Identification Test (UPSIT) to test olfaction in 37 PSP patients (21 men and 16 women) who scored more than 18 in the Mini Mental State Examination (MMSE), 140 non-demented patients with PD (83 men and 57 women) and 126 control subjects (63 men and 63 women). PSP patients were also assessed using the Frontal Assessment Battery (FAB) and the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS Part III).

Results: Mean UPSIT scores were higher in the control than in the PSP and PD groups ($p<0.001$) and higher in the PSP than in the PD group ($p<0.001$) after adjusting for age, gender and smoking history. ROC curves showed suboptimum sensitivity and specificity for the UPSIT in differentiating PD and PSP.

Table 1. (We-301). Best combinations for reliability measures for the UPSIT in the diagnosis of PSP in parkinsonian patients with either PSP or PD

CUT-OFF	Sensitivity	Specificity
17	81.1	55.8
18	78.4	60.5
19	75.7	65.1
20	64.9	73.3
21	59.5	75.6

Cut-off values are inclusive and a higher UPSIT score indicates diagnosis of PSP as opposed to PD.

For PSP patients UPSIT scores correlated with MMSE (Spearman's rho=0.44, p =0.006) but not with disease duration (p=0.6), UPDRS (p=0.2) or FAB (p=0.5). The diagnosis of PSP was confirmed in all six cases who died after the study and underwent post-mortem.

Conclusions: Our study confirms that smell test scores are significantly different in PSP and PD. In the PSP group the UPSIT score strongly correlated with MMSE, indicating that the poor performance might in part relate to cognitive deficit. Although UPSIT scores were significantly different between PSP and PD, the test

alone is not a reliable discriminator due to limited sensitivity and specificity.

We-302

Olfactory heterogeneity in LRRK2 related parkinsonism

L. Silveira-Moriyama, R.P. Munhoz, M. de Jesus Carvalho, S. Raskin, E. Rogaeva, T.S. Moriyama, P. de Carvalho Aguiar, R.A. Bressan, O.G.P. Bassotini, L.A. Andrade, R. Ranvaud, E.R. Barbosa, H.A. Teive, A.J. Lees (London, United Kingdom)

Objective: To evaluate olfaction in LRRK2-related parkinsonism.

Background: Mutations in PARK8 (LRRK2) are associated with autosomal dominant parkinsonism. Previous studies of olfaction in clusters of LRRK2 cases revealed mixed results, and a larger cohort from our group including 19 LRRK2 parkinsonian patients revealed hyposmia. Lewy bodies have been found in the rhinencephalon of LRRK2 patients.

Methods: The 16 item smell identification test from Sniffin Sticks (SS-16) was used to evaluate olfaction in 8 parkinsonian carriers of the G2019S mutation and compared with that of 106 sporadic PD patients and 118 healthy controls.

Results: The mean UPSIT score in G2019S parkinsonian carriers was non-significantly to marginally significantly lower than that in healthy controls ($p=0.07$) and significantly higher than that found in sporadic PD patients ($p<0.001$) when adjusted for age, gender and smoking. See Figue 1. Figure 1 SS-16 scores in PD, PARK8 and control subjects. The median (the horizontal line) is within the box containing the central 50% of the observations (i.e. the upper and lower limits of the box are the 75th and 25th percentiles, respectively): the extremes of the 'whiskers' contain the central 95% of the ordered observations.

Conclusions: Odor identification is heterogeneous in LRRK2 G2019S mutation parkinsonism. Previous reports described pleomorphic pathology in LRRK2 including Lewy body disease and tau accumulation. Further studies of larger cohorts of LRRK2 patients are needed to investigate the underlying reasons for diversity of olfactory function in LRRK2 patients.

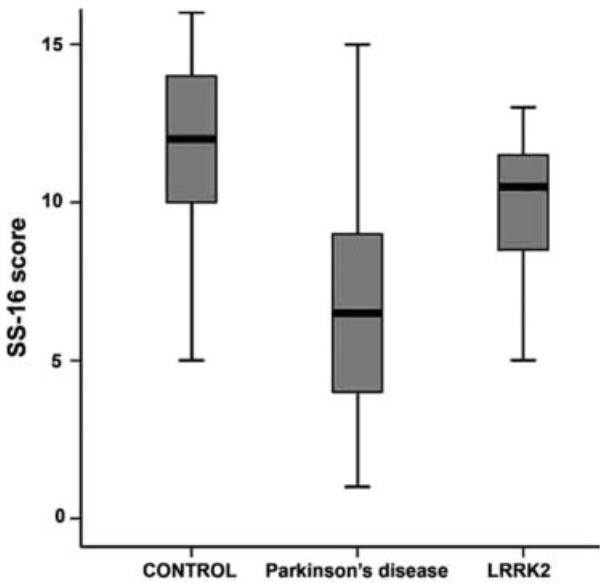

FIG. 1 (We-302).

We-410

A novel presentation of Bickerstaff's brainstem encephalitis with parkinsonism and anti-asialo GM1 antibodies

M. Mathur, K. Dombrowski, A. Jalil, G. Rakocevic, D. Kremens, T.-W. Liang, A. Zangaladze (Philadelphia, Pennsylvania)

Objective: Bickerstaff's brainstem encephalitis (BBE) is a rare post-infectious inflammatory disease that attacks the rhombencephalon and has a spectrum of symptoms including ophthalmoplegia, ataxia, alteration in consciousness or other evidence of central nervous system involvement. We present a case of BBE with parkinsonism in a patient found to have antibodies not previously associated with this condition.

Background: A 31 year-old man presented with rapidly progressive gait imbalance, paresthesias, and blurred vision. Two weeks prior, he had non-bloody diarrhea and fevers to 101F that resolved with Ciprofloxacin. The patient's symptoms began with clumsiness and bilateral feet and perioral paresthesias. Within three days he required assistance to walk due to ataxia and was experiencing dysarthria. Upon admission, the patient was alert with dysarthric speech, delayed saccadic eye movements, dysmetria bilaterally and gait ataxia. His condition worsened during hospitalization when he developed an agitated delirium, ophthalmoplegia, extensor plantar responses, bradykinesia with rigidity and bouts of opisthotonus. After an extensive workup the patient was diagnosed with BBE when he was found to have positive Campylobacter jejuni titers and anti-asialo GM1 antibodies. His exam improved with Methylprednisolone and IVIG, and within one month returned to baseline.

Conclusions: BBE is believed to be part of the clinical spectrum of Guillain-Barre and Miller Fisher Syndrome. These typically occur after an antecedent infection, have similar laboratory findings, and can have anti-ganglioside antibodies on immunological testing. Various infectious agents have been implicated including C. jejuni, as in our patient. BBE is frequently found to have antibodies directed against GQ1b, GT1a, and less commonly GM1 gangliosides. In our case, we suspect the ganglioside antigens are most likely targeted due to cross immunoreactivity with lipo-oligosaccharides of C. jejuni. Anti-asialo GM1 antibodies have also been reported in GBS and its variants as well as multifocal motor neuropathy. We report this patient as a novel example of parkinsonism with Bickerstaff's brainstem encephalitis in association with anti-asialo GM1 antibodies.

We-411

Severe parkinsonism in acute monoxid carbone intoxication

M.A. Rafai, N. Midafi, F.Z. Boulaajaj, B. El Moutawakkil, I. Slassi (Casablanca, Morocco)

Objective: To report case of severe parkinsonism and apathia in acute CO intoxication with typically neuroimaging aspect.

Background: Acute toxic encephalopathy by poisoning to carbon monoxide (CO) is frequent, serious and unknown. Magnetic resonance imaging is of great interest for positive diagnosis while characteristics abnormalities.

Methods: We report a case of a 47 years old woman, admitted for an acute, accidental poisoning to carbon monoxide. The check up on admission found a conscious patient, very anxious with a generalized akineto-rigid syndrome.

Results: The Brain MRI showed typical a symmetric and bilateral pallidums and locus niger hyper-signal. Normobare oxygenation was administered associated a symptomatic treatment (L-Dopa, Peribedil, Piracetam, anxiolytic and anti-depressor drugs) with a stationary motor evolution and thymic improvement.

Conclusions: Typical parkinosian syndrome during intoxication to the CO is rarely documented. However the neuroimaging (Scan, Brain MRI) is very specific showing bilateral gray nucleus signal abnormalities.

We-412

Is arm dystonia in corticobasal degeneration more common on the non-dominant side?

A.Q. Rana (Toronto, Canada)

Objective: We wanted to study the relation of arm dystonia in corticobasal degeneration with handedness.

Background: Corticobasal degeneration is an infrequent cause of atypical parkinsonism. Unilateral arm dystonia may be the presenting symptom in some patients. So far no definite know association has been reported between the side of arm dystonia in corticobasal degeneration and the handedness of patients.

Methods: We did chart review of corticobasal degeneration patients seen in our Parkinson's disease clinic. Four of the patients with corticobasal degeneration seen in our clinic presented with unilateral arm dystonia.

Results: All four of these patients with corticobasal degeneration we had seen were right handed. All of them had developed arm dystonia on the left side(non-dominant side)with typical rigid stiff arm presentation making their left arm useless.

Conclusions: Although number of our patients was very small and this correlation may just be incidental. But this does raise a question, is arm dystonia seen in corticobasal degeneration more common on the non-dominant side? Further observational studies are needed to establish any correlation like this if it ever exists.

We-413

Combination of blephrospasm and apraxia of eye lid opening in progressive supranuclear palsy and its treatment

A.Q. Rana (Toronto, Canada)

Objective: To discuss the coexistance of blephrospams and apraxia of eye lid opening in Progressive supranuclear palsy and its response to botulinum toxin as shown by this interesting case of a patient with PSP who had combination of both blephrospasm and apraxia of eyelid opening and did not respond to Botox.

Background: Some patients with PSP may have apraxia of eye lid opening and others may have blephrospasm. Any of these conditions when present in patients with PSP responds well to botulinum toxin. The combinations of both blephrospasm and apraxia of eyelid opening in PSP is infrequent. The patients with coexisting blephrospasm and apraxia of eye lid opening with PSPS usually do not respond well to Botulinum toxin and may require partial myomectomy in addition to botulinum toxin treatment as the combination of these two treatments is superior to single intervention.

Methods: We report a case of a 67 year old male with progressive supranuclear palsy who had blephrospasm initially and was injected with Botox. He had no response on high dose of botox and was noted to have developed features of aparxia of eyelid opening in addition to blephrospasm and was referred for partial myomectomy.

Results: MRI brain was normal.

Conclusions: About 10-30 % of the patients with atypical parkinsonism and blephrospam who don't respond to Botulinum toxin have underlying apraxia of eyelid opening and combination of partial myomectomy and botulinum toxin ihas been shown better than single intervention. Therefore, patients with PSP who are being treated with blephrospasm and don't respond well shoudl be carefully assessed for apraxia of eyelid opening.

We-414

Multiple system atrophy – Diagnostic in routine clinical practice

S. Skutilova, J. Bednarik (Brno, CZ, Czech Republic)

Objective: Authors present group of 11 patients with the diagnosis propable MSA either striatonigral degeneration type or sporadic olivopontocerebellar atrophy type. MSA is often misdiagnosed and in the beginning of the disease is often mistaken for Parkinson's disease.

Background: The diagnosis is especially determinated by the clinicla finding–parkinson features and or cerebellar features and or autonomic dysfunction, but it is possible to use some examinations giving support to diagnosis of MSA.

Methods: Authors compare results of available examinations: Anal sphincter EMG, testing of autonomic nerve system, brainstem auditory evoked potentionals, brain MRI, neuropsychologic examintation and response to L-Dopa.

Results: EMG of anal sphincter: in 63,7% abnormal finding Testing of autonomic nerve system: in 72,7% abnormal finding BAEP: in 9,1% abnormal finding Brain MRI: brainstem and cerebellar atrophy present in 18,2% Dementia: present in 9,1% No response to L-Dopa present in 72,7% patients.

Conclusions: In routine clinical practise the diagnosis of probable MSA is determined by a/ clinical finding and it's progression b/ poor or no response to L-Dopa c/ abnormal finding at anal sphincter EMG and testing of autonomic nerve system and absence of cognitive impairment.

Th-287

The runny nose sign in multiple system atrophy

R.M. Simoes, A. Constantino, D. Houghton, E. Gibadullina, I. Litvan (Amadora, Portugal)

Objective: The aim of this study was to evaluate the prevalence, characteristics and time of onset of idiopathic reactive nonallergic noninflammatory rhinitis (RR) in multiple system atrophy (MSA).

Background: RR, also called vasomotor rhinitis, is believed to reflect dysfunction of the autonomous nervous system. Its prevalence in Parkinson's disease was recently shown to be higher than in healthy controls.

Methods: Case-control study including 38 patients fulfilling the 2nd consensus criteria for possible or probable MSA and 38 age and sex-matched healthy controls. RR was defined as a recurrent episodic watery rhinorrhea not triggered by allergenic or infectious conditions and with not other apparent etiology. Subjects were administered a standardized interview (by phone or face-to-face) and charts were retrospectively reviewed to characterize the disease.

Results: RR was 2.2 times more frequent in MSA patients than in controls ($p=0.01$). MSA and controls did not differ in co morbidity, except for diabetes ($p=0.001$) which was more common in the MSA group but not related to RR. RR in MSA patients was independent of age, gender, disease duration or severity, MSA motor type, first MSA symptom (whether dysautonomic or motor), cognitive status, co morbidity or medications. Onset of RR was $3,3 \pm 2,2$ years after onset of motor symptoms in 14/18. Skin vasomotor abnormalities were the only dysautonomic feature associated with RR ($p=0.02$). The most common trigger was ingestion of food, regardless of the type of food or its temperature. There were no between-group differences in other triggers.

Conclusions: There is an increased prevalence of a gustatory runny nose in patients with MSA that develops in close temporal relation to motor symptoms. We propose that a runny nose in MSA may be an additional dysautonomic expression of the disease. The association to skin vasomotor changes suggests a specific dysfunction of the sympathetic pathways. These results should be confirmed in future research as the small sample size limits the interpretation of our findings.

Th-288

Objective measurement of different aspects of hypokinetic dysarthria in patients with progressive supranuclear palsy (PSP) as compared to patients with Parkinson's disease (PD)

S. Skodda, U. Schlegel (Bochum, Germany)

Objective: The aim of our study was to measure dysarthria in PSP patients in comparison with speech measures of Parkinson's disease (PD) patients in order to find characteristic differences helpful for

differential diagnosis and for understanding of the underlying pathophysiology.

Background: Besides the typical oculomotor disturbance, gait impairment and axial rigidity, patients with progressive supranuclear palsy (PSP) often suffer from "hypokinetic dysarthria" even in early stages of the diasease.

Methods: 16 PSP patients and 30 PD patients underwent a standardized reading task which was analysed by an audio software (Praat). Measurement of speech variables included first meanF0, jitter, shimmer and noise-to-harmonics ratio (nh-r) as parameters of phonation, second F0SD and F0range as parameters of intonation variablility, third articulatory rate (TSR and NSR) and speech to pause ratio (PR%) as parameters of speech velocity and last fraction of intra-word pauses (Pinw%) as parameter for articulatory precision.

Results: Jitter, shimmer and nh-R were significantly increased in PSP patients as compared to PD patients, whereas gender-based meanF0 showed only a tendency to elevation in PSP. Only in female PSP patients, F0SD and F0range were reduced as compared to the female PD patients. Furthermore, PSP patients showed a significant reduction of articulatory rate and Pinw% was reduced in PSP patients.

Conclusions: According to acoustical analysis, PSP patients' dysarthria is characterized by a disturbed phonation, a tendency to higher average pitch of voice, a decrease of speech velocity and intonation variability as well as a reduction of articulatory precision compared to age-matched PD patients. This characteristical pattern of speech disturbance may be helpful to differentiate PSP from PD. Further studies with higher sample sizes are warranted to confirm our findings and to find correlations to motor impairment and stages of disease in PSP.

Th-289

Degeneration in different parkinsonian syndromes relates directly to astrocyte type and astrocyte protein expression

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Objective: The present study aims to assess reactive changes in different types of astrocytes in Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) to determine any common relationship/s to the severity of degenerative changes.

Background: Reactive astrogliosis is associated with the upregulation of glial fibrillary acidic protein (GFAP) and morphological cell enlargement.

Methods: Formalin-fixed, paraffin-embedded brain tissue from the putamen, pons and substantia nigra was examined from 13 PD, 29 MSA, 34 PSP, 10 CBD and 13 controls.

Results: Classic astrocytic reactivity was observed in MSA, PSP and CBD but not PD, and directly correlated with indices of neurodegeneration and disease stage. About 40-45% of subcortical astrocytes accumulated pathological proteins in PD (α-synuclein) and PSP (phospho-tau) but not MSA or CBD. Protoplasmic but not fibrous astrocytes constituently expressed PACRG as well as ApoD and accumulated abnormal proteins in PD, PSP and CBD but not MSA. PACRG-immunoreactive protoplasmic astrocytes had significantly different responses and severities, which directly correlated with indices of neurodegeneration in PSP and CBD (correlated with parkin expression) but not PD. Non-reactive protoplasmic astrogliosis occurred in PD and MSA, although in PD these astrocytes abnormally accumulated a-synuclein. This suggests an attenuated response in PD and MSA, possibly due to increased levels of α-synuclein.

Conclusions: Our data shows that there is marked but variable pathology in different populations of astrocytes in these parkinsonian syndromes. In MSA, PSP and CBD astrocytic pathology directly related to disease progression.

Th-290

Olfactory function in patients with drug-induced parkinsonism and de novo Parkinson's disease

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Objective: To assess the usefulness of olfactory function test in differentiating Drug-induced parkinsonism from Parkinson's disease.

Background: Drug-induced parkinsonism (DIP) constitutes 15-60% of all parkinsonism case. DIP may be clinically indistinguishable from Parkinson's disease, particularly in the elderly. Parkinsonism symptoms in DIP usually resolve after withdrawal of offending drug, which take up a few weeks to months. However, some patients with DIP don't recover, presumably because they have underlying PD unmasked by offending drug. Therefore it is difficult to differentiate DIP from PD. It is well known that olfactory dysfunction is found in more than 70% of patients with PD. In this study, we investigated olfactory function in patient with DIP to assess its usefulness in differentiating DIP from de novo PD.

Methods: 46 patients with de novo PD, 22 patients with DIP were included in the study. They were consecutively treated at our hospital. DIP was diagnosed using the following three criteria: (1) presence of at least two among the four cardinal signs of parkinsonism, (2) onset of extrapyramidal symptoms during the course of treatment with the offending drug, (3) Improvement of symptoms after discontinuation of the offending drug. Olfactory function was assessed by the means of the Cross Cultural Smell Identification (CCSI) test, a widely used test of odor identification.

Results: The mean age was 68.6 (SD 8.1) in patients with DIP and 67.9 (SD 9.8) in patients with PD. The average duration of parkinsonian symptoms was 14.9 (SD 27.3) in patients with DIP and 23.8 (SD 34.5) in patients with PD. The mean score of Modified Columbia Rating Scale (MCRS) was 7.1 (SD 5.5) in patients with DIP and 8.8 (SD 4.8) in patients with PD. Age, duration of disease, MCRS score were not significantly different between groups. The mean score of Mini-Mental State Examination (MMSE) was 24.7 (SD 4.6) in patients with DIP and 24.2 (SD 4.4) in patients with PD, which were not significantly different. The olfactory function was significantly different between DIP and PD groups. The mean CCSI score was significantly greater in patients with DIP (9.36 ± 1.7; range 6–12) than in patients with PD (6.6 ± 2.7; range 1–11).

Conclusions: Olfactory function test by means of the CCSI may be a useful bed-side method to differentiate patients with DIP from patients with idiopathic PD.

Th-291

An atypical case of Pantothenate kinase-associated neuro degeneration presenting as late-onset parkinsonism

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Objective: To present of a atypical clinical case of PKAN.

Background: Hallervorden-Spatz syndrome (HSS) is a rare autosomal recessive disorder, characterized by juvenile-onset rapid progressive extrapyramidal manifestations and progressive intellectual impairment. The patients were associated with pathological findings included iron deposition in the globus pallidus and substantia nigra pas reticulata. The most important cause of this syndrome is a mutation in the pantothenate kinase 2 (PANK2) gene, located on the short arm of chromosome 20 (20p12.3-13). The cases in which a mutation in PANK2 is identified are termed pantothenate kinase-associated neurodegeneration (PKAN).

Methods: Case report.

Results: A 45 year-old man was presented to our center with a 10 year history of a tremor involving his both hand. His past medical history was unremarkable. There was no history of perinatal complications and his developmental milestones were normal. At his ages of 35, he developed a bilateral postural tremor to his hands and mild

slowness of speech. Symptoms worsened gradually, and he gave up working as a hairdresser due to tremor at age of 40. After then, he had similar symptoms without worsening. His oldest brother also complains of a mild tremor of both hands, and there was no other family history of neurodegenerative disease. At neurologic examination, he showed a masked face, bradykinesia and rigidity in al limbs with predominance in the right side. Postural and actional tremor occurred in his hands bilaterally and tongue tremor was also seen. During walking, he was slow of foot and his left arm swing was slightly decreased. A Brain MRI showed bilateral symmetric hypo-intensity with medial hyper-intensity in the globus pallidus on T2-weighted images. These demonstrated the 'eye-of-the-tiger' sign. Genetic analyses revealed three mutations in the pantothenate kinase 2 (PANK2) gene: 1133A>G (D268G) and 1153del(L385fs) in exon 3 and 1319G>C(R330P) in exon 4. D268G is the known mutations found in PKAN. But, the L385fs and R330P mutations have not been reported yet.

Conclusions: PKAN is resulting from PANK2 mutations. However, PKAN is not a homogeneous disease. Classical and atypical clinical presentations are known. We report an additional case of patient with atypical PKAN presenting as early-onset parkinsonism.

Th-292

Hypodipsia discriminates PSP from PD and MSA

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Objective: To evaluate the sensation of thirst in patients with progressive supranuclear palsy (PSP) compared to patients with Parkinson's disease (PD), multiple system atrophy (MSA) and healthy controls (HC).

Background: The early differential diagnosis of PSP is difficult and most of the false negative cases are attributed to PD and MSA. Some of our PSP patients reported spontaneously a reduced sensation of thirst.

Methods: Using a standardized questionnaire, we evaluated the sensation of thirst in early stage (H&Y $\leq$ 3), non-demented (MMSE $>$ 24), non-depressed (MADRS $\leq$ 7) patients with clinically probable PSP and age-/stage-matched MSA and PD patients as well as age-matched HC.

Results: 69.2% of the PSP patients (N=13; m:f=6:7; age: 62.3±3.8 yrs.; H&Y median 2.0), but only 0.0% of HC (N=13; m:f=6:7; age: 60.3±3.6 yrs.), 7.7% of MSA (N=13; m:f=6:7; age: 60.9±4.5 yrs.; H&Y median 2.5) and 7.7% of PD (N=13; m:f=7:6; age: 61.3±4.5 yrs.; H&Y median 2.5) reported a diminished sensation of thirst (hypodipsia) compared to previous years. Only 23.1% of the PSP patients, but 100.0% of HC, 84.6% of MSA and 76.9% of PD reported that they still experience an increase in their sensation of thirst as a reaction to hot weather. 84.6% of the PSP patients, but only 15.4% of HC, 30.8% of MSA and 23.1% of PD reported that they would only drink because they had to, but not because they felt thirsty. Consequently, 30.8% of the PSP patients, but only 15.4% of HC, 7.7% of MSA and 15.4% of PD reported that they would now drink less than in previous years. Most PSP patients reported that the sensation of thirst would have changed before (55.6%) or with (22.2%) onset of the motor symptoms. 88.9% reported no progressive worsening of this symptom since onset. They reported no association of the onset of hypodipsia with dysphagia (100%), with functionally relevant impairment of locomotion (84.6%) or with the introduction of new medication (87.5%).

Conclusions: In summary, we report hypodipsia as a previously unrecognized symptom in PSP. Since hypodipsia occurs frequently and early in PSP, but is only rarely observed in age-matched HC, PD and MSA, it might prove helpful in the early differential diagnosis of PSP.

Th-293

Transcranial brain sonography findings in discriminating between idiopathic Parkinson's disease and atypical parkinsonism

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Objective: To study the use of transcranial brain sonography in excluding the diagnosis of idiopathic Parkinson's disease in patients with sporadic parkinsonism.

Background: Transcranial brain sonography findings of substantia nigra and lenticular nucleus discriminated between idiopathic Parkinson's disease (PD) and atypical parkinsonian disorders.

Methods: All patients with parkinsonism admitted to our movement disorder clinic from January 1, 2007, through December 31, 2008, who fulfilled clinical diagnostic criteria for PD (150 patients), probable progressive supranuclear palsy (PSP) (32 patients), probable parkinsonian variant of multiple-system atrophy (MSA-P) (18 patients) and 60 control healthy subjects were prospectively studied with transcranial brain sonography by an investigator blinded to clinical diagnoses.

Results: Substantia nigra hyperechogenicity indicated PD rather than atypical parkinsonian syndrome (sensitivity, 89%; specificity 821%; positive predictive value, 94%). Substantia nigra hyperechogenicity was present in 5/60 (8.3%) in normal healthy subjects. Marked hyperchogenicity was found in 94.4% (17/18) patients with YOPD in comparison to 73.5% (97/132) with classical PD (Mann-Witney U test, p=0.045). Third-ventricle dilatation of more than 10mmin indicated PSP rather than PD (sensitivity, 87%; specificity, 91%; positive predictive value 87%). Normal echogenic substantia nigra indicated atypical parkinsonian syndrome (MSA-P or PSP) rather than PD (sensitivity, 82%; specificity, 89%; positive predictive value, 72%). Normal echogenic substantia nigra in combination with lenticular nucleus hyperechogenicity indicated atypical parkinsonian syndrome (sensitivity, 62%; specificity, 98%; positive predictive value, 91%).

Conclusions: Distinct transcranial brain sonography findings can exclude the diagnosis of PD in patients with sporadic parkinsonism. Increased echogenicity of the substantia nigra is predictive for idiopathic PD whereas a low echogenic substantia nigra, particularly when combined with a hyperechogenic lentiform nucleus, strongly suggests an atypical parkinsonian syndrome.

Th-294

Mechanism of the cerebrospinal fluid removal test responsible for improving the gait disturbance in patients with iNPH, as evaluated using the XeCT-CBF method

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Objective: To evaluate changes in the regional cerebral blood flow (rCBF) of idiopathic normal pressure hydrocephalus (iNPH) patients after cerebrospinal fluid (CSF) removal.

Background: Gait disturbance is a cardinal symptom of iNPH and is characterized by a rapid resolution after the removal of a small amount (30 mL) of CSF. Improvement in the microcirculation within the deep white matter compressed by the enlarged lateral ventricles has been speculated, but not verified, to be a major mechanism. As increases in rCBF are coupled with functional activation of the brain, evaluating whether the change in rCBF is a cause or a consequence of the resolution of the gait disturbance is difficult. In the present study, we measured the rCBF of iNPH patients immediately after CSF removal to exclude secondary changes in rCBF.

Methods: The CSF removal test was performed in 17 patients suspected of having iNPH between April 2005 and September 2007 at Keio University Hospital. Gait disturbance was evaluated using the "timed get-up-and-go" test (in seconds). rCBF was measured using the XeCT-CBF method 2 days ahead and/or immediately before CSF

removal. After CSF removal, all the patients remained in the same position and the rCBF was measured again within 30 minutes. The patients who showed a 10% or more reduction in time for the "timed get-up-and-go" test were defined as having a positive result.

Results: rCBF was evaluated in 15 patients; 11 of these were positive and 4 were negative for the CSF removal test. The rCBF was measured 2 days prior to CSF removal in 6 patients, immediately before removal in 5 patients, and both 2 days prior to and immediately before removal in 4 patients. In the patients with positive test results, the increases in rCBF (5-15%) were noted immediately after CSF removal in the areas of the deep white matter adjacent to the lateral ventricle and anterior frontal cortices. In contrast, patients with negative results showed decreases in rCBF in all regions of interest throughout the brain.

Conclusions: CSF removal in patients with iNPH may improve neurological dysfunction, especially gait disturbance, by enabling immediate increases in rCBF in the anterior lobe (both cortex and deep white matter) as a result of the reduction in pressure.

Th-295

Clinical and [^{123}I] FP-CIT SPET imaging follow-up in patients with drug-induced parkinsonism (DIP)

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Objective: Drug-induced parkinsonism (DIP) may develop in individuals treated with dopamine receptor blocking agents (DRBAs). DIP is clinically not easily distinguishable from Parkinson's disease because similar clinical signs may occur in both diseases. In the present study we reassessed clinical features and DAT binding in 19 of the original 32 patients (10 of Group I and 9 of Group II) after a 19- to 39-month follow-up period and tested the effects of chronic levodopa treatment in both cohorts of patients.

Background: Recently we assessed [^{123}I]FP-CIT SPET in 32 consecutive patients treated with DRBAs who had developed DIP (Tinazzi et al. Mov Disord 2008). We observed normal putamen [^{123}I]FP-CIT SPET binding in 18 patients (Group I) and reduced in the remaining 14 (Group II).

Methods: A total of 19 out of 32 patients (10 out of 18 patients of Group I and 9 out of 14 patients of Group II) underwent to a clinical (UPDRS III) and SPECT-DaT Scan re-assessment.

Results: In Group I, [^{123}I]FP-CIT SPET was still normal in all patients at follow-up; DAT binding and UPDRS motor score values did not differ from baseline. In Group II, [^{123}I]FP-CIT SPET was still abnormal at follow-up. Putamen DAT binding was significantly reduced and UPDRS III score higher compared to baseline. Levodopa treatment improved motor symptoms in 3 out of 10 patients of Group I and in 8 out of 9 patients of Group II. No adverse psychiatric effects were observed in any of the patients.

Conclusions: The present study shows that DAT binding imaging may help to identify subjects with DIP secondary to a loss of dopamine nerve terminals in the context of a progressive degenerative parkinsonism. Patients with DIP may benefit from levodopa therapy, particularly when dopamine nerve terminal defects are present and this should be considered in the therapeutic management of these patients.

Th-296

Parkinsonism in HIV-infected patients on highly active antiretroviral therapy

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Objective: To report three patients with relatively young onset parkinsonism which developed in the context of HIV infection and highly active antiretroviral therapy (HAART).

Background: HAART has significantly prolonged the lives of patients with HIV however there is emerging evidence that chronic HIV and HAART may be associated with accelerated neurodegeneration. Recent studies have demonstrated increased alpha-synuclein deposition in the substantia nigra in aging HIV-infected patients.

Methods: Clinical report of a consecutive case series examined independently by both authors.

Results: The patients were HIV-infected males aged between 44 and 55 on HAART(treatment duration 3-10 years). All developed parkinsonism with initial unilateral upper extremity rest tremor, followed by rigidity and bradykinesia and mild gait involvement. Postural stability, however, was preserved. Cognitive, oculomotor, pyramidal, cerebellar and autonomic features were absent. One patient responded well to Levodopa. In all patients parkinsonism developed and progressed in the context of effective HAART (plasma HIV viral load<50 copies/ml). Brain MRI was normal apart from reduced N-acetyl aspartate spectroscopy peaks (relative to creatine) in the caudate in two patients. In two patients cerebrospinal fluid sampled to investigate the development of parkinsonism showed low levels of HIV RNA and one had evidence of inflammation with raised neopterin and β2 microglobulin.

Conclusions: Parkinsonism may occur early in HIV infection reflecting viral infection within the basal ganglia or late in the disease course in combination with HIV dementia. The pattern of parkinsonism in the present series differs from these existing reports: i) patients had chronic HIV infection with viral suppression in the plasma and minor replication in the CSF when symptoms developed, and ii) none had features of dementia. We hypothesize that chronic HIV infection with very low level replication and HAART, particularly protease inhibitors, may predispose to neurodegeneration through persistent low level inflammation, mitochondrial dysfunction and interference with the ubiquitin proteasome pathway.

Th-297

Patient-based evaluation of autonomic failure (AF) symptoms by the SCOPA-AUT scale in multiple system atrophy (MSA)

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Objective: To evaluate AF symptoms through the auto-questionnaire SCOPA-AUT (french version) in MSA patients.

Background: In MSA, AF constitutes the core of the diagnosis of MSA. The SCOPA-AUT (the SCales for Outcomes in PArkinson's disease for SCOPA and autonomy for AUT) has been proposed as a patient-based evaluation of the symptoms of AF in Parkinson's disease (PD).

Methods: Study 1 analyzed SCOPA-AUT in five groups of consecutive in-patients. Study 2 analyzed the SCOPA-AUT compared to the UMSARS (MSA severity) scale in a selected group of MSA patients. Study 1 was a descriptive prospective study of the SCOPA-AUT in five groups of patients who supposely have had various degrees of AF severity: 17 MSA, 17 PD, 15 patients with neuropathy, 16 patients with non-MSA cerebellar disorders, 15 patients non-PD non-MSA parkinsonian syndromes. The goal was to identify differences between these groups. Study 2 compared retrospectively the SCOPA-AUT scores to the UMSARS-II scale scores in 38 MSA patients.

Results: The sexual sphere was difficult to assess by SCOPA-AUT because of the rate of non-answers. The urinary sphere showed significantly more severe scores in MSA patients. The cardiovascular domain (CV) score did not accurately distinguished between patients groups while more than 70 % of MSA patients had orthostatic hypotension (OH). There was a weak correlation (0,23 correlation coefficient) between the global score of SCOPA-AUT and age. There was a moderate correlation (0,52) between the global score of the SCOPA-AUT and the motor severity score of the UMSARS-II.

Conclusions: The SCOPA-AUT seemed useful for screening urinary symptoms in MSA but not accurate enough for differentiating CV autonomic symptoms between MSA, PD, other cerebellar and parkinsonian disorders. There was a moderate correlation between the SCOPA-AUT score and MSA severity rated by the UMSARS.

Th-298

Rehabilitation of dysphagia in progressive supranuclear palsy

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Objective: Test the effects of expiratory muscle strength training (EMST) on the swallow function of persons with Progressive Supranuclear Palsy (PSP) as compared to Parkinson's disease (PD).

Background: Swallow dysfunction in PSP is characterized by difficulty in manipulation of the bolus and reductions in swallow safety, thus leading to aspiration pneumonia, causing respiratory infection and death. No behavioral techniques targeting the swallow musculature have been studied in PSP. Furthermore, a comprehensive description of swallow disturbance in PSP does not exist in the literature, resulting in an incomplete understanding of appropriate therapeutic targets. The innovative technique proposed here for strengthening swallow muscles is physiologically based and mechanistically driven.

Methods: We are completing a blinded, randomized, sham-controlled trial to test the effects of EMST in eight persons with PSP. Following baseline testing, the participants completed four weeks of EMST or sham intervention. Swallowing was assessed as a function of training (EMST/SHAM) and bolus consistency (thin/thick). Measures of swallow safety and timing were completed. Results were compared to eight age and severity matched persons with PD.

Results: The results to date suggest a wide range of response to treatment that appear to be related to disease state and ability to coordinate the physical requirements needed to be successful in using the device. Additionally, participants' degree of cognitive impairment and spasticity of the swallow mechanism appear to be the strongest predictors of baseline functioning. When comparing the PSP and PD groups there were significant differences in swallow transit times (slower for PSP) and trends towards differences in swallow safety (less safe in PSP) before training. Despite this, swallowing related quality of life was not significantly different between groups.

Conclusions: Results support the notion that the mechanisms underlying swallow dysfunction in PSP are distinct from PD. The EMST protocol used previously in PD requires significant modification for those with PSP to receive full benefit. Continued investigation into the swallow pathogenesis in PSP is necessary to identify appropriate therapeutic targets in this population with significant morbidity secondary to dysphagia.

Th-299

Clinical patterns of idiopathic and vascular parkinsonism in Georgian population

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Objective: Parkinsonism is a common clinical entity in the elderly, that's why the recognition of its hallmark features is the important diagnostic step in establishing the exact nature of this pathology.

Background: The aim of this study was to examine the clinical picture of Parkinson's disease (PD) and vascular parkinsonism (VP) in the elderly Georgian population.

Methods: Seventy-two consecutive patients with complete follow-up and medical records for the entire observation period were recruited in 2001-2006 years from three Georgian clinical centers (Tbilisi, n=31; Kutaisi, n=20; Batumi, n=21). All patients underwent cerebral MRI. Patients were examined at baseline and after 6, 12 and 18 months using the Unified Parkinson"s Disease Rating Scale (UPDRS). Criteria for VP were: parkinsonism, presence of vascular lesions on cerebral MRI and exclusion of the other causes of secondary parkinsonism. Statistical analyses were performed using SPSS 9.0 program.

Results: We found that VP differed from PD in the following ways: an older age at onset, a predominant involvement of the lower part of the body and a higher frequency of vascular risk factors. Although PD patients had a longer disease duration, they had lower UPDRS scores at baseline than VP patients. Furthermore during 18 months period we observed significant differences in evolutionary history between the two groups of patients, with the increase of the UPDRS scores in VP than in PD patients. Most often VP can be separated from PD on the basis of the presence of additional focal signs and the absence of typical resting tremor in the upper limbs In addition, neuroimaging studies point out that VP often is characterized by small infarcts within the thalamocortical pathway rather than by frontal or striatal infarcts.

Conclusions: Careful examination of clinical history, symptoms, brain imaging and response to therapy make possible to differentiate PD and VP as two distinct clinical entities. The vivid example of this are data of our clinical investigation (Tbilisi – PD=10, VP=21; Kutaisi – PD=9, VP=11; Batumi – PD=14, VP=7), although the coexistence of PD and a cerebral vascular disease in eldery patients is not uncommon and can complicate the diagnosis.

Th-300

The nigro-striatal pathway in Creutzfeldt-Jakob disease

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Objective: Parkinsonism, chorea and dystonia are well-known clinical manifestations of CJD but lesions of the nigro-striatal pathway have never been studied thoroughly.

Methods: We performed a neuropathological study of the nigro-striatal pathway on 15 sporadic CJD (sCJD), two variant CJD (vCJD) and four controls. Eleven patients presented parkinsonism in the terminal stages of CJD and one at the onset. Two presented chorea, and 16 had myoclonus. Neurone subtype loss, distribution of prion protein (PrP) and alpha-synuclein aggregation were studied on archived autopsy materials and the results were correlated with clinical data.

Results: This study provided evidence of a nigro-striatal pathway damage in CJD. Dopaminergic neurons and striatal outflow neurons were markedly affected in sCJD, while cholinergic interneurons were spared. In CJD with chorea or myoclonus, less pre-synaptic dopaminergic loss was found than in CJD with parkinsonism. In vCJD the striatal pattern of degeneration also involved cholinergic interneurons. PrP deposits were found in the substantia nigra from 11/17 and in the striatum from all CJD cases. Lewy bodies and/or Lewy neurites were present in the substantia nigra and the striatum from three sCJD cases and one vCJD (23-year-old), thus showing that alpha-synuclein aggregation may co-exist with PrP-aggregation.

Conclusions: These findings suggest a possible pathophysiological overlap regarding abnormal protein aggregation in CJD and Parkinson's disease.

Th-301

Multiple system atrophy is not a TDP-43 proteinopathy

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Objective: To examine central nervous system tissue of multiple system atrophy (MSA) patients for evidence of pathological 43 kDa nuclear trans-activating region DNA-binding protein (TDP-43) deposition.

Background: MSA is a sporadic rapid progressive neurodegenerative disorder of adult onset and of unknown etiology, which is clinically characterized by autonomic failure, parkinsonism, cerebellar ataxia, and pyramidal signs in various combinations. Pathological TDP-43 has been shown to be the major protein in amyotrophic lateral sclerosis (ALS), frontotemporal degeneration with ubiquitin positive, tau and α-synuclein negative inclusions (FTLD-U).

Methods: We performed immunohistochemical studies of multiple central nervous system areas by means of the avidin-biotin complex

detection method with 3,3'-diaminobenzidine as chromogen and double-labeling immunofluorescence using Alexa Fluor 488 and 594 conjugated secondary antibodies. Primary antibody included phosphorylation independent and anti-phosphorylated S409/410 TDP-43, α-synuclein 303, α-synuclein 81A, and G protein-coupled receptor kinase-5 (GRK-5) antibodies, in addition to other, routine (immuno-) histochemical techniques. Antigen retrieval methods comprised heat (microwaving with citrate buffer solution) and formic acid pretreatment.

Results: We examined 29 patients with pathologically confirmed MSA including 9 female and 20 males with a median (interquartile range) age of death of 67 (60 to 74) years. We found that about one third of cases showed generally rare TDP-43 pathology. This was located predominantly in subcortical brain areas and comprised mainly dystrophic cellular processes; neuronal cytoplasmic TDP-43 immunoreactivity was encountered only exceptionally. No GRK-5 immunoreactivity was present.

Conclusions: The minor TDP-43 pathology in a subset of MSA cases may represent an age related "incidental" phenomenon. Pyramidal or the subtle neurobehavioral symptoms present in MSA appear not be due to ALS/FTLD-U like inclusion pathology but other causes such as widespread white matter degeneration or non-TDP-43 linked neurodegeneration. The primarily gliodegenerative disease MSA might follow different pathogenetic mechanisms as compared to primarily neurodegenerative diseases linked to pathological TDP-43.

Th-302

The middle cerebellar penducle in diagnostics of MSA and PSP revisited – An MRI study

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Objective: The aim of this study was to characterise the MCP in MSA and PSP using MRI-measurements of ADC and diameter, and especially to investigate the degree of asymmetry of degeneration in the MCP in the patient groups and further evaluate a possible diagnostic use of such finding.

Methods: Thirty-five patients, nine with MSA-C, 11 with MSA-P and 15 with PSP underwent diffusion-weighted MRI. One observer evaluated all examinations blinded to all clinical data. Diameter and ADC-value of both the left and right middle cerebellar peduncle were compared to clinical data. The difference (percent) in average ADC and diameter asymmetry between the left and right MCP was calculated. Two formulas were set up in the aim of expressing differences in the asymmetries between patient groups as simple comparable numbers (factors).

Results: The difference in ADC asymmetry of left and right MCP between patients with MSA-C and patients with PSP was significant ($P < 0.01$). This was also the case in comparing MSA-P and PSP ($P < 0.01$). The difference between patients with MSA-C and patients with MSA-P regarding diameter asymmetry of left and right MCP was significant ($P < 0.01$). This was also the case when comparing MSA-C and patients with PSP ($P < 0.01$). Patients with MSA-C and 3 or more symptoms had significantly lower diameter of MCP than patients with MSA-C and 2 or less symptoms ($P < 0.05$). Significant differences were found between patients with MSA-C and both patients with MSA-P and patients with PSP using formula 1 ($P < 0.01$). Significant differences were found between patients with PSP and both patients with MSA-C and patients with MSA-P using formula 2 ($P < 0.01$). The uses of both formulas in combination thus significantly discriminate between all 3 patient groups on the basis of the MRI-measurements.

Conclusions: The present study demonstrates a significant difference in degree of asymmetry in ADC and diameter measurements between AP-syndromes and presents a novel MRI-based method to help differentiate diagnosing these syndromes.

Th-303

A presumed case of dopa-responsive encephalitis lethargica (von Economo's encephalitis) in a Sub-Saharan African child

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Objective: To report a unique case of postencephalic parkinsonism in a young HIV positive African boy, seen at Moi Teaching and Referral Hospital in Eldoret, Kenya, who improved on Carbidopa-Levodopa treatment.

Background: Postencephalic parkinsonism was first described by Dr. Constantin von Economo in 1917 when he presented his clinical and pathologic findings of encephalitis lethargica (EL) before the Vienna Psychiatric Society. Originially termed the amyostatic-akinetic subtype of EL, postencephalic parkinsonism symptoms include rigidity, bradykinesia, and tremor. Multiple viruses have been associated with acute and chronic parkinsonism, to include influenza, Coxsackie, herpes, and HIV.

Methods: Video footage of the patient was obtained on and off of Carbidopa-Levodopa therapy.

Results: This 9 year-old HIV positive male initially presented with a headache and seizure. His cerebrospinal fluid cryptococcal antigen was negative, he had no exposure to tuberculosis, and his head CT was normal. He was placed on PCP prophylaxis, treated with an antiepileptic, antibiotics, and sulfadoxine and pyrimethamine for presumed Toxoplasmosis. Ten days after his initial presentation he exhibited a frozen gait, with drooling, dysphagia, and bilateral upper extremity resting tremors. After one day of Carbidopa-Levodopa therapy, he was able to ambulate without assistance, sit unaided, and had a moderate reduction in his tremors.

Conclusions: Carbidopa-Levodopa therapy may provide symptomatic benefit in postencephalic parkinsonism in HIV positive patients.

Th-304

Overlap syndromes: parkinsonism and motor neuron disease

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Objective: To review experience with overlap syndromes of motor neuron disease (MND) and parkinsonism.

Background: It has long been recognized that MND can coexist with parkinsonism in different neurodegenerative conditions. The best known of these is the amyotrophic lateral sclerosis-parkinsonism dementia complex (ALS-PDC) of Guam and the Japanese peninsula of Kii. Other syndromes include multiple system atrophy (MSA), post-encephalitic parkinsonism with motor neuron disease, DJ-1 linked Parkinson's disease-dementia-amyotrophy, frontotemporal dementia-parkinsonism-amyotrophy linked to chromosome 17, and spinocerebellar ataxia, type 3 (SCA3). In addition, parkinsonism and MND may co-exist in the absence of any of these conditions, a syndrome called Brait-Fahn disease.

Methods: Using the Columbia University Division of Movement Disorders database, we reviewed 5500 cases of parkinsonism. The cases were assessed for parkinsonism, upper motor neuron dysfunction, lower motor neuron dysfunction, autonomic dysfunction, cerebellar dysfunction, and dementia.

Results: Twenty one cases were identified. Five patients had upper and lower MND and parkinsonism without evidence of other systems involved and were diagnosed with Brait-Fahn disease. Three patients had upper MND and parkinsonism, without evidence of other systems involved, and were diagnosed with PLS and parkinsonism. Five patients had upper and lower MND and parkinsonism with dementia and were diagnosed with frontotemporal dementia-parkinsonism-amyotrophy. Five patients had MND, parkinsonism and autonomic or cerebellar dysfunction, and were diagnosed with multiple system atrophy. Three patients had parkinsonism and MND as part of a much wider neurological degeneration including dementia, brainstem dysfunction, cerebellar dysfunction and autonomic dysfunction. We describe five case reports to illustrate the clinical variations.

Conclusions: MND can rarely be found in combination with parkinsonism. There is clinical heterogeneity among these patients. Thorough neurological exam however, may increase the prevalence of the coexistence of these conditions.

Th-305

Sequential MRI changes in a Parkinson variant of multiple system atrophy (MSA-P)

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Objective: In the current study, the sensitivity of various MRI sequences and sequential changes in signal abnormalities of the dorso-lateral putamen were investigated.

Background: T2-weighted images (T2WI) of MRI or FLAIR showing signal abnormalities at the dorso-lateral putamen are well-known in association with a Parkinson variant of multiple system atrophy (MSA-P). However, reports on their sequential changes (sequences), including those detected by other recording methods, are scarce.

Methods: The subjects were 6 patients with MSA-P who have undergone MRI at least twice over a period of one year or more. All have undergone T1-weighted imaging (T1WI), T2WI, FLAIR, diffusion-weighted imaging (DWI), ADC mapping (ADC map) and T2*-weighted imaging (T2*WI). MRI was conducted a total of 17 times for these 6 patients. The 34 lesions on the right and left were examined by each imaging technique for the presence (or absence) of signal abnormalities at the dorso-lateral putamen. Some patients were also examined by susceptibility-weighted images (SWI).

Results: Among the 34 lesions, signal abnormalities at the dorso-lateral putamen were noted in 32 by DWI, 26 by FLAIR and T2*WI and 20 by T2WI. The lesions with the abnormalities detected by T2WI were also detected by FLAIR, T2*WI and DWI and the lesions with the abnormalities detected by FLAIR and T2*WI were also detected by DWI. Six lesions were detected by DWI only. At 5 lesions, abnormalities were detected by DWI, FLAIR and T2*WI but not by T2WI. When examined sequentially, abnormalities were first detected by DWI, followed by other imaging techniques thereafter. The maximum ADC of the lesions appeared to increase with time; but there were cases in which no changes were noted after having reached a certain level. Those cases that were also examined by SWI suggested that the procedure may be able to depict abnormalities of the dorso-lateral putamen more acutely than by T2*WI.

Conclusions: To depict MRI abnormalities related to MSA-P, DWI was most sensitive. For the sequence of the development of abnormalities, DWI → T2*WI or FLAIR → T2WI was considered.

Th-414

Richardson's syndrome versus progressive supranuclear palsy-parkinsonism (PSP-P): First results of a cross-sectional study

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Objective: To investigate PSP subtypes with state-of-the-art in vivo diagnostics (including neuroimaging, neuropsychological testing, eye motility and acuity measurements, accelerometry, as well as blood and cerebrospinal fluid analyses).

Background: Progressive Supranuclear Palsy (PSP) may not be a single phenotype. A recent retrospective, postmortem study (Williams and colleagues, Brain, 2005) argues for the existence of at least two different subtypes, i.e. Richardson's syndrome (RS, characterized by the early onset of postural instability and falls, supranuclear vertical gaze palsy and cognitive dysfunction), and PSP-parkinsonism (PSP-P, characterized by asymmetric onset, tremor, and a moderate initial therapeutic response to levodopa). To our knowledge, there exists no cross-sectional study which tested this hypothesis for its clinical applicability and relation to specific symptoms and findings *in vivo*.

Methods: Up to abstract submission, a total of 25 PSP patients were included. According to the clinical classification of Williams and colleagues, 10 patients were classified as RS, and 10 as PSP-P. Five patients could not be separated in one of these groups and are therefore named as RS/PSP-P.

Results: Age at study inclusion did not differ significantly between RS (66.5 yrs), PSP-P (66 yrs) and RS/PSP-P (69 yrs, $p=.43$, Kruskal-Wallis Test). Also gender and age at onset of disease did not differ significantly. Median disease duration tended to be longer in PSP-P (4.9 yrs) and RS/PSP-P (5.3 yrs) than in RS (2.8 yrs, $p=.06$). Severity of motor symptoms and cognitive deficits were similar: Median levels of the PSP Rating scale were 35 pts in RS, 34 in PSP-P, and 41 in RS/PSP ($p=.93$). Median levels of the MiniMental State Examination were also comparable between RS (27 pts), PSP-P (25.5 pts) and RS/PSP-P (24 pts, $p=.44$).

Conclusions: These preliminary data suggest that our PSP subgroups are basically comparable with those proposed by Williams and colleagues. The enrolment into this study will end in January 2009. First analyses of our supplementary diagnostics will be carried out and presented.

Th-415

Clinical comparison between atypical parkinsonism and Parkinson's disease

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Objective: To investigate the clinical characteristics of atypical parkinsonian disorders and to determine the clinical significance to differentiate Parkinson's disease.

Background: Atypical parkinsonism (AP) is caused by various neurodegenerative disorders and previously known as parkinsonism plus syndrome. The diagnosis of AP is relevant in clinical practise since prognosis and treatment of patients with these disorders differs from those with Parkinson's disease (PD).

Methods: 67 patients with parkinsonism have been enrolled in according to clinical criteria of the UKBBPD (Gibb, Lees, 1988), NINDS-SPSP (Litvan I.et al., 1996), MSA–(N. P. Quinn, 1994), DLBD–(McKeith I. G. Et al., 1996). The patients were assessed using Hoehn and Yahr stage (HY), Unified Parkinson's Disease Rating Scale (UPDRS), Schwab and England activities of daily living (ADL) score, and de Boer's Parkinson's disease quality of life questionnaire. Using the SPSS software we analyzed the clinical features of AP comparing with PD.

Results: In 67 patients with parkinsonism, 59 patients (88.0%) had PD, 3 patients (4.5%) probable multiple system atrophy (MSA), 4 patients (6.0%) probable progressive supranuclear palsy (PSP), and 1 patient (1.5%) probable dementia with lewy bodies (DLB). Patients with PSP had more late onset of disease (67.6 yrs vs. 62.5 yrs $p<0.05$), and older aged (71.1 yrs vs. 66.5 yrs $p<0.01$) than patients with PD. However there were no significant differences in disease duration, patients with AP had higher motor score on UPDRS III (40.8 vs. 33.7 $p<0.01$), and more severe HY stage (4.0 vs 2.5 $p<0.01$) compare to those with PD. Clinical feature of AP is characterized by absence of rest tremor (1.8 vs. 2.7 $p<0.05$), rapidly evolving postural instability (2.6 vs. 1.3 $p<0.01$), and predominating axial distribution of hypokinesia (10.8 vs. 5.9 $p<0.01$) and rigidity (2.8 vs. 1.7 $p<0.01$). Response to L-DOPA therapy was limited and transient. Neurodegenerative parkinsonism is associated to signs such as supranuclear gaze palsy, early autonomic failure, pseudobulbar palsy and pyramidal or cerebellar dysfunction. Parkinsonism with these disorders is rapidly progressing and leading to severe disability on ADL and PD quality of life questionnaire.

Conclusions: Critical distinctions in clinical features of atypical parkinsonism from PD require different approach in management of these disorders.

Th-416

Atipical parkinsonism associated with cirrhosis: Acquired hepatocerebral degeneration

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Objective: Acquired hepatocerebral degeneration (AHD) is a rare syndrome, characterized by movemet disorders or by neuropsychiatric manifestations, in patients with chronic liver disease. The pathogenic mechanism of AHD is still unclear.

Background: Chronic liver failure may be associated with heterogeneous neurological syndromes, including cognitive impairment, ataxia, postural action tremor and parkinsonism. These findings often occur without signs of toxic-metabolic hepatic encephalopathy and are associated with increased T1 signal intensity in the basal ganglia on magnetic resonance imaging (MRI).

Methods: Case report: A 62-year-old women presented with progressive symmetric akinetic rigid syndrome, postural action tremor, postural instability, inattention, languidness and unhappiness. The treatment with levodopa and citalopram had no therapeutic benefit. Neuropsychiatric tests showed a moderate degree of global cognitive impairment. Electroencephalogram was normal. T1 weighted MRI showed hyperintense lesions in the bilateral globus pallidus, putamen and internal capsules. Extensive blood and urinary tests were normal except for complete blood count, liver function tests and serum ammonia. Serum copper, ceruloplasmin, and urinary copper excretion for 24 hours were all within normal range. There was no Kayser-Fleischer ring on slit-lamp examination. Upper gastrointestinal tract endoscopy has been reported the presence of esophageal varices. Abdominal ultrasonography showed slightly hepatosplenomegaly and increased collateral flow. Liver biopsy specimen revealed micronodular cirrhosis. Dry copper level of liver was measured as 45μg/g and histomorphology of Wilson's disease was not found.

Results: We described here a patient with AHD who presented atypical parkinsonism without history of liver failure.

Conclusions: Cirrhosis related parkinsonism can be clearly distinguished from other forms parkinsonism of clinical, neuroradiological, and biological abnormalities. Manganese accumulation may be responsible for the imaging and clinical findings that secondary to failed hepatobiliary clearance.

Th-417

Preclinical multiple system atrophy: A neuropathological case report in a 81-year- old man with isolated REM sleep behavioral disorder

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Objective: To report the detailed neuropathological brain synucleinopathy with glial cytoplasmic inclusions (GCI) in an asymptomatic 81-year-old man, except for REM sleep behavioral disorder (RBD) since 6-7 years according to the spouse, the death being caused by an acute primary brainstem lymphoma.

Background: To date, the preclinical cases of multiple system atrophy (MSA) are rare (prevalence $<1\%$): only 2 cases in recent neuropathological series (Parkkinen et al, Clin Neuropathol 2007; 26: 276-283, Fujishiro et al, Acta Neuropathol 2008; 116:269-275).

Methods: A 81-year-old man was admitted on december 2007 for falls and slight confusional state since less than 1 month and the MRI showed an infiltrative process in the mesencephalo-diencephalic region with contrast enhancement. Surgery was excluded and the evolution under methylprednisolone led to death, 25 days later. The spouse indicated that her husband was strictly asymptomatic before december 2007, except for a short depressive episode in late september 2007 with a normal brain CT scan. She also mentioned some nocturnal features strongly suggestive of RBD (soccer playing, struggling, falling off bed).

Results: Postmortem analysis showed a diffuse non-hodgkinian centroblastic cerebral lymphoma with large B cells. Moreover, the detailed neuropathological brain examination showed a moderate neuronal loss with gliosis and numerous oligodendroglial and neuronal cytoplasmic inclusions with neurites labelled with alpha-synuclein within medulla, pons, cerebellum and dentate nucleus. The same, more discrete, lesions were present within substantia nigra, basal nucleus of Meynert and centrum ovale.

Conclusions: As in idiopathic Parkinson's disease, the MSA has a preclinical phase, preceding the classical dysautonomic and motor signs.

Th-418

A clinical study of the effect of large volume lumbar puncture on gait in progressive supranuclear palsy

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Objective: To assess the efficacy of a single large volume lumbar puncture (LP) in improving gait in the short term in patients with the three different phenotypes of Progressive Supranuclear Palsy (PSP).

Background: There are several unpublished reports of marked improvement in the gait of patients with PSP hours to weeks after a large volume LP. Symptoms reported to improve include gait freezing and festination.

Methods: 16 patients with PSP (10, Richardson's syndrome (RS), 4 PSP-pure akinesia with gait freezing (PSP-PAGF), 2 PSP-parkinsonism (PSP-P)) underwent three metre and ten metre timed walk tests prior to and 30 minutes after a large volume LP (20–40mls). The fastest of three trials were analysed. We used a 20% change in time to indicate a clinically significant difference.

Results: The mean age of the RS patients was 69.6 years (range 63-80), and mean duration of disease was 4.8 years (2-12 years). Mean severity of PSP was 41/100 (Golbe Rating Scale-GRS). In RS the mean 3 metre time worsened by 3% and mean 10 metre time improved by 3%. A single patient improved by 30% on 10 metre time, and 9% on 3 metre time. Four of 10 patients in this group had non-significant slowing of their gait following LP. The mean age of the PSP-P patients was 71years (68-75), mean duration of disease was 4 years (3-5 years) and severity of PSP was 35/100(GRS). In the PSP-P group mean 3 metre time worsened by 2% and 10 metre time did not change. The mean age of the PAGF patients was 73 years (61-81), mean duration of disease was 6 years (4-10) and mean severity of PSP was 26 (GRS). In this group 3 metre gait time remained unchanged and 10 metre gait time improved by 2% following LP. One patient improved by 25% on 10 metre walk time, and 50% on 3 metre walk time. No patient, particularly the two with improved 10 metre walking times post LP, felt their gait had subjectively improved after the procedure.

Conclusions: This study demonstrates that for most patients with presumed underlying PSP-tau pathology, no clinically significant change in gait when timed over three and ten metres is expected following a large volume LP. Two patients (1 RS, 1 PAGF) responded with a greater than 20% improvement in the ten metre time after the procedure. It is unclear if these represent expected variability in gait, or true single case responses.

QUALITY OF LIFE/CAREGIVER BURDEN IN MOVEMENT DISORDERS

Mo-307

Long-term evaluation of quality of life provided by bilateral subthalamic stimulation in patients with Parkinson's disease

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Objective: The goals of this study were to evaluate long-term benefits in quality of life (Quol) in patients with Parkinson's disease (PD) after bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) and to evaluate the relationship between improvement in Quol and motor, cognitive and mental changes.

Methods: 103 patients who received bilateral STN stimulation implants and participated in follow-up review for at least 12 months were included in the study. 103 patients participated in a 12-month follow-up review, 49 patients in a follow-up review lasting at least 24 months and 15 patients in a follow-up review lasting at least 48 months. Patients' symptoms were assessed pre and post operatively by using the Unified PD Rating Scale (UPDRS) in the "medication-on" and "medication-off' conditions, quality of life was examined using the 39-item PD Questionnaire (PDQ-39). Mattis and MADRSscale and the Beck depression inventory were also evaluated.

Results: The UPDRS activities of daily living (ADL), the motor scores and dyskinesia were significantly improved at 12, 24 and 48 months compared with baseline scores. The perceived health condition improved, in particular ADL, stigma and bodily discomfort. Perceived health condition's variation at one year was correlated with the variation of UPDRS III off/off and with the BDI variations. BDI variations are the cause of 30% of the PDQ 39 variations at 1 year. At long term, the improvement in perceived health condition decreased. The NST stimulation tended to improve anxiety and depression excepting the MADRS at 6 months which was significantly higher. No suicidal attempt were observed in this group.

Conclusions: Depression is with the motor improvement the main factor influencing Quol in patients with Parkinson's disease treated by STN DBS at both short and long term.

Mo-308

Relationships between physical and psychological variables and quality of life in a population of adult members of the French association of Gilles de la Tourette syndrome

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Objective: This study investigated the quality of life (QOL) of Gilles de la Tourette syndrome (GTS) patients and examined the relationship between physical and psychological variables and quality of life. We expected an impairment of domains of QOL with a consistent relationship with the occurrence of comorbid psychiatric disorders.

Background: Several authors have described the clinical impact of tics and associated psychopathologies on social, psychological, educational and economic aspects in GTS patients, but only a few studies have used the term QOL and have used assessments by standardized QOL instruments.

Methods: We report our epidemiological investigation by anonymous national postal survey of QOL of members of the French Association of Gilles de la Tourette syndrome aged 16 years or older. The clinical and QOL measures were collected by 4 questionnaires: a sociodemographic and GTS-related symptoms questionnaire (patient's own subjective view about severity of tics was collected by visual analog scales), the WHOQOL-26, the FSQ, and the SCL-90 R, all validated in French language. we investigated explicitly (regression analyse) the relationships between physical and psychological variables and quality of life in adult GTS population.

Results: A total of 303 patients with GTS aged 16 years or older received by mail self-rating questionnaires. 167 (55%) completed and returned questionnaires. In comparaison to healthy general population our patient group had significantly lower scores in all domains indicating worse QOL. All above, only the psychological variables explained the highest amount of variance in all QOL domains. Tics explained only impairment of physical domain of QOL.

Conclusions: The present study has demonstrated that a relatively high part of the variance of all domains QOL scores was explained by psychological characteristicts. It is therefore important to assess individuals with GTS regarding associated conditions and, in particular, psychological comorbidities. This may can justify important treatment implications, such as the need for treating concurrently both tic and nontic-related impairments, improving functioning more so than treating the symptoms separately.

Mo-309

Management of spasticity and dystonia in children with acquired brain injury with rehabilitation and botulinum toxin A

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Objective: The aim of this observational study was to investigate the effect of a combination of botulinum toxin A (BTX-A) and rehabilitation in children with acquired brain injury (ABI).

Background: There are few reports of spasticity and dystonia management in children with ABI, most of the studies concerning children with cerebral palsy.

Methods: All children, from 2 to 20 years-old, consecutively treated in the department over a 22 month period were prospectively followed-up and clinically assessed. They suffered from ABI responsible for spasticity and/or dystonia with impairment in daily activity living, orthopaedic deformations and/or pain. Injections were performed using electrostimulation without conscious sedation. Doses of BTX-A were administred using recent recommendations. Clinical and functional improvements were evaluated at one month.

Results: 25 children aged 6.3 years-old, 33 months after the injury, were enrolled. They suffered from traumatic brain injury (12), arterioveinous malformation (3), tumor (5), ischemic stroke (3) or anoxia after purpura fulminans (2). Patients received a total of 51 injection protocols. Mean dose in a protocol were 5.41 U Botox®/kg bw (SD=2.14) for the upper limb, 7.78 U Botox®/kg bw (SD= 2.14) for the lower limb and 9.17 U Botox®/kg bw (SD= 2.86) when both limbs were treated. Combination of topic anaesthetic and Meopa® has proven satisfactory in all situations. No serious adverse event was reported. Improvement was observed concerning Ashworth scale ($p<0.0001$), command on antagonist muscles ($p=0.03$ for the tibialis anterior) and goniometry assessment ($p<0.05$). In group of minimally responsive state patients, pain relief and comfort were observed. For the lower limb, functional goals were reached. For the upper limb, Box and Blocks test showed improvement with better utilisation in daily activity living ($p<0,0001$). Overall, 35 treatment sessions led to positive results (68.6%).

Conclusions: This study demonstrated that BTX-A utilization for children with ABI is safe and feasible whatever the type of tonus disorder and the aetiology. Associated with orthosis and physical therapy, BTX-A is an interesting therapy and further research will be needed to identify the most effective therapeutic schedule (dose, delay since injury, age, etc.)

Tu-307

Quality of life in Serbian patients with Parkinson's disease

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Objective: To validate the Serbian version of the PDQ-39, while also providing additional information on the characteristics of this instrument.

Background: The Parkinson's Disease Questionnaire (PDQ-39) is a well validated British scale for the assessment of health-related quality of life (QoL) in Parkinson's disease (PD).

Methods: A total of 102 Serbian PD patients were asked to complete the PDQ-39, a disease-specific QoL questionnaire, as well as the generic, health status questionnaire (SF-36), and the 21 item Beck Depression Inventory (BDI). Neurological examination included the Hoehn and Yahr staging, Unified Parkinson's Disease Rating Scale (UPDRS)-part III, Schwab and England scale, and the Mini Mental State Examination (MMSE).

Results: Internal consistency analysis yielded a Cronbach's a of 0.83. Cronbach's a was above 0.70 for seven out of eight subscales (range from 0.73 to 0.91). A hierarchical structure of the PDQ-39 was shown, with one global higher-order factor and two lower-order factors. The strongest predictor of the QoL in PD was the presence

of depression, while motor disability (UPDRS-part III score) additionally contributed to poor QoL. Cognitive impairment has not been correlated with poor QoL. Also, QoL measures were not different between young- ($\leq$50 years) and older-onset PD patients.

Conclusions: The PDQ-39 is a reliable and valid instrument for the assessment of QoL in Serbian PD patients.

Tu-308

Is the coping style associated with quality of life in persons with Parkinson's disease ?

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Objective: We aimed to study if coping styles are associated with quality of life in persons with Parkinson's disease (PD).

Background: We hypothesized that quality of life (QOL) in persons with PD is determined partly by the way the patients cope with the disease.

Methods: Persons with PD who attended a PD-convention of the Flemish Parkinson League or who were hospitalized in the neurology department of the University Hospital Brussels, completed a number of questionnaires: a self-reported version of the Hoehn & Yahr scale, the Utrecht Coping List and the Parkinson's disease Quality of Life Questionnaire (PDQ-39).

Results: Sixty male and 37 female persons with PD responded (mean age 66.5 $\pm$ 9.9 y, mean duration of PD 10.0 $\pm$ 5.9 y). The PDQ-sum score ranged from 4 to 89/100 (mean 42.4 $\pm$16.9). Multiple regression analysis showed a significant main effect of H&Y-stage of the disease ($F=17.2$, $p<0.001$), but not of gender ($F=3.5$, $p=0.064$) on the quality of life (PDQ-39 sum score). In early stage PD-patients (H&Y I and II) the model consisting of the combination of passive coping, active coping approach and age explained 66.5 % of the variance of the PDQ-sum score. In patients with H&Y IV, passive coping explained 10.1 % of the variance the PDQ-sum score.

Conclusions: We found comparable coping styles in male and female patients with PD. Mainly in the first stages of the disease, passive and active coping styles explain a large portion of the variance of the QOL.

We-303

Pain and quality of life in mild to moderate Parkinson's disease patients

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Objective: We aimed to investigate the influence of pain on the quality of life of patients with mild to moderate Parkinson's disease.

Background: Parkinson's disease (PD) can only be diagnosed when motor symptoms occur. Despite this, there are studies that have shown that nonmotor symptoms have greater significance when assessed by quality of life measures. Pain is a part of the large spectrum of nonmotor features.

Methods: We enrolled 50 patients with established diagnosis of PD consequently hospitalized in the 1st Neurology Clinic in Cluj-Napoca, Romania. Pain was evaluated using the Visual Analogue Scale (VAS) and the Brief Pain Inventory (Romanian version). Depression was measured of the Montgomery Asberg Depression Scale (MADRS). The quality of life was assessed using the Parkinson's Disease Questionnaire (PDQ-39). Upon admission in hospital the following data was taken into account: age, gender, disease duration, disease severity on the Hoehn and Yahr staging scale, medication (daily dose of levodopa and/or dopamine agonist), concomitant diseases and other medication used.

Results: The average age of the patients was 65.71$\pm$ 9.19 years (mean severity of the disease was 2.5 on the Hoehn and Yahr scale). 60% (30 patients of 50) had chronic pain. When taking into account concomitant diseases as a possible cause of pain we noted that the most frequent were osteoarticular and cardiovascular diseases. However, 44 % of the patients considered pain to be caused by PD. The average intensity of pain on VAS was 6 on a scale from 0 (no pain) to 10 (worst pain). The intensity of pain was correlated with higher scores on PDQ-39, indicating that quality of life in PD patients is much affected by pain. Patients, who experienced pain, had also more severe depressive symptoms. No correlation between disease staging and intensity of pain was observed.

Conclusions: Pain should be thought for in any medical examination of PD patients and treated adequately in order to improve the quality of life.

We-304

The impact of young onset Parkinson's disease on quality of life and well-being

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Objective: To investigate the impact of Parkinson's disease (PD) on quality of life in Young Onset Parkinson's disease (YOPD) compared with Late Onset Parkinson's disease (LOPD) in a community based study.

Background: Although YOPD is rare, a recent community based study identified that about 1/3 of PD patients develop disease before the age of 65, and about 5% before the age of 45. The impact of the disease is likely to be different in younger patients.

Methods: We carried out a community based study to determine whether YOPD differed in measure of quality of life compared to LOPD, using the Parkinson's disease specific PDQ-39 scale. Non-motor symptoms were also studied.

Results: We studied 450 PD patients (126 cases from primary care in South Wales and 324 from secondary care in England and Wales). Of these 212 were YOPD patients (onset before 55) and 238 were LOPD (onset on or after 55). The mean age of onset was 45 and 66 years respectively. YOPD patients have significantly higher overall PDQ-39 scores than LOPD (mean score 92.8 vs 83.6, $p<0.001$) and have higher scores for emotional well-being, stigma, social support, communication and bodily discomfort items on the PDQ-39 ($p<0.001$). There was a significant difference in depression between YOPD and LOPD, with YOPD having more severe depressive symptoms (50% YOPD, 34% LOPD $p=0.003$).

Conclusions: Many factors are likely to influence quality of life in YOPD, including variation in disease severity, motor performance and the effect of work and family commitments. Non-motor, particularly neuro-psychiatric symptoms are also likely to be important. Further work will dissect the influence of these factors on the effect of disease on well-being.

Th-306

Consequences of subthalamic deep brain stimulation in patients with Parkinson's disease: The impact of coping and age on change in quality of life and motor functioning

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Objective: To determine whether coping styles predict changes in Quality of Life (QoL), motor impairment and L-Dopa induced motor complications (UPDRS III & IV) after subthalamic nuclei deep brain stimulation (STN-DBS) in patients with Parkinson's disease (PD).

Background: STN-DBS improves motor function and QoL in PD patients, but the impact of coping strategies on these evolutions have rarely been assessed.

Methods: Forty-one patients with advanced PD (29 men and 12 women; mean age: 62.0 ± 8.0; disease duration: 14.5 ± 5.7) completed self-report questionnaires assessing coping strategies (WCC-R), symptoms of depression (BDI-II), anxiety (STAI), and quality of life (PDQ-39, SF-36). Assessments were made at baseline, then 6 and 12 months after neurosurgery (M6, M12).

Results: After surgery, motor function (UPDRS III & IV), global QoL (PDQ-39) and physical component summary (PCS) of the SF-36 improved whilst mental component summary (MCS) deteriorated. The age at inclusion and the mean duration of PD were the best predictors of the global improvement of the PDQ-39 at M6 and M12 and of the PCS at M12. MCS worsened more in older patients, at M6. Coping strategies did not change during the first year post-stimulation. An increased use of problem-focused coping at baseline predicted a higher improvement in motor impairment (UPDRS III) at M12. In addition this way of coping was linked with the evolution of the global QoL, the higher this strategy, the weaker the improvement.

Conclusions: In PD, better psychological adjustment requires being able to adjust the coping to the situation, which is seldom possible for PD patients following neurosurgery. STN-DBS could produce specific disorders of the executive functions, particularly in older patients, and selectively interfere with the normal ability to slow down when faced with decision conflict. This phenomenon could interact with greater coping stability in older patients. Nevertheless, focused-problem coping could be advantageous in terms of medication adherence and health-behaviors.

Th-307

Cause and place of death of patients with idiopathic Parkinson's disease

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Objective: To identify where patients with Idiopathic Parkinson's disease (IPD) die, and the cause of death in these patients.

Background: Over recent years, guidance pertaining to palliative care provision has been produced and the importance of providing high quality palliative care to patients with IPD has been recognised. Current literature provides little data relating to cause of death in Parkinson's disease and, in particular, comparing cause of death between the various parkinsonian phenotypes. No study has previously been done to identify place of death of these patients. Such information guides service provision and helps target optimal end of life care.

Methods: After obtaining ethical approval all patients in a community-based Parkinson's disease population, registered on a Parkinson's disease database who had died between 1999 and 2006 inclusive were identified. Details were extracted from this database and further information obtained from the Office of National Statistics (ONS). Corrections were made for data classified using the ICD 9 classification (prior to 2001) in order to compare accurately with data classified using ICD 10. Trends in cause and place of death were identified. Comparative data was obtained from ONS for a control population.

Results: Of 227 patients on the database who had died, 143 were identified as having IPD according to the UK Brain Bank Criteria. The main causes of death were Parkinson's disease (29%), Ischaemic Heart Disease (12%), Malignancy (12%) and pneumonia (11%). No differences were noted between subtypes. Only 8.4% of patients with IPD died at home compared to 16.5% of the control population, with more dying in care homes. IPD was recorded on the death certificate in only 63% of patients.

Conclusions: Fewer patients with IPD are dying at home compared to the general elderly population. Reasons for this should be sought. Death certificate documentation of IPD is inadequate in 1/3 of certificates; this has implications for research. The ONS classification system appears to lead to a relative increase in classification of Parkinson's disease as cause of death, and a relative decrease in pneumonia as compared to previous literature.

RATING SCALES

Mo-310

Short and comprehensive assessment of praxis production: Reliability and validity of a new test of upper limb apraxia (TULIA)

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Objective: to evaluate reliability and validity of a newly developed test to measure upper limb apraxia (TULIA), which is comprehensive and still short to perform.

Background: Although apraxia may cause considerable disability in movement disorders, its actual contribution to motor impairment remains often uncertain. A reliable and valid assessment is therefore important both for clinical and research purposes. However, only few standardized apraxia scales are available and they do not cover all domains and semantic categories of praxis production (temporal and spatial organization of movement).

Methods: The TULIA consists of 48 items including imitation and pantomime of non-symbolic (meaningless), intransitive (communicative) and transitive (tool related) gestures corresponding to 6 subtests. Items were balanced for kinematic features. A 6- point scoring method (0-5) was used (maximum score 240). Performance was assessed by blinded raters based on videos in 133 stroke patients, 84 with left hemisphere damage (LHD) and 49 with right hemisphere damage (RHD), as well as 50 healthy subjects (HS).

Results: Mild apraxia (score < 194) was found in similar proportions of LHD (43%) and RHD (37 %) patients. By contrast, moderate to severe apraxia (score < 130) was almost exclusively found in LHD patients (25%). The clinimetric findings demonstrated mostly good to excellent internal consistency, inter- and intra-rater (test-retest) reliability, both at the level of the 6 subtests and at individual item level. Criterion validity was evaluated by confirming hypotheses based on the literature. Construct validity was demonstrated by a high correlation (rho = 0.82) with the De Renzi-Test.

Conclusions: These results show that the TULIA is a reliable and valid instrument to systematically assess praxis production. The test can be easily applied and is therefore useful in clinical practice and research. Further evaluation of the TULIA test in movement disorders is expected to identify disease-related patterns of praxis deficits and to allow the investigation of their clinical significance and neuro-anatomical basis.

Mo-311

Unified Freezing of Gait Rating Scale (UFOGS)

J. Crémers, G. Garraux (Liege, Belgium)

Objective: To present a new composite scale aimed to monitor freezing of gait (FOG) severity.

Background: Ten years after diagnosis 50% of patients with Parkinson's disease (PD) experience FOG, which can lead to very poor quality of life (1). There are several clinical tools available to assess FOG but to our knowledge none is able to fully capture the complexity of FOG and the underlying disability.

Methods: Items of the scale were selected from a list of previously published clinical questionnaires and scales. Items were selected in order to assess disability in common daily life situations and to explore different clinical aspects of FOG.

Results: The Unified Freezing of Gait Rating Scale (UFOGS) is divided in two parts: a 10-items questionnaire filled in by the patient (gait during the best state, gait during the worst state, changes in daily life activity due to FOG, longest FOG duration, start hesitation,

turning hesitation, destination hesitation, tight quarters hesitation, FOG during stressful situations and falls due to FOG) and a battery of 10 clinical tests (arising from a chair, walking forwards, turning 360°, turning right, turning left, walking to the right facing forward, walking to the left facing forward, walking backwards, stepping over an imaginary obstacle, walking while performing a dual task). Clinical tests can be easily administered in less than 10 minutes. We propose a 5 point ordinal scoring system (from 0 to 4) similar to that used in the UPDRS. The worst total score is 80.

Conclusions: The UFOGS is designed to become a practical clinimetric tool for the physician to quantify FOG. The scale still needs to be validated and studies are under way to evaluate internal consistency, inter- and intra-rater reliability and responsiveness of the current version. **Reference :** 1. Moore O, Peretz C, Giladi N. Freezing of gait affects quality of life of peoples with Parkinson's disease beyond its relationships with mobility and gait. Mov Disord 2007;22,2192-2195.

Mo-312

Sensitivity and specificity of the finger tapping task for the detection of psychogenic movement disorders

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Objective: To evaluate the ability of finger tapping tests (FTT) to objectively identify clinically established psychogenic movement disorders (PMD) within an outpatient movement disorder clinic.

Background: PMD represent a diagnostically challenging group of patients. FTTs have been used in neuropsychiatric evaluations to identify psychogenic conditions, but their use in movement disorders has been limited to the quantification of upper extremity disability in idiopathic Parkinson's disease (IPD).

Methods: We evaluated the ability of the FTT to objectively identify PMD by screening 195 individuals from a movement disorder clinic with IPD, dystonia, essential tremor, or PMD and compared them to 130 normal adults. All subjects performed six-30 second trials using alternate hands. Mean tapping scores were calculated by averaging the six-30 second trial scores. Variation of effort between trials was measured by calculating the coefficient of variation defined as the quotient of the standard deviation divided by the mean. Mean FTT scores and the coefficients of variation for all five diagnostic groups were compared with an ANCOVA analysis controlled for age. ROC curves were created for the unadjusted raw scores and the ratio of actual/predicted FTT scores (based on age in years) with acceptable cutoff scores defined as ≥ 80% specificity for the diagnosis of PMD.

Results: Mean FTT scores were inversely correlated with age ($r = -0.274$, $p < 0.001$). FTT scores for PMD subjects (mean = 41.72) were significantly lower than all other diagnostic groups after controlling for age ($F = 36.37$, $p < 0.001$). IPD subjects had the lowest scores of the remaining four diagnostic categories available for comparison (mean = 58.78) but were still an average of 17.06 taps faster than PMD subjects. The coefficient of variation was not significantly different between diagnostic groups and ranged from 6.10-11.2%. ROC analysis of the ratio of actual/predicted scores yielded the best sensitivity and specificity for PMD. A ratio of 0.670 or less of age predicted mean FTT score was 89.1% specific and 76.9% sensitive for the diagnosis of PMD.

Conclusions: We conclude the FTT is a simple, easily reproducible test which can provide supportive objective evidence for the diagnosis of PMD.

Tu-309

Graphic of UKPDRS: A practical way for the management of the Parkinson's disease

M.M. Cruzeiro, A. Pacheco, L.A. Pires (Juiz de Fora, Minas Gerais, Brazil)

Objective: This study shows the use of the UKPDRS as a parameter to the management of the therapeutics using table in excel with graphic visualization.

Background: Parkinson's disease (PD) is a degenerative condition of the motor function causing incapacitation and dependence of other people. The PD treatment has improved in the last decade with novels medications. It is possible to use some scales to observe the stage and the conditions of the motor function of the subject.

Methods: It was selected 23 subjects based on reports in the University Hospital of Federal University of Juiz de Fora (UH/FUJF). The sample was composed by nine women and 14 men. The reports with none or only one UKPDRS application were excluded. The UKPDRS was plotted on sheet in excel program containing a graphic for each patient using mental status, daily live activities, therapy complications, motor examination and global score.

Results: The age mean was 57,8 years old (51 to 92). Fourteen patients were males. It was observed improvement and impairment along the clinical history and we could modify the treatment based on UKPDRS graphic information. The best response of the treatment with drugs was observed with levodopa plus benserazide associated or not with pramipexol in intermediate stages and with isolated pramipexol in initial stages of PD. We did not use ropinirole, bromocriptine and pergolide because it did not distributed by the public health system.

Conclusions: The UKPDRS plotted in excel helped in the rapid identification of the therapeutic response and permitted establishment of standard evaluation among the resident physicians.

Tu-310

Scale for the assessment and rating of ataxia (SARA) in Friedreich ataxia patients

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Objective: To assess SARA in Friedreich ataxia (FA).

Background: Simple and appropriate rating scales are required to correctly evaluate treatment efficacy and disease progression. The Scale for the Assessment and Rating of Ataxia (SARA) was validated in patients with dominant cerebellar ataxias and had high inter-rater reliability, internal consistency, validity, and practicability.

Methods: SARA scores in genetically confirmed FA patients were evaluated and compared to ICARS (International Cooperative Ataxia Rating Scale) scores from a previous follow-up study in 107 FA patients (Ribai et al, 2007).

Results: SARA scores (n=114) were performed in 66 FA patients, once in 35 patients (53%), twice in 16 (24%), three times in 14 (21%), five times in one (2 %). On first evaluation, mean disease duration was 18.5± 9.6 years (0.8- 44); mean follow up was 1.56± 0.9 years (0.4-3.1). The mean total SARA score was 23± 10 [4.5 (n=1) to 39 (n=3)] and was higher in wheelchair users ($p<0.0001$). SARA was correlated with disease duration (n=66, $r=0.72$, $p<0.0001$) and duration to wheelchair use (n= 40, $r=0.80$, $p<0.0001$). SARA was also correlated with the length of the GAA expansion on the shorter ($r= 0.44$, $p<0.0003$) and on the longer allele ($r=0.29$, $p<0.02$). The mean annual variation of SARA scores was 1.4± 2.3 (-4.1 to + 7.5, n=48, 3.5/year with a 100 point normalized SARA scale). The mean annual variation of ICARS was of 1.2± 9.4 (Ribai et al, 2007). SARA scores increased linearly with disease duration ($p<0.0001$) and decreased linearly with age at onset ($p<0.0001$); expansion length did not influence SARA. ICARS, however, increased linearly as a function of the expansion on the shorter allele ($p<0.002$) but quadratically with disease duration ($p<0.0001$), leading to a ceiling effect for longer disease durations; in addition, the age at onset interacted with disease duration.

Conclusions: SARA is a valid measure of disease severity and picks up progression in FA patients without ceiling effect. This is a useful tool to be used in routine examinations and clinical research trials.

Tu-311

Severity ranges on the MDS-UPDRS motor examination: Comparison to CGI-severity scores

C.G. Goetz, G.T. Stebbins, V. Simkus (Chicago, Illinois)

Objective: To assess the ranges of scores on the Motor Examination (Part III) of the new MDS-UPDRS that are associated with different severities of PD, determined by the Clinical Global Impression-Severity score (CGI-S) in an outpatient practice.

Background: The MDS-UPDRS is a revision of the original UPDRS with sound clinimetric properties. To date, no study has determined the ranges of scores on the Motor Examination associated with different severity levels based on examiners' global ratings of PD burden.

Methods: A single rater experienced with the MDS-UPDRS rated sequential outpatients with PD during regular outpatient care. He collected the MDS-UPDRS Part III scores along with a CGI-S at each visit. Means and 95% CI of the means were calculated for each level of CGI-S. ANOVA model examined differences of MDS-UPDRS scores among different CGI-S levels. Secondary analyses focused on the published factors of Part III.

Results: 313 PD patients were examined with wide representation of CGI-S ratings of Mildly Ill (N=94), Moderately Ill (N=153), Markedly Ill (N=43) and Severely Ill (N=20). 3 other cases were assigned to Borderline (N=2) and Among the Most Extremely Ill (N=1). Discrete and non-overlapping means [95th CI of the means] for MDS-UPDRS Part III scores were: Mildly ill (30.9 [29.7, 33.1]), Moderately Ill (39.3 [37.5, 41.1]), Markedly Ill (52.4 [48.2, 56.5]), and Severely Ill (59.3 [53.9, 64.6]). MDS-UPDRS Part III scores were significantly different across all CGI-S levels ($F[3,305] = 55.3$, $p < 0.0005$) Examination of the 7 factors comprising Part III revealed significantly progressive increases in five factors (axial function, rigidity, right upper bradykinesia, left upper bradykinesia, and leg bradykinesia) (all p's < 0.0005). Tremor factors (rest and kinetic + posture) did not demonstrate progressive increases with increasing CGI-S scores (p's > 0.12).

Conclusions: MDS-UPDRS Motor Examination scores progress with increasing global PD clinical severity. Factors scores of axial function and bradykinesia appear to be the major components to this progressive increase, whereas tremor measures are not. These data provide preliminary guidelines of MDS-UPDRS scores that represent clinical categories of disease severity and can be used for sample size calculations involving different severity levels of PD.

We-305

Predictors of recurrent falling in healthy older adults: The importance of both executive function and gait

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Objective: To examine prospectively the relationship between executive function (EF), gait and fall risk.

Background: Falls may cause morbidity and mortality especially in the elderly population. While falls are typically multi-factorial, recent studies have demonstrated that executive function may influence gait and fall risk.

Methods: From a cohort of 264 healthy older adults, 203 (mean: 76.0±4.7 yrs) who reported no falls during the year prior to the study were investigated. Subjects were evaluated at baseline and one year later. In between falls were reported via monthly calendars. Subjects completed a computerized cognitive battery that generated aged normalized index of EF. Based on this index, subjects with the upper (better) and lower (worse) quartiles were compared (n= 103). Clinical measures included the Timed Up and Go (TUG), Dynamic Gait Index (DGI), Berg Balance Scale (BBS) and gait under single and dual task conditions.

Results: At baseline, all subjects had normal MMSE mean=28.7±1.2, with no differences between the groups (p=0.15). Fifty-four subjects (26%) had EF scores in the upper quartile (mean 111.8±4.9) and 49 (24%) were in the lower quartile (85±5.1). Small, but significant differences between the groups were observed at baseline in DGI (22.3±1.6 vs. 23.1±1.2; p=0.002), BBS (53.2±2.9 vs. 55.1±1.2; p<0.0001), and TUG (10.17±1.4s vs. 8.8±1.5s; p<0.0001) for the lower and upper quartile groups respectively, as well as comfortable gait speed (p<0.0001) and speed during dual task walking (p<0.0001). Swing percent variability (CV) was higher (worse) in the lower quartile group during gait under single task condition. In addition, 12% of subjects with lower EF had multiple falls during the year follow-up, compared to none in the upper quartile group (p<0.0001). Discriminant analysis demonstrated that TUG, gait speed and DGI can explain 60.4% of the variance between the two EF groups.

Conclusions: Challenging gait assessment tools such as DGI and TUG may predict future falls. Furthrmore, these findings suggest that even in relatively healthy older adults, EF plays an important role in the risk for multiple falls. Although both groups had same MMSE and fall history, individuals with lower EF scores were more prone to falls, affirming the connection between cognition and fall risk.

We-306

An exploratory analysis of the factor structure of the scale for the assessment of positive symptoms (SAPS) in Parkinson's disease patients with psychosis

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Objective: This study examined positive symptoms, particularly hallucinations and delusions, using the SAPS in a group of 60 patients with PDP.

Background: The Scale for the Assessment of Positive Symptoms (SAPS) is one of four recommended scales for the assessment of psychosis in Parkinson's disease as reported by an MDS Task Force. The SAPS was originally developed and validated to assess positive symptoms in patients with schizophrenia. Further study is needed to understand the scale properties in the Parkinson's Disease Psychosis (PDP) population.

Methods: A principle components analysis (PCA) and an exploratory factor analysis with orthogonal (varimax) rotation were performed. The purpose of this analysis was to evaluate the factor structure of the SAPS hallucination and delusion domains (20 items) in this patient population. Symptoms with low incidence (<10% of patients) of moderate to severe ratings were removed from the analysis.

Results: In this study for this population of patients, three dimensions emerge from the hallucinations and delusions constructs. Hallucinations distinctly divide into visual and auditory dimensions and a third dimension was observed for delusions.

Conclusions: Although analysis of a larger set of PDP patient data are necessary to fully address properties of the SAPS, the data reported here provide preliminary insight into relevant scale properties for the PDP population and may support future development of a new scale to measure symptoms of psychosis in the PDP population.

We-307

A case report of 4 patients with Parkinson's disease dementia (PDD) who were assessed pre and post treatment with rivastigmine

C. Johnson, L. Brown (Derby, United Kingdom)

Objective: A review of patients(pts) treated with rivastigmine to examine how useful the Addenbrookes Cognitive Examination(ACE-R) and Neuro-psychiatric Inventory(NPI) are in assessing response to treatment with Rivastigmine in PDD.

Background: Cholinergic deficits are associated with cognitive impairment and neuropsychiatric symptom. Rivastigmine is licensed for the treatment of dementia in Parkinson's disease. The use of ace-

tylcholinesterase inhibitors in pts who have non-cognitive symptoms causing significant distress or leading to behaviour that challenges is supported by NICE. In PDD there is no guidance on how response to treatment should be assessed. The ACE-R is effective in detecting cognitive dysfunction associated with PD. The NPI assesses behavioural disturbances in dementia pts.

Methods: 7 pts with cognitive impairment plus neuropsychiatric symptoms with no contra-indications were included. Baseline assessments were undertaken using the ACE-R and NPI. Treatment with Rivastigmine was commenced at 1.5mg BD increasing at 2 weekly intervals to 3mg BD. Re-assessment was completed with the pts 4-6 weeks after treatment.

Results: 3 discontinued treatment due to side-effects (2 due to nausea and dizziness, 1 hypotension and falls). Those who continued treatment reported overall improvements in their mental function and wellbeing. 3 improved the ACE-R score and 3 had a substantial improvement in the NPI (Table 1).

Table 1 (We-307).

Patient number	ACE-R (pre)	ACE-R (post)	Difference	NPI (pre)	NPI (post)	Difference
1	55	73	+18	18	37	+11
2	65	66	+1	36	4	−32
3	81	90	+9	55	32	−32
4	90	83	−6	65	28	−37

In breaking down the ACE-R by category (Table 2) all 4 pts showed improvement in fluency. Pt 1 showed a substantial improvement in memory and slight improvement in the other sections, pt 2 showed slight improvement within fluency, language and visuospatial but deterioration in other sections. Pt 3 had improvement in all sections where there was a deficit and pt 4 showed improved fluency with no change in memory but deterioration in the other sections.

Table 2 (We-307). Difference in ACE-R score by catagory

Patient Number	Attention and Orientation	Memory	Fluency	Language	Visuo-spatial
1	0	+15	+1	+1	+1
2	−3	−2	+1	+1	+4
3	+3	+5	+4	0	+2
4	−3	0	+3	−2	−5

Conclusions: The ACE-R and NPI can be easily administered in a half hour consultation and provide an objective measure of the cognitive difficulties and neuropsychiatric problems being experienced. This, along with discussion with the patient and carer provided good evidence of a response to treatment with rivastigmine. Further work is needed to prove the effectiveness of the ACE-R and NPI in the assessment of response to treatment with acetylcholinesterase inhibitors.

We-308

Evaluation of patients with tropical spastic paraparesis using the spastic paraplegy rating scale

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Objective: To evaluate the effectiveness of the Spastic Paraplegic Rating Scale (SPRS) in clinical assessment of patients with HAM/TSP.

Background: Tropical spastic paraparesis (TSP) is a myelopathy associated to infection of HTLV-I, clinically characterized by a chronic and progressive spastic paraparesis, related to several degrees of sphincter and sensory disturbances, being predominant in tropical areas. The neurological examination generally shows weakness and spasticity in the lower limbs with an adductor pattern. Commonly, the evolution of the motor disability is analyzed by the Kurtzke Expanded Disability Status Scale (EDSS), which was designed for evaluating patients with multiple sclerosis. However, the progression of other important aspects of the disease – sphincteric complaints and pain – is not mentioned. Such symptoms and signals are very similar to those of the Hereditary Spastic Paraparesis uncomplicated form. The Spastic Paraplegia Rating Scale (SPRS) has been developed in order to measure the severity of this disease.

Methods: We have made a cross-sectional study from a cohort of 197 patients with seropositivity to HTLV-I. 79 from this group presented spastic paraparesis and only 39 had defined diagnose of HAM/TSP, according to new criteria. On those ones, expanded disability status scale (EDSS) and SPRS scales have been applied.

Results: Scores from scales were compared by using Spearman correlation coefficients: SPRS/Kurtze – 0,8033 ($p<0,0001$).

Conclusions: In orphan diseases, such as HAM/TSP, there are few clinical markers to measure disease severity. Scales like SPRS are a useful instrument to quantify the impairment or improvement of the patient during treatment, because it is practical and does not need any specific tool.

Th-308

Validating rating performance of a new rating scale for levodopa-induced dyskinesia (LIDS)

P.A. LeWitt, L.R. Kingery, J. Savola (Southfield, Michigan)

Objective: In order to improve rating capabilities in another fipamezole study, we developed an AIMS modification with enhanced descriptions of involuntary movement intensity (regardless of duration) and a standardized battery of activation procedures to amplify levodopa-induced dyskinesias. We conducted a validation exercise to define rating performance of 70 investigators in the U.S. and 13 in India.

Background: Important therapeutic targets for PD patients chronically treated with levodopa are dyskinesias and shortened duration of drug effect. A novel and promising treatment is fipamezole, a selective α_2-adrenergic antagonist that blocks levodopa-induced dyskinesias in MPTP-lesioned monkeys. An initial proof-of-concept clinical trial using 60 and 90 mg/day showed fipamezole reduced modified Abnormal Involuntary Movement Scale (AIMS) scores by 3.0-3.5 units. Since the 1976 original AIMS, several rating scales (using qualitative descriptors of involuntary movements in body parts) have been used to quantify the severity of dyskinesias.

Methods: LIDS rating categories were: "none", "minimal" (slight in severity), "mild" (amplitude of movements is half the intensity of the most severe that movements could be), moderate" (halfway between "mild" and "severe"), and "severe" (the greatest intensity of involuntary movements possible). Subjects were rated at rest and during speech, calculations, writing, limb movements, and gait. Investigators scored 4 video recordings of PD subjects.

Results: Intraclass correlation coefficients (ICC) evaluated the extent to which ratings were in agreement. For all raters across all 4 videos, the overall ICC was 0.781 ($p<0.001$), similar between U.S. and Indian raters. Limb ratings showed the highest ICC values. We also determined "bias" scores indicating whether investigators tended to "over" or "under" rate (to be presented).

Conclusions: Designed for ease and clarity of rating instructions as well as for standardization of rating technique, the LIDS is in use for determining the primary endpoint of an ongoing PD fipamezole trial (the FJORD study). In the validation exercise, a high level of overall agreement was seen in data from an international group of investigators. These results indicate that reliable rating of dyskinesia can be achieved after training with the LIDS for use in a multi-center clinical trial.

Th-309

Neuropsychiatric inventory in Wilson's disease

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Objective: To use a standardized psychiatric interviews in order to better characterize psychiatric symptoms in a sample of clinically stable patients with Wilson's disease (WD) standardized long-term treatment.

Background: Some form of psychopathologic features is present in approximately 50% of patients with WD.

Methods: The study comprised 50 consecutive, clinically stable and treated patients with WD recruited from the WD Clinical Research Program at the University of Belgrade. Psychiatric comorbidity was assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). Neuropsychiatric symptoms were further evaluated by Neuropsychiatric Inventory (NPI). Wilson's disease caregivers (n=50) were interviewed with the NPI in order to assess the frequency (four point scale) and severity (three point scale) of 10 neuropsychiatric disturbances during last month.

Results: At least one psychiatric symptom was identified at 72% of WD patients: nine patients (18%) had one, 7 patients (14%) had two, and 20 (40%) had ≥three neuropsychiatric symptoms present. None of the patients had delusions, hallucinations and aberrant motor behavior. The most often endosed symptoms were anxiety (62%), depression (36%), irritability (26%), as well as disinhibition and apathy (24% each). The highest mean scores were found for anxiety, depression and apathy. Age and gender, duration of WD, and MMSE were not significantly correlated with either total or the NPI subscores.

Conclusions: The current study suggests that even among stable, long-term treated patients with WD approximately 70% experienced psychiatric symptoms. Evaluating such abnormalities in patients with WD will ultimately benefit patient care.

Th-310

Minimal clinically important change and the MDS-UPDRS motor examination

G.T. Stebbins, C.G. Goetz, V. Siomkus (Chicago, Illinois)

Objective: In a practice setting, to assess the change in the MDS-UPDRS Motor Examination (Part III) score indicative of minimal clinically important change (MCIC).

Background: MCIC represents the smallest difference in a score that is perceived as clinically meaningful. Most studies using scales such as the MDS-UPDRS test statistical significance. For correct interpretation, however, it is essential to know whether the statistical significance reflects differences that are clinically relevant. The MDS-UPDRS is a revision of the original UPDRS and is likely to become the most commonly used scale in PD research. To date, however, the MCIC for the MDS-UPDRS Part III has not been established.

Methods: A single rater experienced with the MDS-UPDRS followed sequential outpatients with PD during regular outpatient care. He collected the MDS-UPDRS Part III scores along with a CGI-C at each visit. The CGI-C measured clinically important change on a 1 to 7 Likert scale. A CGI-C score of 4 = no change and a score of 3 = minimally improved. Cases included all patients who had a CGI-C score of 3 (minimally improved) and a CGI-C score of 4 (no change) on at least one visit each. For all visits with a CGI-C score of 3 or 4, means and 95% CI of the change in Motor Examination Part III MDS-UPDRS scores from the previous visit were calculated. Calculation were made for the total sample and then subdivided by PD severity (mild (HY 1 & 2), moderate (HY 3) and severe (HY 4 & 5)).

Results: Seventy PD patients (mean age =67.8 years (±9.6)) with a CGI-C of both 3 and 4 were examined over a total of 234 visits. MDS-UPDRS Part III change score for CGI-C 4 (no clinical change) was 0.46 [95th CI = -0.05; 0.96] and varied slightly by PD severity (mild = 0.47; moderate = 0.25; severe = 0.80). MDS-UPDRS Part III change score for CGI-C 3 (minimal clinically improvement) was -2.41 [95th CI = -3.17; -1.65] and varied slightly across PD severity (mild = -2.73; moderate = -2.07; severe = -1.70).

Conclusions: This preliminary study derived MCIC scores for the MDS-UPDRS Part III across different levels of PD impairment. The results allow a functional translation of a numeric change into a clinically pertinent change. These results may also be helpful for calculating sample sizes based on expected change scores that are clinically relevant.

Th-311

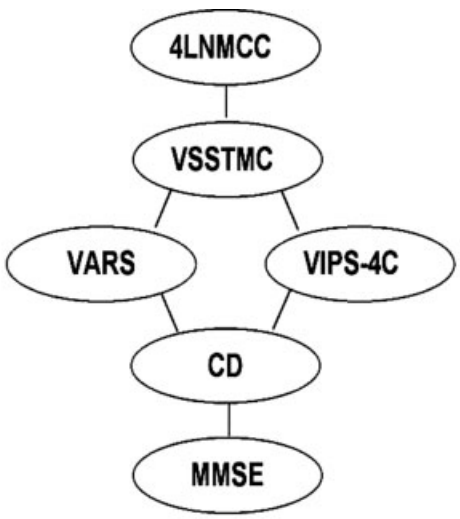
Analysis of clock drawing (CD), Mini Mental Status Examination (MMSE) and quantitative subsystem performance (QSP) in Parkinson's disease (PD) using nonlinear causal resource analysis (NCRA)

R.M. Stewart, G.V. Kondraske, K. Chisty, S. Hussan, M. Movahid (Dallas, Texas)

Objective: To gain insight into the content of selected performance tests by exploring performance theoretic relationships, with particular interest in relationships between cognitive and other tests.

Background: Assessing cognitive function in PD relies on psychometric evaluations such MMSE and CD. While some objective QSP tests focus on motor performance, they involve cognition to some degree (e.g., instructions are given). Using NCRA (Kondraske 2006, CRC Press), we have derived a new method to explore hierarchical relationships among performance measures.

Methods: 197 PD subjects were selected from our clinical database who had evaluable data including CD, MMSE and selected QSP measures. Clock drawing was scored using the Mendez et al method. Using NCRA scatter plot interpretation methods, the hierarchical relationship between selected pairs of measures was systematically evaluated (i.e., identify which measure represents a lower level performance resource and which reflects performance capacity of a more complex system).



Hierarchical relationship between tests studied, determined through use of NCRA methods.

FIG. 1 (Th-311).

Results: Ages ranged from 34 to 90; 74% M and 26% F. MMSE 8-30/30. CD scores 3 to 20/20. The following hierarchical order, starting from that which represents the lowest level performance resource, was found: MMSE, CD, Visual Information Processing Speed with a 4-choice load (VIPS-4C) and Visual-Arm Response Speed (VARS) (both found to be at a similar level), Visual Spatial Short-Term Memory Capacity (VSSTMC), and 4-Limb Neuromotor Channel Capacity (4LNMCC). 4LNMCC is a composite of individual NMCC measures for each limb. No clear type of relationship was found between Finger Tapping Speed (FTS) and any other test, suggesting that it stresses some unique performance resource.

Conclusions: MMSE and CD measure some basic performance resource for which some amount is required in "more complex" tests such as coordination. A good result in a complex test can be used to infer a specific level of cognitive performance resource availability. QSPs that do not focus on cognition could have value in its evaluation. The methodology and logic provide a new approach to study human systems and tasks, especially test tasks.

RESTLESS LEGS SYNDROME

Mo-313

Isolated Restless Arm syndrome associated with severe iron deficiency: A case report

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Objective: To report a patient with primary arm restlessness and severe iron deficiency.

Background: Restless leg syndrome (RLS) affects 10-15% of the population and recent series report some degree of arm paresthesia or restlessness in about 20-50% of cases. However, arm restlessness without leg involvement is relatively rare. While the majority of RLS cases are primary or idiopathic, substantial proportions have been associated with medical conditions.

Methods: Case presentation.

Results: A 68-year-old woman presented with pain and tingling in the right arm that became intolerable in the last two months. She dated the beginning of her complaints, however very mild, at 4 years. At presentation she was complaining of a very disturbing tingling and pain sensation in the inner surface of her right arm for which she underwent several diagnostic procedures with no remarkable results. On close questioning, she denied any discomfort during active hours and reported great discomfort during resting time. Her symptoms were always relieved with restoration of motor activities. The patient denied the actual presence of similar symptoms in her lower extremities, however she admitted the presence of very mild painful leg sensations some 20 years ago for which she sought no medical attention. Her history was only remarkable for the presence of hyperlipidemia and a chronic eosinophilic colitis diagnosed 5 to 6 years ago. The patient's investigations included a cervical MRI and EMG within normal limits. On the contrary, her laboratory examination revealed a moderate anemia with severe iron deficiency (serum ferritin level 5.4 ng/mL) which was associated to her chronic colitis. She was put on an oral iron replacement therapy which resulted in a total relief of symptoms within a week time and no further dopaminergic treatment was required within a year of follow-up.

Conclusions: There are a few remarkable points in this case: arm restlessness is generally reported in severe RLS cases, an association which is lacking here. Furthermore, a profound and unnoticed iron deficiency was disclosed and the sole treatment of this condition was enough to gain full relief of symptoms. Therefore, the present case seems to be a good example to keep in mind both the possibility of an isolated severe arm involvement in RLS and of an adequate treatment solely targeting the underlying pathology.

Mo-314

Thermal hypoesthesia differentiates secondary RLS due to small fiber neuropathy from idiopathic RLS

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Objective: The aim of our study was to assess thermal and mechanical perception and pain thresholds in primary idiopathic restless legs syndrome (RLS) and secondary RLS due to small fiber neuropathy.

Background: Several studies suggested that patients with restless legs syndrome have thermal and mechanical sensory abnormalities.

Methods: We compared 21 patients (age 53.3±8.4, n=3 male) with primary RLS and 13 patients (age 62.4±7.6, n=1 male) with secondary RLS due to small fiber neuropathy with 20 healthy subjects (58±7; n= 2 male). Differential diagnosis of secondary RLS was made based on clinical symptoms, particularly burning feet. A comprehensive quantitative sensory testing (QST) protocol encompassing thermal and mechanical detection and pain thresholds as devised by the German Research Network on Neuropathic Pain (DFNS) was performed upon the dorsum of both feet between 2 pm and 1 am while RLS symptoms were present in all patients.

Results: Patients with idiopathic RLS showed hyperalgesias to heat ($p<0.05$), blunt pressure (PPT: $p<0.001$), pin-prick ($p<0.001$), and vibratory hyperesthesia (VDT: $p<0.01$). Patients with secondary RLS due to small fiber neuropathy showed thermal hypoesthesia to cold (A delta fiber mediated) and warm (C fiber mediated) (all $p<0.001$), and hyperalgesias to blunt pressure ($p<0.05$) and pin-prick ($p<0.001$).

Conclusions: Patients with secondary RLS due to small fiber neuropathy showed significantly increased thermal detection thresholds as compared with idiopathic RLS and healthy controls. Previously demonstrated static mechanical hyperalgesia was confirmed for primary and secondary RLS patients. Furthermore, our results suggest that heat pain hyperalgesia may differentiate primary RLS from secondary RLS due to small fiber neuropathy.

Mo-315

An open label pilot study assessing gender, ethnic, behavioral, and response differences of transdermal rotigotine for the treatment of restless legs syndrome (RLS)

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Objective: To report the benefits and tolerability of rotigotine for the treatment of RLS and response differences based on gender, ethnicity, behavior and sleep patterns secondary to the use of rotigotine.

Background: Dopamine agonists are effective in treating RLS. Rotigotine, a novel transdermal dopamine agonist, with its unique delievery system may allow for a more physiologic dopaminergic stimulation resulting in better symptom control and less side effects.

Methods: A total of 13 patients with RLS were included in the study. The IRLSS questionnaire was used before and at weeks 6, 3 months and in some at 6 months after treatment. Rotigotine was initiated at 2 mg daily and adjusted accordingly to patient's tolerability and response to treatment to a maximum of 6 mg a day. The scores at presentation and at follow up were compared.

Results: Six patients completed at least one follow up visit. The total IRLSS score before and after treatment was 26.7 and 7.6 at 3 months for a 72% improvement rate. The average dose of rotigotine was 2 mg daily in all but 4 mg/d in one. Three patients discontinued treatment due to side effects: dizziness in 2, transient skin discoloration in 1, and headache in 1. Two patients were lost to follow up. A significant improvement in RLS symptom was observed before and after treatment with rotigotine; [(M: 3.04, SD: 0.30)/(M: 0.87, SD: 0.77) $t(5) = 7.2$, $p<0.001$]. A significant difference in the degree of symptom severity before and after treatment was seen [(M: 2.9, SD: 0.27)/(M: 0.67, SD: 0.67), $t(5): 7.3$, $p<0.01$]. Behavioral alterations

caused by RLS improved by 84%. [(before M: 3.25, SD: 0.61) after (M: 0.5, SD: 0.54), t(5): 8.9, $p<0.001$)]. Sleep severity improved by 80%. [(before M: 3.3, SD: 1.03) after (M: 0.67, SD 1.21), t (5): 5.3, $p<0.01$)]. No significant gender or ethnic differences in response to treatment between men and women were observed.

Conclusions: 24 h transdermal delivery of low-dose rotigotine appears to be useful and well tolerated to relieve the nighttime and daytime symptoms of RLS. No significant difference in gender or ethnicity was found. Rotigotine improved behavioral and sleep disturbances induced by RLS.

Mo-316

Carotid intima-media thickness in patients with idiopathic restless legs syndrome

J.S. Baik, J.H. Kim, Y.D. Kim (Seoul, Korea)

Objective: To investigate the carotid intima-media thickness (IMT) in patients with idiopathic restless legs syndrome (iRLS) and to compare with controls.

Background: IMT is increasingly used as a surrogate end point of vascular outcomes, and is a known marker for subclinical atherosclerosis. The dopamine deficiency may provide additional protection from cerebrovascular disease. Some reported Parkinson's disease (PD) was associated with a lower risk of preclinical atherosclerosis. Although RLS may related to dopaminergic system, the risk of preclinical atherosclerotic change in RLS is poor understood.

Methods: Twenty five patients with RLS from January 2007 to August 2008 who were visiting to Sanggye Movement Disorders Clinic, and forty four age-matched healthy controls were involved to this study. Some patients who had previous stroke and RLS with PD were excluded. The CCA-IMT value was measured using the diagnosis software for IMT 'intimaScope'.

Results: In idiopathic RLS patients, eleven was men, forteen was women and mean age was 56.4 ± 13.9 years and the duration of RLS was 14.68 ± 13.31 months. The carotid IMT in iRLS patients was significantly smaller than in controls (0.82 ± 0.14mm vs.0.86 ± 0.16mm, $P=0.016$). There were no differences between iRLS group and control in stroke risk factors including, hypertension, diabetes, hypercholesterolemia, and smoking.

Conclusions: The carotid IMT measurement is used to assess preclinical atherosclerosis. We suggested that RLS patients have a lower risk of preclinical atherosclerosis than healthy controls, although there is no significant difference in multiple regression analysis.

Mo-317

Augmentation in long-term therapy of the restless legs syndrome with transdermal rotigotine – A retrospective systematic analysis of two large open-label 1-year trials

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Objective: To retrospectively and systematically evaluate the long-term data from two open-label rotigotine trials by applying the Max Planck Institute (MPI) criteria both for augmentation and clinically relevant augmentation.

Background: Augmentation of symptoms is the main long-term treatment complication with dopaminergic drugs in restless legs syndrome (RLS). In previous 6-month double-blind RLS trials with rotigotine, a transdermally delivered dopamine agonist, clinically relevant augmentation was observed in 1.5 % of patients.

Methods: Data from two (EU and US) 1-year prospective open-label extension trials of preceding double-blind studies to evaluate the safety, tolerability and efficacy of rotigotine in flexible dosages between 0.5 and 3 mg/24 hours were reanalyzed by three experts. Six-hundred and twenty patients were exposed to rotigotine for a total of 529 years. To assess clinically relevant augmentation, all study visits were systematically evaluated by means of the MPI criteria using the Augmentation Severity Rating Scale (ASRS), IRLS, RLS-6, and CGI, as well as the RLS Quality of Life scale (QoL-RLS).

Results: Sixty patients (9.7%) met MPI criteria for augmentation on at least one visit. The condition was clinically relevant in 18 patients (2.9%) for the 1 year treatment; none of these patients discontinued the trial due to augmentation. No relationship between rotigotine dose and augmentation could be detected. Clinically relevant cases of augmentation according to the expert ratings occurred at any time point of the study period.

Conclusions: This retrospective systematic analysis of a large dataset from two open-label 1-year trials with flexible dosages of the rotigotine patch shows that, at least during the first year of treatment, clinically relevant augmentation is not common. Nevertheless, as with any dopaminergic RLS treatment, a long-term observation is recommended.

Mo-318

Maintenance of efficacy and long-term tolerability of gabapentin enacarbil compared with placebo in subjects with restless legs syndrome

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Objective: To assess the maintenance of efficacy and tolerability of gabapentin enacarbil (GEn) 1200 mg versus placebo in long-term treatment of moderate-to-severe primary restless legs syndrome (RLS).

Background: GEn, a non-dopaminergic treatment, is under investigation for RLS.

Methods: XP060 comprised a 24-week, single-blind (SB) phase (GEn 1200 mg/day) followed by a 12-week, double-blind (DB) phase. SB-phase responders were randomized to GEn 1200 mg/day or placebo during the DB phase (placebo group received GEn 600 mg/day during initial 2-week taper period of DB phase). Doses were administered once daily at 5 pm with food. Primary endpoint: proportion of subjects relapsing (increase in International Restless Legs Scale total score of ≥6 from Week 24 to ≥15, and a rating of 'much worse' or 'very much worse' on the investigator-rated Clinical Global Impression of Change scale, on 2 consecutive visits ≥1 week apart, or withdrawal due to lack of efficacy) during the DB phase. Tolerability evaluations included assessing all adverse events (AEs) during the SB phase and new/worsening AEs during the DB phase.

Results: Of 327 subjects enrolled, 194 subjects (GEn=96, placebo=98) were considered SB-phase responders and randomized in the DB phase. Significantly more placebo-treated subjects relapsed during the DB phase compared with GEn (22.7% vs 9.4%; odds ratio: 0.353; 95% CI: 0.2, 0.8; $p=0.0158$). During the SB phase, the most commonly reported AEs were somnolence (29.8%), dizziness (22.1%) and headache (12.6%). During the DB phase, no AEs were reported by $\geq5\%$ of GEn-treated subjects; nasopharyngitis and viral gastroenteritis were both reported by 5.1% of placebo-treated subjects (GEn-treated subjects: 3.1% and 1.0%, respectively). Most AEs in each phase were mild or moderate in intensity.

Conclusions: Improvement in RLS symptoms provided by GEn 1200 mg once daily is maintained compared with placebo, and treatment is generally well tolerated for up to 9 months.

Mo-319

A randomized, double-blind, placebo-controlled, dose-response study to assess the pharmacokinetics and tolerability of gabapentin enacarbil in subjects with restless legs syndrome

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Objective: To examine gabapentin exposure, efficacy and tolerability across four doses of gabapentin enacarbil (GEn) extended release tablets in subjects with restless legs syndrome (RLS).

Background: GEn, a non-dopaminergic treatment under investigation for the treatment of RLS, provides predictable, dose-proportional gabapentin exposure in healthy adults.

Methods: During a 12-week, double-blind, placebo-controlled, parallel-group study (protocol XP081), subjects with moderate-to-severe primary RLS were randomized to GEn 600, 1200, 1800 or 2400 mg or placebo once daily at 5 pm with food. Plasma gabapentin concentration was measured at Weeks 4 and 12 (0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20 and 24 h post-dose) using sensitive and specific LC-MS/MS methods and data were analyzed by non-compartmental methods. Tolerability evaluation included assessment of adverse events (AEs). Efficacy findings will be presented separately.

Results: 217 subjects were randomized (GEn 600 mg, n=48; 1200 mg, n=45; 1800 mg, n=38; 2400 mg, n=45; placebo, n=41). The half-life of gabapentin (~6 h) was consistent across the dose range and T_{max} was ~7–9 h. Summary statistics for gabapentin exposure in plasma at steady state at Week 4 over the dose range studied were: mean $C_{ss,\ max}$ (μg/mL), GEn 600 mg = 3.86, 1200 mg = 7.14, 1800 mg = 11.4, 2400 mg = 14.0; mean $AUC_{ss,24}$ (μg*h/mL), GEn 600 mg = 49.3, 1200 mg = 96.1, 1800 mg = 141.0, 2400 mg = 176.0. Exposure was not significantly changed at Week 12 and summary statistics were: mean $C_{ss,\ max}$ (μg/mL), GEn 600 mg = 4.14, 1200 mg = 7.15, 1800 mg = 12.0, 2400 mg = 13.3; mean $AUC_{ss,24}$ (μg*h/mL), GEn 600 mg = 51.4, 1200 mg = 95.7, 1800 mg = 146.0, 2400 mg = 173.0. The most commonly reported treatment-emergent AEs in each GEn dose group were somnolence and dizziness, and their frequency tended to increase with dose. Most of these common AEs occurred during the first 2 weeks of treatment and were mild or moderate in intensity.

Conclusions: GEn once daily provides dose-proportional gabapentin exposure over the doses of 600–2400 mg in subjects with moderate-to-severe primary RLS and is generally well tolerated.

Mo-320

Gabapentin enacarbil improves sleep in subjects with moderate-to-severe primary restless legs syndrome

S.E. DeRossett, C.A. Kushida, P.M. Becker, A.L. Ellenbogen, D.M. Canafax, R.W. Barrett (Research Triangle Park, North Carolina)

Objective: To assess sleep outcomes with gabapentin enacarbil (GEn) 1200 mg compared with placebo in subjects with restless legs syndrome (RLS).

Background: Sleep disturbance is a primary complaint of many subjects with RLS. GEn is a non-dopaminergic therapy under investigation for primary RLS.

Methods: XP052 was a 12-week, double-blind, multicenter study. Subjects with moderate-to-severe primary RLS were randomized to GEn 1200 mg (n=114) or placebo (n=108) once daily at 5 pm with food. Co-primary endpoints: mean change from baseline in International Restless Legs Scale (IRLS) total score and proportion of responders (rated 'very much' or 'much' improved) on the investigator-rated Clinical Global Impression–Improvement (CGI-I) scale. Sleep disturbance was assessed using the Medical Outcomes Study (MOS) Sleep Scale and Post-Sleep Questionnaire (PSQ). Adverse events (AEs) were used to assess tolerability.

Results: GEn significantly improved mean IRLS total score vs placebo at Week 12 LOCF (adjusted mean treatment difference for change from baseline: –4.0; 95% CI: –6.2, –1.9; p=0.0003) and more subjects receiving GEn were CGI-I responders (76.1% vs 38.9%; adjusted odds ratio: 5.1; 95% CI: 2.8, 9.2; p<0.0001). GEn improved mean MOS Sleep Scale domain scores from baseline to Week 12 LOCF vs placebo (daytime somnolence: –17.4 vs –9.6, p=0.0018; sleep quantity: 0.8 vs 0.4 h, p=0.0084; sleep adequacy: 27.7 vs 13.4, p<0.0001; sleep disturbance: –29.1 vs –15.5, p<0.0001). Subjects receiving GEn reported higher overall sleep quality, greater ability to function, and fewer nights with RLS symptoms, nighttime awakenings, and hours awake per night due to RLS symptoms vs placebo on the PSQ at Week 12 LOCF (all p<0.05 for distribution of responses). The two most frequently reported AEs (GEn, placebo) were somnolence (27%, 7%) and dizziness (19%, 5%).

Conclusions: In addition to significantly reducing RLS symptoms, GEn 1200 mg once daily significantly improves subject-reported sleep outcomes.

Mo-428

Gabapentin enacarbil relieves pain associated with restless legs syndrome

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Objective: To evaluate the effects of gabapentin enacarbil (GEn) on restless legs syndrome (RLS) symptoms and associated pain.

Background: Painful symptoms may occur in ~60% of patients with RLS (Allen, *et al. Arch Intern Med.* 2005;**165**:1286-92). GEn is a non-dopaminergic treatment under investigation for primary RLS.

Methods: XP052, a 12-week, double-blind, multicenter study, randomized subjects with moderate-to-severe primary RLS to GEn 1200 mg (n=114) or placebo (n=108) once daily at 5 pm with food. Co-primary endpoints: mean change from baseline in International Restless Legs Scale (IRLS) total score and proportion of responders (rated 'very much' or 'much' improved) on the investigator-rated Clinical Global Impression–Improvement (CGI-I) scale. Subjects recorded 'pain associated with RLS symptoms' in the last 24 h on an 11-point scale (0=no pain, 10=most intense pain imaginable) every morning for 7 days prior to assessment. Subjects with other neurologic disease or movement disorders were excluded.

Results: GEn improved mean IRLS total score vs placebo at Week 12 LOCF and more subjects receiving GEn were CGI-I responders (both p<0.001). Overall, 89% and 51% of subjects reported baseline average daily RLS pain scores of >0 and ≥4, respectively. Treatment with GEn reduced mean (SD) pain scores vs placebo for subjects with baseline pain scores >0 (–2.5 [2.32] vs –1.3 [2.07]; adjusted mean treatment difference [AMTD]: –1.1; p<0.0001) and ≥4 (–3.7 [2.18] vs –1.9 [2.36]; AMTD: –1.7; p<0.0001) at Week 12 LOCF. Significantly more GEn-treated subjects reported ≥50% reduction in daily pain scores vs placebo with baseline pain scores >0 (58.6% vs 35.2%; adjusted odds ratio [AOR]: 2.6; 95% CI: 1.5, 4.5; p=0.0006) and ≥4 (75.4% vs 33.3%; AOR: 6.9; 95% CI: 2.9, 16.5; p<0.0001; *post hoc*). The two most frequently reported adverse events (GEn, placebo) were somnolence (27%, 7%) and dizziness (19%, 5%).

Conclusions: GEn 1200 mg once daily significantly improves RLS symptoms in subjects with moderate-to-severe RLS and reduces pain associated with RLS symptoms.

Tu-312

No evidence for cognitive dysfunction or depression in patients with mild restless legs syndrome

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Objective: To assess whether patients with RLS have more cognitive dysfunction and depression than individuals of the same age and education who do not have RLS.

Background: Restless legs syndrome is a common disorder that may interrupt sleep and has been reported to produce daytime fatigue and/or mood changes.

Methods: The Sun Health Research Institute Brain and Body Donation Program (BBDP) database was reviewed for subjects with and without RLS. The diagnosis of RLS was made using the IRLSSG criteria. The 30 item Geriatric Depression Scale (GDS) was used to assess for depression. Neuropsychological testing included: Rey-AVLT, Trails A and B, Stroop, Controlled Oral Word Association,

animal fluency, Judgment of Line Orientation, Digit Span, Folstein Mini-Mental Status Examination (MMSE), and Clock drawing. The mean level of each measure in the RLS group was compared to that of the control group and the statistical significance was calculated by using the two sample *t* test. The prevalence of high GDS scores was analyzed using the Fisher exact test.

Results: A total of 26 subjects with RLS and 208 without RLS (control group) were identified. There was no difference in mean age (RLS, 77 yrs; Control, 78 yrs) or mean duration of education (15 yrs in both groups). The mean RLS rating scale score for the RLS group was 11.0 (SD = 7.6) and the mean duration of RLS was 11.0 yrs (range 1 to 51 yrs). All of the mean cognitive scores were equivalent within one standard deviation of the group without RLS. The mean GDS scores differed by less than 1 point on a 30-point scale.

Conclusions: These findings suggest that older individuals with mild RLS do not have cognitive dysfunction and are not depressed compared with a control group of similar age and education. Further prospectively designed studies of RLS, with appropriate control populations are needed to determine if cognitive or neuropsychiatric symptoms occur in more severe cases of RLS and what factors may be correlated with these disorders.

Tu-314

Double-blind, placebo-controlled treatment of idiopathic restless legs syndrome with pregabalin: Effects on sleep architecture

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Objective: To investigate the effects of pregabaline on sleep architecture in idiopathic RLS.

Background: Pregabalin is an alpha-2 delta receptor agonist that has been approved for the treatment of disorders such as epilepsy, neuropathic pain, generalized anxiety and fibromyalgia. No controlled investigations have been performed so far in restless legs syndrome (RLS).

Methods: The study was designed as a double-blind, placebo-controlled, parallel treatment trial with pregabalin. Following a two-week placebo run-in, subjects with an improvement on the International RLS Severity Scale (IRLS) total score of more than 40% were excluded. Forty five patients diagnosed with idiopathic RLS were then randomized to receive either a 12-week flexible-dose treatment with pregabalin (n=25) or placebo (n=20). Polysomnographic studies were performed at baseline and at the end of treatment.

Results: During the twelve-week treatment period with pregabalin, the IRLS score improved significantly compared with placebo (mean +SD: 19.8±4.2 to 7.4±6.9 versus 21.5±3.8 to 12.8±8.6, p=0.02). The mean effective dose of pregabalin at the end of treatment was 322.50±98.77 mg/day. Treatment with pregabalin also resulted in an improvement in the mean (+SD) periodic leg movement index from 31.25±24.9 to 13.79±14.4, against 33.1±36.3 to 40.98±47.15 (p>0.001) in the placebo group. Furthermore, patients undergoing treatment with pregabalin had a statistically significant increase in time of NREM-sleep and slow wave sleep (p<0.01) and a decrease in percentages of Stage 1 and Stage 2 (p<0.05). Pregabalin was generally well tolerated, and headache, dizziness, postural instability, dry mouth and daytime sleepiness were reported over 5%.

Conclusions: Our results indicate that pregabalin is effective for the treatment of idiopathic RLS and exerts clinically significant therapeutic effects on motor activity during sleep. In contrast to most dopaminergic agents, pregabalin also improved sleep architecture with a pronounced increase in slow wave sleep, and a decrease in Stages 1 and 2. Pregabalin is a promising alternative to existing dopaminergic treatments due to its more pronounced effects on sleep architecture and warrants study in larger, controlled studies.

Tu-315

26-week effects of pramipexole on quality of life in restless legs syndrome

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Objective: To assess the specific effects of pramipexole on quality of life (QOL) in restless legs syndrome (RLS), as rated after longer double-blind treatment than in previous trials.

Background: RLS is known to have an impact on QOL. Pramipexole relieves the syndrome's sensorimotor symptoms, but all double-blind clinical trials have lasted ≤12 weeks.

Methods: RLS patients were randomized to receive 26 weeks of double-blind placebo or pramipexole (individually optimized at 0.125-0.75 mg/d). At baseline and endpoint, patients completed the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). On each of its 8 domains, higher scores, from 0 to 100, indicate better health. Patients also completed the Johns Hopkins restless legs syndrome Quality of Life questionnaire (RLS-QOL). After inversion, the summed score for items 1-5, 7-10, and 13 (each with 5 possible answers) was mapped to the interval 0 to 100, with higher values indicating better QOL. All changes from baseline were analyzed by van Elteren test stratified by country.

Results: In all, 155 to 157 pramipexole and 152 or 153 placebo recipients contributed postbaseline data. On SF-36, baseline medians were ≤67.0 for Bodily Pain, at 50.2, and Vitality, at 56.3. On both these domains, pramipexole was superior to placebo, with median changes of +12.0 vs +9.0 (P=.0179) and +6.3 vs +3.1 (P=.0206), respectively. Other domains showed no median change or the same median improvement for pramipexole and placebo. On RLS-QOL, baseline medians of 72.5 and 70.0 changed by a median +15.0 vs +12.5 (P=.5905).

Conclusions: Across generic and RLS-specific assessment tools, pramipexole-related improvement of QOL at 26 weeks (compared with placebo) was significant for the 2 assessments (bodily pain and vitality) that were most severely affected by RLS at baseline.

Tu-316

Improvement of depressive symptoms, RLS symptoms and sleep in patients with moderate to severe idiopathic RLS and at least mild depressive symptoms under a therapy with ropinirole immediate release: A multicentre, randomised, placebo-controlled study

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Objective: To investigate the effects of ropinirole immediate release (IR) on depressive symptoms, RLS symptoms and sleep in idiopathic restless legs syndrome (RLS).

Background: The treatment of depression in RLS remains a challenge, given the aggravation of RLS by some antidepressants and limited data on the effects of dopamine agonists on mood in RLS. Studies in depressive patients show that ropinirole might have antidepressant properties.

Methods: This German multicentre study included patients with moderate/severe idiopathic RLS (RLS-DI>=11; IRLS Score >=15) and at least mild depressive symptoms (Montgomery-Asberg-Depression Rating Scale/MADRS Score >=12). Exclusion criteria were secondary RLS, sleep disorders, serious psychiatric/internal diseases and acute/anamnestic suicidality. Patients were 3:1-randomised to ropinirole IR up to 4mg/d (to be taken 1-3 hours prior to bedtime) or placebo and double-blindly treated for 12 weeks including an uptitration phase of 7 weeks. Visits were scheduled at screening, baseline and weeks 1, 4 and 12 with additional telephone contacts for dosing decisions.

Results: The prospectively defined modified-Intent-to treat population comprised 231 patients (171 ropinirole, 60 placebo) with >= one intake of study medication and available MADRS score at least

after 4 weeks of treatment. MADRS decreased from baseline to week 12 from 18.8 to 8.7 in the ropinirole group and from 18.4 to 12.1 under placebo (primary endpoint: adjusted mean treatment difference -3.6 (95%-CI: -5,6 to -1,6; $p<0.001$). IRLS decreased from baseline to week 12 by 14.7 under ropinirole and by 10.0 under placebo ($p<0.001$); with ropinirole 84.8% of patients improved by >= 6 points on the IRLS (placebo: 61.7%; $p<0.001$). In the MOS Sleep Scale subdomains (subjective) "sleep quantity", "sleep disturbance" and "sleep adequacy" ropinirole led to greater improvements compared to placebo (each $p<0.001$). The safety analysis confirmed the typical dopaminergic profile.

Conclusions: This randomised placebo-controlled study showed superior effects of ropinirole on depressive symptoms, disturbed sleep and RLS severity in patients with moderate to severe idiopathic RLS compared to placebo.

Tu-317

Efficacy, safety, and dose-response of pramipexole (PPX) in Japanese patients with primary restless legs syndrome (RLS); a randomized, double-blind trial

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Objective: To evaluate the efficacy, safety, and dose-response of PPX in Japanese patients with primary RLS at fixed doses of 0.25 mg, 0.5 mg, and 0.75 mg once daily for 6 weeks.

Background: PPX has been shown as highly effective against RLS in the USA and Europe. In Japanese RLS patients the efficacy of PPX on RLS symptoms has been demonstrated in a placebo controlled polysomnography study only on small number of patients with disorder.

Methods: In a 6-week, double-blind trial, a total of 154 Japanese patients with primary RLS, diagnosed by the 4 criteria of the IRLSSG, and International RLS Study Group rating scale (IRLS), total score >15, were randomized to receive PPX at fixed doses of 0.25–0.75 mg/day. PPX was administered at the initial dosage of 0.125 mg/day for 1 week; then all groups were uptitrated to 0.25 mg/day at week 2; two of the groups were further adjusted to 0.5 mg at week 3, and one group to 0.75 mg at week 4. IRLS and Epworth Sleepiness Scale (Japanese version; JESS) scores, and Clinical Global Impressions-Global Improvement (CGI-I) were assessed at each visit. Pittsburgh Sleep Quality Index (PSQI) was assessed on weeks 0 and 6, and Patient Global Impression (PGI) was assessed at weeks 2, 4, and 6.

Results: At baseline, mean IRLS total scores were nearly identical in the three dose groups (21.4 on 0.25 mg, 22.6 on 0.5 mg, 22.8 on 0.75 mg). At week 6, adjusted mean change of IRLS from baseline in the 0.25, 0.5, and 0.75 mg groups were –12.3, –12.5, and –11.8, respectively; PSQI was –3.2, –3.2, and –2.5, respectively; JESS was –2.6, –3.0, and –2.3, respectively. The IRLS responders rate in the 0.25, 0.5, and 0.75 mg groups at 6 week was 60.4%, 58.5%, and 49.1%, respectively; CGI-I was 77.1%, 75.5%, and 69.8%, respectively; PGI responders was 72.9%, 79.2%, and 67.9%, respectively. The overall frequencies of adverse events (AEs) were not relevantly different among the three groups (0.25 mg, 75.0%; 0.5 mg, 83.0%; 0.75 mg, 84.9%). All observed AEs were rated mild to moderate in severity.

Conclusions: These study results revealed that PPX at all three fixed doses (0.25, 0.5, and 0.75 mg) is highly efficacious for the treatment of primary RLS in Japanese patients, and has a safety and tolerability profile comparable to the one known from studies with Caucasian patients.

Tu-318

The prevalence of restless legs syndrome in Thai Parkinson's disease patients

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Objective: To study the prevalence of restless legs syndrome (RLS) in patients with Parkinson's disease (PD).

Background: RLS is a common neurologic disorder which is underdiagnosed in all parts of the world in spite of being treatable. There have been several studies on the prevalence of RLS in PD in several countries including Japan, India, Singapore, USA and Spain. The prevalence varied greatly in these studies ranging from 0% to 21.9%. There has been no study looking at the prevalence of RLS in patients with PD in Thailand.

Methods: PD patients were consecutively enrolled from movement disorders clinic and interviewed for RLS symptoms. Diagnosis of RLS was made if the patient fulfilled the NIH-IRLSSG diagnostic criteria. Information about the duration, onset and frequency of the symptoms and the amount of distress caused by the symptoms were obtained. Serum ferritin level was obtained from all patients. Patients with a history of end-stage renal disease, peripheral neuropathy, spinal cord diseases and malignancy were excluded from the study.

Results: One hundred and thirty seven PD patients were interviewed. Of these there were four patients (2.9%) who fulfilled the IRLSSG diagnostic criteria but only two patients (1.5%) met the inclusion criteria. One patient was male and the other was female. Both had been diagnosed with PD for three years, had the onset of RLS two years after the symptoms of PD (age at onset of RLS was 73 years in the male patient and 65 years in the female patient) and had Hoen and Yahr stage of 2.5. Serum ferritin level was less than 45 ng/ml in both the patients. One patient had the symptoms once per week while the other had daily symptoms, and the symptoms caused severe and moderate distress respectively. The study is expected to be completed in september 2009. Hence the final results are still pending.

Conclusions: The overall prevalence (four patients) of RLS in our PD patients was 2.9%. When patients with neuropathy, malignancy and end-stage renal disease are excluded, the prevalence falls to 1.5%. In both instances the prevalence is much lower than the prevalence in most countries except in Singapore where the prevalence of RLS in PD patients in a tertiary center was found to be 0% (Tan et. al, 2002). This may be another evidence supporting variable prevalence of RLS in PD in different geographic regions.

Tu-319

Motor performance in patients with restless legs syndrome

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Objective: To analyze motor performance in a large series of patients with idiopathic restless legs syndrome (RLS) and in healthy matched controls, looking for the presence of slowed movements in patients with RLS.

Background: Dopaminergic dysfunction could to play a role in RLS, and patients with central dopaminergic dysfunction exhibit difficulties in performing alternating movements or in the movement initiation. Therefore, we analyzed motor performance in patients with idiopathic RLS and in healthy matched controls.

Methods: We studied 50 patients diagnosed with idiopathic RLS and 100 age and sex matched controls. Evaluation included four timed tests (pronation-supination, finger tapping and movement between two points with both hands, and walking test); and three tests performed on a personal computer (speed for pressing repetitively a key –frequency-, visual reaction time, and movement time with both hands). Comparison between RLS patients and controls were done using the t-test for unpaired samples for those variables normally distributed, and with the Mann-Whitney Rank Sum test for those that did not follow a normal distribution. Bonferroni's test and backward logistic regression were performed for multiple comparison analysis.

Results: In a univariate study, restless legs patients showed lower mean values for right pronation-supination, minimum value for right frequency and movement time, and standard deviation, maximum and rank values of movement time with the left arm; and higher

mean values for left finger tapping, right and left movement between two points, and standard deviation and rank for right and left frequency. With a multivariate study, restless legs patients showed significantly lower mean values for right pronation-supination, minimum right movement time, and rank of left movement time; and higher mean values for left finger tapping and movement between two points, and rank of right frequency.

Conclusions: Motor performance of patients with restless legs syndrome is similar to that of healthy matched controls with the exception of impaired right pronation-supination and better performance of left finger tapping and movement between two points.

Tu-320

Iron deficiency and restless leg syndrome in attention deficit hyperactivity disorder

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Objective: To define the relationship between iron deficiency and RLS in adolescents with ADHD.

Background: Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by pervasive inattention and/or hyperactivity-impulsivity. It has been suggested that ADHD symptoms are associated with restless legs syndrome (RLS), which is a neurological condition that is defined by an irresistible urge to move the legs usually accompanied by or caused by uncomfortable and unpleasant sensations in the legs that begin or worsen during periods of rest or inactivity. Increasing evidence suggests iron deficiency may underlie common pathophysiological mechanisms in subjects with ADHD and with RLS.

Methods: We evaluated 43 ADHD subjects, diagnosed from child and adolescent psychiatrist in Community Centre of Mental Health Nr.1 in Tirana: 39 boys and 4 girls with age 16.3 +/− 2.5 years. The diagnosis of the ADHD was made by child and adolescent psychiatrist according to DSM IV-r Criteria and diagnosis of RLS was made according to the International RLS Group criteria. The patients were evaluated for the iron deficiency (ferritin < 12 ng/ml).

Results: RLS was found in 14 (32.5%) of the 43 ADHD subjects. Parent- and teacher-rated behavioral and emotional problems and the severity of ADHD symptoms were not significantly different between ADHD subjects with RLS and those without RLS ($p>0,05$). The rate of iron deficiency was significantly higher in ADHD subjects with RLS when compared with ADHD subjects without RLS ($p = 0.005$).

Conclusions: Depleted iron stores might increase the risk of having RLS in ADHD subjects. Iron deficiency, which is associated with both ADHD and RLS, seems to be an important modifying factor in the relationship between these two conditions.

Tu-321

Discrete spinal cord functional abnormalities in patients with restless legs syndrome revealed by electrophysiological study of H- and patellar reflexes

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Objective: The objective of the study was to compare the responses of spinal reflexes (as a measure of spinal excitability) in RLS patients at different times of the day as well as with healthy participants

Background: restless legs syndrome (RLS) is characterised by an uncomfortable sensation in the legs, exacerbated during periods of evening inactivity or sleep, resulting in an urge to voluntarily move the legs to relieve the discomfort. The night time expression of RLS symptoms, and lack thereof in the morning, suggest that the aeitology of RLS has a possible circadian influence. RLS is presumed to be caused by a central deficiency of dopamine or other functional abnormalities of the central nervous system and, of particular interest in this study, hyperexcitability of the spinal cord.

Methods: Standard electromyographic techniques were used to quantify patellar and Hoffman reflexes in RLS patients (n=11) and healthy age and gender matched control subjects (CONT, n=9). Biomechanical kinematic analysis was also performed on the patellar reflexes to measure knee angular velocity and displacement. Both reflexes were tested in the evening (PM) and again the following morning (AM). The Visual Analogue Scale (VAS) was used to assess the pain perception of inducing the H-reflex.

Results: The RLS patients had a significantly attenuated patellar reflex amplitude in the evening compared to the control group ($P = 0.04$) and compared to the RLS morning measurements ($P = 0.0078$). Also, RLS patients had significantly less knee angular displacement in the evening ($P = 0.0177$) compared to controls. There were however no significant differences in any of the H-reflex measurements. The VAS pain score recordings were significantly greater in the control subjects than the RLS patients ($P = 0.0451$).

Conclusions: There was no apparent evidence of global spinal hyperexcitability in RLS patients as measured by these parameters. The various changes seen – attenuated patellar reflex amplitude and knee angular displacement, and altered pain perception–do indicate some discrete abnormalities in spinal cord function, amongst RLS patients.

Tu-424

Gabapentin enacarbil improves mood, quality of life, and functioning in subjects with primary restless legs syndrome

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Objective: To evaluate the effects of gabapentin enacarbil (GEn) on restless legs syndrome (RLS) symptoms, mood, quality of life (QoL), and functioning in subjects with RLS.

Background: GEn is a non-dopaminergic therapy under investigation for the treatment of primary RLS. RLS symptoms may negatively impact subjects' mood, QoL, and functioning. The efficacy of GEn on these endpoints was evaluated.

Methods: XP052 was a 12-week, double-blind, placebo-controlled, multicenter study. Subjects with moderate-to-severe primary RLS were randomized to GEn 1200 mg (n=114) or placebo (n=108) once daily at 5 pm with food. Co-primary endpoints were mean change from baseline in International Restless Legs Scale (IRLS) total score and proportion of responders (rated 'very much' or 'much' improved) on the investigator-rated Clinical Global Impression–Improvement (CGI-I) scale. Mood, QoL, and functioning were assessed using the Profile Of Mood State (POMS) and a Mood Assessment Question (MAQ), the Johns Hopkins RLSQoL questionnaire, and item 2 (ability to function in the past week) of the Post-Sleep Questionnaire (PSQ). Tolerability was assessed by the reporting of adverse events (AEs).

Results: GEn significantly improved mean IRLS total score vs placebo at Week 12 LOCF compared with baseline (adjusted mean treatment difference [AMTD] for change from baseline: –4.0; 95% CI: –6.2, –1.9; $p=0.0003$) and significantly more subjects were CGI-I responders (76% vs 39%; adjusted odds ratio: 5.1; 95% CI: 2.8, 9.2; $p<0.0001$). GEn significantly improved POMS total mood disturbance score from baseline (AMTD: –6.9; 95% CI: –11.1, –2.7; $p=0.014$), overall mood (MAQ; $p=0.0008$), mean RLSQoL overall life impact score (AMTD [SE]: 7.8 [1.86]; $p<0.0001$), and ability to function (PSQ, item 2; $p=0.0002$) vs placebo at Week 12 LOCF. The two most frequently reported AEs for GEn and placebo, respectively, were somnolence (27% vs 7%) and dizziness (19% vs 5%).

Conclusions: GEn 1200 mg once daily significantly improves RLS symptoms, as well as overall mood, QoL, and functioning.

We-309

Atypical and interesting cases of restless legs syndrome

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Objective: To describe three atypical cases of restless legs syndrome (RLS).

Background: RLS has only recently been recognized as a medical condition attributable to central nervous system dysfunction. Some causes have been detected; impairments in brain iron availability and hypofunction in brain dopamine signaling. But the precious mechanism of RLS has not yet been detected.

Methods: Three case reports.

Results: Patient 1: A 57-year-old women experienced an uncomfortable urge to move the left leg with during the latter half of each of her three pregnancies (the first was at 24 years of age). That symptom disappeared after each delivery. After these periods, she complained of nighttime awakening by left leg problems during the summer and the symptoms progressed to every days. On laboratory data, there were no signs of anemia. The symptoms subsided with dopamine agonist. This RLS seems to be associated with sex hormone and domapinergic factors but her symptoms almost entirely involved the left leg. Patient 2: A 42-year-old women was admitted with uncomfortable and unpleasant sensations in both legs. Laboratory studies showed iron deficiency anemia (Hb 9.g/dl, serum Fe 22μg/dl), increased protein (146mg/dl) and pleocytosis (39/μl) in the cerebrospinal fluid. She was treated with steroid hormone and iron preparation and the symptoms vanished completely within six months. It was hypothesized that RLS in this case involved two causes, iron deficiency anemia and some inflammation of the central nervous system. Patient 3: A 65-year-old women had been diagnosed as having Parkinson's disease more than ten years. She demonstrated wearing-off symptoms and a sensation of discomfort that difficult to describe in both legs, which considered RLS. Gait disturbance suddenly appeared in one day, and on admission, the new neurological findings were limited to right lower limb monoparesis. We treated her as having fresh cerebral infarction, but she developed right hemiparesis and mild motor aphasia. The brain MRI demonstrated advanced infarction of left frontal lobe. After a few months rehabilitation, she noticed that wearing-off symptoms decreased and RLS disappeared. Recently, deep brain stimulation (DBS) of certain neural nuclei have been shown to improve the symptoms of RLS. The infarction in this case was thought to act as a form of DBS.

Conclusions: Atypical RLS case reports are useful to consider the etiology and the mechanism of RLS.

We-310

Transcranial brain sonography in idiopathic Parkinson's disease with and without restless legs syndrome

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Objective: The purpose of this study is to confirm if there is difference in transcranial sonographic findings between Parkinson's disease with RLS and without RLS.

Background: Echogenicity of substantia nigra (SN) on transcranial brain parenchymal sonography has known to be influenced by the amount of tissue iron contents. Hyperechogenicity of SN determined by transcranial brain sonography (TCS) is a characteristic finding in idiopathic Parkinson's disease (IPD), while restless legs syndrome (RLS) recently demonstrated hypoechogenicity of SN, though the echogenic findings are variable according to the etiology of RLS. RLS is one of the most frequently accompanied sleep problems in IPD but pathophysiologic correlation of these two disorders are not fully elucidated.

Methods: 50 IPD patients(mean age 64 ± 10.3 yrs) and 41 controls (71.6 ± 4.6 yrs) were enrolled and clinical data of history and examination was collected. All subjects answered sleep questionnaire and underwent TCS. Diagnosis of RLS was according to the criteria and subjects who have experienced that congruent with RLS symptoms prior to recognizing parkinsonism were excluded. IPD patients were subdivided with (n=29) and without RLS (n=21) group to compare the sonographic findings.

Results: Although significant hyperechogenicity in both SN area and SN/midbrain ratio was detected in IPD compared with control group ($p<0.001$), there was no significant differences of echogenicity between with and without RLS group. Recognized symptom onset age, disease duration, UPDRS score and other clinical parameters between two groups revealed no statistical differences.

Conclusions: Comorbid RLS with IPD did not have an impact on the sonographic SN findings. This results suggest the possibility that frequently accompanied RLS in IPD might have a different pathomechanism compared with that of idiopathic RLS. Further study with more patients will be required to clarify the relation between RLS and Parkinson's disease.

We-311

A randomized, double-blind, placebo-controlled study to assess the efficacy and tolerability of gabapentin enacarbil in subjects with restless legs syndrome

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Objective: To assess the efficacy and tolerability of gabapentin enacarbil (GEn) 1200 mg and 600 mg compared with placebo in adults with moderate-to-severe primary restless legs syndrome (RLS).

Background: GEn is a non-dopaminergic treatment under investigation for RLS.

Methods: In the 12-week, double-blind, randomized, placebo-controlled PIVOT RLS II study (XP053), subjects received GEn 1200 mg, 600 mg, or placebo (1:1:1) once daily at 5 pm with food. Co-primary endpoints, GEn 1200 mg vs placebo: mean change from baseline in International Restless Legs Scale (IRLS) total score and proportion of responders ('much' or 'very much' improved) on the investigator-rated Clinical Global Impression–Improvement (CGI-I) scale at Week 12 LOCF. Secondary comparison: GEn 600 mg vs placebo for the same outcomes. Tolerability evaluation included assessment of adverse events (AEs).

Results: For the modified ITT population (n=321; GEn 1200 mg=111, 600 mg=114, placebo=96), GEn 1200 mg improved mean IRLS total score vs placebo at Week 12 LOCF (–13.0 vs –9.8; adjusted mean treatment difference [AMTD] for change from baseline: –3.5; 95% CI: –5.6, –1.3; p=0.0015); more subjects receiving GEn were CGI-I responders (77.5% vs 44.8%; adjusted odds ratio [AOR]: 4.3; 95% CI: 2.3, 7.9; $p<0.0001$). GEn 600 mg improved mean IRLS total score vs placebo (–13.8 vs –9.8; AMTD: –4.3; 95% CI: –6.4, –2.3; $p<0.0001$); more subjects receiving GEn were CGI-I responders (72.8% vs 44.8%; AOR: 3.3; 95% CI: 1.8, 6.0; $p<0.0001$). Most AEs were mild or moderate in intensity. The two most commonly reported AEs (GEn 1200 mg, 600 mg, placebo) were dizziness (24%, 10%, 5%) and somnolence (18%, 22%, 2%). AEs led to withdrawal in 7.2%, 6.1%, and 6.3% of subjects, respectively.

Conclusions: GEn 1200 mg once daily significantly improves RLS symptoms compared with placebo. A treatment benefit is also seen with GEn 600 mg once daily. Both doses are generally well tolerated.

We-312

SWITCH: An open-label prospective study of switching from pramipexole to ropinirole in RLS

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Objective: The purpose of this study was to determine if switching to either a 1:4 or a 1:6 ratio of pramipexole (Prx):ropinoro-

le(Rop) was equipotent in patients with moderate to severe primary restless legs syndrome (RLS) currently treated with Prx.

Background: Dopamine agonists are efficacious in RLS and clinicians often switch between therapies for optimal benefit or due to cost. The best strategy to switch from Prx to Rop without losing clinical efficacy remains undetermined.

Methods: SWITCH was an investigator-initiated, open-label study. All RLS medications were stable for at least 4 weeks prior to enrollment and patients were switched overnight to a ratio of either 1:4 or 1:6, Prx to Rop. Clinical Global Impression scales (CGI-I and CGI-S), International Restless Legs Rating Scale (IRLS) and the Epworth Sleepiness Scale (ESS) were obtained at baseline on Prx therapy and at two subsequent visits while on Rop therapy. Tolerability was also assessed. Statistical significance was assessed using $\alpha = 0.05$. Outcome variables included physician-reported CGI-I and subject-reported ESS and IRLS scores. Repeated measures ANOVA was used to examine differences in each outcome measure and Fisher's Exact test was used for differences in tolerability of the drug dose between the two groups. Subjects who withdrew or had their dosage reduced were considered as intolerant of the initial assigned dosage.

Results: Fifteen subjects enrolled, but 2 withdrew and 1 was lost to follow-up. The original 15 patients were used in the analysis of the drug tolerability, but only 12 who completed the entire study were used in the remaining analyses. There were no significant differences for the outcome measures (CGI-I, ESS, IRLS) between groups or between visits. Eight of 9 in the 1:4 group tolerated their dose and completed the study, but only 2 of 6 in the 1:6 group tolerated their dose, suggesting that the 1:6 group did not tolerate the switch as well as the 1:4 group. As the sample size was small, the results were not statistically significant; however, a larger sample size might achieve statistical significance if the trend holds.

Conclusions: A 1:4 ratio of dosing appears ideal when switching moderate to severe RLS patients from Prx to Rop without any worsening of efficacy and tolerability.

We-313

Restless Legs syndrome in adult Celiac disease

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Objective: To evaluate prevalence of restless legs syndrome in a cohort of patients affected by adult celiac disease.

Background: restless legs syndrome (RLS) is a common sensorimotor disorder characterized by an urge to move the legs with unpleasant sensations that occurs or worsens at rest and is relieved by activity. Symptoms usually are worse in the evening or night. This condition, idiopathic in most cases, may be sometimes associated with specific disorders such as iron deficiency. We investigated the prevalence of RLS in adult celiac disease (CD) a condition characterized by several features such as malabsorption related iron deficiency anaemia, neuropathy, irritable bowel syndrome and autoimmune disorders.

Methods: We screened a population of 100 consecutive adult CD patients for CD features, iron metabolism, clinical and neurological conditions. Diagnosis of CD was confirmed by positive duodenal biopsy and tissue transglutaminase antibodies. Presence of RLS was ascertained by the positive answer to the four clinical diagnostic criteria. The International RLS Study Group rating scale was selected to measure RLS severity. Control group consisted of 100 persons enrolled in the general population, matched for age and sex.

Results: We found a 31% prevalence of RLS in the CD population that is significantly different from the prevalence in the control population (4%; $p<0{,}001$). The average severity of RLS in CD population is moderate (17 +/- 6,5). Prevalence of self reported limb movements during sleep is higher in CD patients with RLS (38,7%) than in patients without RLS (15,9%; $p=0{,}025$). In the CD population no statistical correlation was found between RLS and either iron metabolism or gluten free diet. The prevalence of a positive family history for RLS is 25,8% in the RLS population.

Conclusions: RLS is a common condition in CD which does not seem to be caused by malabsorption.

We-314

Effect of tilidin/naloxon for the acute management of RLS-associated periodic limb movements in sleep: An observational study

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Objective: The aim of this observation in our sleep laboratory was to evaluate the acute efficacy of Tilidin solution (in form of drops) fixed combined with the Opioid antagonist Naloxon, for the management of PLM and RLS-related sleep disorders in subjects experiencing moderate to severe RLS symptoms under therapy and requiring additional treatment at night-time.

Background: Low-potency opioids represent a well known optional and effective therapy in the treatment of restless legs syndrome (RLS). Two identified double-blind, randomized trials have demonstrated the effectiveness of oxycodone and propoxyphene concerning relief of RLS symptoms and decrease of periodic limb movements (PLM). Long-term benefit for RLS with opioids has also been described. However, the number of available studies remains limited, particularly in comparison with dopaminergic agents.

Methods: 18 patients (9 men, 9 women; mean age 69,5 years) fulfilling the diagnostic criteria of the international RLS Study Group, were enrolled. Concomittant diagnoses included preexisting sleep apnea (6 patients), polyneuropathy (1 patient) and Parkinson's disease (1 patient). Clinical evaluation consisted of completion of the International RLS Study Group Severity Scale (IRLS) and the Augmentation Severity Rating Scale (ASRS). Patients were studied polysomnographically for one night and were instructed to call the nurse if rescue medication was required due to bothersome symptoms. Outcome measure included assessment of the number of PLM one hour before (baseline) and three hours after treatment as well as estimation of the sleep quality before and after drug administration.

Results: On an average a dose of 40mg Tilidin/Naloxon was given. Compared to one hour before Tilidin administration there was a statistically significant reduction in the number of PLM ($p=0.004$) during the 3 hours after Tilidin application, and a reduction of the wake time ($p=0.004$) as compared to baseline.

Conclusions: Tilidin as solution is effective as additional short term medication on demand for the treatment of patients with moderate to severe RLS-symptoms measured by objective sleep parameters.

We-315

Intravenous iron dextran for severe refractory restless legs syndrome

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Objective: To report the efficacy and tolerability of high dose intravenous iron dextran in medically refractory RLS.

Background: Reduced brain iron is strongly associated with restless legs syndrome (RLS). Oral iron supplements are commonly recommended for RLS but are largely ineffective secondary to poor absorption and poor tolerability at required doses. In contrast, intravenous iron markedly increases body iron stores and has been shown to increase brain iron content. Surprisingly only a few reports have ever presented data on the clinical effect of high dose intravenous iron for RLS.

Methods: We identified 17 subjects (14 female, age 51(12) years) that received intravenous iron for medically refractory RLS. We infused 1 gm of iron dextran over five hours using a standard protocol.

Results: The age of RLS onset was 32(11) years and 11 had a positive family history. Patients were unsatisfactorily treated with 7.9(2.7) RLS medications prior to infusions, including 3.9(1.3) different dopaminergics. Pre-infusion serum ferritin levels were less than 36 μg/ml in 15 subjects, mean of 39(65) μg/ml, but this was not required for inclusion. In ten subjects with a post-infusion ferritin, the serum levels increased from 15(10) μg/ml to 340(201) μg/ml. One subject was lost to follow-up. A 75% improvement in symptoms was reported by 11/16 subjects. Two reported moderate benefit and 3 had no meaningful benefit. Interestingly, the duration until onset of benefit was 4.7(3.8) days. The duration of benefit varied greatly [range: 2 weeks to 14 months], mean 17(18) weeks. Ten subjects reduced or stopped their oral medications after infusion. Iron infusions were repeated iat least once in 10 subjects. Reasons for not currently continuing include lack of benefit (4), high serum ferritin (2), and adverse events (1). One subject had a moderate anaphylactic reaction after administered 500 mg but actually had a very good subsequent clinical response. Two had a rash within a week of infusion and one reported a headache.

Conclusions: Intravenous iron dextran can dramatically improve refractory RLS. Although burdened by a higher rate of anaphylactic reactions, iron dextran may be superior to other intravenous iron preparations.

We-316

Detection of patients with restless legs syndrome in outpatient clinic: Primary results from Slovak Republic

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Objective: This study was aimed to detect and more precisely characterize patients with restless legs syndrome (RLS) using questionaire.

Background: RLS is frequent but extremely underdiagnosed condition. Up to now, a systematic study on epidemiology of RLS have not been done in the Slovak Republic.

Methods: Study sample was created by 555 persons who were recruited in a waiting-room of neurological outpatient clinic. All participants firstly filled a brief questionaire aimed to collect demographic data and than responded to four specific questions, i. e. essential criteria for RLS according to the International Restless Legs Syndrome Study Group. If respondent answered positively, he/she was classified as probable RLS-suferrer. Consecutively he/she underwend a second part of the questionaire. It was applied by physician or trained nurse. This part was oriented to confirmation and particular RLS description. If respondent did not respond positively to all four diagnostic questions, he/she was classified as negative in relation to RLS. The negative state was also approved by repeated questioning by physician or nurse.

Results: In our sample, the criteria for clinical diagnosis of RLS discharged altogether 23.4 % of respondents (in men 18.1 %, in women 26.5 %). Thirty five percent of RLS-suferrers referred daily occurence of RLS symptoms. However, 19 % of them had RLS symptoms one day in month and less. RLS begun in average age of 45.7 ± 16.1 years, and it persisted already for 8.6 ± 8.2 years. Sleep disorders caused by RLS have been referred in 58 % of RLS-suferrers. Familiar occurence of RLS was reported by 41.9 % of patients. RLS-suferrers were more extensive healthcare consumers (RLS-suferrers versus respondents without RLS: number of medicaments (2.6 ± 2.7 versus 2.0 ± 2.5, $p = 0.02$); number of visits of physician in last 3 months (3.0 ± 2.9 versus 2.4 ± 2.6, $p = 0.03$).

Conclusions: RLS is entity with very high prevalence, and significant health as well as economic consequences. Unfortunatelly, the most of afflicted people do not recognize it as treatable disease. Detection of this population by means of simple questionaire, e. g. during waiting for clinical assesment or treatment, is very effective approach applicable in a broad medical practice.

We-415

Restless Arms syndrome: Report of 2 cases

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Objective: To report 2 cases of pure upper limbs (UL) restlessness syndrome.

Background: Restless legs syndrome (RLS) typically is described as an irresistible urge to move the legs, accompanied by unpleasant sensations, that worsens during rest, with partial improvement by moving the lower limbs. The symptoms also get worse or starts in the evening. Some patients with RLS may also have upper limbs (UL) symptoms.

Methods: Report of two cases.

Results: Case 1: a 47 year old male with a 7 month history of UL discomfort, the symptom occurred exclusively while lying in his bed to sleep at night. The sensation was transiently relieved by touching or massaging these areas and by shrugging the shoulders and abducting the arms. There were no symptoms in the lower limbs. Cervical spine MRI and upper limbs EMG were unremarkable. Signs were interpreted as fibriomyalgia and treated with amitryptiline 25mg bd that resulted in significant worsening. Screening for metabolic, inflammatory and hematologic abnormalities, were all negative, including normal iron and ferritin levels. He was started on pramipexole 0.125mg at bed time with excellent response after a six months follow up. Case 2–a 44 year old man initially assessed for an acute peripheral vestibular syndrome. After 3 months, he returned with complaints of bilateral and symmetric UL discomfort that started and worsened in the evening. During the daytime he was unaffected. The unpleasant sensation improved with shaking, rubbing or moving the arms. He never had legs complaints. He was not using any medication. Laboratory testing including glucose, thyroid, renal, hepatic function, ferritin, iron, cervical MRI and upper limbs EMG were done and were all normal. He was started on pramipexole 0.125mg qd, and steadily increased up to 1,0 mg at bedtime, with complete remission of symptoms after 10 months follow up.

Conclusions: Upper limbs involvement in RLS is not rare, but the exclusive involment of the arms without concomitant or subsequent legs symptoms is unusual. The physiopathology of RLS remains only partially explained: abnormal spinal hyperexcitability along several segments of the spinal cord may be the background mechanism, while the triggering mechanism is hypothesized to occur at a supraspinal level most likely involving dopaminergic systems. However, this and other proposed theories fail to explain why symptoms of RLS begin more commonly in the lower limbs.

Th-312

Medical conditions associated with Restless Legs syndrome: Anxiety disorder is on first line

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Objective: Based on recent data about the association between restless legs syndrome (RLS) and different medical conditions, we performed a study on the occurrence of comorbid disorders in patients with RLS.

Background: Several conditions were shown to be associated with restless legs syndrome (RLS), especially anemia and, renal failure, rheumatoid arthritis, fibromyalgia and peripheral neuropathy. These are considered "secondary" forms of RLS. In absence of those medical disorders, RLS is called "primary" or "idiopathic" RLS, the most frequent form of this condition. Nowadays, new comorbidities and risk factors including mood disorders have described in literature.

Methods: Four thousand five hundred patients which have been seen in the general neurology outpatient clinic between 2006 and 2008 were evaluated as retrospectively and 76 patients with RLS were selected, a telephone interview was made with them, and they were invited. Fifty-five patients (34 females and 21males) accepted

and they re-evaluated. The presence of associated conditions was determined by clinical interviews, complete physical and neurological examinations, and blood chemistry and electromyogram when clinically recommended. Also, Hamilton depression and anxiety scales were applied to all patients.

Results: Seventy-six patients (1.6%) of the general neurology outpatient clinic were suffering from RLS. We could re-evaluated 55 of them. Among the RLS subjects, 61.8 % was female (mean age 55±14 years), and 38.2% was male (mean age 61±11 years). RLS symptoms were reported for a mean duration of 5.8±7.4 years (range=1–35 years). Mild-moderate depression was noted in 3 patients (5.4%) and generalized anxiety disorder were found in 13 patients (23.6%) with RLS. Other comorbid conditions were iron deficiency anemia (7.3%), type 2 diabetes mellitus (7.3%), parkinsonism (5.4%), Alzheimer's disease (5.4%) lumbar disc herniation (10.9%), hypertension (12.7%), and obstructive sleep apnea syndrome (9%).

Conclusions: There is a significant relationship between physical and mental health problems and RLS. Our results strongly suggested that it was clear associaton between anxiety disorders and RLS. That relationship might be originated reciprocal interactions and common pathophysiologies. Further investigations are needed.

Th-313

Clinical and genetic study of a large Dutch family with autosomal dominant Restless Legs syndrome

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Objective: To describe the clinical features and to present the results of the genetic analysis of a large Dutch family segregating autosomal dominant RLS.

Background: Genetic factors play an important role in the aetiology of restless legs syndrome (RLS). Familial aggregation has been well documented with up to 90% of the idiopathic cases reporting a positive family history for RLS. During the last decade several loci and association with several genes have been described for Mendelian forms of RLS.

Methods: All living family members were personally examined and an extended pedigree was constructed. Each family member underwent a general medical and neurological examination. An extensive questionnaire was completed, and RLS symptoms were quantified using the International RLS Rating Scale as mild (1-10), moderate (11-20) and severe (21-30). DNA was isolated from peripheral blood. Serum creatinine, hemoglobin and iron levels were also determined to rule out secondary RLS in this family. A genome-wide scan for linkage is in progress using the Affimetrix GeneChip® Human Mapping 250K Array set (~250.000 SNP markers, average intermarker distance ~10kb). Affected-only linkage analysis is performed considering the patients with severe or stably moderate RLS rating scale score as " affected".

Results: Thirty-one family members out of three generations (10 men and 21 women) consented to participate. RLS was ascertained in twenty-six subjects. Mean age at examination was fifty years (20-93). The average age at symptom onset was 17.8 years (6-35). Serum levels of creatinine, hemoglobin and iron all were in normal ranges. RLS symptoms were quantified using the RLS rating scale, with a mean initial score of 12 (0-29) and 12,3 (0-29) after two years. In this family the phenotype is very heterogeneous, including vanishing RLS symptoms in 2 patients during life.

Conclusions: Age at onset in this family is younger (17 versus 27) than described in the literature. Two persons exhibit a vanishing RLS phenotype. Due to large pedigree size and early-onset phenotype, this family has great potential for linkage analysis and the results will be presented.

Th-314

Restless Legs syndrome in stroke patients

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Objective: We conducted an in-patient hospital based cross-sectional study to assess the prevalence of restless legs syndrome (RLS) symptoms in patients with acute stroke and TIA.

Background: It has recently been reported that RLS symptoms may appear following ischemic stroke. Symptoms may be bilateral or restricted to the side affected by stroke. Some cases have been linked to subcortical brain lesions.

Methods: Adults hospitalized with a diagnosis of stroke or TIA underwent an interview according to the International RLS Study Group criteria. Prevalence of RLS was compared with that of a large cohort of adults without a history of stroke, attending their annual check-up.

Results: The prevalence of RLS among stroke or TIA patients was 14% (21/150) compared with 6.7% (103/1537) among controls ($p=0.003$). Among stroke or TIA patients RLS was more prevalent in woman than in men, 22% vs.10% (11/49 vs. 10/101, $p=0.044$). Among 21 patients with RLS, current hospitalization was for ischemic stroke in 12, hemorrhagic stroke in 3 and TIA in 6. Twelve RLS patients listed below had a previous hospitalization for either stroke or TIA: two patients were symptomatic many years before their first stroke, five patients became symptomatic 2-5 years after stroke or TIA, two patients with a stroke 2-7 years earlier became symptomatic one month prior to current stroke, one patient's symptoms exacerbated one month prior to stroke and two more patients had a TIA one month prior to current stroke with RLS symptoms appearing together with the TIA. Nine patients had long standing RLS symptoms with no previous clinical history of stroke.

Conclusions: RLS is more prevalent in stroke or TIA patients as compared with controls. The appearance of RLS symptoms in some patients shortly before the occurrence of stroke or TIA is intriguing.

Th-315

Long-term open-label study to evaluate the safety and efficacy of pramipexole (PPX) in Japanese patients with primary Restless Legs syndrome (RLS)

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Objective: To examine the safety, including the occurrence of augmentation, and efficacy of PPX at flexible doses of 0.25 mg, 0.5 mg, and 0.75 mg once daily for 46 weeks.

Background: PPX, dopamine agonist, has been shown to be highly effective against RLS in long-term trials conducted in Western countries. However there is no report on long-term efficacy and safety of PPX in Japanese patients with primary RLS.

Methods: A total of 141 Japanese patients with primary RLS who completed the prior 6-week randomized double blind trial proceeded to the open-label extension period. Patients were initially given PPX 0.25 mg, and the dosage could be increased to 0.5 mg/day then to 0.75 mg/day, as necessary, every 2 weeks. Efficacy of PPX on RLS symptoms was assessed using standard scales such as International RLS Study Group rating scale (IRLS), Patient Global Impression (PGI), and Clinical Global Impressions-Global Improvement (CGI-I) at each visit (at weeks 2, 4 and every 4 weeks thereafter). Augmentation, defined as the appearance of symptoms ≥2 hours earlier than usual time for ≥5 days/week, was assessed by checking the patients' diary-recorded onset time of RLS symptoms every day.

Results: Of the 141 patients, 123 (87.2%) completed the trial. PPX consistently maintained good RLS efficacy across all endpoints. The mean (±SD) change IRLS total score decreased steadily from 8.7 ± 6.9 at week 4, when optimal doses were being administered to each patient, to 4.9 ± 5.9 at week 46. The mean change in IRLS total score from baseline at week 4 and 46 was -13.5 ± 6.5 and -17.2 ± 6.7, respectively. The responder rates of IRLS, CGI-I, and

PGI increased gradually over time in the 46-week open-label period. Overall, of the patients who responded to PPX in IRLS, CGI-I, and PGI, approximately 80% were under treatment with ≤0.5 mg and approximately 20% under that with 0.75 mg. No specific concerns were found relating to PPX safety and tolerability. A possible augmentation was detected in only 6 of 141 patients during the trial and resolved by increasing and maintaining the dose after the onset for all cases.

Conclusions: Our results revealed that PPX 0.25–0.75 mg/day is considered efficacious, safe, and well tolerated for the 46 weeks of long-term treatment of RLS in Japanese patients.

Th-316

Prevalence of sleep disorders in children with movement diosrders

T.B. Soman (Toronto, Ontario, Canada)

Objective: A pilot study to determine the prevalence and nature of sleep disorders in children with movement disorders.

Background: Sleep disturbances are a common complaint in children with movement disorders like Tourette syndrome (TS). It has been reported that approximately 12-62% of TS patients have increased nighttime awakenings, somnambulism and motor and phonic tics in the sleep. Sleep disturbances are also present in children with dystonia, chorea or choreoathetosis. However, the incidence and frequency of sleep disorders in these patients has not been widely studied.

Methods: Patients, 2-17 years of age, diagnosed with a movement diosrder (dystonia, chorea, athetosis, ballismus, tics, tremor, ataxia, myoclonus and stereotypy) were included. Diagnosis of movement disorders was made in the Pediatric Movement Disorders Clinic by the treating neurologist. In this pilot study parents were asked to complete a validated pediatric sleep questionnaire- *Sleep Disturbance Scale for children* (SDSC). Data was analyzed and results expressed in percentages.

Results: A consecutive cohort study of children at a Pediatric Movement Disorders Clinic included 50 families. Analysis of the SDSC revealed that 40% (20) children had restlessness in sleep. Restlessness was noticed in legs by 18% (9). A complaint of unexplained leg pains was reported in 28% (14) patients. 42% parents reported having seen their child kick at least once or twice in bed while asleep, while 8% noticed more frequent kicks. Groups were divided into Tics/Tourettes and other Movement Disorders for analysis. Leg pains were reported twice as frequently in the tics group-36% vs 17% respectively. Both groups were found to have restlessness; however, children with non-tic group experienced more restlessness (47% vs 25%). Though not conclusive, these results indicate that there could be underlying restless leg syndrome (RLS) or sleep apnea disorders that are underdiagnosed in this population.

Conclusions: 40% **c**hildren with involuntary movement disorders have excessive movements in sleep. The exact nature and etiology of movements needs to be investigated. This pilot study was performed to determine prevalence and identify the group of patients who might benefit from further intervention. We propose to further investigate the "restless" group with sleep studies to determine whether there is a component of sleep apnea, RLS or other sleep disturbances in this population.

Th-317

Peripheral neuropathy in patients with Parkinson's disease and Restless Legs syndrome

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Objective: The goal of the study was to find out the incidence of neuropathy in patients with Parkinson's disease (PD) and to validate higher incidence of neuropathy in parkinsonian patients with restless legs syndrome.

Methods: The study group consisted of 32 patients with Parkinson's disease (PD). 17 of them displayed signs and symptoms of restless legs syndrome (RLS+ subgroup) (mean age 68,5 years) and 15 patients were without RLS symptomatology (RLS- sugroup) (mean age 65,5 years). In all patients we completed clinical neurological exam, Neuropathy Disability Score (NDS), EMG of lower extremities (conduction study, needle EMG), quantitative sensory thermal threshold testing (QS-TTT) and skin biopsy with quantification of density of intraepidermal nerve fibers.

Results: In the whole PD group we found abnormalities of nerve conduction studies and needle EMG (as sign of large fiber polyneuropathy) in 13 patients (40,6%): 6 patients from the RLS+ subgroup and 7 patients from the RLS- subgroup. TTT was normal in 19 patients and abnormal in other 13 patients, while in 23 patients (71,9%) score gives evidence of neuropathy of mild or moderate degree. Decreased intra-epidermal nerve fiber density was found surprisingly in all examined patients.

Conclusions: We didn't confirm the higher occurence of polyneuropathy in parkinsonian patients with the restless legs syndrome that would support hypothesis about the share of neuropathy in pathogenesis of RLS. All tests indicate relativelly high incidence of neuropathy in patients with PD, particularly of small fiber type. It is, however, necessary to disclose the cause of described abnormalities (e.g. influence of antiparkinsonian drugs on the peripheral nervous system, peripheral nervous system manifestation of Parkinson's disease) and their clinical relevance.

Th-318

26-week effects of placebo-controlled pramipexole on overall severity, night/day symptoms, and augmentation risk in Restless Legs syndrome

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Objective: To evaluate overall efficacy, nighttime/daytime efficacy, and risk of augmentation (treatment-associated exacerbation) for pramipexole in restless legs syndrome (RLS), as rated for double-blind treatment longer than studied previously.

Background: In RLS, dysesthesia is worsened by efforts to rest and compels patients to move. The nighttime impact may extend into daytime life.

Methods: For 26 weeks, RLS patients took double-blind placebo or pramipexole (optimized at ≤0.75 mg/d). At baseline and endpoint, they completed the International RLS Study Group's RLS scale (IRLS) and the RLS-6 (ratings from 0 [none] to 10 [very severe]). Three ratings are nighttime problems (sleep satisfaction, RLS severity while falling asleep, and severity during the night), and 3 are daytime problems (severity while resting, severity while active, and daytime tiredness). Patients also marked a 100-mm limb-pain visual analogue scale (VAS). By ANCOVA (adjusted for country and treatment group) or van Elteren test (stratified by country), $P \leq .05$ was considered significant. Augmentation was confirmed/excluded by a blinded expert panel, which reviewed all suspected cases after ≥4 weeks of treatment.

Results: In all, 162 pramipexole and 159 (IRLS/RLS-6) or 158 (VAS) placebo recipients contributed data (Table). On IRLS, adjusted scores improved a mean –13.7 vs –11.1 ($P = .0077$). On RLS-6, nighttime problems improved a median –2.5 vs –2.0 ($P = .0489$) for sleep satisfaction, –3.0 vs –1.0 ($P = .0315$) for severity while falling asleep, and –3.0 vs –2.0 ($P = .0735$) for severity during the night. Daytime problems showed no significant differences, including, for symptoms while active, no median change from low baseline scores. On VAS, pain ratings improved a median –26.0 vs –15.0 ($P = .0916$). Among pramipexole recipients, 18 (11.8%) received expert-panel ratings of augmentation vs 14 (9.4%) for placebo.

Table (Th-318). 26-Week Changes on Efficacy Measures (unadjusted means or medians)

	Pramipexole		Placebo	
	Baseline	Endpoint	Baseline	Endpoint
IRLS mean score	23.9	10.7	23.5	13.2
RLS-6 median scores				
Sleep satisfaction	6.0	3.0	6.0	4.0
Severity while falling asleep	5.0	1.0	5.0	2.0
Severity during the night	5.0	0.0	5.0	1.0
Tiredness/sleepiness	4.0	1.0	4.0	2.0
Symptoms while resting	4.0	1.0	4.0	1.0
Symptoms while active	1.0	0.0	1.0	0.0
Limb-pain VAS median score	50.0	16.0	55.0	27.0

Conclusions: In RLS treated for 26 weeks, pramipexole-related improvement was greatest for nighttime problems (maximally significant while falling asleep), and lower for less severe daytime problems (maximally insignificant when movement would mask RLS). Initially moderate leg pain showed a trend toward pramipexole-related amelioration. Risk of augmentation, judged by experts, resembled placebo.

Th-319

Effects of rotigotine transdermal system on quality of life in idiopathic restless legs syndrome

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Objective: The purpose of this study was to evaluate changes in quality of life (QoL) globally and in particular QoL domains under treatment with rotigotine, a transdermally delivered (patch) dopamine agonist, in patients with moderate to very severe idiopathic RLS.

Background: restless legs syndrome (RLS), if clinically relevant, causes bothersome impairment of QoL and functioning in daily activities.

Methods: Multicenter, randomized, double-blind, placebo-controlled, 4-arm parallel-group trial with 3 fixed transdermal doses of rotigotine 1–3 mg/24h over a 6-month period. QoL was assessed with the QoL-RLS quality of life questionnaire. The scale is analyzed by a total score of 12 items (range 0–60); in addition, four domains of QoL (impact of RLS symptoms, sleep disorders, other features like pain, coping behaviour) as well as a global assessment of QoL "all in all" were evaluated.

Results: A total of 549 subjects (58 ± 11 years, 73% female) were enrolled at 49 sites in 8 European countries and 458 subjects were randomized. The overall mean baseline IRLS score was 28.1±6.1 indicating, on average, severe RLS of the study population. QoL was moderately impaired at baseline (QoL-RLS total score: 32.2 ± 11.8). Between baseline and the end of the trial, the QoL-RLS total score improved significantly more in the pooled rotigotine treatment groups than under placebo ($P<0.001$, effect size ES=0.58). In the 1, 2 and 3 mg/24h rotigotine groups, mean change from baseline in total QoL-RLS score improved by -13.1, -15.7 and -17.5 compared to -7.3 with placebo. With the exception of the subscale covering pain and treatment side effects (ES=0.24), rotigotine showed markedly larger improvements than placebo with regard to the impact of RLS-specific symptoms (ES=0.56), sleep disorders (ES=0.49), and coping with RLS symptoms (ES=0.46) on QoL. QoL "all in all" was much better (ES=0.60).

Conclusions: Rotigotine in dosages of 1 to 3 mg/24h improved overall quality of life and reduced the impact of RLS-specific symptoms, sleep disorders and coping behavior on the patients mood, efficiency and behavior in daily activities in this study.

Th-320

Remission rates with rotigotine transdermal system in idiopathic RLS: Combined results from two 6-month, double-blind, placebo-controlled trials

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Objective: To evaluate the proportion of patients treated with rotigotine in two placebo-controlled trials that achieved complete remission from clinical restless leg (RLS) symptoms.

Background: Rotigotine is licensed in Europe and the US for the treatment of Parkinson's disease and is in development for treatment of RLS. While many dopamine agonists reduce RLS symptoms, they often fail to achieve symptom remission. A key measure of any new RLS treatment will be the rate of symptom remission.

Methods: Pooled data were analyzed from two 6-month, double-blind, placebo-controlled trials. Subjects were stratified by International RLS Study Group Rating Scale (IRLS) sum score at baseline (moderate [IRLS 11-20], severe [IRLS 21-30] or very severe [IRLS 31-40]). Remission rates were calculated as symptom-free remitters (IRLS sum score=0 at trial endpoint) and clinical remitters (IRLS≤10 at trial endpoint).

Results: A total of 843 patients were randomized to placebo or rotigotine (1-3mg/24h). Overall, 24.6% of rotigotine treated patients were symptom-free (IRLS=0) compared to 10.8% for placebo. The clinical remission rate (IRLS≤10) was 49.7% for rotigotine compared to 27.2% for placebo. Analysis of symptom-freedom stratified by baseline symptom severity revealed that IRLS scores of 0 were achieved by 28.5% (rotigotine) vs 16.3% (placebo) of patients with moderate RLS, 24.8% vs 9.2% with severe RLS and 20.5% vs 10.0% with very severe RLS. Similarly, clinical remission was achieved by 59.7% of patients with moderate RLS (rotigotine) vs 48.8% (placebo), 51.3% vs 25.0% with severe RLS and 36.4% vs 14.0% with very severe RLS.

Conclusions: In this pooled analysis, rotigotine treatment resulted in high rates of RLS symptom-freedom and clinical remission. In the lower dose range, higher remission rates relative to placebo were seen in patients with moderate symptoms but at the higher end of the dose range remission rates were higher than placebo regardless of symptom severity at baseline.

Th-321

Restless Legs syndrome and Parkinson's disease: Is there a relation between both disorders?

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Objective: To evaluate the frequency of restless legs syndrome (RLS) in a large cohort of Caucasian patients with Parkinson's disease (PD) and to assess the relation between the presence and severity of RLS and important clinical features of PD.

Background: An association between RLS and PD is suggested by several studies, however evidence is still limited and studies in large patient groups considering the full spectrum of PD are needed.

Methods: In 275 non-demented PD patients, the four diagnostic criteria for RLS as described by the International Restless Legs Syndrome Study Group were administered by a personal interview taken by a RLS trained researcher. In patients with a diagnosis of definite RLS by fulfilling all four criteria, the severity of the RLS symptoms was assessed. Furthermore, in all patients, relevant motor and non-motor symptoms in PD were evaluated.

Results: Definite RLS was present in 11% (n=31) of the patients. In most of the RLS patients, RLS developed after diagnosis of PD (77%). Patients with RLS were more often female (71% vs 31%, $p<0.001$) but no other significant differences existed between PD patients with and without RLS. Within the PD patients with RLS, the RLS severity score correlated positively with PD severity, depressive symptoms, daytime sleepiness, motor problems, cognitive problems,

autonomic symptoms, psychotic symptoms, and motor fluctuations (all p-values <0.05).

Conclusions: This study shows that in a large Caucasian PD cohort, the prevalence of RLS is similar to that in the general population. Firstly, it could be possible that there is no etiologic link between both disorders. Secondly, it could be that the link between both disorders is masked by the diminishing effect of dopaminergic treatment on RLS symptoms. The first explanation is supported by the fact that the presence of RLS was not related to disease-specific features. However, the second explanation is supported by the fact that in most cases RLS occurred after diagnosis in PD and that RLS severity was positively related to the severity of most motor and non-motor symptoms of PD. These results suggest a common pathophysiological mechanism present in both disorders, and dysfunction of the diencephalic dopaminergic pathway could possibly be responsible for the underlying relation between PD and RLS.

Th-419

Dilemma of epilepsy, sleep disorder or movement disorder – A difficult differential diagnosis

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Objective: To present a case which poses diagnostic challenge between frontal lobe epilepsy, sleep disorder and movement disorders.

Background: Patients with nocturnal neurological episodes may have frontal lobe epilepsy, parasomnia or a movement disorder. Sometimes the investigations such as prolonged EEG monitoring, sleep study, or imaging may not be conclusive. To determine exact diagnosis may be a chellange. History taking may be the only tool of making a diagnosis.

Methods: We report a case of 17 year old female who developed episodes of right leg jerking after she would fall sleep starting at age 6 months. She would wake up and will continue to have uncontrollable jerking of her right leg for next 15-20 minutes. These episodes are still occuring at age 17 although have become less intense but much more frequent. She has been on moderate dose of carbamazepine without any success. She had history of mild developmental delay in childhood. She was referred to movement disorders clinic by a general neurologist to rule out paroxysmal non kinesogenic dyskinesia and finally to the epilepsy clinic where diagnosis of frontal lobe epilepsy was favoured.

Results: MRI brain was normal Routine, sleep deprived and ambulatory EEGs were normal while she had spells. A differential diagnosis of frontal lobe epilepsy versus parasomnia such as PLMS was considered, frontal lobe epilepsy was favoured and EEG may have been negative because of deep seated ictal focus.

Conclusions: Patients with nocturnal seizures present a diagnostic dilemma between frontal lobe epilepsy, sleep disorder and movement disorders. Assessment in subspeciality clinic may become necessary to address these chellanging cases.

SPASTICITY

Mo-321

Muscle hyperactivity after stroke: Long term follow up of prevalence and current treatment practice

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Objective: To describe prevalence and current treatment practice of muscle hyperactivity (MHA) after stroke.

Background: MHA after stroke can generate substantial health problems.

Methods: 149 patients (70 females, 79 males, age 60.0y, SD 1.41) with stroke and paresis >24h were recruited and examined neurologically, by Modified Ashworth Scale (MAS) for increased muscle tone (IMT), Spasm Frequency Scale (SFS) for spasms, Medical Research Council Scale (MRCS) for paresis and Global Pain Scale (GPS) for pain 4-6m (V1) and 16-26m (V2) after their stroke. Demographic and therapeutic data were collected additionally.

Results: 97 patients were followed through the observation period, 26 died, 26 couldn't be retrieved. At V1 paresis was remitted in 64% of analysable patients, 36% had residual paresis (2% arm, 1% leg, 33% both). 29% showed MHA. 28% (3% arm, 4% leg, 21% both) had IMT, 16% spasms and 2% action induced dystonia. 13% had IMT related pain, 9% with a GPS score >50. Treatment included rehabilitation (65%), physiotherapy (32%), psychotropics (26%), ergotherapy (21%), analgetics (16%) and spasmolytics (5%). At V2 paresis was remitted in 65% of the patients, 35% had residual paresis (0% arm, 3% leg, both 32%). 5 had identical stroke re-occurrence between V1 and V2 (4 with temporary increased paresis). 33% showed MHA. 32% had IMT (2% arm, 6% leg, 24% both), 13% spasms and 3% action induced dystonia. The number of patients with MAS≥2 in arms increased from 12% to 14% (p=0.81), in legs from 11% to 21% (p=0.30). 13% had IMT related pain, 7% with a GPS score>50. Treatment included physiotherapy (25%), ergotherapy (17%), psychotropics (13%), analgetics (9%) and spasmolytics (7%).

Conclusions: 4-6m after stroke paresis has remitted in about 2/3 of patients. In about 1/3 paresis remains. MHA occurs in almost all of them. Usually it consists of a mixture of dystonia, rigidity and spasticity as tested by MAS. Spasms are less frequent and action-induced dystonia is rare. 16-26m after stroke frequency and morphology of MHA remains unchanged. Spasmolytic therapy is insufficient and rarely includes modern spasmolytics such as botulinum toxin.

Mo-322

Analysis of surgical intrathecal [i.t.] baclofen [ITB] implant results emphasizing revision surgery in a mixed pediatric/adult population

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Objective: Reporting our experience with the surgical complication of the ITB.

Background: Increasingly, spasticity is managed with ITB using surgically implanted programmable pumps [Medtronic, Inc.]. ITB revision surgery unrelated to programmable pump end-of-life is not uncommon, requiring special attention during pre-, intra-, and post-operative management. We retrospectively reviewed our recent revision surgery experience based upon 1) primary implants at our own institution [*"primary-implant-patients"*], and 2) operative revisions for cases originally implanted outside our institution [*"revision-only-patients"*].

Methods: Since 2002 we treated 41 patients [21F/20M; 22 children (14F/8M) vs. 19 adults (7F/12M); 30 *"primary-implant-patients"*: 16 children (10F/6M) vs. 14 adults (5F/9M); 11 *"revision-only-patients"*: 6 children (4F/2M) vs. 5 adults (2F/3M)]. Clinical charts, operative and imaging reports were reviewed to evaluate reasons for revision surgery and diagnostic work-up requirements.

Results: Eight of 30 "*primary-implant-patients"* required 14 revisions and 7 of 11 *"revision-only-patients"* needed 13 procedures. Seven patients with slowly increasing baclofen-resistant spasticity had either 1) unsuspected pump-catheter connector defects [N=4] with a subcutaneously dislocated *i.t.* catheter [N=1], 2) an X-ray-documented pump-catheter connector defect [N=1] or 3) an X-ray-demonstrated fractured catheter with *i.t.* fragment [N=2] requiring laminectomy [N=1]. Injection studies revealed *i.t.* peri-catheter arachnoiditis [N=1; managed without laminectomy], and connector-related dye leakage [N=3]. Implant infections occurred in 4 cases [3 were multiply pre-operated]. Scintigraphy revealed occult CSF leakage [N=1]. Intrinsic pump failure was rare [N=1].

Conclusions: ITB, although very gratifying, has a high, predominantly technique-related complication incidence during implant life. Meticulous surgical technique, high clinical suspicion, appropriate

work-up, and timely surgical management are emphasized to reduce surgical ITB complications.

Mo-323

NT201 (Xeomin®; botulinum neurotoxin free from complexing proteins) is efficacious and well-tolerated in upper limb spasticity of various etiologies

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Objective: Efficacy and safety of NT 201 in patients with upper limb spasticity caused by stroke, brain injury, spinal cord injury, multiple sclerosis or cerebral palsy using different dilutions was evaluated.

Background: NT 201 (Xeomin®; Botulinum neurotoxin type A free from complexing proteins, Merz Pharmaceuticals GmbH, Frankfurt/Main, Germany) did not show formation of neutralizing antibodies in pre-clinical trials nor in upper limb spasticity trials in contrast to a complexing-protein containing product (Botox®, Allergan, USA).

Methods: Responder analysis of at least 1-point improvement from baseline to week 4 on the Disability Assessment Scale [DAS] for the primary therapeutic target after injection of a 20 U/mL dilution or 50 U/mL dilution was evaluated. After injection, observation over a 12-week period was followed by 8 weeks safety follow-up. Botulinum neurotoxin doses were derived from the recommendations from the organization WE MOVE. The individual injection pattern was adapted to patient's needs. A two-sided 95% Newcombe-Wilson confidence interval [CI] for the difference between groups was calculated.

Results: 192 patients with upper limb spasticity caused by either stroke (88%), brain injury (5.7%), multiple sclerosis (0.5%) or cerebral palsy (1.6%) were randomized to the 50 U/mL dilution group (95 patients) or to the 20 U/mL dilution group (97 patients). Limb position (60.4%), Dressing (24.0%), Hygiene (9.4%) and Pain (6.3%) were chosen as primary therapeutic target on the DAS. The maximum injected total dose was 495 units NT 201. Four weeks after injection 57.1% of patients had an at least 1-point DAS reduction from the baseline score for their primary therapeutic target. No dilution group was inferior to each other regarding efficacy. 79.9% of patients and 89.0% of investigators reported an improvement in global assessment of efficacy at week 4. There were no relevant differences regarding safety between groups.

Conclusions: In this trial, NT 201, a highly purified Botulinum neurotoxin type A free from complexing proteins, demonstrated to be efficacious and well tolerated in upper limb spasticity caused by various etiologies in doses of up to 495 units NT 201.

Mo-324

Botulinum toxin type A in the treatment of lower-limb spasticity in children with cerebral palsy

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Objective: The objective of the present study was to evaluate the safety and effectiveness of BoNT/A in the treatment of children with spastic diplegic cerebral palsy.

Background: Cerebral palsy (CP) can be defined as a movement and posture disorder that appears at an early age, is secondary to a lesion or dysfunction of the central nervous system and is not caused by any known progressive or degenerative brain disease. Spasticity in children with CP is a serious problem that affects daily life activities and places obstacles in the path to achieving the rehabilitation goals. Stiffness, restricted movement, the development of contractures and a serious potential for joint complications are associated with muscles affected by spasticity. Botulinum toxin A (BoNT/A), a practical neuromuscular blocking agent that causes a clinical reduction in spasticity in working muscles, appears to have a beneficial effect on the natural history of CP patients with equinus deformity.

Methods: We evaluated the safety and effectiveness of botulinum toxin A (BoNT/A) in the treatment of spasticity in 20 children with spastic diplegic cerebral palsy (CP). All the patients received injections in the gastrocnemius and soleus, and 15 received injections in the adductors. The total dose varied from 70 to 140 U (99.75±16.26 U), or 7.45±2.06 U/kg per patient. to 16 years of age;

Results: The treatment improved the patients' walking and gait pattern significantly. There was also a significant alteration in the heel-ground distance and increased motion of the ankle joint. These structural changes in the feet were sustained until the end of the follow-up, although the same was not observed for the functional parameters. Three patients complained of weakness in the lower limbs.

Conclusions: In conclusion, BoNT/A is safe and effective when used in a single session of injections and produces a sustained structural modification of the lower limbs. However, functional changes are temporary and are only observed during the peak effect of the drug.

Mo-325

Pediatric safety experience with Myobloc®

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Objective: Summarize the Botulinum Toxin Type B (BoNT-B) pediatric safety experience obtained through post-marketing safety surveillance efforts.

Background: BoNT therapy is used to treat pediatric spasticity but the indication is not approved in the US. FDA issued an Early Communication highlighting potential safety concerns with BoNT use in treating pediatric spasticity.

Methods: All cases in the pharmacovigilance data base were tabulated and summarized.

Results: Forty-four cases were reported over 7 years, primarily for treating spasticity. Cases arose from an internal study, published case reports or studies, and spontaneous reporting. Twenty cases were serious; 24 were non-serious. Mean age was 7.5 years, range 2.5 to 17. The mean dose was 11,892 Units, and was greater for serious cases (14,972 Units) than for non-serious cases (9,648 Units). Similarly, greater doses on a Unit/kg basis were reported for serious cases (896 Units/kg) versus non-serious cases (562 Units/kg). Use of untested toxin serotype conversion ratios was associated with higher doses. Adverse event (AE) onset typically occurred within 1-10 days of treatment. Despite high doses on a Unit/kg basis (mean, 716 Units/kg, range 200 to 1,875) among all cases, no overt respiratory impairment was reported. One case was described as botulism. One unrelated death was reported in a study 8 months post-treatment. Feeding tubes were utilized in 2 patients. Frequent events were asthenia, fatigue and lethargy (17); vision abnormalities (14); dysphagia (13); dry mouth (12); and constipation (9). Fewer cases and fewer AEs per case were associated with initial doses $\leq$10,000 Units.

Conclusions: Serious AEs resulting in hospitalization for supportive care were more frequent when initial doses exceeded 10,000 Units. Conservative dose selection is warranted when BoNT-B is used off-label to treat pediatric spasticity. Appropriate dose selection and dose frequency remains to be defined by clinical studies.

Mo-326

Changes in trunk muscle activation and respiratory kinematics during speech following intensive voice treatment (LSVT LOUD) for children with spastic cerebral palsy

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Objective: This study examined changes in trunk muscle activation and respiratory kinematics during speaking tasks in children with cerebral palsy (CP) following an intensive voice treatment (LSVT LOUD).

Background: Children with CP exhibit motor difficulties including those associated with speech. Evidence exists for testing a voice treatment (LSVT LOUD) consistent with principles of activity-dependent neural plasticity in children with spastic CP. Our initial work showed improved acoustic aspects of voice and a corresponding therapeutic effect post LSVT LOUD in children with CP. Underlying physiological changes in speech breathing and chest wall muscle activation patterns associated with post-treatment changes have not been studied. We hypothesized that speech breathing and chest wall muscle activity would improve post-treatment on: (a) speech breathing events, (b) recruitment of muscles and (c) timing and amplitude of muscle activation related to change in lung volume, speech and effort.

Methods: Six children with spastic CP and six controls participated. Surface EMG was recorded on the right side of the body from intercostals, rectus abdominis, obliques, erector spinae and latissimus dorsi muscles. Breathing was simultaneously measured using chest wall kinematic signals from inductance plethysmography. Kinematic and EMG recordings were collected during quiet breathing and speech tasks from baseline, post-treatment and follow-up sessions. Data were analyzed using temporal and spectral techniques.

Results: Findings reflect the refinement of a distributed motor control system and the development of efficiency between synergistic muscle groups relative to inherent and voluntary forces acting on the system post treatment. In addition, the results indicated that post-treatment speech: (a) was initiated at higher lung volumes, (b) was produced using shorter inspiratory durations, and (c) productions included longer breath groups.

Conclusions: The results revealed that physiological aspects of voice and speech production improved in children with CP who received LSVT LOUD. This was accompanied by a therapeutic effect as measured by parent perceptual ratings and clinician preference for post-treated voices.

Mo-429

Elective bilateral above the knee amputation in T4-complete spinal cord injury: A case report

M.S. Jaffe (San Diego, California)

Objective: To discuss amputation as a treatment option for an individual with T4-complete spinal cord injury who had a variety of functional impairments, disabilities, and medical complications due to spasticity.

Background: This case study outlines an individual with T4-complete level injury with Ashworth scale grade 4 spasticity of the bilateral lower extremities.

Methods: A 49 year old male presented to our department of physical medicine and rehabilitation. The patient suffered a T4 complete spinal cord injury from a motorcycle accident in 1986. Due to spasticity the patient developed bilateral hip greater trochanter pressure ulcers requiring multiple debridements and vacuum assisted wound closure devices. The patient's spasticity fluctuated from extensor patterns to flexion patterns forcing his knees up to his chest. The shear forces of his spasticity aggravated his pressure ulcer condition. The patient could only tolerate Baclofen 20-30 mg at night with minimal benefit. Spasticity medication changes were made and an MRI of the patient's T-spine was ordered to rule out the possibility of post-traumatic syringomyelia. The patient was given a prescription for pressure relief ankle foot orthotics to relieve heel pressure. Upon a return visit there was no change in his spasticity level. The patient did not desire a trial of intrathecal Baclofen. The patient brought up the possibility of undergoing bilateral above the knee amputations to improve his quality of life. The patient felt that his lower extremities where heavy, difficult to control for self care and transfers. Over the course of eight weeks, the patient and I had long discussions regarding the risks, benefits, and alternatives to the surgery. We discussed the shift in his center of gravity, wheelchair seating issues, etc.

Results: The patient underwent bilateral above knee amputations. The patient did not desire lower extremity prosthetics. All of the patient's spasticity issues and pressure sores resolved within six months of the amputation.

Conclusions: This case study discusses amputation as a treatment option for a spinal cord injury-complete patient whose lower extremity spasticity had become detrimental to his function and general well being.

Tu-322

Botulinum neurotoxins for post-stroke spasticity in adults: A systematic review

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Objective: The aim of this systematic review was to determine whether botulinum neurotoxin (BoNT) reduced spasticity or improved function in adult patients with post-stroke spasticity.

Background: Numerous treatments are used to reduce spasticity. BoNT injections are employed as focal anti-spastic agents usually as part of complex rehabilitation regimens. There is no consensus as to when BoNT treatment should be initiated, how long it should last or if BoNT treatment improves daily living activities in post-stroke patients.

Methods: Eleven double-blind randomized placebo-controlled trials on post-stroke spasticity met inclusion criteria. They encompassed 782 patients, 767 (98%) of whom received BoNT/A, and 15 (2%) BoNT/B. Most studies used the Ashworth scale as primary outcome measure. Differences between treated and control groups were assessed as categorical or continuous comparisons.

Results: A significantly higher number of patients had a reduction of upper limb spasticity at 4-week and 8-week evaluations in the treatment group compared to placebo. Results on the efficacy of BoNT treatment in different upper limb joints revealed improvement of mean changes in favor of BoNT/A. Standardized mean differences of Ashworth scores were -0.95 ($p < 0.001$) for elbow, -1.35 ($p < 0.0001$) for wrist and -1.07 ($p < 0.0001$) for finger flexor 3-6 weeks after treatment and -0.80 ($p = 0.003$) for elbow spasticity, -0.83 ($p < 0.001$) for wrist spasticity and -0.76 ($p < 0.001$) for finger flexor spasticity 9-12 weeks after treatment. There were insufficient data to establish BoNT/A efficacy on lower limb spasticity or the effect of BoNT/B on the upper and lower limbs. Due to inconsistency and heterogeneity of the available data, it was not possible to perform a meta-analysis on disability and patients' reported outcomes. There was an overlapping safety profile between the treatment and the placebo groups in all trials.

Conclusions: BoNT/A reduces upper limb spasticity in patients post stroke, but the improvement in functional ability remains to be established. This gap needs to be filled by new studies to assess the effect of BoNT in the context of multidisciplinary patient management.

Tu-323

Improvement of Isaacs' syndrome (generalized neuromyotonia) by botulinum toxin injections

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Objective: To report a case of Isaacs' syndrome (generalized neuromyotonia) which was successfully treated with botulinum toxin A (BTA) injections.

Background: Isaacs' syndrome (IS) is a rare disorder characterized by spontaneous and continuous muscle fibre activity. Patients complain of cramps, myokymia and muscle pain. They may exhibit excessive sweating, paresthesias or mild muscle weakness that can lead to severe disability. The terms used to describe this condition include undulating myokymia (Denny-Brown, 1948), continuous muscle fiber activity (Isaacs, 1965), Armadillo syndrome and generalised myokymia, although the term neuromyotonia, proposed by Mertens and Zschocke in 1965, is currently the most widely

accepted. Treatment includes anticonvulsants, baclofen, acetazolamide, immunosuppressive drugs, plasma exchange and immunoglobulin therapy. However, not all patients respond fully. The use of botulinum toxin in neuromyotonia has rarely been reported. We describe a patient with IS, with severe problems in the feet and gait impairment, whose neuromyotonia improved with BTA.

Methods: A 39-year-old woman was diagnosed with IS in 1989. She was treated with carbamazepine, immunoglobulins, phenytoin and acetazolamide, with partial improvement of her symptoms. In the last two years, she developed spasms and contractures in her toes, gait impairment and difficulty wearing shoes. The symptoms occurred spontaneously and were not influenced by movement. She was unable to suppress them. We tried botulinum toxin, with a dose of 1000 U BTA (Dysport®) in the bilateral extensor hallucis longus, flexor digitorum brevis, abductor hallucis and abductor digiti quinti muscles with EMG guidance.

Results: Two weeks later, she noted a functional improvement allowing footwear to be worn comfort and a reduction in symptoms, with decreased spasm frequency, pain relief and improvement of contractures. Two additional injections of 500 U BTA were given at four-monthly intervals with good effect. No adverse event was reported. She is now neurologically stable.

Conclusions: BTA injections should be considered as an option for management of IS. In our patient, significant improvement started two weeks after the injections and lasted about 4 months. Using BTA injections in the involved muscles for treatment of neuromyotonia can be followed by marked functional improvement and reductions of systemic drugs.

Tu-324

Spasticity in public developmental centers for adults with intellectual disability: A survey of medical directors

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Objective: To determine (1) the prevalence of spasticity in developmental centers for adults with intellectual disability (ID), (2) the importance of treating spasticity when present, and (3) which therapies are in use in centers, as reported by medical directors (MD).

Background: Adults with ID are frequently left untreated for non-life-threatening conditions such as spasticity. Our 2001 population survey at a single center found a spasticity prevalence of 35%, that it interfered with care delivery and ADL performance, and that very few patients were treated for the condition. However, it was unclear whether these results were indicative of the population of adults with ID or a single center aberration.

Methods: With IRB exemption, centers were selected at random from a published list of 252 centers in the U.S. Centers that had closed or served other populations in addition to adults with ID were excluded. A movement disorders physician with expertise in treating spasticity conducted the surveys. Medical directors were asked (1) to estimate what percentage of individuals at their facility had spasticity, (2) how important it is to treat when present (5-point Likert scale: very unimportant to very important), and (3) whether each of the following therapies is available to: oral medications, PT/OT, neurotoxin injection, phenol/alcohol injection, orthopedic procedures, neurosurgical procedures, or intrathecal baclofen.

Results: Eleven MDs provided verbal consent and completed the survey. The average prevalence of spasticity at their centers is 33% (range: 13-70%), and they felt it was important to treat spasticity, when present (6 somewhat important, 5 very important). Oral medications and PT/OT were the most commonly available treatments, with 100% of MDs indicating they were available, followed by orthopedic procedures (91%), neurotoxin injection (55%), neurosurgical intervention and phenol/alcohol injection (27%), and intrathecal baclofen (18%).

Conclusions: This survey confirms the results of our single center study in that spasticity is common and felt to be an important problem. More concerning is the relative lack of availability of common treatments such as intrathecal baclofen and neurotoxin injection. More effort is needed for the health disparities faced by adults with ID living in developmental centers.

Tu-325

SPG15 is the second cause of hereditary spastic paraplegia with thin corpus callosum

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Objective: To define the clinical and mutational spectra of SPG15, a complicated form of autosomal recessive hereditary spastic paraplegia (HSP).

Background: HSPs consist in a very heterogeneous group of inherited neurodegenerative disorders. Recently, our group identified *ZFYVE26* as the responsible gene for SPG15. The clinical and mutational spectra of SPG15 are still not well described.

Methods: We analyzed the coding region of *SPG15/ZFYVE26* gene by direct sequencing in a series of 60 HSP subjects, including 30 isolated cases. The mutations predicted to affect the splicing were analyzed on cDNA in 2 patients. The clinical data were collected through the SPATAX network.

Results: We identified 13 novel truncating mutations in *ZFYVE26,* segregating in eight new SPG15 families. Two of three splice site mutations could be validated on RNA. The SPG15 phenotype in 11 affected individuals was characterized by early-onset HSP, severe progression of the disease and mental impairment dominated by cognitive decline. Thin *corpus callosum* (TCC) and white matter hyperintensities (WMH) were MRI hallmarks of the disease.

Conclusions: The mutations are truncating, private and distributed along the entire coding sequence of *ZFYVE26*, which complicates the analysis of this gene in clinical practice. In our series, SPG15 appears as the second most frequent form of HSP-TCC (9.4%) after SPG11. SPG15 and SPG11 share similar clinical and imaging presentations but age at onset is earlier in SPG15. Functional disability seem more severe and clinical and MRI cerebellar involvement more frequent in SPG15 but after a longer mean disease duration. These distinction are however insufficient to infer the molecular diagnosis in front of a single patient.

Tu-326

Repeated injections of NT 201 (botulinum neurotoxin free from complexing proteins) in upper limb post-stroke spasticity patients

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Objective: Long-term efficacy and safety of NT 201 (Botulinum neurotoxin free from complexing proteins, Merz Pharmaceuticals GmbH, Frankfurt/Main, Germany) were evaluated in this open-label extension (OLEX) period in patients with upper limb post-stroke spasticity.

Background: NT 201 (Botulinum neurotoxin type A free from complexing proteins, Merz Pharmaceuticals GmbH, Frankfurt/Main, Germany) did not show formation of neutralizing antibodies in preclinical trials in contrast to a complexing-protein containing product.

Methods: Patients who previously participated in the double-blind, placebo-controlled study, entered the OLEX Period, and were treated with NT 201 (up to five injection intervals) over 1 year (48 to 69 weeks). Parameters were the Ashworth Scale, Disability Assessment Scale (DAS), global assessments, and standard safety testing.

Results: Out of 148 patients who participated in the double-blind period of the study, 145 entered the OLEX Period. 120 patients completed the 1-year trial period. Upper limb muscle groups were treated as clinically indicated (median dose: 400 units, maximum dose: 500 units). Changes on the Ashworth Scale score were highly statistically significant ($p < 0.0001$; Wilcoxon signed rank test) at control visits

during all four injection intervals and in all muscle groups. NT 201 was effective in reducing functional impairment as shown on the DAS (therapeutic domains of hygiene, dressing, limb position, and pain). Efficacy was assessed as very good or good by the majority of investigators, patients and caregivers (range from 56.3% to 85.3%). During the 1-year trial period, adverse events were observed in 56.6% of patients. None of the patients had positive antibody titer tested in the mouse diaphragm assay.

Conclusions: NT 201 was effective and well tolerated following 1-year repeated treatments with a median dose of 400 units in patients with post-stroke spasticity of the upper limb.

Tu-425

Stiff Man syndrome good outcome after methylprednisolone pulse

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Objective: Report one stiff man syndrome with severe spasticity and good outcome after corticosteroid therapy.

Background: Stiff-Man syndrome (SMS) is a rare neurological disease characterized by axial and proximal limb rigidity with painful muscle spasms, trunk and limbs contractions.

Methods: We report a case of a 61 year old man who presented axial muscle rigidity, painful spasms of the trunk and in the upper limbs. Neurological examination reveals paraspinal and abdominal muscle contraction with severe lumbar rigidity associated with adrenergic autonomic dysregulation.

Results: Electroneuromyography showing continuous motor unit activity in limb and axial muscle. No abnormalities were found in the routine haematological and biochemical blood tests, the patient had negative anti-GAD and anti-neuronal antibodies and absence of specific malignancies. The common form of SMS was diagnosed and good improvement was noted after corticosteroid pulse associated with symptomatic treatment combined diazepam, baclofen and physical therapy.

Conclusions: The pathogenesis of Stiff-Man syndrome is unknown but the cause is likely to be autoimmune because of the association with specific autoantibodies (anti-GAD), other autoimmune diseases, paraneoplasic syndrome and response to immunomodulatory therapy. Treatment with GABA-ergic inhibitory drugs with immunomodulation; intravenous immunoglobulin (IVIg), plasmapheresis, and corticosteroid improve both the symptomatology and the quality of life of these patients.

We-317

Effect of extracorporeal shock wave therapy on spastic hypertonia in stroke patients

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Objective: Our purpose is to investigate the the long term effect of extracorporeal shock wave therapy (ESWT) on the muscle hypertonia of the hand and the wrist in patients affected by stroke.

Background: Spasticity is a disabling complication of stroke. Different not invasive treatments are used in order to reduce the muscle hypertonia. Shock waves are defined as a sequence of single sonic pulses characterised by high peak pressure (100 MPa), fast pressure rise (<10 ns) and short duration (10 μs). Shock waves are largely used in the treatment of bone and tendon diseases and on muscular contractures.

Methods: We studied 20 patients affected by stroke associated severe hypertonia in upper limb. An electromagnetic coil lithotriptor (Modulith SLKâ by Storz Medical AG) was used. The pressure pulses were focused in the flexor hypertonic muscles of the forearm and in the interosseus muscles of the hand: 1500 shots were used to treat flexor muscles of the forearm mainly in the middle of the belly, and 3200 shots for interosseus muscles of the hand (800 for each muscle) using an ultrasound pointer-guide. The energy applied was 0.030 mjl mm^2. A placebo stimulation was performed a week before the active stimulation in each patient. NIH scale, Ashworth scale and a video with digital goniometer were performed. The patients were monitored after one, four, twelve and twenty-four weeks from the active treatment.

Results: After active ESWT the patients had greater improvement in flexor tone of wrist and fingers than after placebo stimulation. At follow up visits at one and four weeks a significant decrease of passive muscle tone was noted on the treated muscles in all patients. After 12 weeks from the therapy ten of the twenty patients showed persistent reduction in muscle tone, none of the patients showed a return to the baseline conditions. There were no adverse events associated with ESWT. After 24 weeks 10 patients (50%) showed a persistent effect over the treated muscles. Four patients (20%) showed a further reduction of hypertonia and 6 patients (30%) patients showed a return to the baseline level of spasticity.

Conclusions: ESWT reduce hypertonia of the wrist and finger muscles in all patients after 12 weeks and in 70% of patients after 24 weeks. The effective treatment is different from sham condition.

We-318

Clinical and electrophysiological characteristics of post-stroke spasticity – an attempt to correlate

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Objective: To evaluate patients with poststroke spasticity clinically and electrophysiologically and attempt to correlate clinical severity with electrophysiological abnormalities.

Background: Spasticity is a clinical feature and a physiological phenomenon that is difficult to objectively measure and there are no valid measures that can be applied and repeated easily. This is especially true when treating spasticity as there needs to be a standard measure for followup. Currently there are subjective measurements (Rating scales, tendon jerks, etc.) and objective measurements (ENMG/pendulum tests). Modified Ashworth Scale(MAS) has been found to have less inter and intra-rater variability and hence is traditionally used for assessing spasticity. Subjective tests have inter-rater variability. Hence, if objective neurophysiological testing can be shown to correlate with MAS, then it can be a valuable tool.

Methods: Sixty patients with unilateral poststroke spasticity were evaluated with MAS. The patients were divided into six groups based on the MAS grading and then subjected to electrophysiological evaluation with F waves, H reflex, F wave persistence, F/M and H/M ratios. The abnormalities were then analyzed and an attempt made to correlate with the severity of grading on MAS.

Results: F latency was prolonged in the spastic limb and was statistically significant in MAS grades 2,3 and 4. F/M ratio was higher on the spastic side. F wave persistence was higher on the spastic side and was statistically significantly higher in the higher grades of MAS. H/M ratio correlated directly with the grade of MAS.

Conclusions: Electrophysiological findings correlated well with MAS except between Grades 1 and 1+. Electrophysiology can be a valuable objective measure of spasticity, which can be easily reproduced for followup too.

We-319

Botulinum toxin therapy in chronic lower limb spasticity

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Objective: The objective of this analysis was to assess the effect of BoNTA therapy in lower limb spasticity existing for more than 4 years.

Background: Multiple studies utilizing BoNTA in spasticity of lower limbs exist, however, there is limited understanding of the effect of ongoing injections on chronic spasticity after more than 1 year of treatment. The aim of this study was to analyze the effect of repeated BoNTA injections on locomotion ability and pain in chronic lower limb spasticity.

Methods: 10 patients with lower limb spasticity for more than 4 years, who had been treated with botulinum toxin A (BoNTA; BOTOX, Allergan) for more than 1 year were enrolled. Etiologies of spasticity were: cerebrovascular disease (n=3), cerebral palsy (n=3), multiple sclerosis (n=3), cervical myelopathy (n=1). Patients were treated with BoNTA (t1) and monitored on week 6(t2),12 (t3); 18 (t4) and 24(t5). BoNTA injections were repeated 12 weeks after first injection (t3) if required. BoNTA dosing, adverse events, Ashworth score, 2 minute walking distance, Timed Up and Go (TUG)-Test, VAS and PPI were documented.

Results: Mean (±SD) age at baseline was 59.3±4.6 years. Spasticity had been documented to exist for a mean of 23.9±19.3 years. BoNTA treatment had been regularly for the last 4.0±2.5 years. The mean total dose of a single BoNTA injection was 379±173 U. All patients were treated on t1 and t3. The most frequently injected muscles were soleus, gastrocnemius, adductor muscles and hamstrings. Ashworth score was in mean 2.5±0.7 at baseline, 1.4±0.7 on t4. In TUG-Test a significant improvement from t1 to t4 and t5 was documented (t1: 36 s; t4: 24 s; t5: 29 s). 2 min walking distance increased from 25.5 m (t1) to 49.1 m (t4) and was still 47.4 m on t5. Pain decreased on VAS from 4.5 (t1) to 3 (t4), on PPI from 1.4 (t1) to 1 (t4). There were no SAEs, no treatment had to be discontinued due to AE.

Conclusions: Treatment with BoNTA in chronic lower limb spasticity is well tolerated and effective. In this study the functional benefit was most pronounced 6 weeks after injection as expected, however, 12 weeks after second treatment level of function did still exceed that at baseline. In summary, even in chronic lower limb spasticity after years of BoNTA treatment a further gain of function seems possible. Further double-blind, controlled trials are required to validate the results seen in this clinical setting.

We-320

Treatment of spasticity in the lower limbs with botulinum toxin (Dysport®): A retrospective analysis

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Objective: To evaluate (1) different pattern of spasticity in the lower limbs treated with Botulinum toxin, (2) doses used in the different pattern and (3) adverse events of this treatment.

Background: Spasticity in the lower limbs caused by upper motor neuron lesions is characterized by positive features such as increased muscle tone, negative features such as paresis, pain and late consequences including contracture and fibrosis. Focal treatment of spastic muscles by chemodenervation with botulinum toxin (BoNT) plays an important role in the management of spasticity. Randomized controlled trials (RTCs) have evaluated the efficacy of BoNT in spasticity of various aetiologies in lower limbs and showed improvement of impairment. Despite this evidence of efficacy the usage of BoNT in spasticity in lower limbs in Germany is off-label (except for the use of Botox® in the lower leg of children with cerebral palsy).

Methods: We carried out a retrospective analysis of patients (n=40) who had been treated with BoNT type A (Dysport®) for spasticity in the lower limbs in our out-patient clinic over the last two years (2007-2008).

Results: We identified different pattern of spasticity. The most common pattern involved spastic plantar flexion, sometimes with inversion of the foot and flexion of the toes. Plantar flexion at the ankle was treated most often (n = 17), inversion of the foot alone (n = 4) and flexion of the toes (n = 2) occurred relatively seldom. Hip adductor spasticity was mostly caused by spinal lesions (n = 8). Spastic flexion of hip and knee was treated with good efficacy (n = 6). Very good response to Dysport® treatment was seen in hyperextension of the big toe (n = 3). Doses ranged from 100 units injected in M. extensor hallucis longus and 1250 units injected in the muscles of the adductor group bilaterally. There were no doses exceeding the recommended dose ranges. Muscle weakness occurred as adverse event, but could be managed by dose reduction or change of injection sites.

Conclusions: Treatment with Dysport® in lower limb spasticity was safe, well tolerated and showed in most patients a good clinical outcome with improvement in impairment and function.

We-321

Post stroke spasticity: Somatosensory cortex activation changes after botulinum toxin type A injections

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Objective: The aims of the study were to evaluate the therapeutic effect of BTX-A in the management of spasticity, and to assess the level of somatosensory cortex activation and modulation with this therapy in patients suffering from cerebral spasticity after subcortical stroke.

Background: Intramuscular administration of botulinum toxin type A (BTX-A) features among the most effective measures for cerebral spasticity.

Methods: The patient group comprises 17 subjects (11 males and 6 females), mean age 59.6 years, with a history of ischemic stroke in the middle cerebral artery territory. 9 patients suffered from left-hemispheric stroke and 8 from right-hemispheric stroke. A control group consists of 19 healthy subjects. BTX-A was injected into the most affected muscles: flexor carpi ulnaris and radialis, flexor digitorum profundus and flexor digitorum superficialis. Examinations were performed before BTX-A administration (V0), 4 weeks after the injections (V1) and 12 weeks after BTX-A administration (V2). The spasticity was evaluated using the Modified Ashworth Scale (MAS). Somatosensory evoked potentials (SSEPs) of the median nerve were examined in both upper extremities using a Medtronic Keypoint® device, with off-line analysis of P22/N30 and N20/P23 cortical component amplitudes.

Results: A significant decrease was found for the median MAS in the affected upper extremity (Wilcoxon's test for two dependent samples, $p \leq 0.05$) at time point V1, with consequent return to initial values by V2. No significant effect of BTX-A on cortical components of SSEPs among follow-up was demonstrated (paired t-test, $p > 0.05$). In patients after right-hemispheric stroke, the amplitude of the P22/N30 component at V0 was found significantly higher compared to left-hemispheric stroke. Even stronger difference was observed for the N20/P23 component in V0 and V2 (unpaired t-test, $p \leq 0.05$).

Conclusions: The lack of SSEP amplitude changes over time does not support the participation of somatosensory cortex as a central effect of BTX-A. Relatively higher N20/P23 amplitude in patients with left-sided spasticity may suggest differential involvement of the two hemispheres in the development of spasticity. Study was supported by the grant IGA MZCR Nr. 9920-3/2009.

We-322

Our experience in using the botulinum toxin at spastic children

L. Padure, G. Onose (Bucharest, Romania)

Objective: Bringing in the attention of the entire team of therapeutical benefit of botulinum toxin at the spastic children treated in our clinic.

Background: Spastic pathology, especially cerebral palsy is the first mean of recovery consult for a child with paralysing disorders. The botulinium toxin's experience in neurological pathology in our clinic has been started from 1999. The early treatment adapted to every clinical form (hemi, para, tetraparesis, pyramidal-extra pyramidal syndrome, etc) is used for reducing the cost of the patients' treatment, for increasing the quality of life and social integration of the child in family, kindergarten, day care centre, school.

Methods: Our study group contains 375 children injected with Botulinum Toxin between 2000-2008. In this time 211 were injected

once, 86 twice, 35 three times, 43 four times and more. Botulinum toxin treatment was applied after the exhaustion of all relaxing therapeutically methods.

Results: Results of botulinum toxin therapy for functional level - are distinguishable in time -depends on decreasing spasticity after injection with botulinum toxin -depends on intensive physical therapy, active walking being very important.

Conclusions: Treatment with botulinum toxin is a very important therapeutic part of spasticity recovery in our clinic. With a passing effect it can be used as a therapeutic test before any surgery treatment for equin leg, adduse thighs at the spastic child.

Th-322

The use of complementary therapies for hemifacial spasm

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Objective: To determine the prevalence and factors influencing the use of complementary treatment in patients with hemifacial spasm.

Background: Hemifacial spasm (HFS) is common among Asians and cosmetically unacceptable to many patients. Complementary therapies (CompTh) are frequently sought after by patients with neurological disorders. The use of CompTh in HFS has not been reported.

Methods: We recruited consecutive patients with HFS and administered a structured questionnaire on the frequency of usage of CompTh and investigate the factors influencing the usage. In addition, data on the demographics, severity of HFS, and the use of botulinum toxin were systematically collected.

Results: A total of 96 patients were included. 49 (51%) used one or more forms of CompTh. Thirty-five (71.4%) used one type of CT only and 9 (18.4%) and 5 (10.2%) used 2 and 3 types of CompTh respectively. Different types of CompTh were used by 49 participants, with acupuncture (52.9 %) being the most common, followed by facial massage (17.6 %) and others. Interestingly, only 2 (4.1%) of CompTh users reported the therapies as very helpful, forty-three percent reported the therapies as being sometimes helpful and the rest (53.1%) found the therapies unhelpful. Patients with higher severity of HFS were more likely to use CompTh. Rate of usage of CT was 27.3%, 37.8% and 69.2% among patients with HFS severity of 2, 3 and 4 ($p=0.002$).

Conclusions: At least half of our HFS patients have utilized one or more forms of complementary therapies (acupuncture and facial massage the most common). However, only 4% reported significant improvement with these kinds of therapies. Patients with higher severity of HFS were more likely to seek complementary therapies.

Th-323

The Asian botulinum toxin – A (Dysport®) clinical trial designed for early post-stroke spasticity (ABCDE-S trial)

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Objective: ABCDE-S is a 24-weeks prospective, multicentre, randomised, double-blind, placebo-controlled trial aimed to evaluate the efficacy and safety of one botulinum toxin-A (BoNTA: Dysport® 500 U) injection in early poststroke spasticity (PSS).

Background: Within 12 months, PSS occurs in more than a third of patients, and a proportion will develop disabilities. Notably, about 19% of PSS occur within 3 months. Most studies use BoNTA in PSS after 6 months.

Methods: Asian patients, 18-80 years of age, who had a first ever stroke were recruited from the Philippines, Singapore, Malaysia, Thailand and Hongkong. Eligibility requirements were an Ashworth spasticity scale (MAS) of at least+1 in the upper limb (UL) within 2-12 weeks after stroke, and an MRC weakness of at least grade 2. The primary efficacy variable was reduction of spasticity, based on MAS from baseline of elbow and wrist flexors at week 4. Dysport® 500U(in 2.5ml saline) was injected using a flexible regimen, preferably at the BB, BR, FCR, FCU and optionally at the FDS, FDP and FPL muscles. The MAS score obtained at 4 weeks from baseline of the most affected joint (either elbow or wrist) was assessed across treatment arms using ANCOVA, where pooled country and baseline MAS were treated as covariates. Analysis was conducted applying both ITT and PP analysis sets. MAS scores and safety recording were also done at 2, 4, 8, 12 and 24 weeks.

Results: 163 patients were recruited (Placebo: 83; Dysport®: 80). Protocol deviations excluded 10 patients from the efficacy analysis. ITT or PP analysis at week 4 revealed that MAS scores for the most affected UL joint reduced significantly ($P<0.0001$) by 1.5 in the Dysport®, compared to 0.5 in the placebo groups. Since covariate analysis showed no significant interaction of treatment by country, treatment effect estimates were stratified by MAS score at baseline. Dysport® was significantly more effective than placebo regardless of baseline MAS quartile, and had a sustained efficacy until week 24. There was no significant difference in the distribution of adverse events, 35 (42%) in placebo and 46 (58%) in Dysport® groups.

Conclusions: DYSPORT®500U can significantly reduce UL muscle tone in PSS within 2–12 weeks. The single, low dose, early intervention is safe and is able to have sustained effect until 24 weeks.

Th-324

Autosomal dominant hereditary spastic paraplegia: Clinical and genetic study of 3 Chinese families

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Objective: To investigate the clinical features and screen mutations in the *SPG4*, *SPG6* and SPG3A genes of Chinese autosomal dominant hereditary spastic paraplegia (AD-HSP) patients.

Background: Hereditary spastic paraplegia (HSP) is a group of clinically heterogeneous neurodegenerative disorders. The clinical and genetic character of Chinese HSP patients is unclear.

Methods: We collected all the patients' clinical information and followed up. All PCR products spanning all exons and exon-intron junctures in the *SPG4*, *SPG6* and *SPG3A* genes of eleven patients from three AD-HSP families were directly sequenced. In addition, we used multiplex ligation dependent probe amplification (MLPA) assay targeting *SPG4* and *SPG3A* genes to evaluate large exons deletion or duplicate mutation of these two genes.

Results: Clinical investigations indicated that these three families had a pure form of AD-HSP with the onset age ranged from 1.5 to 40 years old. No mutations in the *SPG4*, *SPG6* and *SPG3A* genes were detected but two novel CGC duplications polymorphisms in exon 1 of the *SPG6* gene by direct sequencing. Two families harbored the same polymorphisms c. *41-44CGC [7] and the other one had the polymorphisms c. *41-44CGC [7]+[9]. However, we found a novel exon10-17 deletion in the *SPG4* gene in one family by using the MLPA method.

Conclusions: Our finding indicated *SPG4* gene played an important role in our pure AD-HSP patients. It is worth screening large exons deletion in the AD-HSP patients without mutation detected by direct sequencing. The other two families might be a new subtype pure AD-HSP.

Th-325

Six cases of SCA3/MJD patients that mimic hereditary spastic paraplegia in clinic

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Objective: To investigate the mutation frequency of SCA3/MJD in patients diagnosed with hereditary spastic paraplegia (HSP) and to characterize the clinical and MR imaging features of this new type.

Background: Spinocerebellar ataxia type 3/ Machado- Joseph disease (SCA3/MJD) is an autosomal dominant neurodegenerative dis-

ease characterized by cerebellar ataxia associated with varying phenotypy which contain pyramidal signs, extrapyramidal signs, peripheral amyotrophy and parkinsonism. It was reported that a few of SCA3/MJD patients manifested spastic paraplegia with or without cerebellar ataxia.

Methods: The collection of clinical data and mutation detection of *MJD1* gene of the patients that represent spastic paraplegia.

Results: *MJD1* gene mutation was found in five probands from 46 autosomal dominant kindreds diagnosed with HSP. Spastic paraplegia with dysarthria may be the common clinical represantation of this new subtype.

Conclusions: SCA3/MJD patients that first manifested spastic paraparesis is not rare in Chinese Han, and *MJD1* gene should be detected routinely in the patients diagnosed with HSP clinically.

Th-326

Progressive spastic paraparesis as a novel presentation of fragile X premutation – A case report

P. Tidswell (Preston, Lancashire, United Kingdom)

Objective: A case report of progressive spastic paraparesis due to fragile X premutation. This novel presentation may suggest significant variability in the clinical phenotype of fragile X-associated tremor/ataxia syndrome (FXTAS).

Background: FXTAS was first described in 2001, and subsequently the neurological clinical phenotype expanded to include for instance, cases with additional pyramidal involvement, or relatively pure ataxia. This case of progressive spasticity suggestive of myelopathy is the first such case reported due to a fragile X premutation, with typical imaging findings of FXTAS.

Methods: A 42 year-old man was first seen in 1997 with a 2 year history of heavy legs, tripping and poor balance. Examination showed pes cavus, possible upgoing plantar responses, a non-diagnostic abnormal gait and low amplitude nystagmus. Initial investigations for primary progressive multiple sclerosis (MRI scan of brain and cervical spine, lumbar puncture and evoked potentials) were negative. He had a male cousin with learning disability due to fragile X mutation. His condition progressed steadily so that by 2004 he required two crutches to walk. He developed urinary urgency, erectile dysfunction and cognitive difficulties, principally memory. MRI scan of thoracic and lumbar spine, and peripheral neurophysiology were normal. A repeat MRI scan of brain (2002) highlighted exuberant falx calcification (not causing compression of brain). Common mutations associated with hereditary spastic paraplegia were negative.

Results: In 2008 the possible relevance of a fragile X premutation was reconsidered, and a third MRI scan of brain undertaken (illustrated). This showed typical radiological features of FXTAS. An expanded CGG triplet repeat in the FMR1 gene was confirmed by Southern blot. Neurological examination showed a severe spastic tetraparesis, minimal low amplitude upper limb postural tremor and non-diagnostic gaze-evoked nystagmus without diplopia, ophthalmoplegia or ataxia. He had mild to moderate short term memory loss. There was no peripheral neuropathy.

Conclusions: Fragile X premutation should be considered as a potential cause of progressive spasticity, even in the absence of significant tremor or ataxia; prompting a detailed enquiry into family history, and repeated MRI brain imaging. The clinical spectrum of FXTAS may be further extended in the future.

Th-327

Classification of posture and movement patterns in patients with arm spasticity and recommendations for treatment with botulinum toxin A (Dysport®): ULTRA class concept (upper limb treatment algorithm & classification)

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Objective: To classify which posture and movement patterns are seen in patients with arm spasticity after stroke. To investigate if recommendations for treatment with botulinum toxin A (BoNT-A) can be deduced from these patterns.

Background: Following many years of experience and confirmed by controlled clinical trials, the use of BoNT-A in post-stroke patients is established as a safe an effective treatment. Many patients benefit from the tone-reducing effects of BoNT-A and show improvements in the areas of impairment (decreased tone of the treated muscles) and activities (reduction in disability measured with the DAS). Depending on the localisation of the lesion, different muscles or groups of muscles are affected by the symptoms of stroke (paresis and disturbances in muscle tone). If a clinically relevant degree of spasticity develops, the combination of the differently affected muscles means that the affected arm remains in a specific pattern. During physical activity (e.g. standing or walking), the spastic pattern becomes more pronounced, due to increases in muscle tone, and is often associated with additional movements.

Methods: Based on a differentiated movement analysis, typical arm spasticity patterns were defined with respect to the position of shoulder, elbow, forearm and wrist joints. Treatment recommendations for BoNT-A with respect to target muscles and doses were drawn up based on these patterns.

Results: Five typical arm spasticity patterns can be distinguished. Pure clinical observation of the posture and movement of the spastic arm in adult post stroke patients is sufficient to classify 95% of cases to one of these five patterns. Within the framework of a recent completed observational study (348 patients), the frequency of occurrence of the different patterns and whether the subsequent treatment with BoNT-A differs according to the pattern type has been investigated.

Conclusions: This classification forms the foundation of a common terminology and facilitates a quick and understandable exchange of information with other physicians. Using validated examinations (range of movement, estimation of muscle tone, pain scales) and tests, treatment relevant changes in these patterns can be documented quantitatively.

SURGICAL THERAPY: PARKINSON'S DISEASE

Mo-327

Violating the ventricular wall increases length of stay following subthalamic DBS surgery for Parkinson's disease

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Objective: To determine if violating the ipsilateral lateral ventricle during Subthalamic DBS surgery increases post-operative length of stay (LOS).

Background: Due to the medial location of the target, surgical trajectories to the subthalamic nucleus (STN) may violate the ipsilateral lateral ventricle. This is generally felt to be safe.

Methods: Retrospective chart review of all STN lead implants for Parkinson's disease performed by one surgeon (RLA) between January 2005 and September 2008. Postoperative MRI was performed in all cases and each scan was reviewed for evidence of ventricular wall violation or other abnormal finding. LOS was recorded for each patient and categorized as routine (ie LOS $\leq$ 2 days) or extended (LOS $>$ 2 days).

Results: 145 leads were implanted in 81 patients over 102 admissions. Each patient underwent detailed neurocognitive testing prior to surgery. 43 patients underwent contemporaneous bilateral lead implants; 23 underwent unilateral implants; and 18 underwent staged bilateral implants. LOS was routine in 86 admissions. Of the 16 instances of extended LOS, 8 were due to transportation/social issues and 8 to surgical complications (1 hemorrhage; 7 altered mental state). Fifteen MRIs demonstrated evidence of ventricular wall violation including all 8 patients with surgical complications. The odds ratio of increased LOS after ventricular wall violation was 39.5

(P<0.0001). The mean age of the patients whose ventricles were violated was greater (67.2 ± 0.9 yrs (SEM)) than those whose ventricles were not (62.9 ± 1.1 yrs: P=0.04, t-test) and the median age of the patients who were adversely affected by the ventricular violation was greater than those who were not (70.5 vs 63 yrs; P=0.02, Wilcoxon).

Conclusions: In this study, violating the ventricular system during STN DBS surgery correlated significantly with postoperative altered mental status and subsequent increased length of stay. The risk of ventricular violation and adverse outcome increased with age. These findings may explain why cognitive complications are observed more frequently in older Parkinson's disease patients and in those undergoing DBS at the STN as compared to the internal pallidum. Care should be taken to avoid violating the ventricle during DBS surgery, particularly in elderly PD patients.

Mo-328

Motor and cognitive effects of subthalamic nucleotomy in one hundred patients with Parkinson's disease

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Objective: To evaluate the long term effects in motor and cognitive functions of unilateral and bilateral subthalamic nucleotomy in a large serie of patients with Parkinson's Disease.

Background: Since 1995 to date we have practised at the CIREN (Havana, Cuba) some STN nucleotomies in patients with PD patients, who had not been previously well controlled with current pharmacological treatments. Here we present and discuss the long term response of subthalamotomy in 100 PD patients (68 unilateral, 32 bilateral).

Methods: All patients fulfilled the diagnostic criteria of the UK Brain Bank Parkinson's disease and had developed refractory motor complications. The guidelines of CAPIT were use for assessment and in addition a battery of neuropsychological tests was applied. Adverse events related to surgery were carefully recorded.

Results: Unilateral Subthalamotomy A significant contralateral motor improvement with 31% overall reduction in off" UPDRS III at 36 month ($p < 0,05$) were observed but ipsilateral motor performance deteriorate up to 20 % at the same time. Pre-existed L-dopa induced dyskinesias, mainly diphasic and dystonic dyskinesias, also improved with significative amelioration only on the contralateral side. Persistent contralateral HCB were observed in 8 patients, that were complete resolved with an ipsilateral pallidotomy without any noticeable adverse event. Non cognitive sequelae were observed but some changes on executive function were demonstrated. Bilateral Subthalamotomy.A significant reduction in the "off" UPDRS score by 47 % at 3 years were obtained. Lesion induced dyskinesias were observed in 4 patients but it have not been a problem at last evaluation. There is no major cognitive deficit in those patients. We have certainly seen nothing close to severe speech or swallowing problems present after bilateral pallidotomy or thalamotomy.

Conclusions: • STN lesion in PD patients has a robust and sustained antiparkinsonian effect with low incidence of hemichoreabalism. • Unilateral STN lesion has an assymetrical antidyskinetic effect that could not be merely explicated by the reduction of DA medication. • Uni or Bilateral STN lesion were not associated with global cognitive or speech impairtment in our patients but induce changes on executive functions.

Mo-329

Effect of subthalamic nucleus lesion on cognitive control of voluntary movements

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Objective: To evaluate the short term effect of subhtalamotomy in (1) motor and (2) cognitive items related to voluntary movement in patients with Parkinson's disease using UPDRS part III and neuropsychologic tests.

Background: The subthalamic nucleus is the most recurred target in functional neuro surgery in Parkinson's disease (PD). In the last decade were described neuropsychologic effects of this techniche in short and long therm. In this investigation we studied the effect of subthalamotomy in cognitive items related to voluntary movements.

Methods: We studied 8 PD patients and 8 matched controls. Motor assessment included UPDRS part III and for cognitive evaluation a battery of neuropsychologic tests like stop signal reaction time; Stroop simple and with interference. PD patients were evaluated before and a month after surgery.

Results: The effect of subthalamothomy in motor signs of PD measured by UPDRS part III improve more than 40%. The effects in neuropsychologic items related to voluntary movements vary in dependence of cognitive complexity or interference and were negative affected in more complex tasks like Stroop with interference.

Conclusions: Beyond the proved benefitial effect in motor signs of PD, the subthalamothomy have other adverses effects in cognition. Those facts support the cognitive role of basal ganglia and particularly of subthalamic nucleus. Also; get focus in the importance of evaluation and follow up for neuropsychologic effects in functional neurosurgery of basal ganglia.

Mo-330

Calvarium erosion resulting from deep brain stimulator wire

K.K. Appleby, L.B. Bahroo, C.G. Kalhorn, F.L. Pagan (Washington, District of Columbia)

Objective: To describe a novel complication seen on autopsy of a patient with Deep Brain Stimulators (DBS).

Background: DBS is a well established treatment for Parkinson's disease, dystonia, and essential tremor. As an increasing number of patients are undergoing placement of DBS, long-term complications of the devices will be realized.

Methods: A case report with relevant literature review.

Results: A 71 year old male with Soletra model bilateral subthalamic nucleus DBS for Parkinson's disease four years prior underwent autopsy after death due to complications of colorectal cancer. Autopsy revealed erosion of the parietal bone underlying the electrode wire. There was no other abnormal pathology found relating to the DBS. There had been no complications or revisions of his DBS. He underwent battery replacement three years after his initial surgery. Standard settings were used.

Conclusions: This case represents a complication seen on autopsy of a DBS patient. To our knowledge this is the first case of bone erosion due to DBS wires. As new DBS technology becomes available, specifically rechargeable batteries and smaller pulse generators implanted in the head, the safety and efficacy should be closely evaluated.

Mo-331

Deep brain stimulator complication due to braided extension wires

K.K. Appleby, L.B. Bahroo, C.G. Kalhorn, F.L. Pagan (Washington, District of Columbia)

Objective: To describe a novel complication of extension wire breakage due to braiding in a patient with Deep Brain Stimulators (DBS).

Background: DBS is a well established treatment for Parkinson's disease, dystonia, and essential tremor. An increasing number of hardware related complications have been reported including breakage due to twisting of extension wires, ie. Twiddler's syndrome. Twiddler's syndrome was first described in patients with cardiac pacemakers but has been seen with other implanted devices including DBS.

Methods: A case report with relevant literature review.

Results: A 49 year old obese female with Kinetra model bilateral subthalamic nucleus DBS for Parkinson's disease (PD) presented 1-1/2 years after placement with new complaints of uncontrolled PD symptoms and her pulse generator "floating." Upon DBS interrogation the device was on but impedence checks were all greater than 4000, indicating an open circuit. Side effects were unable to be induced with elevated voltages or pulse widths. Chest, neck, and skull xrays revealed braiding of the extension wires and a break just distal to the connector site. The patient denied excessive self-manipulation of her pulse generator. She underwent replacement of the pulse generator and extension wires with return of good control of her PD symptoms.

Conclusions: This case represents a hardware complication due to extension wire braiding and breakage. It is an extreme example of IPG migration that we have personally seen with multiple patients in our clinic, especially in those who are obese or thin elderly patients.

Mo-332

Deep brain stimulation in advanced age patients with Parkinson's disease

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Objective: To evaluate the outcome of deep brain stimulation in parkinsonian patients of advanced age (i.e. over 70 years).

Background: Deep brain stimulation (DBS) is widely applied for the treatment of patients with advanced Parkinson's disease. While a short term benefit in old patients has been established, the long term effects are less clear. In this study we evaluated the short and long term outcome in a subgroup of patients that were operated at an age >70 years.

Methods: Twelve patients were included in the study. The mean age at the time of operation was 75.5 years (range 71-82), the mean disease duration 21.3 years (11-39) and the mean follow-up was 4 years (2-6). The main parameter evaluated was the degree of independence, as measured by the Schwab and England (S & E) scale. Additional parameters included daily 'on' time, UPDRS, and PDQ-39. as well as the amount of medication required. The results were compared to those of two control groups. The control group 1 comprised ten patients of similar age, operated before the age of 70 (mean age at operation 67 years, range 66-68, mean follow-up 7.5 years, range 6-9) The control group 2 comprised twelve PD patients matched for sex, age, disease duration and disease severity (estimated by the UPDRS III "off'' score).

Results: Six months after the operation, a clear benefit (i.e. a two-step improvement in the S & E scale) was observed in 9/12 patients (75%); complete independence (i.e.S&E score ≥ 60%) was achieved by 6 patients (50%). In comparison, only 4/12 patients (33%) of control group 2 were completely independent. A similar improvement was observed in 9/10 patients (90%) in the control group I Over the course of the follow up, the benefit was diminished. At 3 years, complete independence was sustained in 2/8 patients (25%) of the study group and 6/10 patients (60%)of the control group I. The results of the study group at 3 and 5 years were not significantly different from those of the control group 2.

Conclusions: The long term results of DBS in advanced age patients are highly individualized. In a few patients, a clear and sustained benefit may be observed, whereas for the majority the beneficial effects tend to vanish after a few years. The degree of independence at the time of operation seems to be the best predictor of the long term effect.

Mo-333

Turning apathetic after subthalamic nucleus (STN) deep brain stimulation (DBS) in a Parkinson's disease (PD) patient with impulse control disorder (ICD)

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Objective: Report an unusual complication of apathy after STN DBS in a PD patient with ICD.

Background: STN DBS is an acceptable treatment for PD patient with ICD, but the outcome varies. Its complications and the optimal stimulation strategies are not well described.

Methods: Hospital chart review.

Results: A PD patient was treated with Levo-dopa and bromocriptine after diagnosis at age 40. He became indulged in gambling 5 year after diagnosis, and had once lost about US$ 25,000 in one night. He took extra doses of dopaminergic drugs, becoming elated, and compulsively visiting video-game center to exhaust his extra energy there. Multiple attempts of lowering drugs failed, related to problematic motor fluctuation and his craving for drugs. STN DBS was performed 11 years after diagnosis in April 2008. Pre-operatively, he was on daily levo-dopa 650mg, and dopamine agonist was taken off. His Unified Parkinson's Disease Rating Scale (UPDRS) was 52 during "off" state, and 2 when he was "on". He had markedly decreased motor fluctuations and dyskinesia few weeks after operation with Levo-dopa 300mg daily. He was on monopolar 60 ms, 130Hz and around 3V bilaterally. His UPDRS off-medication score had improved by 50%. He no longer gambled after DBS. Four months later, he became severely apathetic with loss of all interests and initiatives. He was diagnosed to have apathy but no apparent depression by the psychiatrist. His DBS stimulation was turned off. His apathy score (the Lille apathy rating scale: ranges from -36 to +36, higher score means more apathetic, cut off for normal is -16) before stimulation-off was 23, improved to -12 two days later, yet his motor function deteriorated. The stimulation leads were changed to the highest position bilaterally to minimize limbic spread. He was given a range of voltage to manipulate, so that he could raise the voltage for better motor performance, and decrease it when he was fine to minimize apathy. He has mild apathy but enjoys good functional status with this strategy.

Conclusions: Apathy can be a complication in PD patients with ICD after DBS. Adjustment of stimulation parameters and regime substantially improves this complication.

Mo-334

Cerebral activity changes induced by PPN stimulation in advanced PD patients: A [^{15}O] H_2O PET study

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Objective: To investigate the functional effects induced by unilateral deep brain stimulation (DBS) of the pedunculopontine nucleus (PPN) in advanced Parkinson's disease (PD) using positron emission tomography (PET).

Background: In advanced stages of PD, patients develop disabling axial symptoms, including gait disturbances, freezing and postural instability, poorly responsive to levodopa treatment because secondary to the pathological involvement of non-dopaminergic pathways. The PPN is involved in locomotion, control of posture and balance and some reports have suggested that its activity modulation with DBS may be beneficial in the treatment of axial symptoms, but the mechanisms underlying these effects are still unknown.

Methods: We used [^{15}O] H_2O PET to investigate regional cerebral blood flow (rCBF) in 3 patients with advanced PD implanted with unilateral PPN-DBS because of disabling freezing gait and postural instability. Patients were studied Off-medication with stimulator Off and On, both at rest and during a self-paced alternating motor task of the lower limbs. We used SPM2 for imaging data analysis, threshold $p<0.05$ corrected at the cluster level

Results: During rest, stimulation induced significant rCBF increment in subcortical regions such as the thalamus, cerebellum and midbrain region. During motor performance, stimulation induced significant increased in rCBF in the thalamus, dorsolateral prefrontal cortex (DLPFC), fusiform gyrus. During both conditions, stimulation induced a reduction in rCBF in the anterior and posterior cingulate cortex. When comparing motor task with rest condition, stimulation

induced an increased activity in the medial sensorimotor area extending into caudal SMA, caudal cingulate cortex and DLPFC.

Conclusions: Our findings show that PPN-DBS in advanced PD patients determine rCBF changes within the cerebello-thalamo-cortical motor circuit. Interestingly, during the task PPN-DBS increased neuronal recruitment within the medial sensorimotor areas involved in motor programming and voluntary movements of the lower limbs. Our results suggest that PPN-DBS induces significant functional changes in cerebral areas associated with motor control of lower limb movement.

Mo-335

Deep brain stimulation of the subthalamic nucleus and apathy in Parkinson's disease: Utility of the frontal systems behaviour scale (FrSBe)

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Objective: To specifically study the effect of Subthalamic Nucleus deep brain stimulation (STN-DBS) on apathy by means of the Frontal Systems Behaviour Scale (FrSBe), a brief rating scale which assesses behaviours associated with apathy, disinhibition and executive dysfunction.

Background: STN-DBS significantly improves motor symptoms in advanced Parkinson's disease (PD). However, the effect on apathy is less clear. A few papers report this symptom as one of the adverse behavioural effects of DBS.

Methods: A series of 16 PD patients [6 men; mean age 60.9 years (range 47-73); mean disease duration 13.1 years (range 8-21)] was assessed before (presurgery), and at three months (M3), six months (M6) and one year (1Y) after surgery. The patients underwent a battery of cognitive tests assessing overall cognitive functioning (Mattis Dementia Rating Scale, MDRS), phonemic and categorical fluency tasks. The Beck Depression Inventory (BDI) was used for depression. Apathy was assessed by means of the FrSBe (cut-off score: 65), meaning that a total score of 65 points or above is indicative of apathy.

Results: The FrSBe mean score and the scale's subscores of disinhibition and executive dysfunction did not change between evaluations, while the apathy score was significantly impaired between presurgery (64.2 $\pm$ 15.5) and M3 (72.4 $\pm$ 21, $p = 0.02$), and between presurgery and 1Y (73.2 $\pm$ 15.5, $p = 0.02$). There was no evidence of depression: the mean BDI score did not differ before surgery (15.3 $\pm$ 5.1) and at M3 (17.5 $\pm$ 11.1, $p = 0.9$), M6 (13.3 $\pm$ 8.1, $p = 0.5$) and 1Y (15.8 $\pm$ 7.9, $p = 0.9$) after STN-DBS. We only found a significant impairment in phonemic fluency between the presurgery (11.0 $\pm$ 6.5) and the M3 (7.9 $\pm$ 4.9) evaluations ($p = 0.006$). MDRS did not change between presurgery (128 $\pm$ 10.9) and the 3M (124.3 $\pm$ 12.6, $p = 0.2$), 6M (127.7 $\pm$ 11.5, $p = 0.9$) and 1Y (127.2 $\pm$ 13.8, $p = 0.7$) evaluations.

Conclusions: Our results confirm findings in previous studies that STN-DBS induces apathy, both in short (three months) and in long-term follow-up (at 1 year). The use of the FrSBe may enhance information gathered during the clinical neuropsychological assessment of patients with PD and STN-DBS.

Mo-336

Oscillatory activity quantification of the subthalamic nucleus in Parkinson's disease and a normalization procedure to compare patients with or without prior pallidotomy

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Objective: To quantify the power and site of oscillatory activity in the subthalamic nucleus (STN) in patients with Parkinson's disease (PD) and to develop a normalization procedure to enable comparison between subgroups of PD patients.

Background: Enhanced oscillatory activity of the STN in the 3–30 Hz frequency band has been demonstrated to be a characteristic feature in patients with PD and can be diminished by anti-parkinsonian drugs and deep brain stimulation (DBS).

Methods: Microelectrode recordings (MER) from the STN obtained during DBS surgery, were blindly analyzed. Artefact correction was obtained by visual and auditory check of the spike recordings. For each trajectory the dorsal and ventral borders of the STN were determined from the normalized background activity. For each position inside the STN, with intervals of 0.5 mm, and along the channel, where the permanent electrode was implanted, from the MER the power spectral density (PSD) was calculated and divided into seven frequency bands (3-8 Hz; 8-12 Hz; 12-20 Hz; 20-30 Hz; 30-60 Hz; 60-100 Hz). The spectral power was normalized for each of the bands by dividing the power inside by the total power outside the STN. The size of the STN varied among patients. Therefore, for each patient the length within the STN was normalized by defining the dorsal border as 0 and the ventral border as 1 and dividing this interval into 8 bins. Then the PSD distribution of all different spectral bands along the trajectory inside the STN was averaged for each patient group.

Results: PSD and STN-size normalization procedures made it possible to compare STN oscillatory activity in PD subgroups, including PD patients with or without prior unilateral pallidotomy. Significant differences of spectral power between ipsi- and contralateral STN and at different locations inside the STN were found.

Conclusions: Variations of power spectral density of oscillatory activity inside the STN can be compared between subgroups of patients with PD and yield significant differences if appropriate normalization algorithms are applied.

Mo-337

Cerebral venous infarction: An avoidable complication of deep brain stimulation surgery

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Objective: We review the clinical course of four patients diagnosed with venous infarcts following deep brain stimulation (DBS) in order to clarify their presentation, diagnosis, and outcome.

Background: Despite numerous reports on the compliczations of DBS, there are few observations regarding venous infarction. Characterization of complications will help avoid future incidents, and improve patient outcomes.

Methods: A prospectively-collected database of complications was queried to identify patients who had venous infarcts. The diagnosis was based on: 1) delayed onset of symptoms, and 2) significant edema surrounding the superficial aspect of the implanted lead, with or without typical hemorrhage on CT scan. Their presentations and clinical course were reviewed. Pre- and postoperative images were reviewed to identify the relationship of superficial veins to the DBS lead. Motor symptoms of the affected patients were measured with UPDRS Part III scale.

Results: Four patients with venous infarcts were identified. All had Parkinson's disease (PD), with leads implanted in the subthalamic nucleus (n=2), and the globus pallidus internus (n=2). The trajectory on the preoperative stereotactic MRI scan passed within 3mm of a cortical vein in 2/4 cases. In the other two cases, the presence of superficial veins near the entry site was indeterminate because one patient's preoperative MRI was unusable due to motion artifact, and the other patient was not given contrast for the preoperative MRI. Symptoms of the venous infarct were significant but temporary in all patients, and DBS therapy resulted in improved motor function at 4 month followup.

Conclusions: Cerebral venous infarction is a potentially avoidable complication of DBS surgery. The delayed appearance of post-operative neurological deficits may indicate a potential venous compromise, and many cases of venous infarction may be misclassified as

simple hemorrhage or edema. To minimize the incidence of venous infarction and secondary subcortical hemorrhages, with their associated disabling neurological compromise, careful avoidance of injury or sacrifice of cortical veins is critical. We recommend the use of high resolution, contrasted T1 MRI to delineate cerebral venous anatomy and we also advocate careful planning of the stereotactic trajectory to avoid injury to venous structures.

Mo-338

Accurate and prospective recording of DBS adverse events: Do these complications affect quality of life?

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Objective: We present the results of a prospective, standardized method to record AE's, as well as a review of quality of life (QOL) outcomes in order to gauge the impact of AE's on QOL.

Background: Unlike pharmacological clinical trials, most surgical adverse event (AE) reporting is either unstated or reported as retrospective chart reviews, and is subject to bias. Furthermore, it often discloses only "probable" and surgically-related AE's. Accurately estimating the risk/benefit ratio will assist patients and practitioners in making decisions regarding DBS therapy.

Methods: Complications were prospectively recorded into a database, regardless of severity/probable relation to the procedure. AE's were classified as mild, moderate, or severe (resulting in an unscheduled hospital/clinic visit, >3 day postoperative stay, or a life-threatening event). AE's occurring within 180 days were analyzed to evaluate the impact of complications on the change in QOL, motor, and global impression scales (GIS).

Results: AE's occurred in 146 out of 270 DBS procedures (54%) on 198 patients (PD, n=113; essential tremor, n= 43; dystonia, n= 26, other = 16; Male = 68%, F = 32%). The maximum AE severity was mild in 28 (14.1%) patients, moderate in 35 (17.7%), and severe in 56 (28.3%). 124 DBS procedures had no AE's. Of the 300 AE's, 102 (34.1%) were mild, 106 (35.5%) were moderate, and 91 (30.4%) severe. There was no significant difference between baseline and 6-month QOL score changes between patients with and without AE's (P = 0.58), even when controlling for severity (P = 0.22). There were no significant differences between patients with and without complications in GIS scores or motor improvements in the UPDRS (P = 0.6), DRS (P = 0.35) and TRS Motor/ADL scores (P = 0.57/0.15).

Conclusions: Prospectively tracking AE's may lead to higher recorded AE rates, however, this does not necessarily translate to poorer QOL. We advocate for a community-wide effort to adopt rigorous, standardized adverse event reporting methods to advance the field. University of Florida DBS patients have monthly programming visits up to postoperative month #6, and 4, 6, and 12 months visits for clinical scales. All clinical providers can record AE's on scannable forms for entry into a centralized database, and monthly meetings are held to review recent AEs.

Mo-339

Localization and anatomo-clinical correlation of DBS electrodes contacts in the MLR in Parkinson's disease

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Objective: To report the localization of the most efficient contacts of electrodes implanted billateraly in the pedunculopontine nucleus area (PPNa) of PD patients, and their relationships to rostral brainstem anatomy based on side effects obtained during per-operative microstimulation.

Background: In severe parkinsonism deep brain stimulation (DBS) of the PPNa has been proposed to treat freezing of gait (FOG) symptoms. However, precise localization of the best targets in that area have not been established yet and is still under controversy.

Methods: In 8 PD patients, plots's coordinates were calculated in the Talairach system based on a stereotactic digital tele-radiography carried out during the surgery. The contacts were plotted onto a 3D deformable atlas and onto a proportional stereotactic schema obtained after standardisation of the coordinates. Per-operative microstimulations effects were obtained using 25/130 Hz stimulation. Clinical benefits of PPNa-DBS were evaluated pre and postoperatively with a composite gait score of UPDRS and the Giladi FOG questionnaire.

Results: Per-operative microstimulations of PPNa induced ipsilateral oscillopsia, myoclonia and paresthesia. Clinical benefits on FOG showed that the most benefical contacts were located 4-5 mm posterior to PC and at a depth ranging from -10 to -13 mm below AC-PC line. After standardization and reconstruction using brainstem atlas, those contacts were located just anterior to a line joining the lateral mesencephalic sulcus to the cerebral aqueduc encompassing the posterior part of the PPN pars compacta and the sub-cuneiform nucleus. Bipolar, chronic stimulations in that area were allowed by a lesser effect of electrical current spread to the nearby fibres of the 3rd cranial nerve and to the medial lemniscus.

Conclusions: Anatomical localization of electrode's contacts in PPNa, peroperative microstimulations analysis and clinical evaluation obtained from our 8 patients leaded to identify the sub-cuneiform/cuneiform area located in the posterior tegmentum as a possible most benefical target to implant DBS electrodes to treat FOG symptoms.

Mo-340

Targeting the subthalamic nucleus for deep brain stimulation – A comparative study between magnetic resonance images alone and the fusion with computed topographic Images

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Objective: To test the hypothesis that if Computed Topographic (CT) images fused with Magnetic Resonance Images (MRI) will be superior to MRI alone in targeting the subthalamic nucleus (STN) for deep brain stimulation (DBS).

Background: The targeting methods used in DBS were depend on the facility of the institute and the familiarity of the surgeon. MRI was used to be the only targeting tool in many centers, where the others use image fusion techniques to fuse MRI itself, CT scan or with intraoperative ventriculography for better targeting accuracy.

Methods: In the year 2006 to 2007, a consecutive of 21 parkinsonian patients were enrolled into this prospective cohort study and was divided into two groups for comparison. Group A included 11 patients with 20 procedures of STN-DBS were performed under MRI-directed targeting alone. Group B included 10 patients with 20 procedures were performed under MRI-directed targeting and fused to CT for surgical coordinates. Intra-operative microelectrode recordings (MER) were performed in all procedures. Comparisons were made between the number of MER trajectories, the depth of STN recorded as well as the short term outcome in at least 3 months postoperatively.

Results: In group A (MRI only), 7 patients were followed at least 3 months (mean 5.6±3.2). In group B (MRI fused to CT scan), 6 patients were followed at least 3 months (mean 3.8±1.3). After DBS surgery, in comparing to the baseline l-dopa OFF, UPDRS part 3 were improved by 46±15.9% and 57.6±22.9% in group A/B respectively (l-dopa OFF/DBS ON). With a mean decrement on LEDD of 39.3±26.9% and 47.8±25.4%. Single MER trajectory procedure in group A, B were 45% (N=9/20) and 65%(N=13/20) respectively. The mean recorded STN depth from initial and final MER trajectory in group A, B were 3.6mm(SD=1.7mm)/4.5mm(SD=0.7mm)and 4.3mm(SD=1.8mm)/5.1mm(SD=0.5mm) respective. Where the final recorded STN depth was significantly longer in group B (p=0.0018).

Conclusions: In frame-based stereotactic STN targeting, image fusion technique between CT and MRI has a higher accuracy than

MRI-directed targeting alone. The short term motor outcome on group A/B was comparable.

Mo-341

Subthalamic nucleus-deep brain stimulation modulates thermal sensation and pain thresholds in Parkinson's disease

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Objective: To assess whether subthalamic nucleus-deep brain stimulation (STN-DBS) can modulate sensory (painful and non-painful) thresholds in Parkinson's disease (PD).

Background: PD is associated with various sensory disturbances, including pain. Sensory symptoms can be modulated by L-dopa treatment. In the last decades STN-DBS has been shown to provide significant motor improvement, but its effects on sensory symptoms remain largely unknown.

Methods: Twenty-one PD patients treated by bilateral STN-DBS were evaluated in the off-drug condition (12-hour interruption of antiparkinsonian medication), while DBS was switched on or off. The following sensory thresholds were measured at the hands in both conditions: vibratory, tactile, warm, and cold detection thresholds (DT), and pinprick, heat and cold pain thresholds (PT). Methods of level were used to avoid any influence of changes in motor reaction time. Pain intensity to pinprick, heat and cold suprathreshold stimulations was measured on a visual analogue scale to assess hyperalgesia.

Results: A significant decrease in warm and cold DT, an increase in pinprick, heat, and cold PT, and a reduction of pain intensity produced by suprathreshold stimulations were observed in DBS-ON compared to DBS-OFF condition (paired *t*-test with Bonferroni correction). Conversely, vibratory and tactile DT did not change between both conditions.

Conclusions: STN-DBS was found to selectively modulate thermoalgesic sensation in PD patients. In particular, STN-DBS increased PT and concomitantly reduced pain intensity to suprathreshold stimuli. This study adds to the increasing body of evidence on the non-motor effects of STN-DBS, including in sensory integrative systems.

Mo-342

Levels of the light subunit of neurofilament triplet protein in the cerebrospinal fluid from patients with Parkinson's disease treated with bilateral subthalamic nucleus stimulation

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Objective: To investigate the extent of brain tissue damage in the context of subthalamic nucleus (STN) deep brain stimulation (DBS) for Parkinson's disease (PD), by examining the cerebrospinal fluid (CSF) levels of neurofilament triplet protein (NFL) pre- and postoperatively.

Background: The CSF levels of NFL, a marker of neuronal damage, have been shown to be normal in PD. STN-DBS is an efficient neurosurgical treatment for selected patients with advanced PD. Histopathological studies in PD patients treated with STN-DBS have shown minimal acute tissue damage following STN electrode implantation but no signs of ongoing, long term brain tissue damage (1).

Methods: NFL levels were measured in CSF collected pre- and postoperatively from patients with advanced PD treated with STN-DBS.

Results: The preoperative CSF-NFL levels were normal (median 250, range 250-288 ng/L) in 13 patients and high in 1 patient. Increased CSF-NFL levels at any time point postoperatively were seen in 12 (80%) patients. Three patients (20%) showed no increase in their CSF-NFL levels. The CSF-NFL peak was noted within the first 2 weeks postoperatively in 8 patients and between 2 and 12 weeks postoperatively in 4 patients. CSF-NFL levels normalized at 6 months and beyond in 6 (50%) of the patients showing a postoperative increase. In 5 (42%) patients showing increased CSF-NFL the very last CSF was collected less than 6 months postoperatively (mean 3 months) at which time CSF-NFL was still elevated although clearly decreasing in all but one patient. None of these 5 patients were followed up with more LPs. There was one patient with elevated CSF-NFL levels beyond 6 months. No further CSF was collected from this patient.

Conclusions: The CSF-NFL levels were high directly following the STN-DBS procedure and during the first 6 months postoperatively, indicating an acute neuronal damage. However, they normalized thereafter, suggesting that no ongoing, long term neuronal damage is caused by STN-DBS. Reference: 1. Haberler C, Alesch F, Mazal PR, Pilz P, Jellinger K, Pinter MM, et al. No tissue damage by chronic deep brain stimulation in Parkinson's disease. Ann Neurol. 2000 Sep;48(3):372-6.

Mo-343

Modification of emotional states by bilateral stimulation of the subthalamic nucleus in a patient with Parkinson's disease

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Objective: to assess whether the post-operative psychological symptoms, in a PD patient treated with bilateral STN stimulation, were related to nucleus subthalamicus stimulation. If stimulated related the challenge was to find an optimal balance between motor function and psychological status by changing stimulation settings.

Background: Bilateral subthalamic nucleus (STN) stimulation reduces motor symptoms and Levodopa use in patients with Parkinson's disease (PD) but there is concern about stimulation related emotional and behavioural changes. The present study shows a method of systematic and double blind 'on-off' variation of STN stimulation that allows for controlled tests and statistical analysis of stimulation effects on psychological symptoms in a single case.

Methods: a single case experimental design (SCED) including three conditions: condition 'Off' (no stimulation), condition 'Íntermediate'(free adjustment of stimulation settings) and condition 'Motor optimum' (voltages set at the level of the established motor optimum). Each condition consisted of 5 trials and stimulation order was randomized with the restriction that no more than two successive identical conditions could occur. Psychological symptoms were assessed with Visual Analogue Scales (VAS) that related to seven items: perception, thinking, mood, motivation to attend to the environment, energy/fitness, drive to act and fluency of speech. Item selection was based on information from postoperative interviews. Statistical analysis was restricted to the condition 'Off'and 'Motor optimum'.

Results: VAS scores showed a significant increase (worsening of symptoms) from condition "Off" to condition "Motor Optimum". The average between-treatment difference was least outspoken for Perception, but still significant ($p = 0.047$). For all other symptoms, VAS scores were lowest if the patient was not stimulated ($p=0.012$). At intermediate voltage levels the motor symptoms got slightly worse relative to the 'Motor optimum' condition but psychological symptoms decreased.

Conclusions: the present study demonstrated that a SCED approach, manipulating the stimulation settings is helpful to endorse adverse effects of STN stimulation and to find a compromise between motor improvement and these adverse effects.

Mo-344

Continuous dopaminergic stimulation by intraduodenal infusion of levodopa in advanced Parkinson's disease: Efficacy and safety

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Objective: To evaluate efficacy of continuous intraduodenal infusion of levodopa and safety of this new therapeutic alternative after 6 months of treatment in patients with advanced Parkinson's disease.

Background: When advanced Parkinson's disease (PD) patients experience motor complications despite standard oral treatment, two treatment options are available: deep brain stimulation and subcutaneous apomorphine infusion with respects of indications for each strategy. Continuous intraduodenal infusion of levodopa via a gastrojejunal tube may be proposed at this stage of the disease and the study of indications and clinical results with continuous intraduodenal infusion of levodopa may develop this new therapeutic alternative.

Methods: Seven patients with advanced PD (dementia for all and psychiatric disorders for some of them, axial signs) were treated with continuous intraduodenal infusion of levodopa because the two other strategy of treatment were not available. We evaluated neuropsychological functions, all UPDRS scales, gait and quality-of-life just before treatment onset and six months after treatment end. Moreover, we described all adverse events (early and late) and studied daily levodopa doses before and 6 months after treatment.

Results: We demonstrated an improvement in motor UPDRS (44%), in axial signs (40% for UPDRS part III axial subscore and 12% for gait) and a reduction of fluctuations (37.5%) and dyskinesia (20%) in UPDRS part IV. These significant results are observed without any change in the quality-of-life. Adverse events were due to gastrostomy positioning for four patients, the equipment (pump, connection, inner tube) for all patients and levodopa for four patients. Daily levodopa dose had to be increased 13.5% in order to control symptoms efficiently, without any psychotic complication after six months. The equipment needs however to be improved.

Conclusions: Continuous intraduodenal infusion of levodopa can be considered as a new treatment strategy providing significant improvements in motor fluctuations, dyskinesia and severe axial signs. These results were demonstrated in very advanced PD patients, who had been excluded from previous studies, with cognitive disorders and for some of them dopaminergic psychosis well controlled by medications.

Tu-327

Unilateral STN-DBS in PD: Reappraisal and new insights

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Objective: Consideration of new insights in unilateral STN-DBS, UPDRS III odds ratios in comparative series; segmental evolution in PD and application to unilateral STN-DBS; descriptions of atypical applications of unilateral STN-DB.

Background: -Unilateral STN-DBS methods acquire a relevant value in recent series and case samoples, being observed motor balance improvements (UPDSR III) and ADL-movements inter-relationship, added to improvement rates in bradykinesia -tremor scores. -Unilateral STN-DBS series show a 31 % improvement in general UPDRS III, with ipsilateral UPDRS III transient improvement (17.65 %) and contralateral UPDRS III improvement (45.45 %) -It has been shown a variability in unilateral STN-DBS in series with office-based follow-up variability of 46 % UPDRS III improvement in 5 succesive consultations and 80-81.4 % of UPDRS III improvement in up to 2 consultations.

Methods: -Prevalence odds ratio (OR) in unilateral and bilateral STN-DBS related to significant/non-significant improvement in UPDRS III -Rank correlation between unilateral STN-DBS in refractory PD and UPDRS III improveemnt in unilateral DBS series -Correlation between spontaneous improvement (OFF/OFF) after STN-DBS -Positional basis in unilateral STN-DBS and optimization in subthalamic area /subthalamic nucleus.

Results: -Prevalence OR in significant improvement between unilateral and bilateral STN-DBS is 2.37. Refractory PD series show UPDRS III improvement at 6 months after correct single STN-DBS in r ranges = 0.32 -Unilateral stimulation in dorsal margin /subthalamic area (positional issue) has a rank correlation with optimization in UPDRS III of r=0.86 -Rigidity segmental evolution in ipsilateral and contralateral sides show a peak of 25 % at 6 months, with an improvement post unilateral STN-DBS of 20-28 %.

Conclusions: -Unilateral STN-DBS with 50-54.5 % UPDRS III improvement show spontaneous improvement of 16-25 % in OFF/OFF. -Unilateral STN-DBS with 31-48 % UPDRS III improvement show a linear correlation with OFF/OFF post-DBS of r = 0.49 -Unilateral STN-DBS series with lead 3 active between 0.5-0.7 mm of intercommisural plane may show a linear correlation with optimal results in UPDRS III -OFF/OFF spontaneous improvement of UPDRS III (25 %) at 12 months, in unilateral DBS-STN would be in relationship with segmental progression of rigidity (25 %) at 0-3-12 months of correct diagnostic description.

Tu-328

Task-specific bilateral arm freezing in subthalamic nucleus deep brain stimulation (STN DBS) in Parkinson's disease (PD)

S.A. Ellias (Boston, Massachusetts)

Objective: Characterize bilateral arm freezing during a specific bimanual task in a PD patient after STN DBS.

Background: Gait freezing and difficulty with bimanual tasks are well known in PD. However, task-specific bilateral arm freezing only during a bimanual task has not been well characterized. Some of these results were shown at the Matson Lectures on STN DBS at Brigham and Women's Hospital, Boston MA, June 2003.

Methods: STN DBS was performed in a 56 year old patient (pt.) with 14 yrs of PD (H&Y off 4.0, UPDRS motor off/on 54/30.5). Pre-DBS symptoms included severe bradykinesia, rigidity, and gait freezing. He could not move either leg or left arm during his worst off states. On medications he had severe dyskinesia & required 2 canes to walk. He had no arm apraxia. Movement testing occurred pre-DBS and at 1, 3, 6, 9, 12, & 24 months. Videotaping of arm freezing was at 3 & 5 mo. Clinical visits occurred up to 5 yrs.

Results: Within two months of DBS, bradykinesia, rigidity, fluctuations, and dyskinesia improved. He had no gait freezing, rare dyskinesia and was able to walk without a cane with medications lowered by 90%. At 3-5 mo. with L-dopa only 100 mg per day, he reported arm freezing (AF) for the first time with inabilty to move hands upward from a sink to bring water to his face occurring only when both hands were used together. During testing his arms would freeze only when hands were touching each other in midline while being raised to his face. AF occurred on meds or 12 hrs off meds. AF worsened if avoiding a faucet, or if holding water or if the dorsum of one hand was in the palm of the other. Increasing DBS from 1.3V to 1.8Von either side or together reduced AF for up to 12 hours. Increasing L-dopa partially reduced AF. There was no AF while putting on glasses, while raising each hand independently to the face, or when raising arms together while not touching each other. There was no apraxia when imitating brushing teeth or combing hair. This task-specific AF has persisted at 5 yrs despite changes in voltage, contacts or medicine. Details of stimulator & medicine adjustments and a videotape will be presented.

Conclusions: Persistent task-specific bimanual arm freezing can develop in PD patients with sustained benefit from STN DBS. Similar to gait freezing, the specific arm task involves coordination of two limbs in a task requiring sensori-motor feedback.

Tu-329

Disruption of the melanocortin system caused by bilateral subthalamic nucleus stimulation (STN-DBS) in Parkinson's disease (PD)

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Objective: To determine whether the weight gain after bilateral STN-DBS in PD is related to disruption of the melanocortin system,

i.e., an increase in neuropeptide Y (NPY) and/or resistance to the action of leptin.

Background: The central melanocortin system, responsible for energy balance, is composed of multiple mediators, notably NPY (anabolic effect), which is secreted in the hypothalamic arcuate nucleus, and leptin (catabolic effect), which is produced by adipocytes and inhibits NPY secretion. The weight gain in PD patients after bilateral STN-DBS may in part be related to disruption of this system due to diffusion of the electric current to the hypothalamus.

Methods: This 6-month follow-up study included 37 patients with PD (CAPSIT-PD criteria): 20 who underwent bilateral STN-DBS and 17 controls who refused surgery. Data were obtained at baseline, 3 months and 6 months on neurological and nutritional status, including determination of body mass index (BMI), body composition (impedance) and serum NPY and leptin levels. A general linear model for repeated measures was applied and main confounding factors (diabetes, neuroleptic treatment and change in levodopa equivalent dose) were controlled by multivariate regression analysis.

Results: BMI, NPY and leptin levels changed significantly over time with a distinct pattern in each group. As expected, the BMI increase at 6 months was greater in the surgery group (5.5±6.3% vs. 0.5±3.5% in controls; p=0.031). Control patients exhibited a reduction in leptin level (-2.0±4.3 ng/ml) and a consequent increase in NPY level (72.4±58.7 pmol/ml). However, STN-DBS patients showed an increase in leptin level (3.1±5.0 ng/ml; p=0.001 vs. controls) and also in NPY level (12.1±53.6 pmol/ml; p=0.022 vs. controls), which suggests resistance to inhibition by leptin. This rise in NPY level correlated with higher stimulation voltages but not with changes in levodopa equivalent dose.

Conclusions: Bilateral STN-DBS causes disruption of the melanocortin system, probably related to diffusion of the electric current to the hypothalamus. This mechanism may in part explain the weight gain of PD patients after surgery.

Tu-330

Effects of PPN area stimulation on gait disorders in PD

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Objective: To assess the efficacy of PPN area (PPNa) stimulation on gait disorders in PD, with particular focus on freezing of gait (FOG).

Background: Severe FOG is a common and disabling condition in advanced PD. The initial results of PPNa stimulation appeared encouraging but required confirmation by controlled studies. We initiated a prospective controlled study of PPNa stimulation effects on gait disorders and FOG.

Methods: Six patients with PD and STN stimulation were recruited for bilateral implantation of the PPNa because they progressively developed severe FOG. Our protocol included a double blind randomized crossover study (months 4 to 6) with PPNa stimulation either on or off, and an open assessment one year after surgery. Patients were assessed off and on levodopa. The primary outcome measures were the improvement of a composite gait score and an objective quantification of FOG duration during walking tests. We also assessed global motor functioning, activity of daily living, quality of life and cognition.

Results: No serious adverse event occurred. Postoperative MRIs showed placement of the 12 electrodes in the PPNa, although with some variability from the PPN per se to the cuneiform nucleus. Low frequency stimulation (10-25Hz) was used but induced transient adverse effects at relatively low voltages, requiring bipolar stimulation. Stimulation was eventually set intermittent in all patients due to both tolerance and long carry-over effects. During the double blind study, FOG duration did not change off levodopa, but decreased in two patients on levodopa under PPNa stimulation. One year after surgery, gait disorders and FOG dramatically improved in one patient, moderately in another, and did not change in two. For two others, FOG duration improved while the composite gait score remained unchanged. There was no significant change in global motor functioning, activity of daily living, quality of life and cognition.

Conclusions: Low frequency PPNa stimulation improved gait disorders and FOG in some patients. However, it is a sophisticated procedure for both electrode implantation and patient management. The factors predictive of PPNa stimulation outcomes appear complex and multiple and are currently under scrutiny.

Tu-331

Effects of unilateral pedunculopontine nucleus deep brain stimulation (PPN-DBS) in parkinsonian patients with prominent freezing of gait (FOG)

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Objective: To evaluate the effect of chronic PPN-DBS in a mixed population of parkinsonian patients with prominent FOG.

Background: PPN-DBS has recently been suggested as a possible treatment for refractory FOG. Here we report our experience to date with unilateral PPN-DBS in mixed parkinsonian population, all of whom had severe, refractory FOG.

Methods: 4 pts (3M/1F) with disabling FOG received PPN-DBS at our center. Mean age at surgery was 73 yrs(range 71-76), mean symptom duration was 8 yrs(range 4-13). One patient was diagnosed with primary progressive FOG, two pts with atypical parkinsonism, and one pt with Parkinson's disease who was s/p bilateral STN-DBS with persistent FOG. All 4 pts received unilateral PPN implants, initially. Targeting was achieved by stereotactic MRI and intraoperative MER. Patients were programmed over several sessions and underwent videotaped, on/off medication, pre- and post-operative assessments (UPDRS, FOG-Q (part B) questionnaire, and timed walking tests).

Results: Pts were evaluated 3-7 months post-operatively. A fifth pt had a lead fracture preventing post-op assessment. Typical stimulation parameters used the most ventral contacts in bipolar mode (mean 3.1V, PW60us, freq 25Hz). Overall, there was no significant improvement in objective, validated scales (UPDRS and FOG-Q). We did, however, observe a qualitative change in FOG in all patients; from a baseline festinating, continuous FOG, to smoother gait with more episodic FOG. Three pts experienced a robust transient subjective improvement postoperatively, with mean improvements in; timed walking tasks (26%), FOG-Q score (38%), and UPDRS (II/III) assessing gait, falls, freezing, posture, and stability (32%). Two pts have gone onto bilateral placement, one of them has had persistent improvement in FOG, resolution of falls, and improved mood.

Conclusions: Initial experience suggests that unilateral PPN-DBS shows little persistent benefit for FOG. Although 3 patients showed an initial improvement, this response waned over time. Two patients have gone onto bilateral implantation to date. Additional study is needed to clearly determine the role of unilateral PPN-DBS in parkinsonian patients with refractory FOG.

Tu-332

Pendunculopontine nucleus deep brain stimulation (PPN-DBS)-induced oscillopsia: Implications for mechanisms of visual fixation

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Objective: To present 2 cases of PPN-DBS-induced oscillopsia and discuss the implications of oculographic findings used to assess this symptom.

Background: The PPN is a novel DBS target being investigated for treatment of disabling gait disturbances, e.g. severe freezing of gait (FOG). There are reports of visual symptoms (shimmer or trem-

bling vision) in patients undergoing PPN-DBS. It has been suggested that this shimmer can be used as a marker to localize the therapeutic target in the PPN. Recently, 2 cases were reported in which PPN-DBS-induced vertical oscillopsia was attributed to spread of current to the oculomotor nerve. Here we present 2 pts who experienced similar symptoms and underwent oculographic recordings to evaluate them.

Methods: 2 pts underwent implantation of unilateral PPN-DBS to treat FOG. The first, a 73 yo man with atypical parkinsonism received a left PPN implant (lead-tip coordinates: -4.4mm lateral, -19.4 mm posterior, and -18.3 below the midcommisural point). The second, a 76 yo woman with PD s/p bilateral STN-DBS, received a right PPN implant (+5.8, -17.4mm, and -18.6mm). Both patients had transient robust improvement in FOG. During DBS programming, both patients described a "shimmering" of their vision, the first in a vertical direction, the second horizontal. Oculographic recordings were conducted in both pts.

Results: Regular, rhythmic oscillations were frequency locked (at 10, 25, 50, 65 Hz) and voltage-dependent (with amplitude proportional to voltage of stimulation). Importantly, in accordance with the description of their symptoms, the first pt's eye movements were in a strictly vertical direction, while the second's were primarily horizontal, with square-wave jerk like fixation instability that decreased with stimulation.

Conclusions: Because of the clearly distinct and opposite directionality of the ocular movements recorded in these 2 pts and the clearly frequency-locked and voltage-dependent nature of the movements, we propose that oscillopsia induced by PPN-DBS is the result of electrical stimulation to an area near the PPN in lateral tegmentum of the ponto-mesencephalic junction which may be involved in maintenance of visual fixation.

Tu-333

Case report of successful deep brain stimulation for early stage Parkinson's disease

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Objective: To report an illustrative case of deep brain stimulation (DBS) for early stage PD as part of an ongoing clinical trial.

Background: Our center is conducting a single-blind, parallel-group, randomized pilot assessment of DBS in 30 patients with early PD. DBS is FDA-approved for advanced PD, and extending the therapy for use in early disease holds promise because (1) DBS can decrease anti-PD medication use, delaying or preventing medication-related complications; (2) it provides improvement in quality of life over medication alone; and (3) some have hypothesized DBS may have a disease-modifying effect.

Methods: Eligible patients are between the ages of 50 and 75, have idiopathic Parkinson's disease, have been on levodopa or dopamine agonist therapy for greater than six months but less than four years, and are without motor fluctuations, dementia, or previous brain operation. After a four-part expanded informed consent process and baseline UPDRS testing, 15 subjects are randomized to standard anti-PD medical therapy and 15 to medical therapy plus DBS of the bilateral subthalamic nucleus. All subjects then undergo UPDRS testing at six month intervals for two years.

Results: To date, 26 subjects have enrolled in the study and been randomized (13 medicine, 13 DBS plus medicine). They are 23 men and three women with an average age of 57.9 years, who have been on antiparkinsonian medication an average of 2.1 years at screening. The first patient to complete participation is a white male, aged 58 years at screening. His initial ON-medication UPDRS-III rating was 13 and his full UDPRS was 52, and he was taking 1123 mg of levodopa. He was randomized to surgery. No adverse events related to the surgery or stimulation occurred throughout the follow-up period, and he did not develop dyskinesias. At study exit, his ON UPDRS-III was 14 and full UPDRS was 47, and he was taking 723 mg of levodopa.

Conclusions: In this single case, the severity of treated PD, both motor and overall, did not worsen over the two year period, in spite of greatly reduced anti-PD medication. Moreover, this improvement occurred without related adverse events. If the results of this single case are confirmed in the pilot trial, a multicenter trial should be conducted to investigate the use of DBS in early PD.

Tu-334

New onset reverse sensory gest (rSG) in DYT1 dystonia treated with GPi DBS

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Objective: To discuss rare case of DYT1 dystonia treated with GPi DBS. Later he developed reverse sensory geste to DBS programmer.

Background: Sensory gest are common in about 25% of dystonia and are pathognomic of primary dystonia. Rarely worsening of dystonia with sensory stimulus is described with cervical dystonia. No case of DTY1 with or without DBS has been described with rSG.

Methods: This 14 years had developed generalized dystonia at the age of 8 years and worsened by 12 years to the severity of being bed ridden. At this point his BFM dystonia severity score was 65. He underwent bilateral GPi DBS with excellent response and at 1 month follow up BFM score reduced to 12. At 2 years of follow up his response had deteriorated severely and with best of programming he had poor response to therapy. During programming sessions it was noticed that when ever programmer was brought to chest was he had severe transient deterioration in truncal and facial dystonia, which would disappear on removal of programmer.

Results: This rare case of DYT1 dystonia had developed new onset reverse gest after GPi DBS. This also highlights the modification of mechanism of sensory geste by GPi DBS.

Conclusions: This rare case of reverse sensory gest in DYT1 dystonia, who initially had fair response to GPi DBS, may be an indicator of poor response to GPi DBS.

Tu-335

Atypical speech abnormality following initiation of deep brain stimulation of the subthalamic nucleus (STN-DBS) for Parkinson's disease (PD)

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Objective: To present an unusual speech abnormality following the initiation of STN-DBS that persisted for several months following the cessation of stimulation.

Background: While STN-DBS is an important treatment for PD, speech problems are not improved and sometimes exacerbated by this therapy. Ongoing studies suggest STN-DBS has different effects on voice quality and articulatory fluency. Good control and coordination of both are required for normal speech.

Methods: Bilateral STN-DBS was performed using micro-electrode guided, frame-based stereotactic implantation of DBS leads. Post-operative MRI confirmed lead placement bilaterally in the STN. DBS initial programming was performed three weeks after surgery and adjusted numerous times. Speech was evaluated by a senior speech pathologist using a protocol designed for STN-DBS studies.

Results: A 62 yr old right-handed male with 15 yrs of tremor-predominant PD, confirmed by two movement disorders specialists, developed severe dysarthria several hours after the second programming session, despite symptomatic motor improvement and optimal tremor control. Multiple settings were examined, with no improvement of dysarthria and no return of tremor. A repeat MRI revealed no gross abnormalities. Both stimulators were subsequently turned off with no improvement of speech and no return of tremor over a

period of 4 months. Phonation was viable during vowel prolongation but failed during articulation.

Conclusions: STN-DBS effects are typically reversible after a wash-out period. However, this patient had a persistent speech deficit despite being off stimulation for over four months. A simple lesion effect caused by lead implantation does not explain these findings as the impairment occurred following programming. Post-operative imaging suggests intact leads and accurate placement. Impedance and battery life values do not suggest stimulator malfunction. While the possibility of a psychogenic speech disturbance emerging after successful treatment of organic motor symptoms must be considered, the dysarthria suggests a coordination problem in laryngeal and supraglottal speech processes. Studies to elucidate this unusual outcome are continuing. This case demonstrates that permanent changes can occur following a period of STN-DBS.

Tu-336

Effects of subthalamic nucleus stimulation on cognition and mood in Parkinson's disease (PD)

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Objective: To assess the neuropsychological outcome as a safety measure and quality control in patients with subthalamic nucleus (STN) stimulation for PD.

Background: Deep brain stimulation (DBS) is considered a relatively safe treatment used in patients with movement disorders. However, neuropsychological alterations have been reported in patients with STN DBS for PD. Cognition and mood are important determinants of quality of life in PD patients and must be assessed for safety control.

Methods: Seventeen consecutive patients (8 women) who underwent STN DBS for PD have been assessed before and 4 months after surgery. Besides motor symptoms (UPDRS-III), mood (Beck Depression Inventory, Hamilton Depression Rating Scale) and neuropsychological aspects, mainly executive functions, have been assessed (mini mental state examination, semantic and phonematic verbal fluency, go-no go test, stroop test, trail making test, tests of alertness and attention, digit span, wordlist learning, praxia, Boston naming test, figure drawing, visual perception). Paired t-tests were used for comparisons before and after surgery.

Results: Patients were 61.6 ± 7.8 years old at baseline assessment. All surgeries were performed without major adverse events. Motor symptoms "on" medication remained stable whereas they improved in the "off" condition ($p<0.001$). Mood was not depressed before surgery and remained unchanged at follow-up. All neuropsychological assessment outcome measures remained stable at follow-up with the exception of semantic verbal fluency and wordlist learning. Semantic verbal fluency decreased by $21 \pm 16\%$ ($p<0.001$) and there was a trend to worse phonematic verbal fluency after surgery ($p=0.06$). Recall of a list of 10 words was worse after surgery only for the third attempt of recall (13%, $p<0.005$).

Conclusions: Verbal fluency decreased in our patients after STN DBS, as previously reported. The procedure was otherwise safe and did not lead to deterioration of mood.

Tu-337

Stimulation of the ventral intermediate thalamic nucleus in tremor dominant parkinsonian patients with previous subthalamic nucleus stimulation: A case report

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Objective: To evaluate the clinical efficacy of additional bilateral deep brain stimulation (DBS) of the ventral intermediate thalamic nucleus (Vim-DBS) in a patient with tremor dominant idiopathic Parkinson's disease (PD) and subthalamic nucleus (STN) DBS on rest tremor.

Background: The STN is the target of choice for high frequency DBS in patients with PD. However, in a subgroup of patients with tremor dominant PD tremor is not sufficiently suppressed by STN-DBS.

Methods: Here, we present the case of a 63-year-old male patient with a twelve year history of tremor dominant PD receiving subsequent STN and VIM DBS.

Results: In April 2007 bilateral STN-DBS was performed leading to a mild improvement of overall motor symptoms. However, tremor subscore remained rather unchanged postoperatively, irrespective of STN-DBS being turned on or off (tremor subscore of 21/8 versus 23/8, respectively). Thus, tremor was largely unaffected by STN-DBS alone, still interfering with the patient's activities in daily living. In February 2008 the severity of tremor symptoms was unchanged, and the Unified Parkinson's Disease Rating Scale (UPDRS) was 28/108 in motor part III with dopaminergic medication. Since the patient's disabling tremor remained refractory to medication as well as to STN-DBS, we performed additional bilateral Vim-DBS in July 2008. During additional Vim-DBS, the patient experienced a marked subjective reduction of tremor and the UPDRS motor part III improved by 35% (18/108 on medication). Tremor subscore improved by 71% to 3/28 when Vim-DBS was turned on alone, compared to a subscore of 23/28 without any stimulation or medication at all.

Conclusions: We propose that additional bilateral Vim-DBS may be considered to further reduce tremor symptoms and improve the patients' quality of life in a subgroup of patients with tremor dominant PD that do not sufficiently benefit from medication and STN-DBS alone.

Tu-338

Neuroleptic malignant-like syndrome after discontinuation of deep brain stimulation

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Objective: To describe a case of neuroleptic malignant-like syndrome (NMLS) after discontinuation of bilateral subthalamic nucleus deep brain stimulation (STN-DBS) in a patient with Parkinson's disease (PD).

Background: NMLS is an uncommon, however, potentially fatal complication of dopaminergic treatment. It is characterized by hyperthermia, muscle rigidity, tremor, perspiration, sialorrhea, and elevated creatinine kinase activity. NMLS has been described in patients with PD due to the abrupt discontinuation of L-dopa treatment. There are no reports about NMLS after discontinuation of STN-DBS.

Methods: Case report.

Results: A 58-year-old man with a 15-year history of PD underwent STN-DBS. After surgery, he could reduced dopaminergic medication and his motor function was very much improved. Two years after surgery, he showed manic state suddenly. Due to his manic state he was running in our examination room. We considered that this state was dangerous, so that we turned off the stimulation. A few days after discontinuation of STN-DBS, NLMS appeared. NLMS was improved by fluid therapy, then his manic state was improved. Soon thereafter we started again STN-DBS without medication. Four years after surgery, he got manic state again. We discontinued the stimulation, however, NMLS appeared again. NMLS was similarly improved by fluid therapy. Six years after surgery, the symptom repeated again.

Conclusions: Our case is suggested that NMLS may appeare when STN-DBS was discontinued for several days or more. We considered that NMLS might have been possibly prevented, when he took low dose L-dopa or STN-DBS was continued with low stimulation amplitude level.

Tu-339

Subthalamic nucleus stimulation in patients with Parkinson's disease due to the LRRK2 G2019S mutation

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Objective: To present the outcome of stimulation of the subthalamic nucleus (STN) in patients with Parkinson's disease (PD) carrying the G2019S Leucine Rich Repeat Kinase 2 (LRRK2) mutation.

Background: A single missense mutation (G2019S) in the LRRK2 gene is a common cause for PD in Jewish Ashkenazi patients. Stimulation of the STN is an effective treatment for patients with PD presenting with severe advanced levodopa-responsive parkinsonism.

Methods: Eight patients of Ashkenazi origin, diagnosed with PD according to the United Kingdom PD Society Brain Bank clinical diagnostic criteria were later found to carry the G2019S mutation. The patients were l-dopa responsive but had developed motor complications and prior to the operation they all had severe disability despite medication optimization. The patients were operated between 2001 and 2008 in various centers in Israel, Europe and North America. The average age was 65.1±6.8 years, disease duration 15.5±2.6 years and 6 had a positive family history of PD.

Results: There were no peri-operative complications. At last follow up, 5.1±2.5 years after surgery, UPDRS part II score in off state (activities of daily living), UPDRS part III score in off state (motor examination), and levodopa equivalent daily dose, still showed a significant improvement with STN stimulation., of 40%, 20%, and 29%, respectively. Psychiatric complications occurred, with severe psychotic depression in 2 patients and one case each of apathy, worsening of dopamine dysregulation syndrome, psychosis and cognitive deterioration.

Conclusions: STN stimulation seems to be effective for the motor symptoms in patients with PD carrying the LRRK2 G2019S mutation. However neuropsychiatric complications are not uncommon in this group emphasizing the necessity of a comprehensive neurocognitive and psychiatric evaluation prior to referral to DBS. Further investigations are needed as well as comparison to mutation-negative PD patients.

Tu-340

The impact of deep brain stimulation on parkinsonian gait during dual tasking

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Objective: To evaluate the impact of deep brain stimulation (DBS) on the "dual task" (DT) effect on quality and speed of gait in patients with Parkinson's disease (PD).

Background: Subthalamic DBS relieves many of the motor symptoms associated with PD including certain aspects of gait, however, falls may persist after DBS, perhaps because it does not enhance dual tasking.

Methods: 35 PD patients with DBS (mean age: 63.2±8.5 yrs; mean UPDRS-motor when off stim and off meds: 39.3±13.2) walked off meds/off stim, off meds/on stim, on meds/off stim, and on meds/on stim. In each condition, they performed 3 walking tasks, for 1 min each, while wearing force-sensitive insoles: 1) usual-walking (single task), 2) while subtracting serial 3's (S3), and 3) while generating word lists (verbal fluency, VF). Gait speed, Drag percent (Dpct), a measure of the percent of time spent with one foot on the ground and Drag percent variability (DpctCV) were calculated. These measures reflect the classic stance percent and stance percent CV measures.

Results: Effects of Dual Task: S3 and VF reduced gait speed and increased Dpct and DpctCV under all med/stim conditions. DBS Effects "OFF" Meds: DBS significantly increased gait speed ($p<0.01$) during the three walking tasks compared to the no stim condition. Dpct also significantly decreased during usual-walking ($p<0.003$) and during S3 ($p<0.0004$), but not during VF. DpctCV did not significantly change in response to DBS. DBS Effects "ON" Meds: Although the UPDRS-motor scores improved, gait speed, Dpct and DpctCV did not change significantly during the three walking tasks, compared to the values observed for the same tasks in the on meds, off DBS condition. Effects of DBS on the difference between usual-walking and DT walking: there were no significant changes in the dual task decrement in gait speed, Dpct, or DpctCV, while off or on meds.

Conclusions: Consistent with previous findings, DBS generally enhances motor function and gait speed, especially when anti-parkinsonian medications are withheld. However, with medications, DBS was less effective, and did not alter the DT effects on gait. PD patients tend to walk faster with DBS, but with a similar unfavourable response to DT. Perhaps this creates an unsafe situation and explains the increased fall risk.

Tu-341

Effects of subthalamic nucleus deep brain stimulation on parkinsonian tremor

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Objective: The purpose of this study was to examine the effects of deep brain stimulation (DBS) of the subthalamic nucleus (STN) on resting tremor in patients with Parkinson's disease (PD).

Background: DBS of the ventral intermediate (Vim) nucleus of the thalamus has been the treatment of choice for patients with medication refractory parkinsonian tremor. Recently, there has been evidence that the STN should be another DBS target for patients with tremor associated with PD. It is not currently well known, however, how or to what extent STN-DBS alters the pathophysiology of tremor despite its effectiveness on parkinsonian tremor.

Methods: Study 1: Using the Unified Parkinson's Disease Rating Scale (UPDRS), we evaluated 19 PD patients treated by STN-DBS and 7 PD patients treated by Vim-DBS before, 1, and 6 months after DBS surgery. All these patients had suffered from severe resting tremor rated as 3 or 4 in the off-medication state according to item 20 of the UPDRS in the most affected limb before surgery. Study 2: To evaluate the immediate effect of DBS, from 9 PD patients treated by STN-DBS and 7 PD patients treated by Vim-DBS, we recorded the resting tremor by surface electromyography (EMG) before and after DBS was switched on.

Results: Study1: In 14 of the 19 patients treated by STN-DBS, the UPDRS tremor score was immediately reduced after the start of DBS. In the other 5 patients, the tremor gradually improved after the treatment. On the other hand, all the 7 patients treated by Vim-DBS showed immediate improvement of their tremor. Study 2: Whereas Vim-DBS suppressed the tremor itself or had no effect on the EMG frequency, STN-DBS altered the EMG frequency of the tremor in 3 of the 9 patients. Moreover, in some patients treated by STN-DBS, we observed interesting patterns in their EMG, such as a gradual decrease or fluctuation of the amplitude of EMG grouping discharges just after DBS was switched on.

Conclusions: The effects of STN-DBS on resting tremor in patients with PD were different from those of Vim-DBS. STN-DBS tended to cause progressive improvement over a period of months and to change the frequency and amplitude of the tremor. The results of this study suggest that STN-DBS may modulate the neural networks responsible for resting tremor genesis in PD patients.

Tu-342

Predicting motor outcomes following STN DBS for Parkinson's disease: A probabilistic approach

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Objective: To examine the use of a novel, probabilistic algorithm to subgroup characterisation in Parkinson's disease and determine the relationship between phenotypic presentation and motor outcome in a consecutive cohort of 50 patients with PD undergoing STN DBS.

Background: Previous studies examining motor outcome following STN DBS for Parkinson's disease have focused on comparing patient subgroups defined by deterministic criteria. In light of the variable and overlapping phenotypes observed in Parkinson's disease, a probabilistic approach to clinical subgroup characterisation may yield better predictors of patient outcome following surgery.

Methods: The statistical model was initially applied to a baseline cohort of 351 patients with idiopathic PD with the aim of deriving patient subgroups based on tremor, rigidity + bradykinesia, and axial + postural disturbance sections of the UPDRS III. Following the definition of three such subgroups from the model, it was then applied prospectively to 50 patients with PD treated with STN DBS. From this analysis we sought to explore how the DBS population differed from a random PD cohort and how results related to pre-operative symptomatic profile. Outcomes examined were reduction in l-dopa equivalent dose, relative benefit of stimulation plus or minus medication and the relative benefit of stimulation versus pre-operative medication benefit.

Results: Patients best described by moderate rigidity + bradykinesia scores experienced a larger change in l-dopa equivalent dose on average. On the other hand, patients with moderate to high scores for rigidity + bradykinesia and axial +postural disturbance had both a higher average relative benefit of stimulation alone and relative benefit of stimulation versus preoperative medication benefit. All subgroups appeared to respond equally when comparing benefit of stimulation plus medication.

Conclusions: Further refinement of this model may lead to further predictive markers of individual outcome following STN DBS.

Tu-343

Stability of effects of STN stimulation for Parkinson's disease and cost of treatment at 5 years: A single-centre study from India

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Objective: To assess the stability of effects of STN stimulation and cost of treatment at 5 years.

Background: There are limited data on the stability of effects of STN stimulation in Parkinson's disease (PD).

Methods: We assessed a cohort of 45 consecutive patients with PD who received STN stimulation over 8 years (mean age 55 ± 10.9 years, mean duration of disease 11 ± 5.7 years). UPDRS, timed tests, Goetz scale, a detailed neuropsychological battery, Beck's depression inventory and PDQL for quality of life (QOL) were used. Both direct and indirect costs of treatment were calculated.

Results: In the drug "off " state, UPDRS II, III, IV A,B, sub scores of the 3 cardinal motor signs of PD, and scores of timed tests remained improved from baseline at 1, 3 and 5 years ($p<0.001$). At 5 years, compared to year 1, there was a decline in UPDRS I ($p=0.006$), II ($p=0.006$) and III ($p=0.001$) in "off". There was a significant improvement in UPDRS II and III (<0.001) in "on" and in early morning dystonia ($p=0.001$) only at 1 year. At 5 years, compared to year 1, there was a decline in "on" UPDRS III ($p=0.001$) and sub scores for gait (<0.0001), stability ($P<0.0001$) and speech ($p=0.002$). Improvement in total QOL and its sub scores for parkinsonism and social functioning and reduction in equivalent daily dose of L-dopa remained significant until 5 years ($p<0.001$). Clinically significant adverse events that appeared by 5 years were dysarthria, psychosis, cognitive decline and falls. There was a significant reduction in the total annual cost of medical treatment by 64% in the first year, which was sustained ($P<0.0001$). The cost of surgery and related expenses was 16 times the per capita income. By 5 years, 9 patients needed battery reimplantation, which amounted to 40% of the expense of the initial surgery.

Conclusions: Substantial benefits of STN stimulation on the 3 cardinal motor signs, motor fluctuations, dyskinesias and total quality of life in advanced PD are stable up to 5 years. By 5 years, there is a decline in speech, balance, stability, ADL and systemic and emotional components of QOL and new adverse events can appear. This is in line with 2 previous reports. STN surgery is expensive but can reduce the total annual cost of treatment until battery replacement is warranted.

Tu-344

Analysis of the exclusion causes for bilateral subthalamic deep brain stimulation

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Objective: To evaluate exclusion causes for bilateral subthalamic deep brain stimulation (STN DBS).

Background: DBS is an effective treatment of advanced Parkinson's disease (PD) capable improving motors symptoms. Proper patient selection is crucial for adequate surgical outcome. Following the broad outlines of international guidelines, the inclusion and exclusion criteria can vary from center to center. There are a relatively few published studies on the exclusion causes and refusal rates for bilateral STN DBS.

Methods: We analyzed the preoperative evaluations in the Department of Neurology, University of Pecs, Hungary. 109 consecutive patients with proposed medically untreatable idiopathic PD (71 males, 38 females, age: 62.8 ± 9.2) were referred for STN DBS.

Results: Out of 109 potential candidates, 48 (44%) patients were considered as a good subject for surgery, while in the remaining 61 (56%) cases we did not offer the option of DBS. The diagnosis of idiopathic PD could not be established in 17 patients. Eleven patients had too mild symptoms, whereas, 20 patients had one, 3 patients had two and 2 patients had three absolute contraindications. The most frequent absolute contraindications were the presence of psychotic symptoms, severe cognitive impairment and the disease duration less than 5 years. Surgery was not offered in eight candidates, where no absolute, but at least two relative contraindications were identified. The most frequent relative contraindications were the mild cognitive impairment; age over 70 years and drug-induced psychosis in the history.

Conclusions: Our study emphasizes the importance of strict preoperative evaluation in identifying etiologies other than idiopathic PD, evaluating the severity of symptoms and the contraindications of the surgery.

We-323

Hardware-related complications of deep brain stimulation: A review of 221 cases

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Objective: To determine the incidence of long-term hardware-related complications of deep brain stimulation(DBS).

Background: Deep brain stimulation (DBS) is an established procedure for the treatment of movement disorders and pain. Chronic electrical stimulation conveys several advantages over lesioning: it is nonablative, and its effects can be modified or reversed. As with any implanted system, however, DBS introduces a new set of problems related to the hardware.

Methods: The study design is a retrospective chart review of two surgeons, single-institution experience with DBS in 221 consecutive cases from Jan 2006 to August 2008. Two patients were excluded because the procedure was aborted owing to hemorrhage. 219 patients received 328 permanent DBS electrode implants.

Results: The follow-up time was range 3–35 months. The mean follow-up period was16.1 months. Overall, 26 patients (11.9%) had 26 hardware-related complications involving 21 (6.4%)of the electrodes. There were 5 lead migrations, 4 short or open circuits, 12 erosions and/or infections, 2 foreign body reactions, and 3 cerebrospinal fluid leak. A significant finding was a high number of complications involving erosions or infections.

Conclusions: Long-term follow-up reveals that hardware-related complications occur in a significant number of patients. Factors that lead to such complications must be identified and addressed to maximize the important benefits of DBS therapy.

We-324

Pallidotomy abolishes STN lesion induced dyskinesias in Parkinson's disease without further deterioration

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Objective: To evaluate the long term effects of pallidotomy in motor function (1) and cognition (2) in patients with Parkinson's disease and dyskinesia.

Background: The potential to induce severe HCB remains as the principal concerns for applying subthalamotomy in PD. Pallidotomy eliminate contralateral L-Dopa Induced Dyskinesias in PD patients and can control other types of Dyskinesias and spontaneous hemibalism in non PD patients. Here we report the effect of pallidotomy on severe dyskinesias induced by surgical lesion of STN in 8 PD patients.

Methods: From eighty nine patients with PD operated at CIREN (Havana,Cuba) between 1995 and 2004. eight cases exhibited a severe contralateral hemichorea-ballism that was treated with ipsilateral pallidotomy. All of them were evaluated before surgery and after each procedure. UPDRS-III was used for motor evaluation. Dyskinesias were evaluated topographycaly using the OBESO scale in the contralateral hemibody. Cognitive profile was assessed by standards NPS battery.

Results: Dyskinesias were abolished in all cases but antiparkinsonian efficacy of the STN lesion was maintained after the pallidal lesion (UPDRSm post STN vs post Gpi lesion, $p < 0.8$). The double lesions were not associated with any new neurological deficit. Assessment of cognitive functions showed no difference between pre-operative and post-pallidotomy performance. There was no behavioral disorder, limb apraxia or defect in fine motor skills and speech. Gait and balance were unchanged or improved with respect to baseline. Indeed, one of these patients has been thoroughly studied considering both cognitive and motor control functions without detecting any major deficit, other than reduced capacity for implicit learning on the operated side.

Conclusions: Our experience permit us to suggest that pallidotomy suppress hemibalism induced by STN lesion in PD patients with out further side effects.

We-325

Deep brain stimulation of the subthalamic nucleus improves bradykinesia in Parkinson's disease

H.A. Miranda, A.P. Duker, F.J. Revilla (Cincinnati, Ohio)

Objective: To measure the effects of bilateral and unilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) on bradykinesia.

Background: Bradykinesia is a motor sign of Parkinson's disease (PD); STN DBS is an accepted treatment option for PD. Several studies have reported improvement in bradykinesia in PD after STN DBS. The majority of studies measure bradykinesia using only clinical rating scales.

Methods: Bradykinesia was measured using the gyro-based G1 Motion Analysis System (Neurokinetics, Inc, Edmonton, AB) (G1MAS). The G1MAS consists of gyro sensors for monitoring motion in limb segments; measures Angular Velocity (AV). Gyro sensors were mounted on the ventral aspects of both forearms proximal to the wrist crease and in the dorsal aspect of the second falange of both index fingers. Each subject was asked to perform two tasks: hand rotation in a pronation-supination motion and finger tapping. Subjects with PD and STN DBS were studied in the practical OFF state (dopaminergic medications held overnight) in 4 conditions: both stimulators OFF (Both-OFF), left ON-right OFF, left OFF-right ON and both stimulators ON (Both-ON). During each condition bradykinesia was evaluated in both arms using the UPDRS and G1MAS. Examiners and patients were blinded to stimulation condition. Average AV was calculated. AV in the Both-OFF condition was compared with the unilateral and Both-ON conditions. The effects of ipsilateral (Ipsi-ON) and contralateral (Contra-ON) stimulation were compared. Subjects with hand tremor rated >1 on UPDRS were excluded. Only the extremity with the greatest amount of bradykinesia in the Both-OFF condition was used in the analysis.

Results: We studied 23 patients; 14 were included (10 men). Age was 61.2 +/-5.9 years, duration of disease was 13.9 +/-2.9 years. The root mean square (RMS) of the AV was calculated. Anova Two-Factor Without Replication (ANOVA-TFWR) of RMS AV for finger tapping was statistically significant ($p=0.0074$). Tukey's Post Hoc

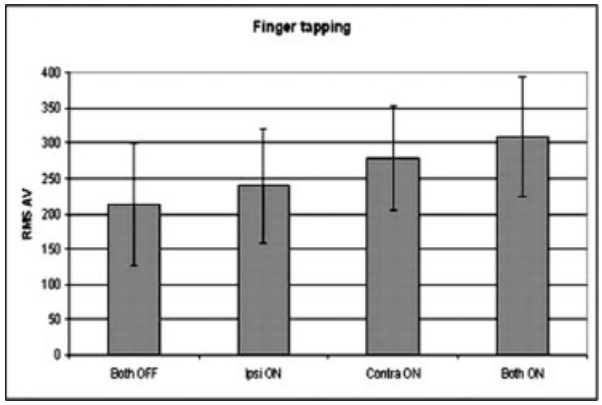

FIG. 1 (We-325).

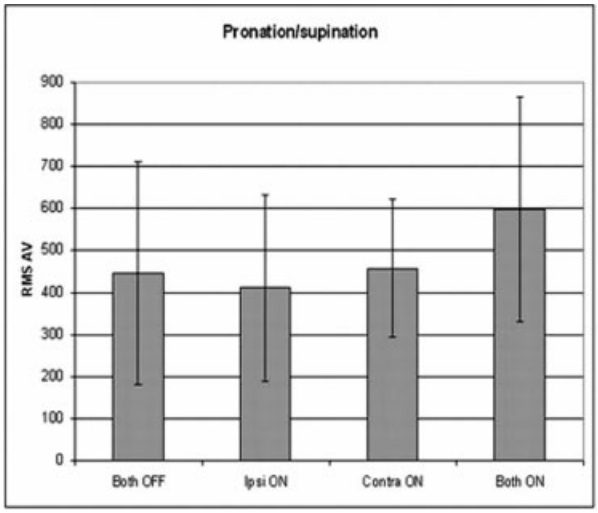

FIG. 2 (We-325).

Test analysis (TPH) showed: Both-ON > Both-OFF ($\alpha=0.01$), Both-ON > Ipsi-ON ($\alpha=0.05$) and Contra-ON > Both-OFF ($\alpha=0.05$). ANOVA-TFWR of RMS AV for pronation-supination was statistically significant ($p=0.0058$). TPH showed: Both-ON > Both-OFF ($\alpha=0.05$) and Both-ON > Ipsi-ON ($\alpha=0.01$).

Conclusions: Bradykinesia in PD improves with bilateral and contralateral STN DBS as measured by objective methods.

We-326

Bilateral subthalamic stimulation for Parkinson's disease deteriorates frontal cortex function in early periods after operation

S. Natori, G. Oyama, Y. Shimo, N. Hattori (Tokyo, Japan)

Objective: To evaluate the effect of the deep brain stimulation (DBS) of the bilateral subthalamic nucleus (STN) to the function of the frontal cortex after within one month operation in 15 patients with Parkinson's disease (PD) using a sequential button press task (BPT).

Background: Deep brain stimulation (DBS) of the bilateral subthalamic nucleus (STN) has been widely accepted for treatment of advanced Parkinson's disease (PD). Several studies have been done about the effect of STN-DBS for cognitive function, however, there is a little study about the effect for visuo-motor skill learning which is very important for learning skillful motor action. In previous study, the functions of the frontal cortex (dorso-lateral prefrontal cortex: DLPFC, pre supplementary motor area: pre-SMA, supplementary motor area: SMA) and anterior part of the caudate play important role during early stage of this skill learning. In this report, we assess the effect of the STN-DBS on motor skill learning using button press task.

Methods: We applied a sequential button press task (BPT) (Hikosaka et al 2002) with 15 PD patients before and after within one month bilateral STN-DBS operation. Patients performed same sequence for three days: one trial/ one day. We used two parameters to assess the accuracy and speed of the performance: the number of error trials and the performance time.

Results: The score of UPDRS PART 3 showed no difference between before and after the STN-DBS operation during performing the task. Although we didn't find statistical difference in performance time in any of the 3 days, we found that STN-DBS increase the number of error trials ($p<0.01$ two-factor ANOVA with repeated measures).

Conclusions: Our results may suggest that STN-DBS is able to deteriorate the function of pre-SMA and DLPFC together with anterior part of the caudate after the early period of operation.

We-327

A prospective and controlled study into the effect of subthalamic nucleus stimulation on freezing of gait

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Objective: To investigate whether freezing of gait (FOG) is affected by bilateral subthalamic nucleus (STN) stimulation in comparison to continued best medical treatment in PD patients.

Background: Previous studies suggest that STN-stimulation improves levodopa-responsive FOG, but induces FOG in some cases. However, this was never compared with a control group.

Methods: We consecutively recruited 13 patients who underwent STN stimulation, and 15 controls eligible for surgery but on continued best medical treatment. Inclusion criteria: disease duration >5 years and medication-resistant tremor or a combination of disturbing motor fluctuations and dyskinesias. Exclusion criteria: cognitive decline, H&Y IV-V in *on* and persistent psychosis or depression. A clinical test battery was performed before surgery (T1) and 6 months after (T2). Primary outcome was the new Freezing of Gait Questionnaire (NFOGQ). Secondary outcome was the UPDRS III. Statistical analysis included non-parametric tests.

Results: At T1 no significant differences were found between the control and STN group for age, NFOGQ, UPDRS III and H&Y scores. Five out of 15 controls and 4/13 STN patients experienced *on*-FOG ($P=0.88$) at T1 and most patients in both groups (14/15 and 11/13) had *off*-FOG ($P=0.46$). At T2 11 controls and 10 STN patients were retested. Overall no significant group differences were observed in change scores over the study period. Within-group analysis revealed that the STN group showed a significant improvement of 18% ($P=0.01$) of the NFOGQ score at T2. In 4/10 STN patients *off*-FOG and in 5/10 *on*-FOG disappeared completely. However, 2/10 developed *on*-FOG and 1/10 *off*-FOG post-surgery. Controls remained stable on the NFOGQ-score. The number of controls with *off*-FOG also stayed constant over 6 months and in 1/11 *on*-FOG disappeared. Conversely, 3/11 controls developed *on*-FOG. UPDRS-III *on*-scores improved in the STN group ($p=0.009$) whereas controls tended to deteriorate with time ($p=0.8$).

Conclusions: It was confirmed that after STN stimulation subjects showed overall improvement of FOG, but also developed FOG as a new symptom in 2 cases. In non-operated patients, o*ff*-FOG remained stable and *on*-FOG increased. With the current sample size, this pattern was not significantly different from the STN group.

We-328

Brain tissue changes following deep brain stimulation

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Objective: To analyse histopathological changes in 10 patients treated with DBS.

Background: Deep brain stimulation (DBS) with electrodes implanted in the thalamus, the subthalamic nucleus or pallidum rapidly gained acceptance for the treatment of movement disorders. Although more than 50,000 patients have received DBS treatment, only few histopathological studies have been published so far, most of them case reports.

Methods: Postmortem analyses including histopathological studies were performed on 10 patients (8 with Parkinson's disease and 2 with essential tremor) with a total of 17 DBS electrodes (2 in the globus pallidus, 5 in the thalamus, 10 in the subthalamic nucleus) up to 8 years after surgery. Three patients had died from cardiovascular events; the remaining died from sepsis.

Results: Only minor astrogliosis around the electrode shaft was found in the majority of subjects analysed. However, in few cases piloid gliosis was prominent. In 3 cases lymphocytic infiltrates (predominantly T-cells) mainly around the distal electrode tract and/or the nearby blood vessels were noted. Further, multinucleated giant cells of the foreign body type were present in the immediate vicinity of the DBS electrode in 5 patients. Additionally, scattered eosinophils in the surrounding gliotic tissue could be detected in one case. No clear differences between the active site of DBS (that is one of the four contacts of the electrode) and the rest of the DBS electrode were found. In 4 patients, a cone shaped bilateral frontal lobe damage associated with minor focal haemorrhage was found at the electrode entry site in the brain, which was not apparent in postoperative imaging due to artefacts caused by the DBS electrode. Apart from the cortical entry zone of the electrode only one case showed an appreciable amount of haemosiderin at the electrode tip.

Conclusions: DBS causes moderate tissue changes, in particular astrogliosis, including gliosis of the piloid type. In 50% of cases multinucleated giant cells were present along the electrode tract. For unknown reasons 3 patients with different causes of death also showed inflammatory responses in the vicinity of the electrode. The clinical significance of frontal lobe damage due to electrode implantation is unclear at present. However, all these changes did not impede successful long-term stimulation.

We-329

Anesthesia for deep brain stimulation in adults and children: Evolution of technique

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Objective: Patients for deep brain stimulation (DBS) present a number of anesthetic challenges. Anxiety, fear and discomfort must be managed in order to produce a cooperative patient and coherent state. A dedicated team of neuroanesthetists and operating room staff were assembled to meet these goals and determine which agents and techniques would benefit most patients.

Background: The sequence of events during DBS includes analgesia and cooperation for headframe placement followed by comfort and lack of movement during diagnostic studies such as magnetic resonance imaging (MRI). The operative procedure requires compliance and participation for optimal recording and assessment for side-effects. Short-acting agents are used for brief periods to accomplish these goals and newer agents and techniques may be incorporated based on patient needs.

Methods: Following approval by the investigational review board, anesthetic charts of patients were reviewed retrospectively to determine: type of anesthetic agent(s) used, performance and effectiveness of a "scalp block" technique, duration of the procedure and intraoperative complications.

Results: A total of 220 charts were reviewed from 2005- 2008. Patients ranged in age from 6 to 81 years. The anesthetic technique was gradually adapted to include minimal or no sedation for headframe placement (except for pediatric patients). Propofol infusion was used for MRI in patients with claustrophobia or uncontrolled tremors. A scalp block with bupivacaine performed in the operating room under sedation produced satisfactory analgesia for long periods of time. Agents for sedation were limited to propofol and the gradual use of dexmedetomidine for very difficult patients. General anesthesia was only used for one patient and depth of sedation was monitored using bispectral index (BIS).

Conclusions: Anesthetic management of patients for DBS requires understanding of the underlying disease and co-morbidities as well as patience and flexibility. The experience of anesthetizing a wide range of patients with Parkinson's disease, essential tremor, dystonia and other pathologies provided an opportunity to test a variety of anesthetic options. We discovered over time the most effective techniques to improve intraoperative efficiency and patient well-being.

We-330

Motor and neuropsychological outcomes of bilateral STN DBS in advanced Parkinson's disease (PD)

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Objective: To assess long term motor and neuropsychological effects of high frequency STN DBS in advanced PD.

Background: Data on long term outcome of motor and neuropsychological functions following DBS for PD is scanty.

Methods: Sixty patients who underwent bilateral STN DBS were followed prospectively after surgery. We evaluated subjects using the Unified Parkinson's Disease Rating Scale (UPDRS) preoperatively, 12 months after surgery and at a long term follow up visit. We compared postoperative UPDRS scores and medication dosages with preoperative values. Neuropsychological assessment was done in all patients before and after bilateral implantation of electrodes. All patients were assessed using MMSE, Trial making, Stroop test, Rey auditory verbal learning test, Verbal N back test and Verbal fluency before and 12 months, 24 months and 48 months after surgery and compared using Wilcoxon signed rank test.

Results: Sixty patients who underwent bilateral STN DBS at our center since 2001 were studied. Mean age and duration were 56.4±10.1 years and 10.7±4.3 years respectively. There was a significant 42% mean reduction in the UPDRS motor scores from 55.4 ±14.1 to 32.2 ± 12.5 in off medication status at 12 months. Levodopa requirement postoperatively decreased significantly by 43% from a levodopa equivalent dose of 855 ± 367mg to 492 ± 228 mg. At one and two years post surgery, the patient cohort showed a statistically significant decline on measures of verbal fluency, executive functioning, working memory and delayed recall ($p<0.001$). Except for delayed recall, no statistically significant difference was found in neuropsychological parameters at four years when compared to one year followup. Even at four years the cohort had a cognitive profile similar to age matched normal control population.

Conclusions: In this cohort of subjects with advanced PD, bilateral STN stimulation improved off medication motor function, reduced time spent in medication off state and reduced medication requirements up to four years after surgery. Lack of significant cognitive impairment after DBS further supports the use of this surgical approach for treating motor symptoms of PD.

We-331

Changing from high to low frequency stimulation of the STN in Parkinson: Enthusiasm from a case report

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Objective: Our goal was to evaluated the effect of low frequency stimulation on FOG, sleep, depression, QOL and parkinsonism.

Background: Improvement in freezing of gait (FOG) in patients with Parkinson's disease (PD) was recently reported after changing the frequency of STN stimulation to 60 Hz. There is a possibility that at this frequency the STN be driving the PPN.

Methods: We evaluated one patient who had had STN DBS and still experienced significant FOG. The patient is a woman with a 11 year history of PD, a good response to levodopa, who had STN DBS 5 years ago because of fluctuations resistant to pharmacological manipulations. Her parameters were 2.5 and 3.3 volts, 120 and 150 micro sec (pulse width), 130 Hz on the right and on the left respectively. Both sides were on bipolar mode. She was taking 1880 mg of levodopa and amantadine 100 mg per day. She was evaluated with UPDRS, PDQ-39, Yesavage depression scale, MoCA, WOQ, Lickert scales, TUG, part of the Pittsburgh Sleep scale and force plates before and six weeks after her STN DBS was changed from 180 to 60 Hz. For the force plates, patients were asked to stand for 30 seconds eyes open and eyes closed. All medications and other DBS parameters remained unchanged between the evaluations.

Results: The results are given in the table.

Table (We-331). Results

	Time 0	6 weeks
Moca (/30)	22	21
updrs 1	3	1
updrs 2 on	15	6
updrs 2 off	17	14
updrs 3	49.5	29
updrs 4	3	1
pdq 39	53	37
Yesavage depression scale (/30)	12	13
WOQ	14	10
lickert fog	5.2	0.8
TUG	26	16
Sleep (hours)	10	8.5
Insomnia (points/42)	9	0
range ap eyes open	42,9	31,3
range ml eyes open	31,7	25,5
range ap eyes closed	74,1	53,6
range ml eyes closed	40,8	31,2

Her change appreciation was 6,7 over 10 cm on a Lickert scale where 0=worst deterioration, 10 best improvement and 5 cm no change.

Conclusions: Decreasing STN DBS frequency to 60 Hz helped in a clinically significant way the FOG in this patient. We could also observe a change in the general appreciation of change, the QOL, the bradykinesia and sleep quality. Laboratory measurement showed a decrease in sway both in the antero-posterior and in the medio-lateral directions. Although this report can cause enthusiasm, it needs to be extended to more patients and over a much longer period of observation.

We-332

Post-traumatic hyperkinesias in patients with Parkinson's disease with stimulation of the subthalamic nucleus

K.A.M. Pauls, C. Reck, M.T. Barbe, M. Maarouf, V. Sturm, G.R. Fink, L. Timmermann (Cologne, Germany)

Objective: Here, we describe a new clinical entity of pathological transient hyperkinesias after trauma in patients with Parkinson's disease (PD) with bilateral deep brain stimulation (DBS) in the subthalamic nucleus (STN), and discuss possible pathophysiological mechanisms and treatment options.

Background: Deep brain stimulation is today an established treatment option for advanced PD. Perioperative complications and side effects such as infections, hardware problems, electrode dislocation and misplaced or fractured leads have been reported in numerous publications.

Methods: Three PD patients treated with bilateral deep brain stimulation in the subthalamic nucleus (STN-DBS) were observed and treated after they had had a trauma (falling or being hit by something), followed by severe hyperkinesias.

Results: The hyperkinesias lasted several hours to days and were self-limiting and completely reversible with time. They could be controlled by transiently decreasing stimulation amplitudes. In one patient, a reversible short circuit was documented in one of the stimulation electrodes, suggesting changes in tissue conductivity. No hardware damage occurred in any of the patients.

Conclusions: Trauma can cause transient hyperkinesias in PD patients with STN-DBS. These hyperkinesias are self-limiting and usually benign, but monitoring and adjustments in therapy may be necessary. Potential pathophysiological mechanisms are discussed.

We-333

Value of subthalamic multiple microelectrode recordings and intraoperative stimulation in Parkinsons disease

C. Reck, M. Maarouf, L. Wojtecki, S. Groiss, E. Florin, V. Sturm, G.R. Fink, A. Schnitzler, L. Timmermann (Cologne, Germany)

Objective: To evaluate contribution of intraoperative multiple microelectrode recordings to benefit of deep brain stimulation electrode placement in the subthalamic nucleus in patients with Parkinson's disease.

Background: Microelectrode recordings (MER) and the intraoperative evaluation of stimulation effects are a promising tool in patients with Parkinson's disease (PD) for targeting deep brain stimulation (DBS) electrodes in the subthalamic nucleus (STN). However, it remains unclear how MER by multiple electrodes in combination with stimulation may contribute to a deviation of the MRI-guided centrally planned electrode, to a beneficial electrode placement and, hence, good clinical outcome.

Methods: We performed MER and intraoperative stimulation in 20 PD patients (31 hemispheres) using simultaneously up to five parallel MRI-guided micro-macroelectrodes during implantation of deep brain stimulation electrodes in the STN.

Results: Electrodes were implanted in 65% at the center of the dorsolateral STN–suggested by MRI–but deviated in 35% from the predetermined trajectory (decentral). DBS significantly improved the UPDRS (Unified Parkinson's disease rating scale) part III by 55% in medication OFF and by 69% in medication ON. A comparison between centrally and decentrally placed electrodes revealed no difference in stimulation parameters and the clinical outcome as measured by UPDRS hemibody score.

Conclusions: These findings clearly show that the implantation decision based on combined intraoperative monitoring using multiple MER and test stimulation resulted in a great beneficial stimulation effect. We suppose that implantation solely based on individual MRI could have led to non-optimal placement of electrodes and consequently reduce the improvement of clinical outcome.

We-334

Deep brain stimulation of the subthalamic nucleus improves balance in Parkinson's disease

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Objective: To measure the effects of high frequency bilateral and unilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) on balance in Parkinson's disease (PD).

Background: Clinical effects of DBS of the STN on balance are not well understood. Balance impairment and falls due to postural instability are a major cause of disability in PD. Few reports have directly addressed how STN DBS affects balance using appropriately designed methods. We hypothesized that balance, as measured by static posturography, improves after STN DBS.

Methods: Twenty one PD patients underwent bilateral STN DBS (15 men). Age was 58.8 $\pm$ 5.1 years, duration of disease was 14.6 $\pm$ 3.3 years. Sway Area (SA) and Sway Length (SL) were measured on a strain gauge type force platform system to obtain parameters of static posturography at 30 second intervals in 4 conditions: both stimulators OFF, both ON, left only stimulator ON and right only stimulator ON, in the practical-off state. Trials were conducted on a firm surface, with eyes open (EO-firm), and eyes closed (EC-firm). The same tests were repeated while the subject was standing on a foam surface (EO-foam, EC-foam). Examiners and patients were blinded to conditions.

Results: Data were analyzed for 16 subjects: Compared with stimulation OFF, SL improved ($P<.0001$, ANCOVA) in unilateral and bilateral stimulation in the EO-firm and EC-firm conditions. This difference was not significant when adjusting for tremor clinical ratings (Scheffe method). SA was not statistically different between stimulator conditions.

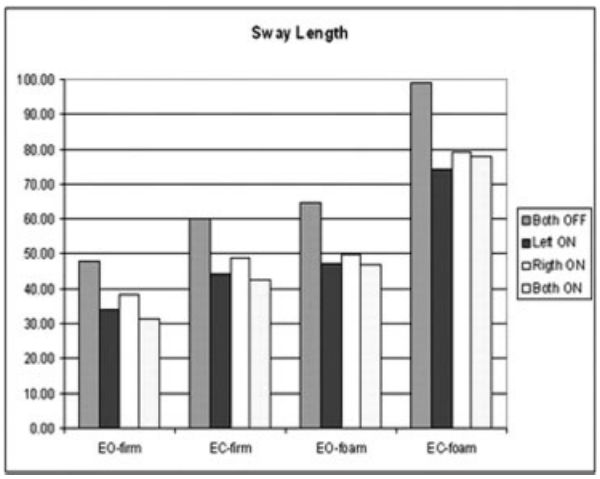

FIG. 1 (We-334).

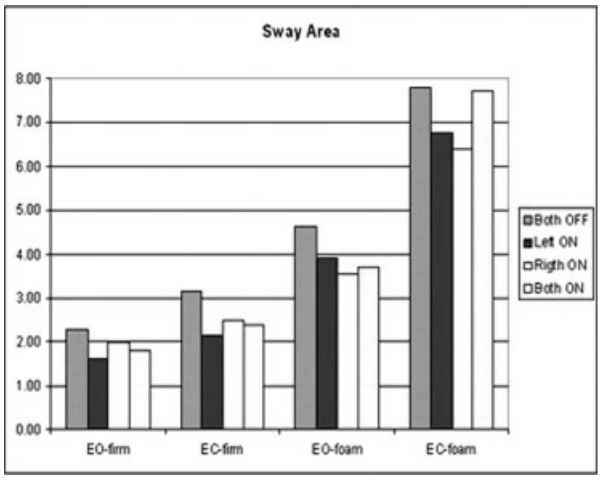

FIG. 2 (We-334).

Conclusions: STN DBS improves balance in PD, as measured by static posturography. Tremor may either directly affect balance or alter its measurement by this method. Further studies are warranted to explore this issue.

We-335

Use of 3 Tesla MRI for direct localization of subthalamic nucleus: Preliminary experience and comparison with conventional targeting

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Objective: To evaluate feasibility, reliability and possible advantages of employing 3-Tesla (3T) MRI in subthalamic nucleus (STN) targeting in advanced PD. Efficacy of this approach was assessed by comparison of surgical and neurological outcome in two groups of patients treated with same selection protocols and materials but different imaging technique.

Background: The STN is the optimal target for DBS in advanced PD. Conventional imaging approaches rely most frequently on the use of direct stereotactic 1.5T targeting or registration of non stereotactic 1.5T imaging and stereotactic CT. 3T MRI in pre-operative STN localization has been previously described[1], but concerns still remain on the presence of distortion artifacts hampering stereotactic precision of the procedure[2]. We believe that fusion with 1T stereotactic images may increase stereotactic precision.

Methods: Thirteen patients with advanced PD underwent STN-DBS (M:F=8:5; mean age 52y). According to the different targeting method they were divided into two groups: Group A (5 patients, 1T stereotactic MRI alone) and Group B (8 patients, 3T non-stereotactic MRI fused with 1T stereotactic MRI). Intraoperative microrecording and macrostimulation were performed in each case.

Results: At 6 months follow-up, mean UPDRS III score reduction (med-off/stim.-on vs. preoperative med-off) was respectively 69% in Group A and 73% in Group B ($p=0.015$). Postoperatively, a statistically significant reduction in antiparkinsonian treatment was also present in Group B compared to Group A. The preoperatively planned "central" track proved to be the most clinically effective in 1/10 leads for Group A vs. 12/15 for Group B ($p<0.001$).

Conclusions: 3T MRI, associated with intraoperative microrecording and macrostimulation, seems to be accurate in DBS targeting, allowing to obtain very satisfactory clinical benefit.

References 1) Slavin KV, Thulborn KR et al: Direct visualization of the human STN with 3T MR imaging. AJNR AM J Neuroradiol 27:80-4, 2006 2) Mack A, Wolff R et al: Analyzing 3T MRI units for implementation in radiosurgery. J Neurosurg 102 Suppl:158-164, 2005

We-336

Does deep brain stimulation of the STN in advanced Parkinson's disease change habitual physical activity?

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Objective: This study aimed to objectively quantify the amount of habitual physical activity before and after deep brain stimulation of the sub-thalamic nucleus (DBS-STN) using an activity monitor (accelerometer).

Background: A recent randomised long-term assessment of surgery for PD (PD SURG) evaluated the efficacy of DBS-STN compared to medical therapy in patients with advanced PD not adequately controlled by current medication. The study demonstrated a significant improvement in quality of life however the impact of surgery on changes in habitual physical activity is unknown.

Methods: 18 people with PD were recruited. Activity was measured 6 months (P3) and 6 weeks before surgery (P4) and at four time points after surgery (6 weeks (T1), 3 (T2), 6 (T3), 12 months (T4)) during which participants were asked to wear an activity monitor (activPAL^{TM}) for 7 days. Percentage time sitting/lying, standing, walking and the number of transitions from sit-stand were determined. Additional measures of motor severity and function were made and assessments were carried out in the home. Regressions of measures of each outcome against time (P3-T4) provided variance ratios and associated p values for the null hypothesis (no change over time). A P value of 0.05 was considered significant.

Results: DBS-STN does not significantly increase the percentage time sitting/lying, standing, walking or the number of transitions from sit-stand over the 12 month period following surgery compared to before surgery despite significant improvements in motor symptom severity (freezing of gait, $P\leq.0001$; Hoehn and Yahr, $P=.005$) and function (Nottingham Extended Activities of Daily Living, $P=.01$).

Conclusions: Improvement in clinical symptoms does not reflect the impact on the amount of habitual physical activity. Addressing behavioural change through rehabilitation to maximise the effect of surgery may be necessary to modify habitual activity. These are interesting results and may point to caution in the way we interpret commonly used clinical tests.

We-337

Improvement of gait and resolution of mycolonus with high frequency stimulation of the rostral brainstem. Case report

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Objective: We report a case of a 68 year old woman with 15-year history of PD with bilateral STN stimulators with deepest contacts activating the rostral tegmentum of the brainstem, presumed to be in the region of the PPN who showed marked improvement of her balance and freezing of gait at high STN frequencies of 170 HZ. In addition, she now has recent onset myoclonic jerks in the setting of dementia that resolve with deep brain stimulation.

Background: Freezing of gait and poor balance are well known disabling features of advanced Parkinson's disease and other atypical parkinsonian syndromes. Recently the Pedunculopontine nucleus (PPN) has obtained more attention, as its stimulation has been linked to improvement of axial symptoms and freezing of gait in Parkinson patients and respective animal models. PPN that is located in the rostral tegmentum of brainstem, measured 5mm away from STN has been loosely defined as the mesencephalic locomotor region. Deep brain stimulation of the PPN at low frequencies (20Hz) have shown significant improvement of gait in patients with advanced PD (Pereira. et.al); whereas higher frequency stimulation of PPN (100 HZ) produced worsening postural stability (D. Nandi et.al).

Methods: MRI measurements showed the caudal tip of the right electrode to be at the ponto-mesencephalic junction. The inferior tip of the right electrode was measured at 22mm caudal, 13mm lateral to the AC/PC line, and was at the posterior commissure level. The inferior tip of the left electrode was 16mm caudal, 15mm lateral to the AC/PC line, and was at the posterior commissure level. Both stimulators had frequency of 170 Hz, case positive, contacts 1 and 2 negative. The patient was examined off and on cabidopa/levodopa as well as with both stimulators on, both off, and then with each stimulator off.

Results: We documented the significant improvement of her gait stability and freezing with the stimulators on at the above mentioned DBS settings. She also had recent onset of myoclonic jerks of unknown etiology that resolved with the stimulators on with these settings.

Conclusions: The observation of this patient indicates that there may be other approaches in stimulating the mesencephalic locomotor region. In addition, the rostral brainstem may be a potential target for treatment of myoclonus with deep brain stimulation surgery.

We-338

Impulse control disorder in STN-DBS cases in PD patients

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Objective: To elucidate risks of impulse control disorder (ICD) in Parkinson's disease (PD) after subthalamic deep brain stimulation (STN-DBS), and discuss appropriate peri- and post-operative management methods to control ICD.

Background: ICD such as hypersexuality (HS), pathological gambling (PG), compulsive shopping (CS), binge eating (BE) is considered to be a relatively rare complication with PD therapy. However, some risk factors of ICD in PD treatment shares same medical condition with indicative conditions of STN-DBS; younger disease onset, higher dose dopamine replacement therapy.

Methods: We reviewed medical records of thirty-five PD patients who underwent STN-DBS in 2007 and 2008. ICD was interpreted as positive 1) if there were any kind of behavioral changes related sexuality, gambling, shopping or eating in peri-/postoperatively, and 2) at least one of family members or care-giver recognize as abnormal, and 3) caused any kind of social problems. The related behavioral change (BC) such as punding (PU), social mal-adjustment (SM) or hypomania (HM) was also evaluated in a same manner.

Results: Eleven patients showed any kind of ICD or BD peri-/postoperatively. There was PG in two, HS in four, CS in one, PU in one, SM in two, HM in two patients. Suggested triggers with retrospective investigation were increment of stimulation amplitude in three, medication increment in one, unknown in one case. In six cases, ICD/BD occurred within two months after STN-DBS surgery with no or minimal stimulation and without any medicational change, which suggests that implantation itself can be the trigger. In these cases, doses of both levodopa and dopamine agonist (DA) were not reduced preoperatively. ICD/BD recovered after reduction of medication combined with initiation/adjustment of stimulation in those implantation triggered six cases.

Conclusions: Our data suggest ICD/BD can be more common with STN-DBS in PD patients, and perioperative sustained doses of both levodopa and DA is one of risk factor. Preoperative dose optimization considered to be able to lower the risks of ICD/BD.

We-339

Deep brain stimulation (DBS) in Parkinson's disease (PD) patients-carriers of mutations in the glucocerebrosidase (GBA) gene

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Objective: To describe 3 cases of Ashkenazi Parkinson's disease (PD) patients who underwent bilateral STN stimulation in Israel and were found to be carriers of GBA mutations.

Background: Mutations in the GBA gene are associated with increased risk to develop PD. GBA mutations also correlate with earlier age of PD onset and increased disease severity.

Methods: The patients fulfilled UK PD Brain Bank clinical diagnostic criteria, were L-dopa responsive, and had motor complications prompting referral for STN stimulation therapy. Physicians were unaware of GBA status prior to surgery. Gaucher disease was diagnosed in a first-degree family member (daughter) of one patient.

Results: All 3 subjects had early onset PD (31, 34, 47 years). Disease duration before DBS was 28, 20 and 6 years; the patients were 57, 52 and 53 years respectively at time of surgery. Two patients are carriers of the N370S GBA mutation, and one patient was diagnosed with the more severe IVS2+1 GBA mutation. Before surgery patients had normal cognitive function, though two of them had mild attention deficits. There were no intra/ post operation complications. DBS parameters coincided with accepted parameters for PD patients. The patients with N370S GBA mutations exhibited clear motor improvement on DBS with significant reduction in L-dopa dosage. The IVS2+1 GBA mutation carrier exhibited mild improvement. One N370S patient developed severe depression 3 weeks after surgery and was treated pharmacologically with improvement. Two years after surgery he was diagnosed with dysexecutive syndrome with affective changes not seen previously. The IVS2+1 carrier experienced profound weight gain (16 kg) 6 months post surgery, and developed severe eyelid apraxia that responded well to botulinum treatment. The N370S carrier with the latest disease onset and earliest DBS introduction had prominent improvement after the surgery. Outcomes in the other patients were not satisfactory.

Conclusions: To our knowledge, this is the first description of outcomes of DBS in PD patients who are GBA mutations carriers. These data represent anecdotal clinical descriptions of individual cases. Further observations are needed to better understand the benefits of DBS procedures in this population.

We-340

Globally increased cerebral blood flow (CBF) during high-frequency deep brain stimulation of the subthalamic nucleus (STN-DBS) in Parkinson's disease (PD)

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Objective: Global effects of bilateral STN-DBS on CBF were studied in subjects with PD. The determination of global effects is critical to characterizing regional changes associated with specific behaviors.

Background: While STN-DBS has become a popular and effective therapeutic tool in the treatment of PD, the mechanisms of action are not fully understood. High-frequency stimulation is believed to mimic the effects of a lesion, producing reversible changes in the basal ganglia. Local effects on surrounding white matter are also thought to occur.

Methods: Two sets of 12 H20 PET scans were performed on 7 PD subjects with bilateral STN-DBS, once with the stimulators ON, once with the stimulators OFF, on separate days. There were 2 replications of a rest state and 5 speech tasks. Composite images were created from the initial 6 (first half) and the subsequent 6 scans (second half). Regions of interest encompassing each slice were applied to 59 slices. CBF was measured at 3 thresholds: maximum CBF, mean CBF of voxels at the upper 10% of activity, and mean CBF of all voxels (100%).

Results: Results were analyzed using nonparametric statistics to avoid assumptions about the underlying distributions of CBF values across conditions. For maximum CBF, there was a significant decrease in the second half during DBS OFF [Wilcoxon Signed Ranks Test, $Z = -2.37$; $p = 0.018$] but not during DBS ON. Maximum CBF was also lower during DBS OFF [$Z = -2.37$; $p = 0.018$] than during DBS ON in the second half. Similar results were obtained for the upper 10% CBF condition: CBF decreased in

the second half during DBS OFF [Z =–2.37; p = 0.018] and CBF was lower during DBS OFF compared to DBS ON [Z =–2.37; p = 0.018] in the second half of the study. Time was not a significant effect for the 100% CBF measure.

Conclusions: CBF was stable when STN-DBS was ON, but global CBF decreased over time in the DBS OFF condition. Models of the mechanism of STN-DBS have focused on specific changes in the role of the STN in the basal ganglia, and on local field effects. The present results demonstrate a third mechanism of action in STN-DBS: a global effect on CBF. This mechanism may play a role in therapeutic response, undesired side effects, or both. [Supported by R01 DC007658].

Th-328

Long term bilateral stimulation of the pedunculopontine nucleus improves balance and gait stability and alleviates falls in Parkinson's disease

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Objective: The aim of this study was to determine the effectiveness of deep brain stimulation (DBS) of the pedunculopontine nucleus (PPN) on stability and gait in Parkinson's disease patients.

Background: The PPN is a known locomotor center that also processes sensory & behavioural information. It is located in the brainstem and has connections with the basal ganglia & spinal cord. It has a possible role in mechanisms of axial symptoms and postural instability in PD. The PPN contains mainly cholinergic neurons and constitutes a different movement control pathway from that of the dopaminergic system.

Methods: Six PD patients (63-73 yrs) whose predominant disability related to gait stability and function were selected for PPN DBS. Duration with PD ranged from 8-18 years. Patients were levodopa responsive but drug refractory. In our series of bilateral PPN DBS patients pre- and post-operative assessment of UPDRS part III and qualitative and quantitative gait analysis where performed. Participants also completed the freezing of gait (FOG) questionnaire.

Results: There was sustained improvement in hesitancy, freezing and falls. There was a 65% improvement in FOG, reduction in the number and duration of freezing episodes (gait initiation and during gait), and a commensurate reduction in falls. Patients walked with the same cadence, but demonstrated reduced double-support time and increased stride length and walking speed post-operatively. Similarly, the range of hip, knee and ankle motion was increased following the procedure and was likely related to the increase in stride length.

Conclusions: DBS targeting of the PPN provides significant improvement of stability and gait performance. The PPN appears to be a viable target for DBS in PD patients with predominantly gait and stance stability problems.

Th-329

Risk factors for intracranial hemorrhage during deep brain stimulation surgery

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Objective: To evaluate the incidence and risk factors for asymptomatic and clinically significant intracranial hemorrhage (ICH) during deep brain stimulation (DBS) surgery following implantation into the subthalamic nucleus (STN), ventralis intermediate nucleus of the thalamus (VIM), and globus pallidus internus nucleus (GPi).

Background: While the risk of ICH during DBS surgery is thought to be low, the risk factors for the development of such hemorrhage are not well defined.

Methods: All DBS surgeries at our institution performed over a 24 month period for treatment of movement disorders were included in this study. Information was collected on the indication for surgery, patient demographics, anatomic target, use of microelectrode recording (MER), number of MER passes and trajectory of electrode insertions, type and location of ICH, clinical consequence of ICH, and potential risk factors for ICH (age, hypertension, diabetes, and use of anticoagulant medication). Logistic regression was used to analyze factors that predicted the development of hemorrhage.

Results: One hundred thirty-five charts with 246 lead implantations were reviewed and 4 patients (2.96%) were demonstrated to have had clinically significant ICH (defined by new neurologic symptoms lasting >24 hr). Routine post-operative head CT was performed in 113 patients (84%), and in 23 (20.4%) asymptomatic ICHs were detected. No variables, including single vs multiple MER passes, HTN, DM, use of anticoagulants, anatomic target, and electrode trajectory predicted clinically significant ICH. In a univariate model, age predicted asymptomatic ICH (p=0.024); however, this significance was lost in a multivariate model of all factors.

Conclusions: The incidence of clinically significant ICH in our study was 2.96%. Multiple vs single MER passes did not increase the risk of ICH. Age appeared as a risk factor for asymptomatic ICH but its association with clinically significant ICH was not clear.

Th-330

Deep brain stimulation – Timing of generator replacement

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Objective: Deep brain stimulations (DBSs) have been used in various centers in the treatment of patients with movement disorders and the other diseases. Most patients treated by DBS achieved stable and notable reduction of their symptoms. However, the pulse generator for DBS needs the surgical replacement because of the battery depletion. Here, we examine the relationships between the timing of generator replacement and the stimulation parameters affecting battery depletion.

Methods: Seventeen patients underwent generator replacement in our institute and were included in this study (14 Parkinson's disease (PD), 1 dystonia and 2 intractable pain). Mean time between generator implantation to replacement was 49 months (range 24 to 70 months).

Results: Stimulations using double electrode contacts as the cathodes or high voltage rapidly depleted the batteries. Six patients needed to reduce the stimulation voltage and 4 patents required higher power output. In 8 out of 17 patients, symptomatic deterioration occurred before generator replacement and their batteries were exhausted almost completely. All deteriorated symptoms recovered after generator replacement.

Conclusions: Various stimulation parameters (electrode contact, frequency, pulse width, voltage) participate in the depletion of the pulse generator. And the exhaustion of the generator result in the symptomatic deterioration of treated patient. It seems to be desirable to perform generator replacement in advance of complete battery exhaustion and symptomatic deterioration of treated patients.

Th-331

Deep brain stimulation of the subthalamic nucleus. Our experience in 53 patients

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Objective: The aim of this study is to present the results of DBS in STN in 53 patients and to analyze the surgical morbidity and mortality of the procedure.

Background: Subthalamic deep brain stimulation (DBS) has become the standard surgical therapy for medically refractory Parkinson's disease (PD) since stimulation of the STN improves all cardinal features of PD.

Methods: Between 2003 and 2007, we implanted 105 DBS systems (52 bilateral, 1 unilateral) in 53 patients (34 male, 19 female). Mean age of patients was 61,4 years (38-75 years) and the average duration of the disease was 15,1 years (7-29 years). The clinical rat-

ing tests included: the Unified Parkinson's Disease Rating Scale (UPDRS), the Hoehn and Yahr and the Swab and England scales. The quality of life was assessed with the Parkinson's Disease Questionnaire 39 (PDQ39). Preoperatively, all patients were assessed in "on" and "off" condition and postoperative evaluations were performed at 6 and 12 months in medication "on" and "off" condition and stimulation "on" and "off" condition.

Results: Bilateral STN-DBS resulted in a significant reduction in UPDRS motor scores (off 65,7%, on 20,2%), in Hoehn and Yahr and the Swab and England (off 58%, on 12%). The quality of life improved in 50 patients (n=94%). Complications occurred in 6 patients (11.3%); these included: infection in 2 (3.8%), hemorrhage in 2 (3.8%) and pulmonary embolism in 2 cases (3.8%). All complications were managed conservatively and the patients recovered without any permanent sequelae. No perioperative death occurred.

Conclusions: Bilateral STN stimulation is an effective and safe treatment for patients with advanced PD and contributes to the improvement of parkinsonian symptoms. The risk of associated surgical morbidity is acceptable.

Th-332

Evaluation of brain damage during movement disorders surgery with the utilization of the S100b protein

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Objective: The aim of this study is to measure the degree of brain damage generated during the passing of a) microrecordings electrodes, b) macrostimulation electrodes and c) permanent stimulation electrodes and try to associate the number of inserted electrodes with morbidity.

Background: Despite of subthalamic deep brain stimulation (DBS) wide acceptance, there is considerable variability in the technical approach. An important controversy in DBS is whether the use of multiple simultaneous tracts for the microelectrode recordings (MERs) is associated with a higher hemorrhage and complication rate. On the other hand S-100b protein has been established as a biochemical marker of brain damage as well as a responder to therapy and prognosticator.

Methods: Between 2003-2007, 43 patients underwent surgery for the implantation of 85 STN-DBS leads. In all cases five simultaneous tracts were utilized for MERs. All patients underwent measurements of serum S-100b prior to the operation, intraoperatively after the: a) burr hole placement, b) insertion of microrecording electrodes, c) during the macrostimulation, e) end of operation and finally on the 1st postoperative day.

Results: We noticed only two cases of increased S-100B protein. In all other cases serum S-100b protein was within normal values and remained within the normal value during the procedure. No association was found between the number of inserted electrodes and the number of complications

Conclusions: These results, strongly suggest that there is no statistically significant difference between the number of electrodes used and the a) degree of brain damage generated, b) morbidity in movement disorders surgery.

Th-333

Comparison of surgical outcomes with unilateral, staged bilateral, and bilateral subthalamic stimulation for advanced Parkinson's disease

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Objective: We aimed to evaluate the risks and benefits of unilateral and bilateral STN DBS surgery. We have retrospectively analyzed surgical outcomes of the patients underwent unilateral, staged bilateral, and bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) for the advanced Parkinson's disease.

Methods: Twenty-four patients with advanced Parkinson's disease underwent unilateral STN DBS surgery, which included the initial cases of staged bilateral surgery (unilateral group), 20 patients underwent staged bilateral surgery (staged bilateral group), and 16 patients underwent bilateral surgery (bilateral group). We evaluated the patients with Unified Parkinson's Disease Rating Scale (UPDRS) part III, levodopa equivalent daily doses (LEDD), surgical complication and stimulation-related adverse effects. We aimed to evaluate the risks and benefits of unilateral and bilateral STN DBS surgery. We have retrospectively analyzed surgical outcomes of the patients underwent unilateral, staged bilateral, and bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) for the advanced Parkinson's disease.

Results: The mean preoperative UPDRS part III during off/on periods were 49/31 in the unilateral group, 33/17 in the staged bilateral group, and 39/23 in the bilateral group. The mean preoperative LEDD were 614 mg, 641 mg, and 727 mg. The mean postoperative UPDRS part III were 27/23, 21/18, 20/18. The mean postoperative LEDD were 492 mg, 340 mg, 356 mg. The surgical complication rates were 8%, 10%, and 0%. The stimulation-related adverse effect rates were 29%, 30%, and 25%.

Conclusions: Unilateral STN DBS is an effective treatment for selected patients with advanced PD. However, most of the patients need bilateral STN DBS surgery. Unilateral STN DBS may be an alternative to bilateral STN DBS for the elderly, patients with asymmetry of parkinsonism, and the patients at risk of stimulation-related adverse effects.

Th-334

Bilateral deep brain stimulation of the subthalamic nucleus in Parkinson's disease: A large single centre study of motor effects and severe adverse events

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Objective: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is associated with significant improvements of motor function and motor complications in patients with advanced Parkinson's disease (PD).

Background: Long-term results have been reported only in a few studies and mainly from multicenter studies. The frequencies of severe adverse events (AE) related to the surgical procedure have varied considerably in previous reports.

Methods: All PD patients treated with bilateral DBS of the STN at Rikshospitalet University Hospital 2001-2006 were included in this retrospective study. Patients were examined preoperatively, at 3 months after surgery and then annually. Motor function was assessed in the medication 'off' and 'on' states using the Unified Parkinson's Disease Rating Scale motor part (UPDRS-III). Medical records were examined for the occurrence of severe AEs.

Results: 125 patients with PD were treated with STN-DBS in this period. Average disease duration before the procedure was 11.1 years (range 4-23 years). None of the patients died of causes related to the surgical procedure. There were no symptomatic intracranial hematomas or intracranial infections. 14 severe AEs directly related to the surgery occurred. The mean UPDRS-III score 'off' medication improved significantly from 40.3 ± 13.2 at baseline to 19.9 ± 8.5 one year after implantation (51%, $P<0.001$). The daily dosage of dopaminergic medication was significantly reduced from 1044 to 489 levodopa equivalents (53%, $P<0.001$). Follow up of 2.8 ± 1.6 years demonstrated a deterioration of motor function, with an average annual increase of UPDRS-III score of 2.5 points. The patients' disease duration prior to surgery and preoperative UPDRS-III scores 'off' medication decreased during the study period.

Conclusions: STN-DBS is a safe procedure with a low frequency of severe AEs. Improvement of motor function is comparable to previously published data. STN-DBS is an effective long-term treatment for advanced PD. Motor function deteriorates slowly,

probably related to the natural progression of PD. Towards the end of the study patients with less advanced disease were treated with STN-DBS, indicating changes in inclusion criteria in this six year-period.

Th-335

Subthalamic deep brain stimulation for young onset Parkinson's disease

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Objective: The aim of this study was to confirm the long-term effectiveness of subthalamic deep brain stimulation (STN-DBS) for young onset Parkinson's disease (YOPD).

Background: STN-DBS has been ensured its long-term benefit in treating PD. However, YOPD is definded as Parkinson's disease diagnosed between the ages of 21 and 40 years with different clinical features and management strategies in comparison with idiopathic PD.

Methods: Among consecutive 101 PD patients with bilateral STN-DBS in our hospital from February 2003 to January 2009, sixteen YOPD patients (2 female, 14 male) with mean age 40.9±9.5 year old were enrolled. The average disease duration was 10±7.2 years. The mean post-operative follow up was 26±19.3 (3∼60) months by using Unified Parkinson's Disease Rating Scale (UPDRS) and mini-mental status exam (MMSE). Student t test was used for statistical analysis.

Results: The post-operative UPDRS total scores, part I, part II, part III and part IV in DBS on/med off all showed significant improvement ($p < 0.05$) comparing to pre-operative med off baseline. The levodopa equivalent daily dosage also decreased by 60.6±30%. The MMSE did not show deterioration. In terms of complication, there were 8 patients with transcient stimulation-related dyskinesia, which subsided after active stimulation adaptation and/or adjustment. Three patients had stimulation related neuropsychological sequelae including hedonistic homeostatic dysregulation, mania, and impulse control disorder, which improved after psychiatric consultation. There had neither surgical nor DBS-related permanent complication such as intracerebral hemorrhage except one patient with hardware failure (battery).

Conclusions: Albeit higher stimulation-related dyskinesia and neuropsychiatric issues, bilateral STN-DBS has effective long-term benefit for YOPD patients concerning risk-benefit ratio.

Th-336

STN DBS versus GPi DBS in refractory freezing of gait in Parkinson's disease: A case report

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Objective: To describe a Parkinson's disease (PD) patient with severe freezing of gait not alleviated by bilateral globus pallidus (GPi) DBS but improved dramatically with subthalamic nucleus (STN) DBS.

Background: STN and GPi DBS are both established treatments for PD, with each target improving cardinal motor symptoms. Unfortunately freezing of gait (FOG) is not always improved with DBS especially if it occurs in the "on medication" state. We present a case of a PD patient whose FOG was not alleviated by GPi stimulation but was eliminated by STN stimulation.

Methods: The patient, a 62 year-old man with PD for 12 years, developed FOG just prior to having bilateral GPi DBS surgery in 2003. Despite marked improvement in cardinal motor features and motor fluctuations, his FOG increased in severity and was debilitating. In 2005 the patient underwent additional surgery where bilateral STN DBS leads were placed. On- and off-medication UPDRS motor scores and Stand-Walk-Sit (SWS) testing were performed preoperatively and at 6 and 24 months postoperatively for both GPi and STN DBS treatments. Typical DBS parameters were used (2.4-4.0 V, 60-90 microsec, 185 Hz).

Results: There was similar improvement in the off medication UPDRS motor score for both GPi(39%) and STN(41%) treatments compared to baseline at 6 months. At 24 months, STN(50%) DBS was more improved compared to GPi(32%). However, there were significant differences in the SWS scores, better reflecting the degree of FOG. After 6 months of GPi DBS, there was an 88% worsening in the off medication time to complete the SWS test and continuous freezing of gait and at 24 months, freezing persisted. In contrast after 6 months of STN DBS, the off medication time to complete the SWS test was similar to baseline and there were no episodes of freezing. Similar results were seen at 24 months. No further motor improvement was seen when both GPi and STN leads were used together.

Conclusions: In this case of a patient treated initially with bilateral GPi DBS and then bilateral STN DBS, stimulation of the STN proved to be much more effective than GPi stimulation for the treatment of FOG.

Th-337

Pre-selection for deep brain stimulation in patients with Parkinson's disease: The STIMULUS screening tool

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Objective: To evaluate the usefulness of an online screening tool (*Stimulus*) to assist neurologists in deciding which patients with Parkinson's (PD) should be referred for the consideration of deep brain stimulation (DBS).

Background: Deep brain stimulation (DBS) is an effective treatment in well-selected patients with advanced Parkinson's disease (PD). However, the identification of appropriate candidates it is often difficult for referring neurologists.

Methods: The *Stimulus* tool was based on the recommendations of an international expert panel, who assessed the appropriateness of referral for 972 theoretical patient profiles. The tool allows the user to select a patient profile and to see the related recommendation on referral (appropriate, inappropriate, uncertain). The tool was disseminated via local educational meetings, and its use was monitored via an online program. Data included the patient profile, panel recommendation, referral decision, and 6-months follow-up information.

Results: Between 01/02/2007 and 01/01/2009, 2859 patient profiles were entered by 249 referring neurologists in 5 European countries and Canada. Referral intentions were strongly associated with the panel recommendations; positive intentions were seen for 3%, 33% and 74% of patients for whom the tool recommendation was inappropriate, uncertain and appropriate respectively. Follow-up at 6 months showed that 29% of patients for whom a positive referral intention was documented had actually been referred to a DBS centre. Principal reasons for not referring a potentially appropriate candidate were 'patient's reluctance of brain surgery' (53%) and 'patient still undecided' (40%). For patients referred to a DBS centre and having a completed evaluation (n=121), the predictive value of the tool recommendations for final selection decisions was high, with an acceptance rate of 78% in those with an appropriate referral according to the tool. This is considerably higher than the average acceptance rate in patients for whom no pre-selection procedures are applied (around 50%).

Conclusions: The *Stimulus* tool has the potential to increase the quality of referral decisions for DBS consideration in patients with PD. However, data show that the actual decision for referral is strongly determined by patients' perceptions and preferences.

Th-338

Evoked magnetic fields from subthalamic deep brain stimulation in Parkinson's disease measured by magnetoencephalography

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Objective: To measure an evoked magnetic field from subthlamic deep brain stimulation (STN DBS) in Parkinson's disease (PD).

Background: As DBS is investigated for a variety of potential indications, there is an increasing need to understand how neurostimulation modulates brain activity to exert its clinical effects. Gaining such knowledge could potentially improve the efficacy and safety of DBS in established indications and guide future therapeutic strategies. Although the mechanism of DBS is poorly understood, recent studies suggest that alterations in the rhythmic activity of the basal ganglia–thalamic–cortical (BG-Th-CTX) system underlies its remarkable efficacy. Magnetoencephalography (MEG) measures magnetic fields associated with electrical activity within the brain and has excellent temporal and spatial resolution, making it a potential tool to investigate the therapeutic mechanism of DBS.

Methods: Five subjects with advanced PD who had undergone unilateral STN DBS participated in the study. Evoked responses to DBS pulses at 2 Hz were measured in the "practically defined off" medication state with the patients awake and at rest. Event detection and averaging were used to characterize the kinetics of the evoked responses.

Results: STN DBS at 2 Hz evokes a polyphasic magnetic field with components at short latencies (P1 onset 8.6 $\pm$ 3.5 ms, P1 peak 13.6 $\pm$ 3.9 ms, P2 onset 27.0 $\pm$ 8.9 ms, P2 peak 34.8 $\pm$ 9.2 ms) in the gamma frequency range (40–50 Hz). Shorter latency responses (less than 5 ms following the DBS pulse) and longer latency responses (beyond P1 and P2) were observed in individual subjects.

Conclusions: These preliminary data demonstrate that cortical evoked magnetic fields from STN DBS in PD can be measured using MEG.

Th-339

Effects of subthalamic nucleus lesions and short-term stimulation upon striatal glutamate release in awake intact and 6-hydroxydopamine-lesioned rats

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Objective: To compare the effects of lesions and stimulation of the subthalamic nucleus (STN) upon striatal glutamate levels in awake, intact and 6-hydroxydopamine (6OHDA)-lesioned rats.

Background: Despite being widely accepted as therapy, the mechanisms by which neurosurgical interventions benefit patients with Parkinson's disease are not known. In order to investigate whether glutamate may play a role, we compared the effects of STN lesions and short-term STN stimulation upon striatal extracellular glutamate levels and immunogold-labeled glutamate in presynaptic striatal terminals in intact and 6OHDA-lesioned rats.

Methods: Two weeks after unilateral 6OHDA lesions rats underwent implantation of a striatal microdialysis probe and either implantation of a stimulating electrode or an electrolytic lesion of the ipsilateral STN. One week later striatal microdialysis was performed for 6 hours while awake. Rats with stimulating electrodes received 2 hours of STN stimulation. Parallel groups of rats without microdialysis probes were perfused for electron microscopy (EM), and the striatum dissected for glutamate immunogold labeling. Rats with electrodes implanted were perfused either immediately following 1 hour of STN stimulation, or with no stimulation (sham stimulation).

Results: Stimulation of the STN for 6 hours in awake intact or 6OHDA rats did not have any effect upon striatal glutamate levels as determined by microdialysis. This was supported by the finding that there was no change in EM presynaptic glutamate immunogold labeling after 1 hour of stimulation, as compared with placement of the STN stimulating electrode alone. In intact animals there was a trend to increased striatal glutamate levels in rats with STN lesions, however, in 6OHDA-lesioned rats, levels were decreased.

Conclusions: Short-term stimulation of the STN did not affect striatal glutamate levels in either intact or 6OHDA-lesioned rats. STN lesions tended to increase levels in intact rats, but decreased levels in 6OHDA-lesioned rats, reversing the increase due to dopamine depletion. These findings suggest that lesions and stimulation have divergent effects upon striatal glutamate, and, as we have found with studies of dopamine metabolism, have state-dependent effects in intact vs 6OHDA-lesioned rats.

Th-340

Gamma knife subthalamotomy in Parkinson's disease: Long-term follow-up

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Objective: To assess the long-term outcome of unilateral Gamma Knife subthalamotomy in Parkinson's disease.

Background: Chronic STN stimulation is an established treatment for complicated PD. Bilateral subthalamotomy may induce significant and long-lasting results when DBS is not available. However, which alternative can be proposed for patients with surgical or medical contraindications for electrodes implantation? Gamma Knife thalamotomy is an effective therapy for treating disabling tremor. This technique encounters very few contraindications as it is done without craniotomy. We report the outcome of 3patients with severe PD who underwent unilateral Gamma Knife subthalamotomy.

Methods: Three PD patients with severe motor complications were assessed before surgery. Although, all of them had a good motor response to levodopa without axial symptoms or cognitive impairment, STN DBS was contraindicated. Patient 1, a 53-year-old man had a severe diabetes mellitus with vasculopathy at the MRI. Patient 2, a woman aged of 68 years had ventricules enlargement. Patient 3, a 64-year-old man had diabetes and ventricules enlargement. A unilateral Gamma Knife subthalamotomy on the most affected side was proposed. STN lesioning was performed with Leksell Gamma unit with a single exposure through a 4mm collimator. The radiosurgical dose at 100% was 110Grays.

Results: Unfortunately, patient 2 died of an aggressive gastric cancer 9months after radiosurgical procedure. However, she reported motor improvement 3months after surgery. Patient 1 and 3 had equivalent evolution. At 3 months, they reported mild unilateral dyskinesia. At 12 months the motor improvement was of 51% for patient 1 and 58% for patient 3 without dyskinesia. The LEDD decrease was 45% and 35% respectively. At 18 months, both patients experienced sudden severe akinesia that mimic hemiparesia. The MRI showed typical gamma knife induced ring-enhancing lesion within the STN associated with vasogenic edema that encompasses SN. The symptoms resolved spontaneously in less than 2 months. 3years after radiosurgery, patient 1 remains stable although axial symptoms emerge. Patient 3 has only a slight intermittent tremor without akinesia or rigidity after 2 years.

Conclusions: Gamma Knife subthalamotomy may be an alternative treatment for severe PD patients with contraindications for DBS.

Th-341

Dramatically efficacy of deep brain stimulation for a patient with Parkinson's disease with olfactory hallucination

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Objective: To describe Parkinson's disease (PD) with olfactory hallucinations and it's treatment.

Background: Olfactory hallucinations have been rarely described in patients with PD. In addition, there is a few report how to manage

olfactory hallucinations in PD. We describe a case of PD who improved dramatically her olfactory hallucinations.

Methods: A 65-year-old woman presented with tremor of left arm and bradykinesia in 1998 at the age of 54. She was diagnosed with PD and started on cabergoline with significant benefit in 2002. Then, we additionally prescribed amantadine hydrochloride and zonisamide. After the additional treatment her tremor and bradykinesia were ameliorated. Since February 2005, she had sudden onset of olfactory hallucinations.

Results: Although brain MRI was normal findings, SPECT of brain showed hypoperfusion in the basal ganglia. Marked reduced uptake was seen in cardiac 123I-MIBG scintigraphy. The olfactogram was performed and showed dissociation level between smell detection and recognition threshold. Quetiapine temporarily improved olfactory and auditory hallucinations, however, the effect lasted only for three months. She improved a mental symptom when she started to take entacapone, On the other hand, the improvement of motor function was poor. The mental symptom improved by electroconvulsive therapy (ECT). However, the effect was again temporary and she complained hallucination. Therefore she underwent STN-DBS due to mainly motor function declined. As a result, she showed almost normal motor function.

Conclusions: This case report is an important and very rare case who showed olfactory hallucination in PD. Although hallucination is common symptom in PD, olfactory hallucination is rare. DBS cases usually aggravate for a mental symptom, but this case did not aggravation for her mental symptom and motor function. In this case, STN-DBS was effective dramatically.

Th-342

Electric current distribution in the pedunculopontine nucleus region: A 2D atlas-based structural computational model

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Objective: To construct an atlas-based anatomical computational model for estimating and visualising the electric field around the deep brain stimulation (DBS) electrodes implanted in the pedunculopontine nucleus (PPN) region for alleviating akinesia in Parkinson's disease (PD).

Background: The PPN is emerging as a novel target for DBS in PD to specifically treat intractable axial symptoms such as gait freezing and loss of postural control. The PPN lies within the brainstem reticular formation and projects to the thalamus and the spinal cord. It is an elongated neuronal collection, lying in the gray matter medial to the medial lemniscus system and lateral to the decussation of the superior cerebellar peduncle. Detailed structural MRI studies, including diffusion tensor imaging and probabilistic diffusion tractography, have been attempted to help better delineate the PPN to aid surgical targeting.

Methods: We took a computational modelling approach to estimate and visualise the induced electrical field in the PPN region. We constructed a 2-dimensional structural model, and included anatomical features by basing the model on a standard, and widely used stereotactic atlas. We quantitatively investigated changes in the electric field generated at different target positions in the PPN region, focussing on the spread of current within the PPN and into surrounding regions.

Results: Simulations of this structural model show that the location of the electrode has a significant effect on the shape and strength of the electric field, as the induced current spread is dependent on the biophysical properties of the surrounding tissue. For example, the proximity of fibre tracts such as the medial lemniscus and the superior cerebellar peduncle restrict the spread of current due to the low conductivity of white matter relative to grey matter.

Conclusions: These results provide quantitative visualisation of the induced current spread in the PPN and surrounding structures due to DBS in an atlas-based model. In turn, the image-based patient-specific model in 3D with more complexity in the biodynamic properties of the brain tissue can be developed to aid surgical targeting, and to assist the appropriate configuration of the DBS paradigm in individual patients during post-implantation programming.

Th-343

Deep brain stimulation for movement disorders in a series of 276 patients

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Objective: To discuss the therapeutic effect of deep brain stimulation for movement disorders in a series of 276 patients.

Background: DBS has become an increasingly common surgical treatment of movement disorders. However, many aspects of this promising intervention remain uncertain.

Methods: A consecutive series of 276 patients with movement disorders underwent DBS performed by the same operative team at Xuanwu Hospital, Beijing. These patients suffered mainly from Parkinson's disease (PD), essential tremor (ET), dystonia (DT), and tourette syndrome (TS).

Results: Significant improvement of motor abilities (UPDRS) was observed in PD patients by 45.6%. There was a significant association of non-motor symptoms (NMS) score in PD patients with Hoehn-Yahr stage($r=0.49$, $p=0.00$). Six items of NMS (pain, paraesthesia, insomnia, vivid dreaming, restless legs, weight loss) were significantly less reported by PD patients postoperatively (Pearson Chi-square test, P, 0.00$\sim$0.02). Stimulation of the ventral-internal nucleus of the thalamus is an effective treatment for ET with sustained long-term effects. The individual improvement rate of DT varied from 22.0% to 95.8% followed by delayed but steady progress. Patients with TS showed substantial reduction of tics and compulsions.

Conclusions: According to STN-DBS for PD and Gpi-DBS for TS, detailed neuropsychological evaluations may become helpful to further understand the mechanisms underlying some aspects of the clinical features. Good results have been achieved in patients with primary dystonia due to undergoing GPi or STN DBS. However, without controlled studies evaluating, the optimal stimulation target for different subtypes of dystonia is unknown.

Th-344

Is REM sleep behavior disorder associated with a less favorable outcome of STN-DBS in PD?

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Objective: To assess whether the presence of REM sleep behaviour disorder (RBD) influences the long-term outcome of Parkinson's disease (PD) patients undergoing Subthalamic Nucleus deep brain stimulation (STN-DBS).

Background: RBD is a parasomnia characterized by loss of muscular atonia and complex motor behaviours during REM sleep, frequently reported in PD patients. Recent evidence suggests that RBD is associated with specific motor features, including akinetic rigid disease type and increased frequency of falls. PD patients undergoing STN-DBS show improvement of cardinal symptoms; however, in the long-term some patients develop axial symptoms with a progressive increase in gait dysfunction. The observation of the development of gait disorders after years of successful STN-DBS in patients displaying clinical symptoms of RBD, prompted us to wonder whether the presence of RBD would influence the long-term outcome of STN-DBS.

Methods: Forty-one consecutive PD patients treated with bilateral STN-DBS were assessed. The presence of RBD was diagnosed by clinical history. The Unified Parkinson's Disease Rating Scale was used to compare the on- and off-medication conditions preoperatively and the on-stimulation/ on- and off-medication condition 1 and 3 years postoperatively. The general linear model for multivariate

measures was used to analyse the interaction of RBD with STN-DBS outcome measures.

Results: RBD was present in 12 out of 41 patients (29%) undergoing STN-DBS. Patients with RBD showed a significantly poorer outcome three years after STN-DBS compared to patients without RBD, in particular for axial symptoms.

Conclusions: We suggest that the presence of RBD may be associated to a greater risk of developing resistant axial symptoms during the STN-DBS follow-up. However, further studies involving a larger number of patients are necessary to assess if the presence of preoperative RBD may be considered a risk factor for a less favourable outcome in the long-term.

Th-345

Asymptomatic deep venous thrombosis in advanced Parkinson's disease: Implications for DBS surgery

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Objective: To determine the incidence of deep venous thrombosis (DVT) in patients with advanced Parkinson's disease (PD) undergoing STN-DBS surgery.

Background: Patients with PD are at increased risk for asymptomatic leg DVT. Pulmonary embolism is the second cause of death in advanced disease after pneumonia. DBS surgery is considered at high risk for venous thromboembolism in the lower limbs and a specific prophylaxis is recommended and commonly applied.

Methods: Dopper ultrasonographic examination of the leg veins was performed on two groups of PD patients: 1. 70 advanced PD patients [24 females/46 males, mean age 58.7 years, mean disease duration 11.7 years, mean H&Y off score 3.2, mean UPDRS IIII off score 41.6/108] 2. 41 advanced PD patients undergoing STN-DBS surgery [15 females/26 males, mean age 57.0 years and mean disease duration 12.1 years, mean H&Y off score 3.1, mean UPDRS IIII off score 43.8/108].

Results: The doppler ultrasonographic examinations demonstrated that 3 (4.3%) out of the 70 advanced PD patients had asymptomatic DVT. Despite none of the 41 patients undergoing STN-DBS had DVT before surgery, 3 patients (4.9%) developed asymptomatic DVT shortly after surgery (mean 8.5 days).

Conclusions: We confirm previous studies suggesting that patients with advanced PD are at risk for asymptomatic leg DVT and show that this is a clinically relevant problem in patients undergoing DBS surgery.

SURGICAL THERAPY: OTHER MOVEMENT DISORDERS

Mo-345

Control of tremor in multiple sclerosis with bilateral stimulation of the caudal zona incerta

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Objective: To undertake a retrospective analysis of the effect of chronic deep brain stimulation (DBS) on tremor control in patients with Multiple Sclerosis (MS). We present our case series of ten patients who presented with a mean disease duration of 10.4 years (range 3-18 years).

Background: The caudal Zona Incerta (cZI) has previously been shown to be an effective target in the treatment of tremor associated with Multiple Sclerosis[1]. We stimulated the cZI nucleus in 10 MS patients with a mean age of 41.6 years. Response rates for tremor secondary to MS are significantly lower than those for Essential Tremor with average reduction in MS tremor scores after DBS ranging from 30-60%.

Methods: Under GA, a modified Leksell frame was applied and high resolution MR images were acquired, enabling cZI target definition and planning. Bilateral cZi DBS Medtronic 3389 electrodes were inserted and connected to a Kinetra generator. Patients were assessed using the Fahn-Tolosa-Marin (FTM) tremor rating scale at baseline, and followed up for a mean period of 15.3 months (range 4.0-26.4 months). The primary outcome measure was the change in the total FTM score and in the individual severity (A), functional (B) and ADL (C) subscores.

Results: DBS of the cZI achieved improved tremor control in all patients with a mean improvement of 46% (11-83%) in the total FTM score. Improvement in scores for part A, B and C of the FTM rating scale were 66.5% (21-100%), 41.3% (14-76) and 31.9% (4-86) respectively. Analysis of the scores according to the severity of MS showed that those with moderate MS (ambulatory) had a 44.6% higher response rate when compared to those with severely disabling MS (wheelchair-bound). Refer to graph.

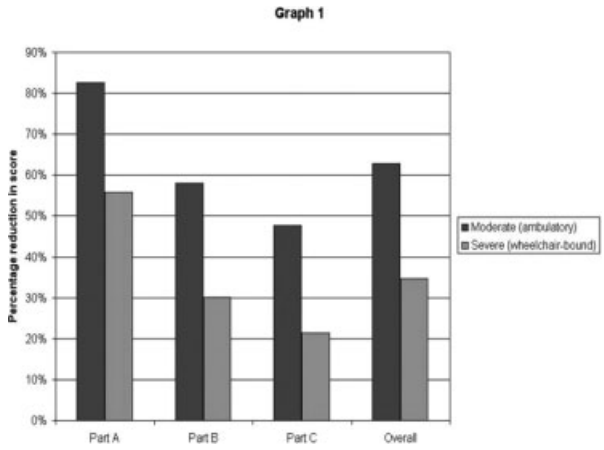

FIG. 1 (Mo-345).

Conclusions: Chronic deep brain stimulation of the cZI can be an effective treatment, however our experience suggests that this is dependent on the pre-operative severity and progression of MS. Careful patient selection is therefore important for maximising therapeutic benefit. [1] Plaha P, Khan S, Gill SS. Bilateral stimulation of the caudal zona incerta nucleus for tremor control. J Neurol Neurosurg Psychiatry 2008. 79; 504-513

Mo-346

DBS in pantothenate kinase deficiency

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Objective: To report a case of a 16-year old female with pantothenate kinase deficiency who underwent right-sided GPi deep brain surgery (DBS) with minimal post procedure benefit in chorea, but no benefit in dystonia.

Background: Pantothenate kinase deficiency (Hallervorden- Spatz) is a form of familial brain degeneration with iron deposition due to mutation of the PANK2 gene. Clinical presentation varies from gait problems, rigidity, bradykinesia, dystonia, choreoathetosis, tremor, spasticity, dysarthria, and later dementia and seizures. No effective therapy is available for this disease. Several authors report DBS improves dystonia and choreoathetosis.

Methods: A 16-year old female presented at age 13 with walking, balance difficulties and facial grimacing. Falls started several months later. Neurological examination showed flexion toe dystonia in both feet, choreoathetoid movements in the left sided extremities with predominance in the left leg, mild left-sided spasticity and severe facial dystonia with dysarthria. Due to rapid symptomatic worsening, espe-

cially gait, and minimal response to current medication (carbidopa/levodopa, carnitine), right-sided GPi DBS was performed. Dystonia UPDRS score was 10.5 (maximum of 44) before and 20 three and six months after DBS. Initially, high frequency stimulation was applied (electrode 1 negative, 2 positive, amplitude of 1.5V, pulse width 90μs, rate 50Hz) and later low frequency stimulation (electrode 2 positive, 1 negative, amplitude 2.0 V, pulse width 270μs, frequency 50 Hz), but both produced subjective and objective worsening of her gait. Choreoathetoid limb movements were the only improvements observed.

Conclusions: Pantothenate kinase deficiency is a rare neurodegenerative disorder without a known cure. DBS has been reported to have mild transient benefit in dystonia. Our patient showed benefit in limb chorea, but no benefit in dystonia in high and low frequency DBS 6 months post-procedure.

Mo-347

Thalamic DBS for tremor in IgM paraproteinaemic demyelinating polyneuropathy

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Objective: To present a case of DBS for neuropathic tremor.

Background: Postural tremor is a common symptom in IgM paraproteinaemic demyelinating polyneuropathy. We present a patient with disabling, drug-resistant tremor due to neuropathy associated with anti-myelin-associated glycoprotein IgM antibodies (anti-MAG) that was successfully treated by bilateral deep brain stimulation (DBS) of the ventral intermediate thalamic nucleus (VIM).

Methods: Case report.

Results: A 58-year-old man, with negative family history, had been diagnosed with IgM monoclonal gammopathy and demyelinating neuropathy associated to anti-MAG, three years before. He presented postural and action tremor of both upper limbs that had appeared a few weeks after onset of the first sensory symptoms, and worsened over time. Whereas weakness and sensory loss responded satisfactorily to immunoactive therapies, tremor persisted and was resistant to symptomatic drug treatment. As it became severe and was source of incapacity in the daily activities, bilateral DBS of VIM was implanted and led to great improvement of tremor (video will be presented).

Conclusions: DBS of VIM is a well-established therapeutic option in disabling, drug-resistant tremor in Parkinson's disease and essential tremor. Tremor in IgM paraproteinaemic demyelinating polyneuropathy shares many clinical features with essential tremor, with presence in posture and action, predominantly affecting distal rather than proximal muscles, and similar frequencies. To our knowledge, only one patient with unilateral DBS for neuropathic tremor has been reported so far, for a 72-year-old man suffering from neuropathy associated with monoclonal IgM gammopathy. In this report as in ours, DBS of VIM gave an excellent result. In conclusion, severe, drug-resistant tremor in IgM paraproteinaemic demyelinating polyneuropathy seems to be a good indication for DBS of VIM. Effect of DBS for this condition as for tremor associated to other peripheral neuropathies needs to be confirmed by larger studies.

Mo-348

Combined neurostimulation therapy (DBS and SCS) for orthostatic tremor: A case report

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Objective: To report the short-term outcome of combined Ventrointermedial deep brain stimulation (Vim-DBS) and Spinal Cord stimulation (SCS) in a patient with medically refractive Orthostatic Tremor (OT).

Background: OT is a condition characterized by unsteadiness when standing accompanied by a characteristic 13–18 Hz rhythmic tremor in the lower limb muscles in orthostatisms. The pathophysiological mechanisms of OT is still debated. Although OT is generally thought to originate from a central oscillator in the brain, some authors have suggested a spinal source of the tremor.

Methods: A 58-year-old woman had a 8-year history of feeling of unsteadiness during stance, increased while standing still and relieved by walking. The diagnosis of primary OT was confirmed by EMG evaluation. Medical treatment was ineffective and because of an increased disability for daily life activities, she was assessed for surgery. In January 2007 she underwent bilateral Vim-DBS. Electrodes were positioned with intraoperative neurophysiological monitoring. The best clinical effects were obtained with a chronic low-frequency stimulation (20Hz), she was able to stand for prolonged period. Considering the unsatisfied response, in July 2008 the patient underwent an implantation for SCS. Two octapolar percutaneous electrodes were inserted at lumbar site and were advanced over several segments in the epidural space allowing testing for several spinal cord levels and assessing for optimal electrode position. The final placement was on the midline with the upper extremity of the electrode located at T8. No adverse events were observed.

Results: No significant benefits were observed with the SCS alone. Otherwise the simultaneous stimulation of VIM-DBS and SCS was extremely effective to control the tremor and improved the ability to stand still (from pre-op 120 sec to >9 min in the post-op). The efficacy of the stimulation has remained unchanged over the last 6 months.

Conclusions: Our preliminary data, although requiring a neurophysiological validation, support the hypothesis of a "double modulation" (central and spinal) in the neuronal network originating the OT.

Mo-349

Lifetime of impulse generators for deep brain stimulation in dystonia

C. Blahak, H.-H. Capelle, H. Baezner, T. Kinfe, M.G. Hennerici, J.K. Krauss (Mannheim, Germany)

Objective: To investigate the lifetime of bilaterally implanted Soletra impulse generators (Medtronic, Minneapolis) depending on stimulation settings and total electrical energy delivered (TEED) in patients with chronic bilateral deep brain stimulation (DBS) of the globus pallidus internus (GPi) or the thalamic ventral intermediate (VIM) nucleus for dystonia.

Background: The efficacy of bilateral pallidal and thalamic deep brain stimulation (DBS) in generalized and segmental dystonia is well documented, but little is known about the lifetime of implanted pulse generators (IPG).

Methods: We analyzed the adjustment of stimulation settings over time and the IPG lifetime in 19 consecutive patients with generalized (n=2) or segmental (n=17) dystonia who underwent DBS surgery between 2001-2006. 17 patients had DBS of the GPi, two patients of the VIM. TEED was estimated using a previously proposed equation [(voltage^2 x pulse width x frequency)/impedance]. Statistical analysis included non parametric testing for unpaired (Mann-Whitney-Test) variables and Spearman correlation test.

Results: Up to December 2008, in 17 patients 59 IPGs were replaced due to low-battery signalling or end of life. Mean IPG lifetime was 25.5+/-10.4 (range 16-60) months, mean stimulation intensity applied throughout the lifetime cycle 4.2+/-0.9V, mean stimulus frequency 132.0+/-5.1Hz and pulse width 210μs in all patients. We found an inverse correlation between IPG lifetime and both mean stimulation intensity ($r=-0.78$; $p<0.001$) and TEED ($r=-0.74$; $p<0.001$). Mean IPG lifetime was not different between monopolar and bipolar stimulation mode (26.2+/-9.2 vs. 25.1+/-11 months; $p=0.42$), but mean stimulation intensity (3.7+/-0.6V vs. 4.5+/-0.9V; $p<0.001$) and TEED (381+/-128 vs. 588+/-218 $p<0.001$) applied

throughout the lifetime cycle were significantly lower in patients with monopolar stimulation.

Conclusions: Mean lifetime of Soletra IPGs for DBS in dystonia is notably lower than the previously reported lifetime of almost identical Itrel II IPGs in patients with subthalamic nucleus (STN) DBS for Parkinson's disease (PD). This difference in IPG lifetime is primarily caused by a higher mean stimulation intensity and pulse width usually required for DBS of GPi and VIM in patients with dystonia, resulting in a higher TEED compared to STN-DBS in PD patients.

Mo-350

Micrographia induced by bilateral pallidal deep brain stimulation for segmental dystonia

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Objective: To evaluate and measure the degree of micrographia induced by bilateral chronic deep brain stimulation (DBS) of the globus pallidus internus (GPi) in patients with segmental dystonia analyzing pre- and postoperative handwriting samples.

Background: GPi-DBS has been established as an effective and safe therapy for dystonia. In general, side effects are rare. Parkinsonism due to lesions in the GPi has been reported in single cases secondary to brain hypoxia, after pallidotomy and recently also following DBS of the GPi. In our prospective series of DBS of the GPi for segmental dystonia, some patients report mild micrographia and hypokinesia as side-effects of chronic DBS, particularly with high stimulation intensities.

Methods: We analyzed the height and width of a predefined handwriting sample in 11 consecutive patients (mean age 57.6±13.6 years) with segmental dystonia preoperatively and at a median of 7 months (FU1) and 17 months (FU2) post DBS surgery. None of the patients had involvement of distal arm and hand function in dystonic symptoms, and none reported typical capsular effects with GPi-DBS. Statistical analysis used non parametric testing for paired variables (Wilcoxon rank test) and Spearman correlation test.

Results: Maximum height of handwriting characters significantly decreased from 15.7±4.0mm (mean+/-SD) preoperatively to 13.5±4.1mm at FU1 ($p=0.036$) and 12.5±2.2mm at FU2 ($p=0.008$), and width of the handwriting phrase sample decreased from 121.3±36.1mm preoperatively to 105.8±33.5mm at FU1 ($p=0.013$) and 103.6±33.7mm at FU2 ($p=0.009$). The decrease in height and width did not correlate with stimulation intensity at FU1 and FU2 (height: $r=0.13$; $p=0.57$; width: $r=-0.06$; $p=0.78$).

Conclusions: Chronic bilateral GPi-DBS significantly decreases height and width of a predefined handwriting sample in patients with segmental dystonia. We postulate that this phenomenon reflects a disturbance of basal ganglia function in terms of a mild and thus for not fully appreciated hypokinetic syndrom as a side-effect of chronic bilateral GPi-DBS. Contrary to clinical assumptions on the occurrence of hypokinesia, the intensity of stimulation did not correlate with severity of micrographia in our study.

Mo-351

Prevalence of Twiddler's syndrome as a cause of deep brain stimulation hardware failure

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Objective: To describe the presentation, diagnosis, treatment and prevalence of Twiddler's syndrome in the DBS population.

Background: DBS for the treatment of movement disorders has resulted in positive clinical outcomes, but there have been complications. Patients with cardiac pacemakers have been reported to suffer from Twiddler's syndrome, which has been described as the conscious or subconscious manipulation of implantable chest generators, leading to twisting and ultimately fracture and/or device failure. One such case has recently been reported in DBS for ET. We report three cases of Twiddler's syndrome in DBS patients within our practice.

Methods: We reviewed an Institutional Review Board-approved DBS database for cases of hardware malfunction. Of 362 leads implanted in 226 patients were 17 hardware malfunctions. Among these 17 hardware malfunctions, 5 of them were due to Twiddler's syndrome in 3 patients. We review the presentations, radiographic findings, interrogation data, risk factors, treatment, as well as the published literature.

Results: Three cases of Twiddler's syndrome were identified, occurring in 1.3% of patients and in 1.1% of leads. One patient presented with pain, tingling, high impedances and low current drains, and radiographic evidence of fracture. The second patient presented with pain over the hardware, tremor recurrence, and abnormal device interrogation. Intraoperatively, pocket laxity was found. The third patient presented with a sensation of generator mobiity, was found to have excessive laxity in her generator pocket during operative revision. All patients eventually had their generators sutured to fascia to prevent further Twiddling.

Conclusions: As the use of DBS increases, recognition of unique complications such as Twiddler's syndrome will become clinically important. Recurrence of symptoms, pain along the path of the hardware, abnormal impedances/current drain, and radiographic signs such as an obvious break, or more subtly, twisting of the extension cable, should alert the DBS team to the possibility of failure of the DBS system and a Twiddler's syndrome. Securing the IPG within its pocket can be effective treatment for Twiddler's recurrence. More studies are needed to identify risk factors for the development of this complication.

Mo-352

Rehabilitation and orthopedic management of Stiff Person syndrome

A.C. Clairmont, K.E. Lindberg, N. Goldstein (Columbus, Ohio)

Objective: We report the case of a 71-year-old female with increasing persistent painful muscle spasm in her left followed by right lower limb. She presented with a several month history of aching and stiffness about her knees, attributed to osteoarthritis. She then deteriorated rapidly, became unable to walk, and was admitted to hospital. Serum studies positive for anti-amphiphysin antibodies and electrodiagnostic studies showing continuous motor unit activity supported the diagnosis of Stiff Person Syndrome and suggested malignancy. She was treated with IVIG and plasmapharesis. Imaging studies found malignancy of the breast. Treatment was right mastectomy and chemotherapy for invasive ductal carcinoma. During inpatient rehabilitation, she hobbled with a walker, secondary to stiffness, spasm, decreased range of motion of the left knee and severe stiffness and orthopedic deformity of her left ankle and foot. Physical therapy modalities including serial casting were utilized. Pharmacological management of her spastic dystonia included Tizanidine 24 mg/day, Baclofen 80mg/day, Gabapentin 1600 mg/day and ultimately transition to intrathecal baclofen (ITB) pump, which was side-effect limited to 800μg/day. She improved with ITB therapy but continued to have severe plantar flexion spastic dystonia, inversion of forefoot and hyperflexion of the toes. Six % phenol-mediated Tibial and Peroneal neurolysis and Botulinum toxin type A injections of 1000 units of to left leg muscles were performed. Spastic dystonia resolved but severe contracture remained. Orthopedic surgical specialists were consulted and offered opinions including left below knee amputation. We recommended splitting the tibialis anterior tendon with transplant to the lateral dorsal foot, tibialis posterior and flexor digitorum longus tenotomy, and tendo-achilles lengthening. These recommendations were implemented. Intense physical therapy followed surgery. Within 2 months, she was ambulating unlimited distances with a wheeled walker, today walks independently, and is completely assimilated into the community. Maintenance therapy: ITB at

800 micrograms/day, no oral anti-spasticity medication or neurotoxin injections.

Mo-353

Deep brain stimulation for Holmes' tremor

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Objective: A retrospective review of 8 patients in whom we have inserted deep brain stimulators to treat medically intractable Holmes' tremor.

Background: Deep brain stimulation is a recognised treatment for several tremulous conditions however it has not previously been reported in a case series of patients with Holmes tremor. Elements of this abstract were presented at the 151st Society of British Neurological Surgeons Conference published in the British Journal of Neurosurgery (2008) 22:2, 169–186.

Methods: Electrodes were implanted unilaterally into the VOP nucleus of the thalamus in all patients. In one case an additional electrode was inserted unilaterally into the GPi. Surgery was carried out between 1999 and 2007 by 1 surgeon. Patients were assessed preoperatively and during clinical follow-up (median length of longest follow-up = 22 months). Tremor severity of each body region was rated by 3–4 independent blinded observers, using Bain's rating scale. Clinical scores were augmented with electromyograph (EMG) recordings and quality of life data in a subset of patients. Quality of life was measured using Functional Life Profiles, collected by self administered questionnaire.

Results: There was a significant 74.8% improvement between preoperative clinical scores and clinical scores with Vop-stimulation on ($p \leq 0.0001$; Wilcoxon Signed Ranks Test). The EMG data is consistent with this, with a significant overall improvement between the pre-operative and post-operative assessment with stimulation on (mean = 79.3%; n=3, p=0.01). These findings are also consistent with the improvement seen in quality of life, although statistical significance could not be calculated for this data set. There were no serious complications.

Conclusions: Deep brain stimulation is an effective treatment for medically intractable Holmes' tremor.

Mo-354

Effects of contact location in a cohort of 41 parkinsonian treated by deep brain stimulation of subthalamic nucleus area

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Objective: We carried out a study in order to explore systematically effectiveness and anatomical localization of the four contacts of both electrodes in 41 parkinsonian patients treated by bilateral DBS-STN.

Methods: The surgical procedure was based on direct STN targeting. Preoperatively, we performed a White Matter Attenuated Inversion Recovery (WAIR) T2-weighted sequence to visualize both the stereotactic markers and the subthalamic anatomy of nuclei and bundles. Several structures of the subthalamic region were segmented manually on the coronal plane. Post operative imagery was then performed after electrodes implantation. A pseudo coronal plan was then reconstructed along the main axis of the electrode using surgerical software (iplan/ BrainLAB). Localization was determined by superimposing postoperative with preoperative imaging. We were then able to define the membership of each contact within the different structures of subthalamic area (substancia nigra, subthalamic nucleus, zona incerta, forel field). At the three-month follow-up, we systematically explored the acute motor effects of the four contacts of the electrode (328 contacts). Clinical evaluation used subscores of the UPDRS III (rest tremor, finger taps, tap heel on ground, arm and leg rigidity).

Results: We will discuss relation between anatomical locations of contacts and clinical benefits after deep brain stimulation of subthalamic area.

Tu-345

Long-term deep brain stimulation for essential tremor: 12-year clinicopathologic follow up and literature review

D.J. DiLorenzo, J. Jankovic, R.K. Simpson, H. Takei, S.Z. Powell (Houston, Texas)

Objective: To describe the clinical course and postmortem pathological findings in a patient with essential tremor (ET) treated with deep brain stimulation (DBS) for 12 years and to review the autopsy literature on DBS cases.

Background: Although DBS has been used to treat tremors and other movement disorders for nearly a quarter century, the long-term effects of chronic stimulation on the human brain are not well characterized.

Methods: This 75 year old woman had a 13-year history of progressively disabling ET prior to initial implantation of bilateral quadripolar Pt/IR DBS electrodes in her Vim thalamic nuclei in 1996. She received immediate relief of arm tremor. Final stimulation parameters were 2.5/2.8v, 185/135Hz, 90/60s, on L/R sides respectively. She derived marked therapeutic relief of her tremor until her death from natural causes at age 88. Detailed histological examination was performed, and all postmortem DBS cases were reviewed after Medline search of the literature.

Results: Electrode catheter tracts were rimmed by a 20-25 m thick fibrous sheath, with foreign body type multinucleated giant cells and surrounding reactive gliosis. Lymphocytic infiltration, with T more than B cells, was seen by L26 immunoreactivity with CD3 (T cells) staining predominating over CD20 (B cells). H&E stains of the cerebellum showed axonal spheroids and Purkinje cell loss. Literature search revealed 42 cases implanted with a total of 61 electrodes with adequate clinicopathological analyses. The indications for DBS in these cases included Parkinson's disease (26 electrodes in 16 cases), chronic pain (23/20), ET (4/2), multiple system atrophy (4/2), epilepsy (2/1), and choreoathetosis (2/1). The average implant duration was 22 months (range: 0-146). The present case, with autopsy 146 months after initial implantation, represents the longest follow-up of all postmortem DBS cases reported.

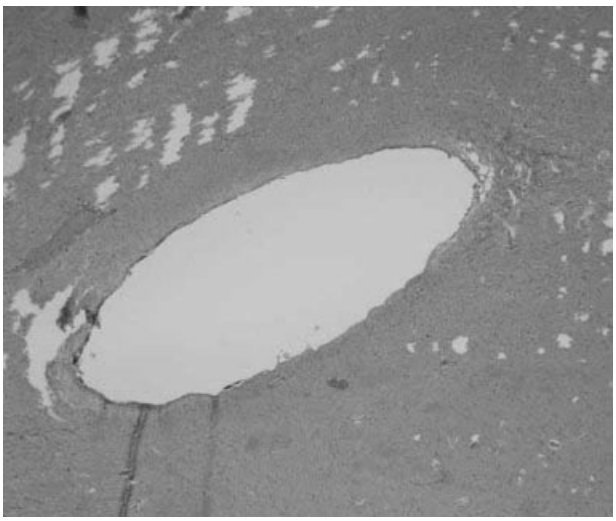

FIG. 1 (Tu-345).

Conclusions: Besides mild cerebellar pathology, consistent with the diagnosis of ET, the histopathological examination more than 12 years after initial implantation revealed only minimal foreign body reaction and gliosis around the implanted electrodes. This case, which represents the longest reported clinicopathologic follow-up from DBS implantation to autopsy, supports the long-term safety of this therapeutic intervention.

Tu-346

Spinal cord stimulation for painful legs and moving toes syndrome

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Objective: We report patient with a possible central form of PLMT who had a striking response to continuous stimulation delivered by a spinal cord stimulator.

Background: Painful leg and moving toes (PLMT) syndrome is a rare disorder characterized by constant and excruciating pain in the lower limbs accompanied by varied involuntary movements in the toes. The etiology is unknown and treatment in all forms (peripheral and central) remains disappointing.

Methods: A 63-year-old female patient presented with moving toes and progressive sharp pain in her lower extremities. She had previous traumatic L4/5 fracture and resulting back pain. Five years ago, she developed symmetric onset of radicular pain and diffuse leg aching, with progression to her arms Her neurological exam showed intermittent, though sometimes sustained, flexion/extension of toes, ankle inversions and hip flexion/adduction. Brain MRI revealed basal ganglia signal abnormalities involving bilateral globus pallidus, right striatum and left internal capsule that were stable on serial imaging. MR-spectroscopy, spinal MRI, EMG/nerve conduction study were unrevealing. A diagnosis of PLMT was made. Involuntary toe movements improved with botulinum toxin injections, but the pain component remained refractory to this treatment. Since her pain escalated despite extensive drug regimens including gabapentin, baclofen, clonazepam, trazodone, and narcotics, she underwent a trial of epidural spinal cord stimulation by dorsal T10 laminectomy for insertion of a Resume II electrode.

Results: Postoperatively she experienced an acute remarkable benefit from the epidural stimulation at low voltage and underwent implantation of the internal pulse generator. The voltage parameter had to be adjusted in the following months to maintain the significant pain relief. Final settings were PW=120us and rate=50Hz at 2.8 V. The abnormal movements diminished markedly and pain resolved almost immediately during stimulation.

Conclusions: This is the third case reported of PLMT successfully treated by spinal cord stimulation and the first to possibly result from a central etiology. Longer term follow up will be required before we can routinely consider it in the treatment of pharmacologically resistant cases.

Tu-347

Long term effects of pallidal deep brain stimulation in tardive dystonia

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Objective: Here we show the long term effect of continuous bilateral GPi DBS in tardive dystonia on motor function, quality of life (QoL) and mood.

Background: High frequency stimulation of the internal globus pallidus (GPi) is a highly effective therapy in primary dystonia. Recent reports have also demonstrated almost immediate improvement of motor symptoms in patients with tardive dystonia following pallidal deep brain stimulation (DBS).

Methods: Nine consecutive patients undergoing DBS for tardive dystonia were assessed during continuous DBS at three time points: 1 week, 3-6 months and last follow-up at the mean of 41 (range 18-80) months after surgery using established and validated movement disorder and neuropsychological scales.

Results: One week and 3-6 months following pallidal DBS motor scores BFMDRS (Burke-Fahn-Marsden Dystonia Rating Scale) were ameliorated by 56.4 ± 26.7 % and 74.1 ± 15.8 %, the disability scores by 62.5 ± 21.0 % and 88.9 ± 10.3 % and AIMS (Abnormal Involuntary Movement Scale) by 52.3 ± 24.1 % and 69.5 ± 27.6 %, respectively. At last follow-up this improvement compared with the presurgical assessment was maintained as reflected by a reduction of the BFMDRS movement by 83.0 ± 12.2 %, the disability scores by 67.7 ± 28.0 %, and the AIMS score by 78.7 ± 19.9 %. QoL improved significantly in physical components, while there was no change in the affective state. Furthermore cognitive functions remained unchanged compared to presurgical status in the long term follow up. No permanent adverse effects were observed.

Conclusions: We conclude that pallidal DBS is a safe and effective long-term treatment in patients with medically refractory tardive dystonia.

Tu-348

Deep brain stimulation (DBS) for hyperkinetic disorders

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Objective: Evaluate the results of Deep brain Stimulation in hyperkinetic disorders.

Background: DBS has been widely used in Parkinson's disease, tremor and dystonia with good surgical results. This study report the application of the DBS to hyperkinetic disorders considered as uncommon.

Methods: 7 patients with different pathologies (chorea/acanthocytosis, ortosthatic tremor, upper limb dyskinesia, Tourette syndrome (two cases), hemichorea/ballism and writing cramp with action tremor) were treated surgically with DBS in the Vop-Vim and GPi.

Results: All the patients improved the scores used for assessment in different percentage after surgery. The patient with hemichorea/ballism and orthostatic tremor had a benefit of 80% of improvement. The chorea/acanthocytosis and the upper limb dyskinesia had a benefit between 50-70% and Tourette cases and writing cramp a 50% improvement.

Conclusions: 1) The hyperkinetic disorders considered as uncommon may be improved with DBS. 2) The benefits obtained are not inmediate and programing need more time. 3) The Vop-Vim and the Gpi has been the targets selected.

Tu-349

Rescue of post-DBS benefit by correction of lead migration in a patient with dystonic head jerking

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Objective: To present a single unique case of ventral lead migration with imaging following globus pallidus interna (GPI) DBS for dystonia.

Background: Deep brain stimulation is an efficacious treatment for medication-refractory dystonia as well as for tardive and other dystonia subtypes. A worsening clinical response to DBS, coupled with evidence of a lead shift on imaging, serves as the hallmark for lead migration. Its incidence is likely under-reported as many centers do not routinely perform post-operative imaging.

Methods: A 26 year old right-handed man developed 'tremors' in his arms and hands following seven years of treatment with multiple neuroleptic agents administered for hallucinations accompanying psychotic depression. His most troubling symptom was painful nonfixed retrocollis which left his head at nearly 90 degrees to his spinal axis.

The movements evolved over a 12 month period to include the neck, arms and hands. He presented with a geste antagoniste, comprised of holding a cell phone to his left ear with his left hand, which improved his retrocollis enough to allow him to lie supine. DBS leads were implanted bilaterally into the GPI according to our standard protocol.

Results: Two months following activation of the DBS, he was able to sit for long periods and to walk without support. The retrocollic jerks diminished 40-50% and his neck pain was reduced. Six months postoperatively these benefits waned. Despite multiple programming adjustments of the active contact, voltage, and frequency, his clinical condition as assessed by the Unified Dystonia Rating Scale worsened. At 13 months following his implantations we removed and reimplanted the leads. A preoperative CT revealed his left and right electrodes to be 15.6mm and 4.6mm displaced, respectively. The left lead was coated with a mix of dura and scar tissue material and presented significant resistance when removed.

FIG. 1 (Tu-349).

Conclusions: Lead migration should be suspected when there is a loss of benefit following DBS implantation, especially in patients with frequent head movements. Imaging can be used as a screening measure to hasten diagnosis and treatment of this important surgical complication. In patients with neck hyperkinesis, as seen in our case, lead migration should be screened for as a serious and correctible complication.

Tu-350

Vim DBS in spinocerebellar ataxias with intention tremor

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Objective: To study effectiveness of Vim deep brain stimulation (DBS) on daily functioning in spinocerebellar ataxias (SCA) with intention tremor.

Background: Vim DBS is a procedure in the treatment of various types of tremor. There have been some case reports illustrating improvement of daily functioning after Vim DBS in SCA patients, and it has been proposed that Vim DBS could improve not only tremor but also ataxia in SCA.

Methods: Four patients with SCA (2 female and 2 males, age 45, 53, 57 and 64 years, 1 sporadic SCA and 3 familial SCA) were treated with Vim DBS, unilateral surgery for 1 patient and bilateral surgery for 3. Tremor severity and functional disability were assessed with Fahn-Tolosa-Marin Tremor Rating Scale.

Results: Vim stimulation alleviated intention tremor in all patients and led to substantial improvement in daily functioning. Although disability from ataxia remained, the disease progression appears to be stable or slower after the surgery. One case who underwent bilateral Vim DBS showed improvement in speech.

Conclusions: Vim DBS can be a useful treatment option for SCA patients with disabling tremor. Alleviation of tremor is a major contributor to improvement of daily functioning, and Vim DBS could improve ataxia by modifying activities in the cerebellothalamocortical projections or by activating cerebellar function through the cerebellothalamic afferents.

Tu-351

Deep brain stimulation in Huntington's disease – Report of a case

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Objective: To describe a Huntington's Disease (HD) patient who underwent bilateral deep brain stimulation (DBS) of the internal globus pallidus (GPi) with 18 months follow-up after surgery.

Background: HD is an autosomal dominant trinucleotide repeat disorder characterized by progressive psychiatric, cognitive and motor symptoms. Motor symptoms range from choreatic hyperkinesias to dystonia and akinetic-rigid symptoms. Medical therapy is limited and leads to symptomatic relief only. Indications for DBS in HD are rare, and there are only few reports on the efficacy of bilateral GPi stimulation in treating motor symptoms of HD.

Methods: A 30 year old male patient with a 9 year history of clinically manifest HD presented a severely disabling choreo-dystonic syndrome with consecutive injuries and multiple decubital ulcers at the back, the bottom and the head due to the excessive involuntary movements. Conservative treatment approaches including amantadine, olanzapine, tetrabenazine, tiapride, sulpiride and perphenazine in adequate dosages had been performed over a period of several years with only marginal effect on the motor syndrome. When the patient was admitted for treatment evaluation, the treatment regime comprised tetrabenazine (225mg/day), haloperidol (15mg/day), tiapride (300mg/day), and amantadine (400mg/day). Due to the insufficient motor symptom control by best medical treatment, bilateral DBS of the GPi was performed.

Results: During the post-operative period the choreo-dystonic movements improved markedly. At the 18-month post-operative visit, there was a continued positive effect on choreo-dystonic movements, whereas medical therapy could be reduced. The treatment regime then included tetrabenazine (150mg/day), olanzapine (10mg/day) and amantadine (300mg/day). Stimulation parameters were set at 2.0V and 130Hz on either side.

Conclusions: This case report demonstrates the efficacy of GPi stimulation in controlling the severely disabling movement disorder in a young HD patient. Overall, GPi stimulation was well tolerated, and the quality of life had markedly improved in this patient. The effects of GPi stimulation by DBS demonstrated in the present patient are in agreement with previously published case reports.

Tu-352

Long-term follow-up of pallidal deep brain stimulation for secondary dystonias

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Objective: To evaluate long-term outcomes of pallidal deep brain stimulation (DBS) as a treatment of advanced, disabling secondary dystonias.

Background: Pallidal DBS is a safe and effective treatment for advanced, medically refractory primary dystonia. The efficacy of

DBS in secondary dystonia is controversial and outcomes vary greatly with etiology.

Methods: We retrospectively reviewed the clinical outcome of 10 patients with secondary dystonias treated with GPi DBS for at least one year in two major movement disorders centers. Outcome was assessed based on the percentage improvement of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) at final follow/up visit as compared to baseline.

Results: Three patients had tardive dystonia, two dystonia secondary to perinatal hypoxia, two secondary to basal ganglia strokes and one each had dystonia secondary to post-encephalitic brain lesions, anoxic brain injury (prolonged status epilepticus) and methylmalonil aciduria. Patients with *tardive dystonia* showed best outcomes after DBS implants (65% on average, sustained at 3.5 years follow up), followed by patients with dystonia secondary to perinatal hypoxia (50% on average, up to two years follow up). All other patients improved between 30% and 50% (over three years of follow-up), with dystonic symptoms due to methylmalonil aciduria improving the least (28% at 2 years follow up). There was a negative correlation between age at onset, age at surgery and BFMDRS percentage improvement (Multivariate correlations, Spearman's Rho test, $p < 0.05$). There was no significant difference between BFMDRS percentage improvement of subjects with ($n = 7$) and without ($n = 3$) MRI brain lesions (47 ± 25 vs. 60 ± 35).

Conclusions: Among secondary dystonias, patients with *tardive dystonia* show best long-term outcomes after pallidal DBS. The limited number of patients and heterogeneous etiologies do not allow an evaluation of outcome predictors. However, younger age at onset and at surgery were associated with better DBS outcome. Further studies with larger patient populations are warranted to better understand the therapeutic role of DBS for secondary dystonias.

Tu-353

Longitudinal study of microlesion effect on bradykinesia after subthalamic nucleus deep brain stimulation surgery for Parkinson's disease

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(Aurora, Colorado)

Objective: To study longitudinally, off therapy, a quantitative measure of bradykinesia before and up to six months after bilateral subthalamic nucleus deep brain stimulation (STN DBS) surgery in patients with Parkinson's disease (PD).

Background: Alleviation of some PD symptoms immediately after STN DBS surgery is recognized and attributed to a "microlesion" effect. A significant improvement of bradykinesia is seen immediately after microelectrode recording with further improvement after placement of DBS electrode. We were interested whether this improvement persisted at the time of initial programming and after six months when the medications and DBS were withdrawn.

Methods: The root mean square of angular velocity (Vrms) of 10 seconds of repetitive wrist pronation-supination (qrWPS) was measured off therapy before surgery (24 hours off long acting (LA) and 12 hours off short acting (SA) medications), then immediately prior to initial programming session (off medications for the same time, three to four weeks after surgery) and after six months of DBS treatment (48 hours off LA and 36 hours off SA medications, off DBS for 17-24 hours). The data at all three points were collected in 49 cases. The mean interval between the pre-operative and last data point was 6.5 months, ranging from one to twelve months.

Results: The preoperative mean Vrms was 404.186 deg/sec. On the day of initial programming the mean Vrms was 481.65 deg/sec. That was significantly better than pre-operative ($p<0.011$), suggesting that the "microlesion" effect still persisted. At six months the mean Vrms was 269.336 deg/sec, worse than pre-operative and pre-programming ($p<0.001$), suggesting that the effect had worn off and the bradykinesia continued to progress.

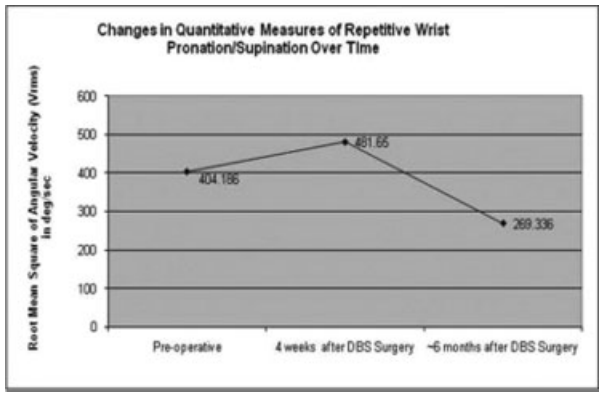

FIG. 1 (Tu-353).

Conclusions: Bradykinesia shows significant improvement at the time of initial programming three to four weeks after surgery. The effect disappears and bradykinesia progresses after six months of STN DBS. This suggests that "microlesion" has a significant, but short lasting effect on bradykinesia. This finding is clinically significant and has to be accounted for during initial programming and subsequent stimulation adjustments. More adjustments might need to be done within the first months after initiation of stimulation to counteract the progression of bradykinesia.

Tu-354

Number of microelectrode recording passes during bilateral staged vs. unstaged deep-brain stimulation surgery for Parkinson's disease

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Objective: To compare the number of microelectrode recording (MER) passes required to accurately localize the dorsolateral aspect of subthalamic nucleus (STN) on the side of the brain implanted first vs. second during staged vs. unstaged bilateral deep-brain stimulation (DBS) surgery for Parkinson's disease (PD).

Background: During stereotactic brain surgeries—DBS implantation in particular—brain shift can be significant enough to cause discrepancy between the calculated and actual location of the intended target. As a result, neurophysiologic mapping may become more difficult during prolonged surgeries. Additionally, patient fatigue impairs cooperation with testing, which may also obfuscate intra-operative monitoring. Therefore, more MER passes may be required to achieve adequate localization of the STN on the second side of the brain as compared to the first when the bilateral implantation is performed in one setting. In contrast, when bilateral placement is staged, fewer passes may be required for adequate localization of the STN.

Methods: We reviewed operative reports of 49 patients who had undergone bilateral STN-DBS surgery for PD. Of these, 25 were staged and 24 were implanted in single setting. The total number of MER passes needed to determine final placement of the DBS lead was calculated.

Results: The average number of MER passes needed for precise localization of STN during unstaged bilateral STN-DBS surgery was 2.5 on the side of the brain that was implanted first, and 3.16 on the side of the brain that was implanted second. With staged bilateral surgery the number of MER passes was 2.88 on the first side and 2.16 on the second. The number of MER passes on the second side of the brain was higher during unstaged surgeries (3.16 vs. 2.16, $p=0.089$).

Conclusions: Our data suggest that fewer MER passes are required for precise localization of the dorsolateral aspect of the STN

for DBS placement when bilateral implantation is staged. We postulate that high accuracy of DBS electrode placement in both hemispheres with fewer penetrations in the brain is achieved in staged implantation. Further investigation is required to establish the relationship between the number of MER passes, intra- and post-operative complication rates, and therapeutic effects of DBS.

Tu-355

Effects of thalamic deep brain stimulation for Tourette-syndrome on the sense of smell

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Objective: To explore the involvement of the thalamus in the sense of smell by assessing patients with Tourette syndrome (TS) who underwent thalamic deep brain stimulation (DBS).

Background: The thalamus is involved in the transmission of sensory information to the cortex across all modalities with the exception being the sense of smell. However, findings form microelectrode recordings in animals, odor dysfunction in humans suffering from focal thalamic lesion, and recent functional brain imaging studies point to an involvement of the medio-dorsal thalamus in the sense of smell. Deep brain stimulation (DBS) targeting the centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus is a promising treatment for patients with severe Tourette syndrome (TS) and can be used to further assess thalamic involvement in the sense of smell.

Methods: Four patients with TS treated with DBS were assessed with Sniffin' Sticks, a well established measure for assessing odor threshold (best score: 16) and odor discrimination (best score: 16). Two patients with TS were assessed with DBS-OFF and then with DBS-ON, while the others were assessed in reversed order. Performance with DBS-OFF compared with DBS-ON was analysed using the Wilcoxon-Test.

Results: Odor discrimination with DBS-ON (10.0 +/- 2.3) was significantly ($p = 0.04$) worse than with DBS-OFF (11.8 +/- 2.0), while odor threshold was not significantly different (DBS-ON: 6.5 +/- 1.5; DBS-OFF 7.2 +/- 2.3; $p = 0.55$).

Conclusions: Whereas none of the participants reported a disturbance of the sense of smell as a side effect of DBS, subclinical impairments can be found. As odor threshold was unaffected by DBS the results point to an involvement of the targeted thalamic area in cognitive functions related to the sense of smell. Studying a larger number of patients with TS and DBS is necessary to confirm present findings.

We-341

Ten to five years follow-up after subthalamic DBS for advanced Parkinson's disease

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Objective: to assess clinical impact of subthalamic DBS after long-term follow up.

Background: subthalamic DBS has proven its efficacy in controlling motor symptoms of Parkinson's disease. An increasing mess of data is growing concerning the long-term follow-up of implanted patients. The aim of this study was to retrospectively review the clinical data of patients operated on for bilateral subthalamic DBS at our Institution with more than 5 years of follow-up.

Methods: 95 consecutive patients were included in the study. Clinical assessment was performed at baseline, 1 year,5 years and at the actual time postoperatively, by means of UPDRS evaluation in both "on" and "off"-medication. L-dopa equivalent dosage, surgical and stimulation-related adverse events were considered.

Results: mean age at surgery was 58 years. Mean UPDRS III in "off"-condition was 42 (±15) pre-operatively, 19 (±13)at 1 year follow-up and 29 (±12) at 5 year follow-up. Baseline L-dopa equivalent dosage was 1400 mg at baseline, 650 at 1 year and 670 at 5 year. 24 patients experienced hypofonia/disartrhria, 5 had eyelid apraxia, 3 developed depression. 1 patient had an intracranial haemorrhage, 3 had infections requiring substitution of the prosthetic materials and 1 had an extension wire fracture.

Conclusions: subthalamic DBS is an effective and relatively safe treatment for advanced Parkinson's disease. The beneficial effect is maintained longer than 5 years, in both UPDRS III improvement and reduction of medications. However, worsening occurs over time, due to disease progression.

We-342

Dancing neurostimulators in a patient with myocolonus-dystonia (DYT11)

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Objective: To show a rare surgical complication in a patient with Myoclonus-Dystonia (MD) who received quadruple electrodes for DBS (VIM and GPI bilaterally; two Kinetras©).

Background: MD is a rare, hereditary movement disorder presenting with juvenile onset of myoclonus and dystonia. MD is known to be associated with disorders of the epsilon sarcoglycan gene and has been classified as DYT 11 in the genetic classification of dystonias. Clinical symptoms develop progressively, typically starting at early childhood leading to severe dysability. Therapeutic approaches include oral drug treatment, Botulinum Toxin injections and deep brain stimulation (DBS).

Methods: Case report

Results: The now 30 year old, female Patient developed symptoms of myclonus and dystonia in early childhood. First signs of the disease were myoclonic movements of the head and extremities. With disease progression in her teenager years dystonic symptoms developed including cervical dystonia and dystonic posturing of the extremities especially the left arm. The diagnosis of DYT 11 Dystonia was established by genetic testing at the age of 18. Therapeutic approaches (including Tetrabenazine, Artane, Clonazepam, Botulinum Toxin) showed insufficient symptom relief. The patient was evaluated for DBS in 2005 and received quadruple electrodes for DBS (VIM and GPI bilaterally) in 2006. Myoclonus decreased by 60% and cervical dystonia decreased by 70% (individual outcome will be presented elsewhere). There was only slight effect on the dystonic posturing of her left arm. Two years after surgery dysaesthesias and pain in the region of the neurosimulators developed. At presentation we noticed "up and down dancing" of the neurostimulators correlating to head rotation probably caused by shortening of the stimulator-wires due to connective tissue transformation. Surgical revision showed complete relief of these symptoms. (Video will be presented)

Conclusions: Quadruple electrodes for DBS (VIM and GPI) can lead to distinct reduction of myoclonus and dystonia in patients with DYT 11 MD. Rarely surgical complications develop in the course of the disease after implantation of neurostimulators. Technical improvement of stimulating devices (for example smaller devices) might reduce these complications.

We-343

Chronic thalamic stimulation in the management of multiple sclerosis related tremor

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Objective: To evaluate the effect of Vim stimulation in MS related tremor.

Background: About 50-75% of MS patients suffer from action tremor due to lesioned cerebellar pathways. In most cases, this tremor poorly responds to medication. Consequently, stereotactic surgery has been performed in patients with incapacitating tremors.

Methods: The position of the Vim relative to the intercommisural line was identified by CT-MRI image fusion, according to a stereotactic atlas. Electrode trajectories were planned to avoid the ventricle and blood vessels. Test stimulation for each electrode was performed every millimeter along the track within the Vim. During the operation, the patient was awake and the adequate placement of electrode was determined as the site in which the stimulation suppressed tremor with the lowest electrical intensity and without side effects. The patients were objectively assessed with the Fahn-Tolosa-Marin tremor rating scale and the TADL questionnaire preoperatively and six months after surgery.

Results: A 33-year-old male patient presented with impaired coordination, a worsening action tremor of the upper extremities and progressive gait ataxia at hospital four years ago. Diagnosis of primary progressive MS was made. All available medical treatment could not prevent disease progression to an EDSS score of 7.0. Bilateral Vim stimulation was performed leading to a significant reduction of tremor severity (-73%) and tremor related disability (-58%) 6 months after surgery. A 42-year-old male patient was admitted with a 13-year long history of relapsing-remitting and secondary progressive type of MS. Treatment resistant intention tremor of the upper extremities had increased over the last four years. The EDSS score was 6.5. Bilateral Vim stimulation resulted in a decrease of tremor intensity (-47%) and an improvement of the TADL score (-42%) 6 months later.

Conclusions: Vim stimulation has been effective for the suppression of tremor in our MS patients. Small studies demonstrated a lasting reduction in MS tremor up to 4 years, whereas improvement in functional ability did not maintain long-term due to the progression of other MS symptoms. Vim stimulation in MS related tremor is less validated than in essential or parkinsonian tremor and indication criteria need to be established.

We-344

Holmes tremor responding to dual electrode thalamic deep brain stimulation

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Objective: To report 2 cases of unilateral Holmes tremor successfully treated with dual electrode deep brain stimulation (DBS), targeting thalamus and subthalamic area.

Background: Holmes tremor is difficult to treat, particularly the kinetic tremor component–which often remains disabling despite good suppression of resting and postural tremor with Vim DBS.

Methods: Case 1 is a 28-year-old male who developed tremor in his left upper extremity during recovery from a severe traumatic brain injury. Case 2 is a 55-year-old female developed tremor after thalamic infarction at the age of 20 due to posterior cerebral artery occlusion. With the assistance of microelectrode recording and macrostimulation, one electrode was placed in the anterior portion of Vim, and another 2mm anterior in the ventral Vop extending down to the zona incerta and subthalamic area. Electrode location was confirmed with post-operative imaging.

Results: Stimulation at all sites (Vim, Vop, ZI and STN) resulted in tremor suppression, with the most effective single site being Vop. Dual Vop + Vim stimulation gave additive tremor reduction, but did not worsen ataxia. Polygraphic EMG-accelerometric tremor recordings were performed pre-operatively, and post-operatively both OFF and ON stimulation using clinically optimal stimulation parameters. The OFF stimulation findings were similar to those pre-operatively. In both cases, stimulation resulted in marked tremor suppression, including >85% suppression of kinetic tremor, and was associated with significant functional gains. Both patients turn off the stimulation during the night and neither patient has experienced loss of efficacy over 10-12 months follow-up.

Conclusions: We propose that dual thalamic stimulation can provide effective long term tremor suppression in a condition that is otherwise resistant to medical and standard surgical therapy.

Table (We-344). Amplitude change with DBS

	Case 1	A 28-year-old male post-traumatic tremor		Case 2	A 55-year-old female, posterior thalamic stroke	
Tremor	Amplitude (OFF stim, mm)	Amplitude (ON stim, mm)	benefit (%)	Amplitude (OFF stim, mm)	Amplitude (ON stim, mm)	benefit (%)
Resting	4.4	1.1	75	1.5	0.3	80
Postural	35	<1	>95	80	2.5	96
Drawing spiral	8.5	<1	>90	34	4.7	86

We-345

Pantothenate kinase-associated neurodegeneration dystonia treated with subthalamic nucleus deep brain stimulation. Preliminary report

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Objective: To evaluate safety and efficacy of STN DBS among PKAN patients.

Background: No protocol for pantothenate kinase-associated neurodegeneration (PKAN) has been established yet. The authors present a group of patients with diagnosed PKAN treated with subthalamic nucleus deep brain stimulation (STN DBS).

Methods: Material and methods: Three patients aged 12-24 with diagnosed PKAN were treated with STN DBS in 2008. Clinical status of the patients was evaluated with scales and video recorded. With direct and indirect method (MRI/CT) location of STN were identified. Under general anesthesia the electrodes were placed that was confirmed electrophysiologically. The electrodes ware externalized and LFP were evaluated. Position of the electrodes were confirmed with MRI. IPG were internalized on the third day following implantation of the electrodes.

Results: Clinical status of the patients improved in three months follow up. No complication related to the surgery were noted.

Conclusions: Further observations on larger group of patients are needed to evaluate advantage or disadvantage of STN target over GPi target for DBS implantation among PKAN patients.

We-346

Deep brain stimulation for dystonic cerebral palsy: Early experience

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Objective: To evaluate our early experience with DBS in children and young adults with dystonic cerebral palsy.

Background: Many patients with cerebral palsy have a significant component of dystonia which does not adequately respond adequately to other treatment modalities. Many patients have persistent dystonic movements that interfere with function despite treatment with pharmacologic interventions including trihexypnenidel and/or baclofen either orally or via intrathecal infusion.

Methods: 7 patients with dystonic cerebral palsy underwent bilateral GPi DBS implantation. Surgery was performed with patients awake (6/7) utilizing image guidance and MER monitoring. Intra-operative motor testing demonstrating passive muscle relaxation and/or improvement in active motor control further confirmed placement. Patient progress is tracked using multiple rating scales, patient, caretaker and therapist reports and video recording.

Results: Average age at DBS implant is 16.8 yrs (range 8-26). One patient (age 11) has been explanted secondary to infection and is not included in the current analysis. Follow-up has ranged from 2 -13 months. Younger patients (≤12 yrs; n=2) had less fixed contractures and lower disability scores at the time of implant. All families report some improvement by 6 months after implant. Average settings older patients: V=3; PW= 225; Rate=120 Hz; younger patients (4 leads) V= 3; PW= 210; Rate= 112.5 Hz.

Table (We-346). DBS Patients

	DMS (Dystonia Movement Sore)	DS (Dystonia Disability Score)	BAD (Barry Albright)	GMFCS (Gross Motor Function)
Baseline				
<12 yrs (4 leads)	90.8	20	22	4.5
>12 yrs (8 leads)	80.1	31.7	26.5	5
Follow-up				
<12 yrs (4 leads)	49	21	22	5
>12 yrs (4 leads)	48.5	24.5	24.5	5

Average rating scores.

Conclusions: Our findings suggest that for patients with dystonic cerebral palsy, DBS can alleviate some of the dystonia and improve function. All families report subjective improvement and a high degree of satisfaction with the surgical experience. DBS surgery can be successfully performed on young children while awake with an appropriate support team. MER is valuable to confirm anatomic localization, especially electrode depth. Used individually, current rating scales do not adequately characterize the dystonia-related disability associated with cerebral palsy. Earlier intervention in younger patients with less disability (contracture load) may be more beneficial for patients and aid in reducing caretaker burden.

We-347

Improvement of tics after subthalamic nucleus deep brain stimulation

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Objective: To describe the effect of subthalamic nucleus (STN) deep brain stimulation (DBS) on tics in a patient with Parkinson's disease (PD) and Tourette syndrome (TS).

Background: DBS of the medial thalamic nuclei and globus pallidus internus (GPi) has been tried in the treatment of refractory TS. STN is the target most commonly used for PD. More recently, STN DBS has shown to improve obsessive compulsive disorder, which is considered within the spectrum of TS.

Methods: A 38 year old man with an 8 year history of PD who developed dyskinesias and motor fluctuations underwent bilateral STN DBS. He also had a history of TS since childhood. At the time of surgery he had both motor and phonic tics. Tics were mild in intensity and caused moderate social disability.

Results: At one year follow up STN DBS produced a 57% improvement in the motor part of the Unified Parkinson's Disease Rating Scale and dopaminergic medication was reduced by 56%. Stimulation was monopolar, at 60 usec and 130 Hz. Amplitude was gradually increased up to 3.0 volts for the left electrode and 3.2 for the right. Tic frequency decreased by 97% as scored on a 10 minutes videotape by a blinded investigator. Switching stimulation off produced an immediate increase in tic frequency (from 5 tics to 48) but not a complete return to baseline pre-DBS. Immediate relief of tics occurred after turning the stimulation back on.

Conclusions: This report suggests that STN may be a potential target for DBS in TS. Although amelioration of tics can be in part explained by the chronic reduction of dopaminergic medication, the effect of STN stimulation on tics was evident after switching the stimulation off. From a pathophysiological perspective, stimulation of the STN would influence nearby structures such as the substantia nigra that have been related with stereotypies and tics. Furthermore, because of the small size of the nucleus, STN DBS might allow modulation of limbic and sensorimotor circuits more easily than DBS of the GPi or thalamus, which may be of relevance in TS.

We-348

Deep brain stimulation (DBS) of the globus pallidus interna (GPi) in satus dystonicus

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Objective: Status dystonicus is a relatively rare but devastating complication of dystonia which is refractory to medical treatment and associated with significant morbidity. A number of small case series point to pallidal stimulation as an effective treatment. We present our experience of 3 paediatric patients with secondary dystonia.

Background: Case 1 was an 11-yr-old girl with generalised dystonia secondary to cerebral palsy, who had 6 previous admissions in status and was ventilated on presentation. Case 2 was a 10-yr-old girl with Hallervorden-Spatz-Syndrome who had been on intra-thecal baclofen. Case 3 was a 4-yr-old boy diagnosed at the age of ten months with dystonia secondary to an unknown degenerative brain disorder. Neither were ventilated on presentation, but were heavily sedated on intensive care.

Methods: Under GA, bilateral Medtronic-3389 electrodes were inserted into the GPi. The stimulation parameters were optimised over the following months. Patients were assessed using the Burke-Fahn-Marsden Rating Scale (BFM) at baseline and a follow up of 34, 21 and 3 months for patients 1, 2 and 3 respectively.

Results: Refer to table 1. The first patient recovered from status 24 hours post-operatively, but four months later developed sepsis and the DBS system was explanted. She then remained status free for 2 years, was re-admitted with another episode and had revisional surgery. Subsequently she has been status free for 3 years. Our second patient recovered from status within 24 hours of surgery and has been stable for four years. DBS led to the resolution of status and a 75% improvement in her BFM movement sub-score. The last patient recovered from status within hours of surgery. His case was complicated by hydrocephalus that was treated with a VP shunt. There was an 85% improvement in his BFM movement sub-score and a significant reduction in his medication. Stimulator Off/On assessments revealed continuing benefit to his dystonia, resulting from pallidal stimulation rather than the resolution of hydrocephalus alone.

Table (We-348). Results

Patient	Pre-OP BFM M/D	Immediate Post-OP	3-6 Months Post-OP	Latest Follow-up	Medication Reduction
Patient 1	96/29	Recovered from status	90/29	90/29	Moderate reduction
Patient 2	120/29	Recovered from status	46/27	29.5/26	Minimal reduction
Patient 3	104/29	Recovered from status	15.5/29	n/a	Significant reduction

M = Movement D = Disability.

Conclusions: Although DBS may not result in a reduction in the BFM rating-scale; it is effective in reversing status where maximum medical management fails. As this is a rare and potentially fatal complication, modelling clinical trials is difficult and our evidence will be accumulated from small studies.

We-349

Actual performance of the rechargeable Medtronic implantable pulse generator (Activa-RC) for deep brain stimulation (DBS) therapy in dystonia: A case report

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Objective: To report on the frequency of recharging required by the newly developed rechargeable Medtronic implantable pulse generator (Activa-RC) for deep brain stimulation (DBS) therapy in dystonia.

Background: DBS has become a common therapeutic approach to patients with various forms of primary or secondary dystonia. The advertised battery life for the newly developed Activa-RC for DBS therapy is up to nine years, with daily or weekly recharge options. However, no published clinical data exists with regards to Activa-RC battery life and its recharging frequency requirements. Previous experience with non-rechargeable Medtronic implantable pulse generators (IPG: Kinetra, Soletra, Itrel) suggests battery performance can vary markedly with parameter settings (stimulation amplitude, pulse width, frequency and mode (bipolar/monopolar)).

Methods: We describe our experience with the first Activa-RC implanted for the treatment of dystonia by our group, involving a 32-year-old woman with bilateral GPi-DBS for generalised non-DYT1 dystonia.

Results: The patient underwent successful bilateral GPi-DBS implantation in March 2000 and subsequently the IPG (Kinetra) was replaced nine times up to August 2008, owing to high parameter settings (bipolar stimulation at 7.0V, 240μs and 180Hz bilaterally). To avoid the hazards involved in such frequent revisional-surgery an Activa-RC was implanted in January 2009. On the above parameters, recharging of the stimulator was required for 30 minutes per day. Excluding the costs of surgery and/or its complications, the cost for the 9 IPG (Kinetra) replacements required in this case amounted to €115,000. During the same nine year period the cost would have been €16,000, if as expected, one Activa-RC would have been required.

Conclusions: Activa-RC has the potential to greatly decrease the cost of treating dystonic patients with GPi-DBS but may require more frequent recharging than previously believed. This has life-style implications for the patient and may potentially have an effect on Activa-RC battery life. A long-term audit is needed to ascertain if Activa-RC lifespan is dependent on the recharging frequency and whether its clinical efficacy is generally consistent with previously published data for non-rechargeable IPG systems.

We-350

Camptocormia – Response to bilateral globus pallidus interna stimulation in three patients

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Objective: To document clinical, quality of life, neuropsychological, neurophysiological and dopamine transporter imaging data and responses to bilateral GPi stimulation in 3 patients with camptocormia.

Background: There are infrequent reports of the use of DBS in the treatment of camptocormia.

Results: Case reports: 1. Dystonic camptocormia. This 67 year old man presented with a 10 year history of camptocormia and jerky abdominal wall movements. His trunk flexed to 90^{o} on standing and jerking movements pulled his trunk forwards. There was no evidence of parkinsonism. Neuropsychological assessment was normal. MRI brain & spinal cord was normal. DaTSCAN showed mildly reduced tracer uptake in the right putamen tail. Surface EMG from rectus abdominis while standing revealed myoclonic bursts. Bilateral GPi DBS led to benefit within one month; at 6 months he could stand upright and walk unaided. Rectus abdominis myoclonic bursts were suppressed. Battery failure at 23 months led to immediate return of symptoms. 5 year follow-up assessment reveals sustained major benefit. **2. Camptocormia and parkinsonism.** This 63 year old woman was diagnosed with parkinsonism aged 47 years (left limb bradykinesia, reduced dexterity and dystonic posturing). Aged 49 years she acutely developed severe camptocormia. MRI brain & spinal cord was normal. DaTSCAN demonstrated markedly reduced basal ganglia tracer uptake bilaterally. Neuropsychological testing revealed mild depressive features. Bilateral GPi DBS was commenced at age 58 years. At 2-years, camptocormia was unchanged but modest improvement of her parkinsonism was noted. **3. Camptocormia and parkinsonism.** This 62 year old woman was diagnosed with parkinsonism aged 48 years when she developed right hand rest tremor. Aged 57 years she developed severe camptocormia and prominent motor fluctuations. DaTSCAN revealed reduced uptake in the putamen bilaterally. Neuropsychological testing was normal. 6 months after bilateral pallidal DBS surgery there has been modest improvement in her parkinsonism and in the degree of camptocormia.

Conclusions: In the patients whose camptocormia was associated with parkinsonism, response was poor in one case and modest in the other. Dramatic benefit in the patient with dystonic camptocormia is sustained at 5 year follow up.

We-351

Treatment of cervical dystonia with deep brain stimulation (DBS) of the globus pallidus interna (GPi)

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(Bristol, United Kingdom)

Objective: We present our experience with 6 patients who had severe, chronic and medication-resistant cervical dystonia, which on the background of previously published case series provides cumulative evidence for DBS as an effective treatment in this condition.

Background: Cervical dystonia is the most common form of focal dystonia and is usually complicated by pain in 75% of sufferers resulting in significant disability and deterioration in their quality of life. A significant proportion of cervical dystonia is medically refractory to treatments such as botulinum toxin. DBS is a safe and reversible procedure and it's application in the treatment of spasmodic torticollis has been well documented; however the largest open-label and blinded studies only look at small numbers of patients up to a maximum of ten.

Methods: Under GA, our modified Leksell frame was applied and high resolution MR images were acquired, enabling GPi target definition and planning. Bilateral Medtronic 3389 DBS electrodes were inserted using our unique guide tube method and these were then connected to a DBS Kinetra generator. The Kinetra generator was switched on immediately after surgery, and the stimulation parameters were optimised over the following weeks. Patients were assessed using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) at baseline and at a mean follow-up of 25.7 months.

Results: The primary outcome was the TWSTRS severity subscore and secondary outcomes included the disability, pain and total TWSTRS score. The TWSTRS severity subscore improved from a mean (SD) of 20(6.5) before surgery to 7.86(7) post DBS, with an average improvement of 64 %. The total TWSTRS score improved from 45(15) before surgery to 10.7(9.6); average improvement of 76.5%. The Disability and Pain subscores improved from 15.5(5.7) to 1.7(2.98); average improvement of 87.63%; and from 9.75(6.45) before surgery to 1.86(2.6); average improvement of 69.7%. One patient had a stimulation related complication which resolved completely.

Conclusions: Our results are comparable to other case series in the literature and support the safety and the efficacy of DBS of the GPi as a treatment for patients with severe cervical dystonia who remain resistant to optimum medical treatment.

Th-346

Effect of spinal cord stimulation on pain and axial symptoms in progressive supranuclear palsy with intractable low back pain

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Objective: To assess the effect of spinal cord stimulation (SCS) on postural instability/gait difficulty (PIGD) and intractable low back pain in patient with progressive supranuclear palsy (PSP).

Methods: We report a 71-year-old man with a 6-year history of PSP who was conducted SCS for intractable low back pain. His parkinsonian feature consisted of supranuclear gaze palsy, axial rigidity/

bradykinesia, and PIGD. He developed lumbago at his age of 60 and was diagnosed with lumbar spondylosis. The low back pain with refractory to analgesic therapy gradually deteriorated over past several years, and which contributed to the progression of PIGD. We performed SCS therapy for intractable low back pain and evaluated the influence on PIGD in addition to effectivity for pain. The assessment battery included the Wong-Baker Faces Pain Rating Scale, visual analog scale pain score, and PSP Rating Scale. Postural instability was also evaluated by using stabilometer.

Results: Dual quad electrode was placed in the posterior epidural space at the Th9 vertebra level. After successful SCS trial, pulse generator was implanted in the left side of the lateroabdominal subfascialis. The setting after the implant was pulse width of 360μs, frequency of 15Hz, and amplitude using four different programs varied from 1.8 to 3.2V. The patient experienced dramatic pain relief, and PIGD also showed a partial amelioration.

Conclusions: The lumbago in Parkinson-plus syndrome is a factor causing deterioration in PIGD. SCS is an additional therapeutic tool for improvement of ADL, especially in parkinsonian patients who show deterioration of axial symptoms associated with intractable low back pain.

Th-347

Neuropathic pain in Parkinson's disease: Prevalence, interest of DN4 questionnaire

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Objective: to determinate the prevalence of chronic pain in Parkinson's disease (PD), especially of neuropathic pain, and to evaluate the interest of DN4 questionnaire to identify neuropathic pain in PD.

Background: PD patients experience pain with various clinical descriptions and various etiologies. Some kind of pain is related to motor symptoms whereas other is primary sensory complaint unrelated to motor disability and looks like neuropathic pain. The prevalence of neuropathic pain in PD is not established, and the interest of the DN4 questionnaire to identify specific neuropathic pain in PD is unknown.

Methods: We prospectively included all non demented patients with PD, hospitalized in the Abnormal Movement Unit of Toulouse Hospital in France between February to December 2006. In all PD patients with chronic pain (at least 6 months), pain questionnaire was collected. PD related pain was defined if 3 of 5 following items were positive: 1 beginning with PD or related to motor fluctuations, 2 location of pain in the most affected limb, 3 improvement by dopaminergic agents, 4 no other etiology of pain, 5 patients attributing his pain to PD. Neuropathic pain was defined if 2 of the 3 following items were positive: 1 aching, numbness, tingling, burning, vibrating, lancinating pain, 2 non radicular systematization, 3 involving the most affected parkinsonian limb. In addition in all PD patients, DN4 questionnaire was performed.

Results: 135 PD patients were included. 71% of the PD patients were painful. Among these painful patients, 66% had PD related pain. Among PD related pain, 70% of the patients had neuropathic pain. Mean DN4 score was 2.4 ±2.02 in our population: 3.15 ±1.88 for the neuropathic pain group and 0.78 ±1.21 for non neuropathic pain group ($p<0,0001$). DN4 sensibility and specificity were respectively of 37% and 100% with the classical threshold of 4 and was respectively 63% and 100% with a threshold of 3.

Conclusions: Prevalence of chronic pain, especially neuropathic pain is high in PD. This is in accordance with previous studies that have shown lower objective and subjective pain thresholds in Parkinson's disease. Epidemiologic research on neuropathic pain in PD is hampered by lack of adequate case identification instruments since the DN4 seems to be specific but no sensitive to identify neuropathic pain in PD.

Th-348

The number and nature of emergency room encounters in patients with deep brain stimulators

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Objective: To review the number and nature of emergency room encounters in patients with deep brain stimulation (DBS) devices implanted for movement and neuropsychiatric disorders.

Background: As more and more DBS patients are implanted worldwide (currently >40,000), there will be a need to better understand the best management of these patients when they present to an emergency room setting.

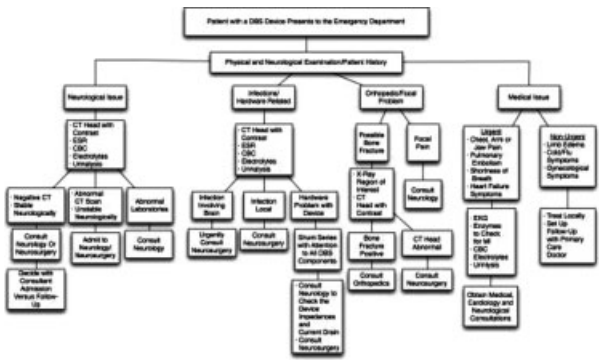

FIG. 1 (Th-348).

Methods: The cohort of encounters reviewed included 215 unique patients with DBS implantation who were identified using an IRB approved database and a paper chart review. Patients in the study included those implanted at University of Florida (UF), as well as those implanted at outside institutions, so long as they were followed at UF.

Results: The cohort included n=215 DBS patients. Of those who presented to the ER (n=55), the average age was 53.1 (range = 10-80 years). Reasons for presentation to the ER: neurological (54.6%), infections/hardware issues (27.9%), orthopedic/focal problems (10.5%), and medical issues (7%).

Table(Th-348). Complications Categorized by Major Subsets

Neurological (54.6%)	Infection/Hardware Issue (27.9%)	Orthopedic or Focal Problem (10.5%)	Medical Issue (7%)
Headache: 22.1%	Local Infection: 13.9%	Focal Pain: 10.5%	MI: 1.2%
Mental Status Change: 15.1%	Hardware Removal: 3.5%	Fracture: 0%	Swelling: 1.2%
Fall: 4.6%	Non-DBS Infection: 9.3%		Tubes (e.g. PEG): 4.6%
Hallucinations: 1.2%	Fever: 1.2%		
Syncope: 9.3%			
Panic Attacks: 2.3%			

Legend: This chart is a representation of the complications and percentages when divided into neurological, infection/hardware issue, orthopedic/focal problems, or a medical issue.

Headache was the most common complaint within the neurological category (22.1%), followed by change in mental status (15.1%), and syncope (9.3%). When examining the data by ER diagnosis, change in mental status occurred most commonly in Parkinson's disease (19.6%). Falls were most common in essential tremor (27.2%), and headache for the dystonia group (52.1%). 25.6% of all 215 patients presented to the ER at least once. Across all diseases, mental status change was the most common indication for an ER encounter (6%). Parkinson's disease patients most commonly presented with altered mental status (8%), essential tremor patients revealed a high preponderance of falls (6.5%), and dystonia patients tended to present with headache (7.1%). In total, 29 patients arrived at the ER for DBS related issues (23.2%).

Conclusions: A large number of patients with DBS will present to the ER for many reasons, the majority of which will not be related to their DBS device.

Table (Th-348). Relatedness of DBS Visits in the Limited Cohort Presenting to the Emergency Room

Disease	(n)	DBS Related	Unrelated to DBS
Parkinson's disease	125	29 (23.2%)	22 (17.6%)
Essential Tremor	46	6 (13%)	5 (10.9%)
Dystonia	28	19 (67.9%)	4 (14.3%)
Other (MS, OCD, Other Tremors)	16	1 (6.3%)	0 (0%)

Legend: This chart is a representation of the number of patients for DBS related and DBS non-related visits to the emergency room for specific diseases.

Neurological issues were the most common chief complaint, with individual differences depending on the underlying disease. DBS patients usually present to the ER for non-DBS related causes, and in addition to device management, regular standard of care should apply to treatment approaches.

Th-349

Chronic thalamic deep brain stimulation in ataxia telangiectasia (A-T; Louis-Bar-Syndrome)

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Objective: To evaluate the efficacy of chronic DBS of the nucleus ventralis intermedius (VIM) in cerebellar symptoms in a patient with genetically proven ataxia telangiectasia (A-T; OMIM 208900).

Background: VIM DBS is a well established treatment for essential tremor and recently has been shown to be effective in various other types of tremor. In cerebellar disease DBS may also be successful, although the clinical differentiation between tremor and ataxia often is difficult and safe predictions on stimulation effects can barely be made.

Methods: This 71-year-old woman developed coarse resting and action tremor in her right leg at the age of 32, which gradually generalized and later on was associated with dysarthria, bradykinesia, gait ataxia, intention and head tremor, titubation, and dystonic elements. In her sixties, she became wheelchair bound. Tremor was disabling making even eating and drinking on her own impossible. Various oral drugs failed, so she consented to undergo DBS. Preoperatively, she showed severe gait ataxia, marked titubation and head tremor, 4-5 Hz, 20-30 cm amplitude resting and postural tremor of the upper extremities, action and intention tremor indistinguishable from kinetic ataxia, and marked dysarthria. Quadripolar electrodes were placed stereotactically bilaterally in the VIM. During test stimulation, resting tremor vanished immediately and postural tremor improved. Postoperative stereotactic CT confirmed accurate placement of electrodes.

Results: The most responsive symptoms were distal tremors (action > postural > resting). Titubation moderately improved, but required high voltages which as a side effect reproducibly worsened dysarthria and weakness and some instability of her left leg. Postural instability, gait ataxia, and speech did not improve. With K1 3.5 V, 210 ms, 130 Hz, 0 -, 1 +, and K2 3.5 V, 210 ms, 130 Hz, 4 -, 5+ resting tremor amplitude was 5 cm, postural tremor was suppressed for 10 s until 5-10 cm postural tremor recurred. Action tremor was well controlled so that she could feed and drink and wash her upper body on her own again. 12 months follow-up revealed a sustained effect.

Conclusions: VIM DBS is also lastingly effective in complex cerebellar tremors, but suppresses distal components best. Titubation may improve, but requires high charge densities.

Th-350

Motor Gpi DBS for rare movement disorders. Reports of three cases of chorea and NBIA

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Objective: to assess the efficacy of motor Gpi bilateral DBS for highly disabling movement disorders refractory to conservative therapies.

Background: During recent years DBS has been proposed as add-on therapy for multidisciplinary treatment regimes for complex movement disorder and neuropsychiatric diseases such as Tourette syndrome, refractory obsessive-compulsive disorder, refractory depression. Treatment refractory chorea and neurodegeneration with brain iron accumulation (NBIA) have been previously treated with DBS aswell. We describe our experience with two patients affected with important choreic manifestations and one patient diagnosed with NBIA characterized by dystonia and parkinsonian tremor.

Methods: The first patient was a 28 years-old male with juvenile–Westphal variant–Huntington's chorea, with important psychic deterioration together with rigidity, and choreic movement of the trunk and of the limbs preventing him from walking. The other patient was a 35 years-old female affected by choreic movements of the upper limbs determining important limitations of all the daily activities. She previously undergone right thalamotomy by age 16 with temporary amelioration of symptoms. The third patient was a 38 years-old female diagnosed with NBIA after multiple MRI controls documenting brain accumulation in Gpi bilaterally.

Results: The three patients were treated with multiple drugs therapies, and with Botulinum toxin type A intramuscular infiltration without durable improvement of their clinical pictures. Bilateral DBS at the Gpi posterior (motor) part was undertaken for the three patients. Improvement of the clinical picture was documented for the three patients.

Conclusions: our encouraging results show palliation of symptoms and confirm DBS as a significant adjunctive therapeutical instrument with low morbidity in experienced hands, that has to be considered also for those patients whose general condition could rise problems concerning long-term conservative treatments.

Th-351

Nucleus accumbens (NAC) deep brain stimulation (DBS) in refractory Tourette syndrome (rTS): Our experience with de-novo and rescue surgery in 4 patients

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Objective: to discuss our results with NAC DBS for rTS as a treatment modality tailored on clinical picture of the patient.

Background: Invasive treatment for Gilles de la Tourette syndrome (TS) has shown interesting results in a number of published reports, and is evolving into a promising therapeutic procedure for those patients demonstrating disabling clinical pictures, who are refractory to conservative treatments. There are however important issues concerning the stimulated target, with different nuclei currently under investigation. An important question concerns whether the clinical features of the syndrome can be matched with a specific target. In this sense, deep brain stimulation for Tourette syndrome may in the future be tailored utilizing specific target regions for individual clinical manifestations. In our early experience we failed to address non-motor clinical symptoms with the thalamic target in Tourette syndrome.

Methods: follow-up evaluation showing failure of the thalamic DBS to address comorbid manifestations of TS was considered an indication to rescue procedure with NAC DBS.

Results: We therefore explored the option of a "rescue" procedure for our Tourette patients with persistent obsessive-compulsive disorder following Ventrooralis/CentroMedianus-Parafascicularis deep

brain stimulation. Following two cases where rescue leads were effective, two additional procedures were performed (Anterior Limb of the Internal Capsule plus entrooralis/CentroMedianus-Parafascicularis and Anterior Limb of the Internal Capsule de novo) with perhaps slightly better results on comorbid obsessive-compulsive disorder, although the number of observations was notably low.

Conclusions: The effects seen with using Anterior Limb of the Internal Capsule were less than hypothesized for use in Tourette syndrome.

Th-352

Unsuccessful revision of Vim DBS leads in essential tremor (ET) patients with late failures: Three cases

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Objective: To report outcome in 3 patients with ET treated with Vim DBS with good initial response followed by worsening of tremor, unimproved by revising lead location.

Background: ET consists of both postural and kinetic tremor. The kinetic component can be severe, progress with age and cause functional disability even in patients receiving Vim DBS. Though progression of disease is likely the main contributor, tolerance and suboptimal lead location are offered as alternative explanations for worsening tremor in Vim DBS patients.

Methods: Case report and literature review.

Results: We operated on 3 patients with advanced ET, with documented effective and stable suppression of postural and kinetic tremor with Vim DBS, both intraoperatively and postoperatively for a mean duration of 15 months (range 12-18 months). From this point on, these patients showed waning tremor suppression despite increasing stimulation (mean voltage 4.3V, PW 60-90), prompting repeat neuroimaging to assess lead location. In all 3 cases, lead locations were thought to be too lateral and in 2 cases too posterior to achieve a good effect based on stereotactic coordinates relative to the posterior commissure. Unilateral revision of the lead was made contralateral to the dominant hand in all 3 cases. This led to modest or transient improvement in kinetic tremor control (TRS items 11,12,15), despite good intraoperative tremor control. Tremor cell identification was uncertain in two cases. Decisions on lead location were therefore dependent upon effects of intraoperative macrostimulation. Lead tip location was revised to a more medial, anterior and inferior location. Details of lead location at AC-PC plane and at active contact will be shown.

Table (Th-352). Summary of revisions of VIM DBS for late failures in ET

Case	Age/disease duration	Baseline/on DBS modified TRS score	Lead tip rel to PC before revision	Lead tip rel to PC After Revision	Interval Between 1st surgery & revision	Revision intraop findings	Pre- revision/ Post- revision on DBS mTRS score
1	68, >40y	19 → 6; rest 0→0; post 3→1; FNF 4→1; writ 4→2; spiral 4→1; pour 4→1	x=15, y=4, z=-6	x=9, y=6, z=-6.5	7y	Good tremor control at 3V 0+ 1- PW 90 identified 185Hz, no tremor cells	n/a → n/a*; rest 0 → 0; post 0 → 0; FNF 1 → 1; writ 2 → 2; spir -- → --; pour 4 → 2
2	64, >45y	10→ 4; rest 0 → 0; post 2→0; FNF 2 → 0; writ 2 → 2; spir 2 → 1; pour 2 → 1	x=15, y=3, z=4	x=8, y=7.5, z=-2	8y	Good tremor control, no tremor cells identified	18 → 11*; rest 0 → 0; post 3 → 1; FNF 4 → 2; writ 4 → 3; spir 4 → 2; pour 3 → 3
3	69, 30y	N/A, operated on elsewhere	x=15, y=8, z=-1	x=12.5, y=8, z=-3	8y	Tremor cells identified, good tremor control	20 → 14; rest 1 → 0; post 3 → 0; FNF 4 → 2; writ 4 → 4; spir 4 → 4; pour 4 → 4

PC, posterior commissure; mTRS, modified Fahn Tolosa Marin Tremor Rating Scale score (dominant hand only, items 5/6, 11, 12, 15); *only transient benefit lasting 2–3 wks between programming sessions.

Conclusions: Three patients with ET developed severe kinetic tremor following an initial positive and durable response to DBS which did not improve after lead location was revised to a more medial and anterior position. Our experience supports the idea that suboptimal lead location combined with progressive disease are both likely to contribute to late failures of VIM DBS for tremor. Revision of DBS lead location for waning tremor suppression should be weighed carefully given the difficulty we encountered assessing correct lead location with intraoperative electrophysiology.

Th-353

The effect of GPi-DBS combined with thalamotomy in patient with secondary focal dystonia

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Objective: The effect of Gpi-DBS combined with thalamotomy to the secondary focal dystonia.

Background: Deep brain stimulation (DBS) has been applied to medically refractory dystonia for recent decade, although its primary mechanisms of action are yet poorly understood. At this time, patient with primary generalized and segmental dystonia and patients with complex cervical dystonia are thought to be the best candidates for pallidal DBS. Nevertheless, outcome of DBS for patients with secondary dystonia is controversial.

Methods: Case report.

Results: A 31-year-old man had suffered from the involuntary movement of right arm since 12 years old. His past medical history was unremarkable. There was no history of other psychiatric illness, antipsychotic drug use, or familial illness, except a mild head contusion history at 6 years old. At neurological evaluation, he exhibited repetitive involuntary movement of right arm associated with rotational torticollis and elevation of the right shoulder. His intelligence was normal. Routine blood studies, celuroplasmin and gene study for DYT1 and Huntington gene were normal. Brain MRI revealed focal high signal changes at left peritrigone area in T2 image, suggesting of unusual white matter injury or demyelination. MR spectroscopy demonstrated the non-specific decrease of N-acetylaspartate, which suggested of non-tumorous lesion. He underwent frame-based, MRI-guided stereotactic placement of DBS leads into the globus pallidus internus and stereotatic left thalamotomy. There was an immediate and dramatic reduction of abnormal movement after surgery.

Conclusions: Outcome of DBS for secondary dystonia has been less predictable. One possible predictive factor has been suggested is the presence of a normal structural brain MRI. Our case showed dramatic improvement of dystonia in spite of structural abnormalities.

Th-354

Outcome of pallidal stimulation in primary and secondary axial dystonia

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Objective: Axial dystonia is a rare disorder of sustained, involuntary contractions of the muscles of the axial skeleton. Primary axial dystonia is generally seen in children. Secondary axial dystonia may be tardive, usually following neuroleptic administration. The resulting severe abnormalities of both sitting and standing posture are very significantly disabling as may be seen in our two videos.

Background: Bilateral stimulation of the globus pallidus internus (GPi) with deep brain electrodes has been successfully used for other types of primary dystonia and secondary dystonia including tardive dystonia.

Methods: Two patients, one with tardive axial dystonia and one with late onset primary axial dystonia underwent insertion of bilateral globus pallidus internus deep brain stimulator electrodes.

Results: Case 1. A 55-year-old man with medically refractory tardive dystonia and dyskinesia following treatment with neuroleptics

for 22 years for a schizophrenia-like illness, which was well controlled on olanzapine. He complained of facial grimacing, neck extension, jerky back extension and recurrent falls. He felt unable to go out, run or work. Examination showed severe dystonia and dyskinesia. There was blepharospasm, marked retrocollis and abnormal gait. Bilateral GPi stimulation at 2 volts bilaterally (60 μs, 130 Hz) lead to a marked reduction in dystonia. Walking distance is about 1 mile. This difference is illustrated with pre- and post-operative videos. He has now found voluntary work. **Case 2.** A 50-year-old with a 10 year history of progressive primary axial dystonia. This mainly manifested as axial retrocollis, present when sitting but worse on standing so that his spine was severely, painfully arched. He could not walk around his house nor could he eat, drink, wash or dress without help. After bilateral GPi stimulation at 2 volts (450 μs, 140Hz) gait was significantly improved. Pre- and post-operative videos are supplied for comparison.

Conclusions: Both patients showed a functional improvement in axial dystonia following pallidal stimulation. We can confirm the favourable outcome seen in other reports.

Th-355

Effects of pallidal deep brain stimulation in primary dystonia: A case report

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Objective: To describe a patient affected by primary generalized dystonia (not DYT1 carrier) who markedly improved after chronic bilateral deep brain stimulation (DBS) of the globus pallidus internus (GPi).

Background: Deep-brain stimulation is a reversible neurosurgical procedure that has been used for the treatment of pharmacoresistant primary generalized dystonia.

Methods: A 16- year old male patient with generalized DYT1 negative juvenile onset dystonia was followed up for two years postoperatively. He was videotaped, the severity of dystonia was evaluated with the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) before and at several intervals after surgery during neurostimulation. He had bilateral implants; DBS settings were increased to achieve best clinical response; typical parameters were 120 sec and 145 Hz at maximum tolerated voltage in a unipolar mode.

Results: Three weeks after surgery we observed statistically significant improvement in his rating scores(BFMDRS total score 77 preoperatively/24 postoperatively). Dystonic postures and movements of the axis and limbs responded to DBS while speech and swallowing were unchanged.

Conclusions: Our experience confirms that GPi DBS is an effective treatment in a selected patients with medication refractory primary generalized dystonia.

Th-356

Pedunculopontine nucleus stimulation in pure akinesia with gait freezing

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Objective: To report the 6-month outcome of a patient with pure akinesia with gait freezing (PAGF) who was treated surgically with bilateral stimulation in the region of the pedunculopontine nucleus (PPN).

Background: PPN stimulation has been proposed as a surgical target for the treatment of drug-refractory freezing in Parkinson's disease. Freezing of gait is a particularly disabling feature of PAGF. PAGF is defined by the presence of gradual onset of freezing of gait or speech; absent limb rigidity and tremor; no sustained response to levodopa; and no dementia or ophthalmoplegia in the first five years of disease and is most often associated with underlying PSP-tau pathology.

Methods: This 74 year old man was seen 8 years after first developing progressive gait slowing, rapid hypophonia and micrographia. He had never had any response to dopaminergic medications and satisfied the proposed clinical diagnostic criteria for PAGF. A cardiac MIBG scan was normal, and brain MRI showed only mild generalised atrophy without focal changes or severe vascular disease. Gait evaluation prior to the operation included the Freezing of Gait Questionairre (FOGQ) and a simple "figure of 8" obstacle path. A double blinded gait evaluation was undertaken in the 'ON' and '36 hours OFF' stimulation state six months following the operation using the same obstacle path.

Results: The pre-operative FOGQ score was 54. There were no complications from the surgical procedure. Post-operative imaging confirmed the location of the electrodes within the region of the PPN. Weekly programming sessions were undertaken, adjusting the low frequency stimulation of the PPN (range 20-30Hz), different electrode combinations (monopolar and bipolar) and voltages (0-3.5V). At 3 months post-implantation the FOGQ improved to 32. There was, however, no subjective improvement in function despite this. Although the patient tended to freeeze less when walking outside, he continued to have difficulty in the small areas at home and when walking through doorways. On blinded gait analysis the patient did not notice any differences in his walking. Blinded clinical evaluation was unchanged from the pre-operative state.

Conclusions: This single case report has not shown any clinically significant improvement in freezing, start hesitancy or mobility with low frequency PPN stimulation in a patient with PAGF who has never respoded to dopaminergic medications.

TICS/STEREOTYPIES

Mo-355

Long-term outcome of thalamic deep brain stimulation in two patients with Tourette syndrome

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Objective: To report on the long-term (6 and 10 years) outcome in terms of tic reduction, cognition and mood and side-effects of medial thalamic DBS in two previously described Tourette patients.

Background: Thalamic deep brain stimulation for intractable Tourette syndrome has been introduced in 1999 by Vandewalle et al. and in 2003 the efficacy and safety of this intervention has been reported up to five years of follow-up. Since then multiple case reports with beneficial tic reduction have been published.

Methods: We compared the outcome of two patients at 6 and 10 years after surgery with their preoperative status and after 8 months and 5 years of treatment, respectively. Standardized video recordings were scored by three independent investigators. Both patients underwent (neuro)psychological assessment at all time points of follow-up.

Results: Tic improvement observed at 5 years in patient 1 (90.1%) was maintained at 10 years (92.6%). In patient 2 the tic improvement at 8 months (82%) was slightly decreased at 6 years (78%). During follow-up, case 1 revealed no changes in cognition, but case 2 showed a decrease in verbal fluency and learning which was in line with his subjective reports. Case 2 showed a slight decrease in depression but overall psychopathology was still high at 6 years after surgery with an increase in anger and aggression together with difficulties in social adaptation. Besides temporary hardware related complications no distressing adverse effects were observed.

Conclusions: Bilateral thalamic stimulation may provide sustained tic benefit after at least 6 years but overall improvement is not obvious. To maximize overall outcome attention is needed for postoperative psychosocial adaptation, already prior to surgery.

Mo-356

Striatal cholinergic neurons, a key for stopping stereotypies

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Objective: Determine the role of cholinergic interneurones of the dorsal striatum in cocaine-induced stereotypy.

Background: Stereotyped behaviour is a key symptom of various diseases such as stereotypy movement disorder, Tourette syndrome and TICs. In a rat model of cocaine-induced stereotypy we have shown a functional imbalance between the limbic/prefrontal (PF) and the sensorimotor basal ganglia circuits. One feature of this imbalance is an increase of dopamine (DA) and a decrease of acetylcholine (ACh) release in the limbic/PF but not in the sensorimotor territory of the dorsal striatum, during strong cocaine-induced stereotypy. In the present study we focused on the mechanisms contributing to the arrest of stereotyped behaviour by analysing: 1- the striatal DA and ACh releases during the time when stereotypy decreases and stops 2- the impact of striatal cholinergic transmission on the duration of stereotypy.

Methods: Combined behavioural, neurochemical (release of DA and ACh using microsuperfusion device *in vitro* and *in vivo*) and pharmacological (raclopride, scopolamine, injected during the strong cocaine-induced stereotypy either intraperitoneally (i.p.) or in the limbic/PF territory of the dorsal striatum; AF64A, a cholinergic toxin injected bilaterally in the limbic/PF territory) approaches were used to analyse the role of striatal cholinergic interneurones in the rat model of cocaine-induced stereotypy (sensitization with cocaine 25 $mgKg^{-1}$: 2 injections i.p. per day, 5 days; withdrawal: 4-6 days; challenge injection: cocaine 15 or 25 $mgKg^{-1}$).

Results: When the intensity of stereotypy decreased until its end, while DA release remained high, the ACh release came back to its basal level in the limbic/PF territory of the dorsal striatum. By blocking the DAD2 inhibitory control on ACh neurones, raclopride at a low dose restored the level of ACh release in the striatum and stopped the stereotypy around 5min after its injection. In contrast, blocking the postsynaptic effect of ACh by scopolamine as well as lesioning cholinergic interneurones increased the duration of cocaine-induced stereotypy.

Conclusions: Our data suggest that cholinergic interneurones of the limbic/PF territory of the dorsal striatum play an essential role in stereotyped behaviour.

Mo-358

The execution of unimanual and bimanual repetitive finger movements in patients with Tourette syndrome

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Objective: To analyze the performance of repetitive, externally paced, opposition finger movements in patients with Tourette syndrome (GTS).

Background: GTS is a neurodevelopmental disorder characterized by the presence of vocal and motor tics. The pathophysiology of GTS is uncertain even if an abnormal organization of areas involved in motor control (sensorimotor cortex, basal ganglia, and corpus callosum) has been suggested. The characteristics of the execution of unimanual and bimanual finger opposition movements in GTS have not been investigated so far.

Methods: Eight patients with GTS (mean age 11.8 $\pm$ 2.95 years) and 13 age-matched normal subjects (NS) (mean age 12.4 $\pm$ 2.06) entered the study. All the subjects were right handed. They wore a sensor-engineered glove on both hands and were asked to perform the following tasks: 1. sequential unimanual task (right hand, uni-SEQ) of opposition of the thumb to index, medium, ring and little finger, following an acoustic cue at 1-1.5-2 Hz; 2. bimanual sequential task with both hands (bi-SEQ). Inter tapping interval (ITI), Touch duration (TD) and percentage of correct sequences were analysed.

Results: In the uni-SEQ task, patients with GTS showed an increased TD ($P<0.05$) and a decreased ITI ($P<0.05$) at all the rates compared to NS. The percentage of correct sequences was lower in GTS than in NS ($P<0.05$). During the bi-SEQ task, no difference was found between GTS and NS in the two phases of movement (ITI and TD). NS showed, at all the rates, a lower number of correct sequences performed with the left hand compared to the right hand, GTS patients performed with the left and right hand the same number of correct sequences at 1.0 and 1.5 Hz.

Conclusions: When performing repetitive finger opposition movements with their dominant hand patients with GTS showed subtle alterations in the touching phase and performed a lower number of correct sequences. Differently, when required to perform the task bimanually, GTS patients showed a better performance. These preliminary results suggest that patients with GTS have an alteration in the organization of movement during the execution of unimanual tasks, while during the execution of a bimanual task they present an enhanced control of movement.

Mo-359

The use of levetiracetam to treat tics in children and adolescents with Tourette syndrome

Y.M. Awaad (Riyadh, Saudi Arabia)

Objective: To evaluate the effects of levetiracetam on motor and focal tics, behavior, and school performance in children and adolescents with tics and Tourette syndrome.

Background: Some drugs currently used to treat tics have drawbacks, including the risk of side effects such as tardive dyskinesia. Therapeutic options with better safety profiles are needed. Levetiracetam is an anti epileptic drug with atypical GABAergic effects that might be beneficial for this indication.

Methods: 24 patients, age:=; 18 years, with tics and Tourette syndrome were enrolled in this prospective, double- blinded placebo randomized study for 8 weeks. Each group had 12 patients. The initial starting dose of levetiracetam was 250 mg/d. The dosage was titrated over 3 weeks to 1,000 to 2,000 mg/d. Clinical outcomes were assessed with the Clinical Global Impression Scale, Yale Global Tic Severity Scale, and Revised Conners' Scale.

Results: 10 out of 12 patients in the Levetiracetam group showed improvements based on all of the scales used and 4 patients improved with regard to behavior and school performance. 2 patients dropped out. 9 patients out of 12 patients in the placebo group showed no improvement, one patient showed a great placebo effect, and 2 patients dropped out of the study. Levetiracetam was generally well tolerated. 2 patients discontinued because of exaggeration of pre-existing behavioral problems.

Conclusions: Levetiracetam may be useful in treating tics in children and adolescents. Given its established safety profile, levetiracetam is a candidate for additional evaluation.

Mo-360

Tourette syndrome in the movies: A critical review

B.R. Barton, G. Stebbins, K. Kompoliti (Chicago, Illinois)

Objective: To analyze portrayals of Tourette syndrome (TS) in movies.

Background: Neurological disorders are portrayed in film with varying degrees of accuracy, as demonstrated in studies evaluating movie portrayals of coma, epilepsy, and dementia. Of all movement disorders, TS lends itself to frequent depiction given the often dramatic manifestations of tics or their accompanying comorbidities.

Methods: Using internet search engines, we identified 23 full-length television or theatrical-release movies released since 1991, excluding documentaries, specifically depicting characters with TS or referencing TS. 17 were obtainable for review. 4 only briefly referenced TS with comedic references to coprolalia and were not included in the analysis. The remaining 13 films, featuring portrayals of 14 TS characters, were independently analyzed by two movement disorders physicians using pre-defined criteria. Accuracy of tic depiction was assessed on a scale of 0 (inaccurate) to 10 (highly accurate)

for motor tics, vocal tics, and medical context. An score of 7 was considered the minimal score for "medical accuracy."

Results: 8 films had major recurring characters with TS, and 5 had briefer depictions. Average accuracy of tic depiction was: Motor 7.0 (SD 2.9), Vocal 6.2 (SD 3.6), and medical context 4.3 (SD 3.5). The most common comorbidities depicted were OCD (64%) and affective disorder (43%). Films portrayed TS as predominately a male disorder (71%), involving eyes (92%) and neck (100%). Estimated proportion of portrayed motor tic types was 82.5% simple vs. 17.5% complex, and vocal tic types 48% simple vs. 48% complex. Whereas coprolalia is an uncommon feature of TS, it was highly represented in movie portrayals of TS, occurring in 8/12 characters with vocal tics. Neurobehavioral comorbidities overshadowed tics in 4 TS characters. Only 3 films were deemed minimally fair and accurate depictions of TS by both reviewers ($>$ 7 mean accuracy score on the three indices).

Conclusions: While increasing public awareness, few films portraying TS are medically accurate. The high prevalence of coprolalia, movement and vocalization patterns atypical of tics, and exotic comorbidities misrepresent TS in the movies and create the risk of miseducation.

Mo-361

Coordinated care models for Gilles de la Tourette syndrome: Impact on co-morbidities and patient health perception

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Objective: To assess two different models of patient care for children with Gilles de la Tourette syndrome (GTS).

Background: Children with GTS seen in our clinic are typically evaluated by a neurologist and a neuropsychologist, who develop a treatment plan. Patients are seen in quarterly follow-up and parents are expected to follow through independently with treatment recommendations. We considered that a patient liaison who proactively contacted parents to encourage follow through would improve clinical outcomes. Consenting families were randomized to either: 1) standard clinic care coordinated by the neurologist and neuropsychologist, or 2) standard clinical care supplemented by the addition of a clinical coordinator, who checks on the status of the patient on a monthly basis.

Methods: 56 children with GTS seen at baseline were assessed using the Yale Global Tic Severity Scale, WISC-III Coding, WISC-III Symbol Search, Underlining Test, Sentence Memory, and Fluency Test. Behavioral scales included the Leyton Obsessional Inventory, Children's Yale-Brown Obsessive-Compulsive Scale, ADHD Rating Scale, Personality Inventory for Children, TNO-AZL Children's Quality of Life Scale (TACQOL), and a measure of general health perception, the Home Side Effects Rating Scale. Parents in the coordinator group were contacted by an independent clinician once a month to check on the child's status and encourage following through with the treating physician's recommendations. The above measures were repeated after 12 months.

Results: The mean total time invested by the liaison coordinator over the 12 months was 9.2 hours per patient. In spite of this involvement, for 29 measures, there was no significant improvement for the coordinator group. The coordinator group did significantly improve on two attention tests (WISC-III Coding and Symbol Search) but also worsened on the ADHD rating scale.

Conclusions: The addition of a clinical liaison to the treatment team did not substantially improve the impact of co-morbidities, quality of life, or perception of health status in patients with GTS. Given the personnel and financial investment of this model, we cannot consider this to be a useful adjunct to the care already provided by the neurologist and neuropsychologist.

Mo-430

Myobloc responsive tics triggered by unpleasant sensation: A report of 2 cases

M.V. Alvarez (Lackland AFB, Texas)

Objective: To discuss safety and efficacy of Myobloc in Tics triggered by unpleasant sensation.

Background: Tics are voluntary repetitive movements in response to an urge. Although seen rarely, complain of a disabling and unpleasant sensation, similar to an "itch", which always preceded the tic movements had been described. This sensation would thus be viewed as a trigger for the movements. While not the first treatment of choice, Botulinum Toxin has shown positive effects in the treatment of some refractory tics.

Methods: Case report.

Results: Case 1 48 year old school teacher with history of left mouth, neck, and shoulder "shrug" triggered by intractable left scapular pruritus for 30 years. Except for the embarassing, and disfiguring constant "shrugging", she didn't find any other effective treatment that would decrease her pruritus. Her examination revealed repetitive pulling/shrugging of her left platysma, lower mouth, and shoulder. Myobloc was injected to the site where she complained of pruritic sensation. She reported relief: sensory urge and movement reduced by 50%. With no reported side effect, she continues to receive injection every 12-14 weeks for 12 months now. Case 2 28 yo man with Arnold Chiari-II presented with 15 year history of neck shaking triggered by an unpleasant urge "pinching" sensation to the right side of his neck, which is worse especially when he is under stressful situation. His examination revealed a repetitive headshaking and neck flexion in response to subjective "pinching" sensation. Attempt to control movement leads to a more violent shaking. With negative work up and ineffective medication, he opted for myobloc injection to his neck area where the "pinching" sensation is generated. With no reported side effect, he continues to receive injection every 12 weeks and reports 50% improvement of symptoms each time after treatment.

Conclusions: For decades, we have experienced the efficacy and safety of botulinum toxin in cosmetic dermatology, hyperhidrosis, involuntary movements, pain, and other neurological disorders. In this case report, myobloc has been shown effective in reducing movements in 2 cases of Tics by reducing the unpleasant sensory triggers or urge (ie pruritus and "pinching" sensation). Findings on these 2 cases suggest that Myobloc has potential to reduce peripheral sensitization to unpleasant sensation such as pruritus and pain like "pinching" sensation.

Tu-356

Lack of tic suppression in a case of accumbens/capsular region deep brain stimulation for Tourette syndrome

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Objective: To investigate the effect of anterior limb of internal capsule/nucleus accumbens (ALIC-NA) DBS on mild motor and vocal tics in Tourette syndrome (TS).

Background: The optimum target to treat symptoms of TS with DBS is unknown. Earlier lesional therapy had used thalamic targets for TS, as well as ALIC targets for other psychiatric disorders. Evidence regarding the efficacy of DBS targets for symptoms of TS can help define those targets' suitability. We report here the efficacy of DBS of the ALIC/NA in a patient with OCD and TS on his touretism.

Methods: A 33 year-old man received bilateral ALIC-NA DBS. One month following implantation, a post-operative CT was obtained to verify lead location. For the first six months following the implants, Yale Global Tic Severity Scales (YGTSS) and modified Rush Videotape Rating scales (RVRS) were obtained, as well as clin-

ical examinations by a specialized neurology and psychiatry team. Follow-up included 30 months of data.

Results: Total YGTSS scores worsened by an average of 17% during the first 6 months. RVRMS also worsened. There was a lack of clinically significant tic reduction over the 30 months of follow-up although subjectively the patient noted mild improvement.

Conclusions: DBS in the ALIC-NA failed to effectively address mild vocal and motor tics in a patient with TS and severe comorbid OCD.

Tu-357

Aripiprazole in adolescents affected by Tourette syndrome

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Objective: This work illustrates the results of a retrospective, observational study aimed at assessing the usefulness and the effectiveness of Aripiprazole for the treatment of motor and vocal tics in 40 adolescents with Tourette syndrome.

Background: Typical and atypical neuroleptics represent the mainstay of drug therapy of motor and vocal tics in Tourette syndrome (TS), despite the limited response and poor tolerance to the side effects of these drugs.

Methods: A case series of 40 consecutive patients with TS (M=28, F=12; age range: 11-22 years), were treated with Aripiprazole. All patients were initially assessed with semi-structured diagnostic interviews and self-report inventories. Many young patients presented additional co-morbid disorders: 3 out of 40 with ADHD; 8 with OCB, 7 with OCD, 3 with ICD; 3 patients presented borderline cognitive organization. 20 subjects presented TS without co-morbid disorders and 16 showed coprolalia. In 29 patients the treatment with Aripiprazole was started after withdrawal of other anti-tic medications; 11 patients were drug naïve. All patients were treated with a dose between 5-15 mg daily for a period from 3 to 36 months.

Results: 34 patients showed a significant and persistent response assessed by the YGTSS scores; the reduction of frequency and severity of tics leaded to a significant lowering of total impairment. 1 patient interrupted the treatment for occurred hypokinesia, another one for drowsiness; 4 subjects did not respond to the drug. Only mild and transient side effects were reported in the other patients.

Conclusions: Treatment with low dose of Aripiprazole seems to be useful and effective in TS, well tolerated by youths, with few mild side effects.

Tu-358

Prevalence and clinical characteristics of tics and other repetitive movement disorders in children with mental retardation

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Objective: To evaluate the prevalence and clinical characteristics of tics and other repetitive movement disorders in children with mental retardation (MR).

Background: Tic disorders and stereotypies have been associated with MR, however little is known about the prevalence and their association with specific mental retardation disorders.

Methods: This study is part of an ongoing large-scale, community-based epidemiologic survey of the prevalence of tic disorders in children and adolescents, aged 6-16 years in Burgos (Spain). Children with MR attending special education schools were evaluated by trained observers and a neurologist. Possible tic disorder was defined by completing ad hoc questionnaire by teachers, observers, and parents. Ascertaine diagnoses was given by the neurologist based on DSM-IV TR criteria. X^2 tests were used for comparisons.

Results: Of the 111 children, 57 children (48%) with a mean age of 11.4 ± 3.3 years, 60 % males, 40 % females, consented to participate, including 8% subjects with mild, 71% with moderate and 21% with severe MR. Tics disorders were found in 28 children (49 %, CI 95% 32.1-62.1) and stereotypies and mixed repetitive behavior (MRB) in 17 (29%, CI 95% 17.9-41.7 respectively). The most frequent tic disorder was Tourette syndrome (61%) followed by motor and vocal chronic tic disorders (25%, 3%, respectively). MRB was more frequent in girls with autism spectrum disorders (ASD) (p=0.01, p=0.04, respectively). Instead, tics and stereotypies were equally seen in boys and girls and equally associated with MR secondary to cerebral palsy, chromosomal disorders, ASD, and other causes of MR (p>0.05). The sensitivity for tic disorders was moderate among teachers (66%), observers (55%) and parents (77%) but excellent using any of them (90%).

Conclusions: Although possibly influenced by selection bias, repetitive movement disorders are frequent in patients with MR. In this population, tic disorders and stereotypies should be considered part of a clinical spectrum of repetitive behaviors secondary to basal ganglia circuit disturbances. For epidemiologic studies looking at fluctuating disorders such as tics, multiple sources appear to be adequate for routine screening in this population.

Tu-359

Tourette syndrome in adults

R.N. Gelineau-Kattner, J. Jankovic, A.L. Davidson (Houston, Texas)

Objective: To examine the clinical characteristics of adult population of patients with Tourette syndrome (TS) as compared to childhood TS.

Background: TS, as defined by DSM-IV-TR, specifies as one of four diagnostic criteria the onset of the disorder before age 18. As a consequence, the clinical phenotype and natural course of TS in adults has not been well studied.

Methods: Clinical data, including gender, age, duration and types of tics, co-morbidities, family history, and medications for all new patients with TS in the past 5 years who at their initial evaluation at the Movement Disorders Clinic at Baylor College of Medicine were 50 years old or older were retrospectively reviewed. They were compared to a population of all TS patients evaluated in our clinic between 2003 and 2006, whose age was $\leq$ 18 (N = 221, mean age 12.9 ±3.2 years).

Results: Of the 40 adult patients with TS, 31 (77.5%) had onset of their tics before age 18, and males had a significantly earlier onset of tic symptoms than females (p=0.003). Three of the 40 patients (7.5%) experienced their first symptom at or after the age of 50. The prevalence of coprolalia (7.5%) and copropraxia (2.5%) as well as ADHD (37.5%) was lower in the adult TS patients than in the younger TS clinic population (coprolalia = 18.6%; copropraxia = 6.8%; ADHD = 68.8%). The prevalence of obsessive-compulsive disorder was the same (58.5% in adult TS vs. 58.4% in younger TS clinic population).

Conclusions: The occurrence of TS in adults is similar in its components and clinical characteristics to those of childhood onset, suggesting that environmental stresses in the course of aging do not exert a robust effect on the evolution and natural course of TS-related symptoms. Additionally, the majority of adult patients with TS experienced their first symptoms before age 18, indicating that adult TS largely represents a re-emergence or exacerbation of a childhood disease. The lower prevalence of complex tics, including coprolalia and copropraxia, in adult TS patients suggests that age-related neuroplasticity is able to compensate for the underlying TS-related deficit.

Tu-360

Repetitive behaviours in patients with Tourette syndrome

K. Gocyla, A. Kalbarczyk, P. Janik (Warsaw, Poland)

Objective: To examine the frequency and associations with comorbidities of significant RBs.

Background: Repetitive behaviours (RBs) are amusing disturbances of Tourette syndrome (TS) that do not fulfill strictly the criteria

for motor tics nor compulsions. Although they are seen in many patients with TS their frequency and clinical significance remain unclear.

Methods: 92 subjects with TS (14 females and 78 males, aged: 6-54) were included into the study. The data entry form including the data from medical history and neurological examination was used. Only significant RBs often occurring or affecting the daily functioning of the patients were considered.

Results: At least one RB occurred in 85.9% of patients. Nail-biting was the most common one followed by smelling/sniffing non-food things (54.4% and 38.0%, resp.). There were on average 3.1 ± 1.94 (range: 1-11) RBs per each TS patient. Mean age at tics and first RB onset did not differ significantly (7.7 vs 8.3 years, resp.). All RBs were present before the age of 19. All RBs but rocking followed the onset of tics. Almost half of the patients with rocking developed it before the onset of tics in contrast to cutting-self, skin picking and nose-picking that never preceded tics. RBs appeared after tics in 51.2% of patients with nail-biting up to 88.9% with cutting-self. In 28.2% of patients RBs preceded the onset of tics by 4.3 ± 2.8 years on average (range: 1-11). In this group 90.9% of patients developed one or two RBs before the onset of tics. In most of TS patients RBs ceased or were present continuously. In the minority of cases RBs ran an intermittent course. There were positive associations between presence of RBs and comorbid psychiatric disorders, behavioural problems, severe tics and coprolalia.

Conclusions: RBs occur in the majority of TS patients and may precede the onset of tics. The appearance of RBs is associated with more severe form of TS.

Tu-361

A randomized, double-blind, placebo-controlled study of topiramate in the treatment of Tourette syndrome

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Objective: To investigate the change in severity of Tourette syndrome (TS) tic symptoms following treatment with topiramate as monotherapy or as an add-on to established, stable, chronic therapy when compared to placebo as measured by the Yale Global Tic Severity Scale (YGTSS).

Background: Dopamine receptor blocking drugs and dopamine depleting drugs have been traditionally used to control tics in patients with TS, but these neuroleptics are associated with potentially limiting side effects. Preliminary data suggested that topiramate may have a role in the management of TS patients with moderate to severe tic symptoms.

Methods: This is a randomized, double-blind, placebo-controlled, parallel group study which consisted of three phases: 1. Screening/Washout; 2. Double-Blind (titration: up to 6 weeks; maintenance: 4 weeks); and 3. Taper. The study medication (or placebo) was titrated up to 200 mg/day or the subject's maximum tolerated dose or adjusted by the investigator according to age. To be included in the study, subjects required a DSM-IV diagnosis of TS, 7-65 years of age, moderate to severe symptoms (YGTSS ≥19), and marked impairment with a rating on the Clinical Global Impression (CGI) scale severity score of ≥4, and were taking no more than one drug each for tics or TS co-morbidities.

Results: There were 29 patients (26 males), mean age 16.5 ± 9.89, randomized and 20 (69%) completed the double-blind phase of the study. The primary endpoint was Total Tic Score, which improved by 14.29 ± 10.47 points from baseline to visit 5 (Day 70) with topiramate (mean dose 118 mg) compared to only 5.00 ± 9.88 point change in the placebo group ($p = 0.0259$). There were also statistically significant improvements in the other components of the YGTSS as well as improvements in various secondary measures, including the CGI and premonitory urge CGI[Q1]. No differences were observed in the frequency of adverse events between the two treatment groups.

Conclusions: This double-blind, placebo-controlled trial provides evidence that topiramate is a safe and effective drug for the treatment of moderately severe TS.

Tu-426

Improvement in vocal & motor tics following DBS of motor GPi for Tourette syndrome, not accompanied by subjective improvement in quality of life – A case report

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Objective: To present a patient with Tourette syndrome (TS) treated with DBS of the motor Pallidum (GPi).

Background: Patients with medically refractory TS have had improvement in motor and vocal tics following DBS of various brain targets (medial thalamus, motor GPi and limbic GPi). Whether stimulation of different targets leads to differing effects on specific symptoms of TS, and also on patient quality of life is unclear.

Methods: This patient had the onset of tics at age 3. He exhibited multiple vocal and motor tics, injurious behaviour and compulsive behaviours and was diagnosed with attention deficit disorder and TS. Despite multiple medications he remained severely disabled. Haloperidol, Methylphenidate, Lorazepam & Mirtazepine were continued in view of their subjective benefit. Pre-operatively he had 106 motor tics/compulsions and 20 vocal tics at rest in 5 minutes and scored 81/100 on the Yale Global Tic Severity Scale. Bilateral electrodes were implanted in the posteroventral GPi. Post operative stereotactic MRI is shown in Figs 1 & 2.

Results: Post operative stimulation programming was complicated by an acute worsening in anxiety requiring prolonged hospitalisation for stimulation adjustment. Monopolar stimulation through contacts 1 and 5 at 2.0V, 150us, 170Hz led to an improvement in tics without

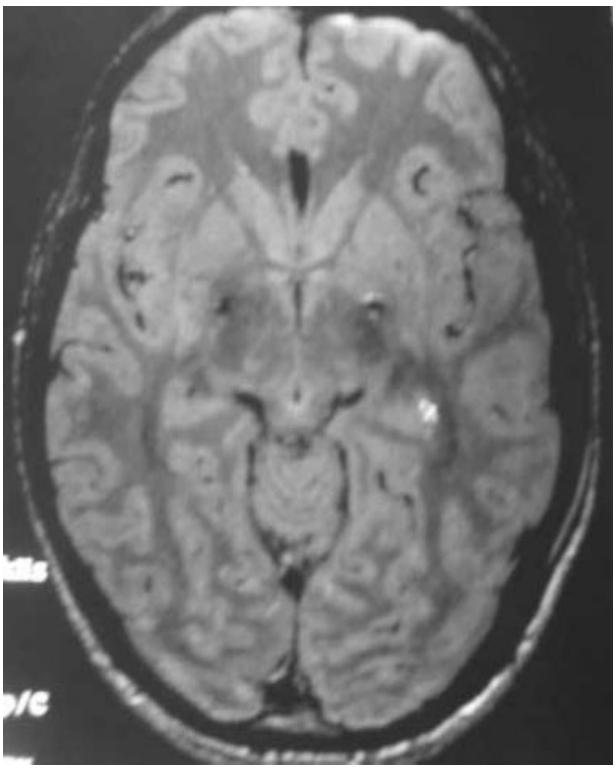

FIG. 1 (Tu-426).

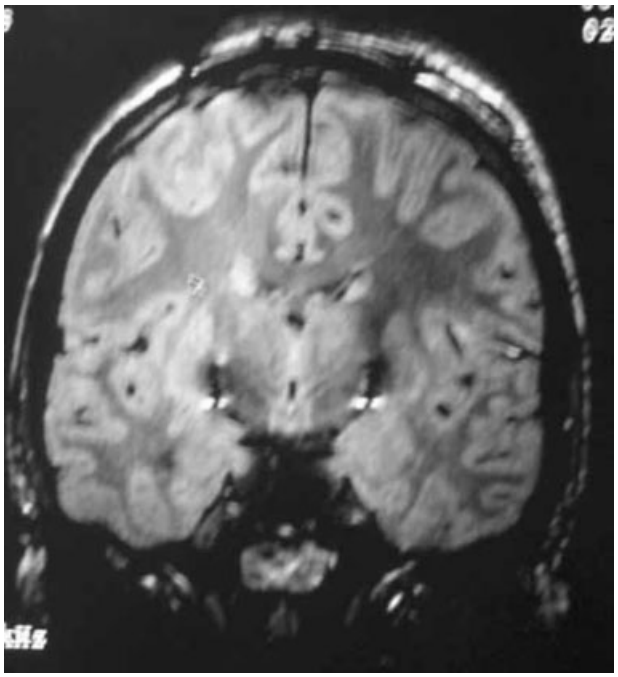

FIG. 2 (Tu-426).

provoking further anxiety at the time of discharge. At 3 and 6 month follow up assessments, he had a near complete resolution of both motor and vocal tics while at rest (12 and 2 respectively in 5 minutes) but on attempting to speak, he had recurrence of disabling vocal tics. He felt very lethargic but had a sense of inner tension and subjectively felt he had had no improvement in his quality of life as a result of surgery. On turning the stimulation off, he had a dramatic re-emergence of vocal and motor tics at rest and he requested that the stimulation be switched on.

Conclusions: GPi-DBS may be successful in reducing tic frequency and severity in the early stages following surgery without concomitant improvement in subjective well being. Possible explanations include the electrode target and adaptation to altered life-circumstances. Longer term follow up is warranted.

We-352

Glutamic acid and gamma-aminobutyric acid (GABA) concentrations in serum of patients with Tourette syndrome

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Objective: To analyze the concentrations of glutamic acid (Glu), gamma-aminobutyric acid (GABA) and glycine in serum of patients with Tourette syndrome (TS). To determine the associations of levels of analysed neurotransmitters with age at onset of tics, patients' age, severity of tics, duration of the disease and comorbidities.

Background: Abnormal concentrations of excitatory and inhibitory neurotransmitters are implicated in the pathophysiology of TS.

Methods: 67 patients with TS, aged 16-59, and 57 normal controls, aged 19-37, were studied. Mean age at the examination was similar in both groups (24.6 ± 8.0 vs. 25.6 ± 3.7 years, resp.). 67% of TS patients were not treated at the time of examination. Treatment in the remaining patients was stopped at least 48 hours before blood sample taking. Demographic and clinical data were obtained using data entry forms. Blood samples were taken after 12-hour fasting to determine levels of neurotransmitters and HPLC technique was used.

Results: The TS group had higher concentration of Glu ($p<0.05$) and lower concentration of GABA ($p<0.05$). Similar concentrations of glycine were found in both groups. There was no difference regarding analysed neurotransmitters between treated and not treated TS patients. Glu concentration was significantly higher in patients with severe tics ($p<0.05$). The positive correlation between the number of comorbidities per individual and Glu concentration was observed (Spearman $r=0.34$; $p<0.05$). Patients with obsessive-compulsive disorder had higher concentration of Glu and those with learning disorder had decreased concentration of GABA. Glycine concentration correlated negatively with the number of behavioral problems in TS patients with comorbidities. There was no correlation between concentrations of examined neurochemicals and patients' gender, age at tics onset, age at examination, disease duration and positive family history.

Conclusions: Abnormal serum levels of Glu and GABA can be potentially useful as markers of TS. Abnormalities in the serum excitatory/inhibitory system are associated with more severe form of TS and may reflect the changes within the brain.[1.] The paper was presented at the 20th Meeting of Polish Neurological Society in Wroclaw on Sep 03-06, 2008.

We-353

Coprolalia and copropraxia in Polish patients with Tourette syndrome

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Objective: To examine the frequency, associations with comorbidities and impact on patients' daily functioning of coprophenomena.

Background: Involuntary expression of socially unacceptable words (coprolalia) or gestures (copropraxia) are the best recognized symptoms of Tourette syndrome (TS).

Methods: 92 subjects with TS, aged: 6-54, were studied. The data entry form including the data from medical history and neurological examination was used.

Results: Coprolalia occurred in 27.2% of patients; copropraxia in 5.4% of patients. In 15.4% of TS patients both coprophenomena were present. Coprolalia was significantly higher in females compared to males (50% vs. 23%, resp.; $p=0.371$). Mean age at onset was 14.2 ± 6.4 (range: 6-33) years for coprolalia and 11.4 ± 3.6 (range: 7-16) years for copropraxia. Coprophenomena started about 4 years after the onset of tics. In only one patient with severe comorbidities coprolalia was the initial symptom of TS and began at age 6; in 24% coprolalia began in adulthood. Coprolalia and copropraxia had an intermittent course in 68% and 80% of patients, respectively. There were positive correlations between appearance of coprophenomena and other psychiatric disorders, behavioral problems and non-tic non-compulsion repetitive behaviors. Anxiety, conduct disorder, obsessive-compulsive disorder, depression, self-injury behaviour and anger control problems were significantly more often seen in patients with coprophenomena. The presence of coprophenomena was associated with more severe tics. 84% of patients reported significant influence of coprophenomena on daily living, relations with family and work/school. Only 16% of patients stated that coprophenomena had not influenced their daily living.

Conclusions: Coprophenomena affect ¼ of patients with TS and may appear at any age. The appearance of coprophenomena is associated with more severe form of TS and poorer quality of life.[1] The paper was presented at the 20th Meeting of the Polish Neurological Society in Wroclaw on 3rd-6th Sept 2008.

We-354

Weight and height distribution in children with Tourette syndrome

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Objective: To investigate whether untreated children with Tourette syndrome have height and weight differences compared to age and gender matched controls.

Background: Children with TS as a whole have been reported to have lower than normal height and weight, while BMI is normal. This is hypothesized to indicate a possible dopaminergic over activity in the hypothalamo-pituitary axis.

Methods: Weight and height of consecutive patients with TS under the age of 20 years were recorded. Patients were considered to be untreated if they had never been exposed to any medication to treat tics and/or TS co-morbidities. Age and gender specified standardized weight z-score and body mass index (BMI) z-scores were compared between the TS group and the CDC normative data from 2000 using one-sample t-test.

Results: A total of 131 patients (106 males, 25 females), younger than 20 years (mean age 12.2 years (SD 3.6, range [5, 19]), were included. Of those, 60 had never been exposed to medications. Untreated patients had a significantly higher age and gender adjusted average weight compared to the CDC sample's mean ($p = 0.004$), with the height difference not reaching significance ($p = 0.52$): weight percentile z score = 0.43 (SD = 1.12); height percentile z score = 0.09 (SD = 1.11). When all patients were assessed (N=131), their average age and gender adjusted weight was also significantly higher than the CDC sample's mean ($p < 0.0005$) with the height difference not reaching significance ($p = 0.08$): weight percentile z score 0.63 (SD 1.09); height percentile z score 0.17 (SD 1.10).

Conclusions: Un-medicated TS children are heavier than the general population. The fact that their height fits within the normal range argues against a generalized hyperdopaminergic state affecting Growth Hormone function in this population. Medication treatment increases weight further, alerting physicians to monitor weight carefully in treating TS children. One limitation of this study is that the norms used for comparison date from 2000. Such data may not accurately reflect the current weight norms in the context of public health reports that average US children are increasingly heavy.

We-355

Substance use disorder in adult Tourette syndrome

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Objective: To evaluate the frequency and nature of substance use disorder (SUD) and its clinical correlates in adult Tourette syndrome (TS).

Background: Behavioural and psychiatric co-morbidity, including obsessive-compulsive disorder (OCD), ADHD, and other impulse control disorders are frequently observed in TS patients. Prior studies have linked drug abuse with ADHD in patients with and without tics. However, the frequency and pattern of drug abuse as a possible expression of compulsive or impulsive behavior, or as a response to the tic disorder, has been little studied in TS.

Methods: SUD was investigated by retrospective review of clinical records of 63 adult TS patients, aged 36.8 ± 13.6 years, followed at a University-based TS clinic for 7.8 +/-6.2 years. DSM-IV criteria were used for TS and comorbid conditions except for adult ADHD where proposed DSM-V criteria (Barkley et al, 2008) were applied. Patients with and without histories of SUD were compared using assessments of ADHD, self-injurious behaviors (SIB), other co-morbid mood and behavioral disorders, and ratings of tic and OCD severity (YGTSS and YBOCS scores).

Results: Eleven patients (17%) had a history of SUD, drugs alone or in combination including alcohol (n=7), benzodiazepines (4), cocaine (3), marijuana (3), opioids (3), and methamphetamine (n=1). One patient died unexpectedly of a drug overdose. Severe SIB was limited to two patients with cocaine/polysubstance abuse, who exhibited severe tics. In one case, recognition of cocaine abuse was delayed. Marijuana was used to calm tics and anxiety but caused significant apathy in one subject. Comorbid conditions in SUD patients included bipolar disorder (n=2, 18%), intermittent explosive disorder (n=2), childhood-onset ADHD (n=1), and probable adult ADHD (n=1). Patients with SUD did not differ from other TS subjects in frequency of ADHD, nor in severity of tics or OCD. Three (27%) had a family history of drug/alcohol abuse, which was comorbid with tics/OCD in two cases.

Conclusions: SUD is not uncommon in adult TS and may both drive and be driven by tics (cocaine and marijuana use, respectively). SIB may be aggravated by cocaine or predispose to polysubstance dependence. SUD does not appear to be related to OCD in TS but comorbid bipolar disorder, intermittent explosive disorder and ADHD represent risk factors. Unreported cocaine abuse should always be considered as a possible contributing cause of severe tics and SIB in TS.

We-356

Time processing in children with Tourette syndrome

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Objective: To analyse temporal information processing in patients with Tourette syndrome (TS).

Background: TS is characterized by dysfunctional connectivity between prefrontal cortex and sub-cortical structures. Since time processing is regulated by the same circuitry, we hypothesized abnormal time processing in TS.

Methods: We analysed time reproduction of sub-second (500, 600, 700, 800 and 900 msec) and over-second (1500, 1600, 1700, 1800 and 1900 msec) time intervals in 9 medication-free children with TS-only (without major psychiatric co-morbidities) and 10 age-matched healthy children, by means of a time reproduction task which used visually cued intervals. Tic severity was assessed by the Yale Global Tic Severity Scale; the IQ of both groups was assessed by the Brief IQ version of the Leiter International Performance Scale-Revised (Leiter-R); attention difficulties was measured in both groups using the two Attention subtests of the AM battery of the Leiter-R, Sustained Attention (SA) and Divided Attention (DA); working memory was tested using the Digit Span subtest of the Wechsler Intelligence Scale for Children Revised (WISC-R).

Results: Children with TS-only reproduced in an overestimated fashion over-second, but not sub-second, intervals. The precision of over-second intervals reproduction correlated with tic severity, in that the lower the tic severity, the closer the reproduction of over-second intervals to their real duration. Time reproduction performance did not correlate with IQ, attention and working memory in either group.

Conclusions: Time processing abnormalities in children with TS-only seem specific for over-second intervals, consistent with dysfunctional time processing within the dorso-lateral prefrontal cortex. Our data also support an enhanced cognitive control in TS children, probably facilitated by effortful tic suppression.

We-357

Bradykinesia in patients with obsessive-compulsive disorder

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Objective: To evaluate whether bradykinesia is present in patients with obsessive compulsive disorders (OCD) and to assess its correlation with the other OCD features.

Background: The pathophysiology of OCD is thought to be due to a dysfunction of the cortico-striato-thalamo-cortical circuits.

Methods: Twenty-three patients were enrolled in the study. Diagnosis of OCD was made according to the DSM-IV. Inclusion criteria were age 18 years and a total score ≥ 14 on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Exclusion criteria were current or lifetime psychiatric disorders on DSM-IV Axis I, II or III and use of antipsychotic medications in the preceding month. Bradykinesia was assessed with the motor section of the Unified Parkinson's Disease Rating Scale Part III (UPDRS III; items 18,19,23-27, 29 and 31). Mental slowness was assessed with the specific item of the Y-BOCS. The HAM-D and the HAM-A were administered to evaluate the presence

of depressive and anxiety symptoms. The CGI was used to evaluate the severity of the psychiatric disorder. The Wechsler Adult Intelligent Scales-Revised (WAIS-R) was used to assess the Full Scale IQ.

Results: Bradykinesia (mean ± SD score 5.1 ± 1.4) was present in 8 of the 23 patients (34.8%). Mental slowness was present in 21 of the 23 patients (91.3%). Severity of bradykinesia was not related to any specific demographic features, whereas it correlated with the severity of compulsions ($r=0.58$, $p<0.01$). Bradykinesia was inversely related to the IQ (verbal $r=-0.55$ $p< 0.05$; performance $r=-0.52$ $p<0.05$; total $r=-0.58$ $p<0.01$) as measured by WAIS-R, independently of possible confounders (age, disease duration, depression). Patients with bradykinesia scored significantly lower in the Digit symbol coding than patients without bradykinesia.

Conclusions: Bradykinesia clinically assessed is present in about one third of OCD patients. OCD patients with bradykinesia have more severe compulsions and are more affected in nonverbal performance than patients with OCD but without bradykinesia.

We-416

Stereotypy following status epilepticus due herpetic encephalitis. Probable Kluver-Bucy syndrome

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Objective: To report a 34-years-old female who developed an odd stereotypic behavior after status epilepticus due herpetic encephalitis with prominent hypersexuality.

Background: Stereotypy is an involuntary, coordinated, paterned, repetitive, thythmic, purposeless but seemingly purposeful or ritualistic movement. Sometimes distinguishing stereotypy from other movements is important and often difficult with tics and mannerisms being the most likely to cause confusion.

Methods: Case Report: This patient was admitted in our hospital complain of headache, fever and somnolence in the past 24 hours. A CSF analyses revealed pleocytosis with lymphocytes predominance. Couple days later the polymerase chain reaction for HSV DNA revealed positive. She was then diagnosed as having herpetic encephalitis and treated with intravenous acyclovir 10 mg/kg. A continuous electroencephalography demonstrated that those episodes were convulsion coming from the temporal lobes and were occurring every 2-5 minutes. After the treatment initiation for the seizures the patient status worsened and she has to be intubated and ventilated. In the ICU, during the recovery time, she started to present repetitive movements, like scratching her face (video). Those movements was precipitated by touching the face and were so intense that she developed a skin abrasation in her face. She denied pleasure and was concerned about that problem.

Results: Brain MRI showed bitemporal acute lesion with increased signal intensity in both temporal lobes and mesial structures. One month after the hospital discharge his husband reported that she developed prominent hypersexuality. She solicited several intercourse in the same day with multiples orgasms. He denied dietary changes, increased appetite, loss of normal fear or emotional changes, but she complaint of memory difficulties. The stereotypy remain besides carbamazepine (1200 mg/day) and haloperidol (2mg/day) treatment.

Conclusions: Stereotypies are classically associated occurring in autistic, retarded, psychotic, congenitally blind, and congenitally deaf. We report an unusual case of stereotypy following status epilepticus due herpetic encephalitis in a patient with a probable Kluver-Bucy syndrome.

We-417

Videotape analysis of childhood masturbation mimiking as paroxysmal dystonia

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Objective: To highlight the profile childhood masturbation by analysing the video tapes.

Background: Masturbation or self gratification behaviour in children is often misdiagnosed as paroxymal dystonia. Although a normal behaviour in childhood, it is frequently unrecognised because of absence of genital manipulation.

Methods: Six patients presenting to movement disorder clinic over a period of 5 years with suspected paroxysmal movement disorder were detremined to have postures and movements associated with masturbation. We reviewed the clinical history examination and video tapes of these patients.

Results: Our patients had severe features in common: (1)Onset after the age of 3 months and before 2years; (2)all were female babies; (3)stereotyped episodes of variable duration; (4) vocalisation with grunting; (5)flexion and adduction of hips with charecterstic posturing; (6) no genital manipulation; (7)movements were obsereved in supine rather than prone position; (8) no aleration of consciousness; (9)Cessation of movements with distraction; (10) normal neurological examination.

Conclusions: The identification of these common features should assist in the proper diagnosis and eliminate the need for extensive and unecessary testing. Direct observation or video tapes are useful in identification of child hood masturbation.

Th-357

Multiple targets deep brain stimulation (DBS) for the treatment of refractory Tourette syndrome (rTS): Our experience with a long-term follow-up evaluation

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Objective: To evaluate DBS as a tailored treatment on the basis of the clinical history (conservative treatments undertaken, social integration disorders) and of the clinical picture (comorbidities) expressed by the patient.

Background: Tourette syndrome (TS) is a complex neuropsychiatric syndrome with a wide range of behavioral comorbidities for which DBS has recently demonstrated to be a promising add/on treatment.

Methods: DBS for refractory TS was undertaken using three different target. A total number of 79 procedures were undertaken. Thirty-six patients with GTS who were resistant to at least six months of treatment with both standard and innovative medications, as well as psycho-behavioural techniques, were submitted to DBS.

Results: Vo/CM-Pf: most of the procedures (67 procedures) were performed at this target. With respects to the classical Vandewalle target, in our procedures we shifted the trajectory 2 mm anteriorly in order to include a larger part of the Ventralis oralis nucleus, on the basis of previous findings by Hassler and Dieckmann and in order to obtain a more important influence over the anterior "associative" thalamus. NAC: 10 procedures were undertaken targeting nucleus accumbens, on a total number of 5 patients. Out of these 5, only one patient was treated at NAC alone, while of the other four, three were treated also with bylateral Vo/CM-Pf and one at motor Gpi bylaterally. NAC was treated with DBS as a "rescue surgery" in patients in which severe behavioral comorbidities failed to respond to improving tic manifestations after a first DBS procedure. On the basis of promising improvement of behavioral comorbidities, one patient expressing important comorbidites was treated during the same DBS procedure, at Vo/CM-Pf and NAC bylaterally. Gpi: only one patient was treated with DBS at this target, because of a clinical picture dominated by dystonic tics. In a staged second procedure, DBS was undertaken also for the NAC target bylaterally, because of relentless behavioral obsessive comorbidities.

Conclusions: TS is a complex syndrome with multiple neurologic and behavioral features: this should focus on the possibility to treat multiple targets tailoring on the specific clinical features of the patient.

Th-358

Inverse relationship between thalamic and orbitofrontal volumes in obsessive-compulsive disorder: Magnetic resonance imaging study and meta-regression

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Objective: To investigate the relationship between thalamic and orbitofrontal volumes in patients with obsessive-compulsive disorder (OCD) relative to healthy controls by conducting a magnetic resonance imaging (MRI) study and a meta-regression.

Background: OCD is a frequent, disabling and chronic psychiatric condition. In the past two decades, many MRI studies have explored the volumes of brain regions in OCD and reported a smaller volume of the orbitofrontal cortex (OFC) and a larger volume of the thalamus compared to healthy controls. Here, we investigated the relationship between thalamus and OFC volumes in OCD patients relative to healthy controls by conducting a MRI study and a meta-regression that included data from five independent MRI studies.

Methods: MRI volumetric measurements of the thalamus and OFC were obtained in 16 OCD patients without comorbidity and 16 comparison subjects matched for age, sex and educational level. Partial correlation analyses that controlled for intracranial volume (ICV) were performed to explore relationships between thalamic and OFC volumes in each group. In order to assess the speficity of this relationship, we conducted similar analyses with non-OFC (the anterior cingulate cortex) as the cortical volume. Finally, by using data from previous published volumetric MRI studies, we conducted a meta-regression exploring relationships between volume changes in the thalamus and OFC.

Results: Results showed that thalamic volumes were significantly negatively correlated with OFC volumes in OCD patients ($r=-0.83$, $p<0.001$), but not in healthy subjects ($r=-0.15$, $p=0.59$). No significant relationship between thalamic and non-OFC volumes was found neither in OCD patients ($r=0.03$, $p=0.91$) nor in comparison subjects ($r=-0.23$, $p=0.40$). Furthermore, meta-regression analyses showed that previously reported volume changes in the thalamus were significantly correlated with OFC volume changes ($r=-0.71$, $p<0.05$), but not with non-OFC volume changes ($r=0.07$, $p=0.86$).

Conclusions: Although our results do not allow to establish any causal relationship, they suggest that brain structural alterations would be related in OCD.

Th-359

Age at tic remission in patients with Tourette syndrome

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Objective: To examine the natural history of tics in Tourette syndrome (TS).

Background: Previous studies have suggested that tics in TS begin at a mean age of 6 years, peak in severity around age 11, and then lessen or resolve in more than half of the patients as they grow into adulthood. Data to define the age at tic remission or time course of comorbid ADHD or OCD are lacking.

Methods: Subjects aged 13 to 31 were recruited through the University of Rochester TS Clinic. Subjects completed a brief questionnaire consisting of four questions about tic, ADHD, and OCD symptoms: (1) age at onset, (2) age at peak severity, (3) age at which symptoms began to lessen, and (4) age at which symptoms essentially stopped. The mean ages of occurrence for each of these milestones was then determined.

Results: 53 participants (79% male, mean age 19.36 ($\pm$ 5.3) years) completed the survey. Mean age at tic onset was 7.9 ($\pm$3.6) years, followed by an average peak in tic severity at 12.3 ($\pm$4.61) years of age. This period of heightened tics was followed by a lessening of symptoms which occurred at 14.8 ($\pm$3.7) years of age. Essential tic remission occurred at a mean age of 17.4 ($\pm$ 3.8) years. 83% reported that their tics had lessened over time, and tics had essentially stopped in 32%. Previously diagnosed ADHD or OCD was present in 68% and 72%, respectively. The mean age at OCD onset was 9.2 ($\pm$5.0) years while the mean age at ADHD onset was 7.9 ($\pm$3.5) years. Reported peak symptom severity occurred at 12.6 ($\pm$5.5) years for OCD and at 10.8 ($\pm$3.8) years for ADHD. Mean age at symptom lessening for OCD was 15.1 ($\pm$5.0) years, and at 14.0 ($\pm$2.9) years for ADHD.

Conclusions: The results of this study confirm the TS milestones, time course, and improvement or remission rates reported in previous studies. This study also provides more specific data for the age when tic remission can be expected to occur and may be useful when designing prospective studies.

Th-360

Extrastriatal abnormalities of dopaminergic function in Tourette syndrome: An FLB 457 PET study

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Objective: To evaluate extrastriatal dopamine (DA) D2/D3 receptor binding and DA release in patients with Tourette syndrome (TS) using Positron Emission Tomography (PET).

Background: Accumulated evidence from pharmacological trials and select postmortem analyses suggests that abnormalities of dopaminergic neurotransmission play a key role in the pathogenesis of TS. However, most previous attempts to elucidate the nature of these abnormalities using PET ligands with preferential binding in the striatum have generated equivocal or contradictory findings. Another approach has therefore been to evaluate the dynamic aspects of DA function in TS by inducing striatal DA release with an amphetamine challenge. Using this method striatal DA release has been reported increased from 21% to 50% in TS patients compared to controls. However a substantial body of evidence has also implicated extrastriatal abnormalities in TS, yet the neurotransmitter function of these regions has remained largely unexamined.

Methods: We initiated a PET study using [11C]- FLB 457, a D2/D3 DA receptor ligand with sufficient affinity to allow quantification of binding potentials in extrastriatal regions, in conjunction with an amphetamine challenge to evaluate both extrastriatal DA D2/D3 receptor binding and DA release in a group of 8 adult TS patients who were both treatment naïve and lacking in significant psychiatric comorbidities. We compared binding potentials in these patients to a group of age and sex matched controls.

Results: At baseline, TS patients showed decreased binding of [11C]FLB 457 relative to control subjects bilaterally and broadly in cortical and subcortical regions outside the striatum, including the cingulate gyrus, middle and superior temporal gyrus, occipital cortex, insula as well as thalamus. Amphetamine challenge induced DA release in both control and TS subjects bilaterally in many cortical regions; however in the TS patients, these regions of increased DA release were significantly more widespread and extended more anteriorly to involve anterior cingulate and medial frontal gyri. Conversely, and in contrast to healthy controls, no significant dopamine release was noted in the thalami of TS patients.

Conclusions: Our data suggest global abnormalities of dopaminergic function in TS.

Th-361

Antisaccade and countermanding tasks as pathophysiologic paradigms of motor control in Gilles de la Tourette syndrome (GTS)

P.C. van Meerbeeck, S. Rivaud, Y. Worbe, P. Pouget, A. Hartmann, B. Gaymard (Paris, France)

Objective: To investigate the motor inhibitory abilities of adult patients with GTS by coupling the oculomotor antisaccade task (AS) and the countermanding (CTM) paradigm.

Background: To date, impairment of the fronto-striato-thalamo-cortical loops represents the most consensual pathophysiological hypothesis in GTS. While appropriate oculomotor tasks may investigate the inhibition exerted by the frontal cortex on the basal ganglia and the motor cortex, previous eye movement studies in GTS have, however, provided conflicting results. The CTM task evaluates the ability

to withhold a planned ocular movement in extremis. Compared to the AS task, motor inhibition in the CTM task seems more complex and probably controlled by distinct neuronal networks.

Methods: To evaluate the inhibitory activity of the frontal cortex, a comprehensive oculomotor testing–combining prosaccade, AS and CTM tasks in a single-session–was performed in 22 adult patients with GTS and 22 matched healthy controls. Patients were recruited through the French National Reference Center for GTS.

Results: On the CTM task, 64% of GTS patients showed normal motor inhibition, while 36% of them presented abnormally low withholding rates. Clinical features did not differ between both groups. On the AS task, 64% of the GTS patients showed abnormally increased error rates compared to healthy subjects, without any correlation between clinical features and performances. One poor performer on the CTM task had normal AS performances, while 57% of poor AS performers had normal CTM performances. Neuroleptic treatment did not alter AS or CTM performances, but modified behavior after STOP trials in the CTM task.

Conclusions: The CTM paradigm enables to detect motor control

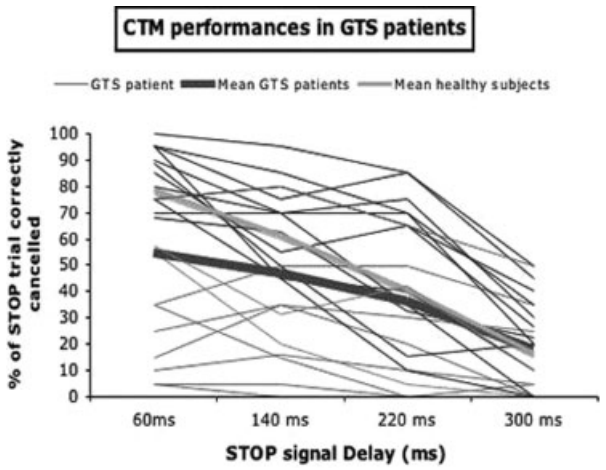

FIG. 1 (Th-361).

deficits in 1/3 of TS patients, whereas AS task detects inhibitory deficits in 2/3 of them. Performances on both tasks were independent of clinical features and not interrelated. Discrepancy between performances in AS and CTM tasks in some patients supports hypothesis of a double dissociation, i.e., that AS and CTM are processed by distinct inhibitory neural networks. These results confirm that motor control deficits exist in most adult GTS patients and that the coupling of both paradigms may improve inhibition deficit detection in these patients.

Th-362

Motor tics of the neck: A possible cause of stroke and brachial plexopathy in a child with Tourette syndrome

P.C. van Meerbeeck, E. Deniau, A. Hartmann (Paris, France)

Objective: To highlight the potential dramatic consequences of tics involving the neck in GTS patients and discuss treatment options.

Background: Motor tics may produce disabling physical sequelae, even they do not consist of self-injurious behaviors: six cases of myelopathy secondary to violent flexion or extension of the neck have been previously reported in GTS patients. However, cases of cervical artery dissection or traumatic plexopathy have never been described.

Methods: Case report.

Results: A 13-year-old boy presented motor and vocal tics from age of 7, meeting criteria of GTS. Despite treatment, he kept severe motor tics consisting in strong sudden neck extension. On May 2007, he suddenly developed weakness of his left arm. Brain MRI showed both acute striatal ischemic stroke and less recent cerebellar stroke on the right side. Axial MRI and MRA disclosed dissection of the right vertebral artery. Comprehensive blood examination was normal, hereditary or acquired coagulopathy was excluded, transthoracic and transesophageal echocardiography, as well as the 24-hour electrocardiography were normal. Striatal stroke was imputed to an embolic migration from the left vertebral artery to the left middle cerebral artery through the posterior communicating artery. Initial anticoagulant therapy was followed by antithrombotic treatment, without any further ischemic recurrence. However, tics of neck extension persisted with a waxing and waning course and led, one year later, to a traumatic brachial plexopathy confirmed by EMG.

Conclusions: Besides their social inconvenience, motor tics in GTS may also cause severe osteoarticular or neurological lesions. In addition to myelopathy, tics involving the neck may also induce cervical artery dissection or traumatic plexopathy. The therapeutic consequences will be discussed (behavioural therapy, pharmacotherapy, botulinum toxin injections, deep brain stimulation).

Th-420

Bilateral synchronous hemifacial spasm (HFS) after bilateral Bell's palsy (BP)

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Objective: To describe clinical and electrophysiological findings in patient with bilateral synchronous HFS.

Background: HFS is characterized by irregular, clonic contractions affecting the muscles innervated by the ispilateral facial nerve. Bilateral HFS has been reported only in a handful of patients with and without a history of previous facial palsy. In reported cases the onset of HFS is not simultaneous and muscle contractions are not synchronous. Women are more commonly affected and the left side is typically more severely involved.

Methods: Case report.

Results: A twenty six year old gentleman developed bilateral BP, which has interfered with his ability to smile or close his eyes. His facial strength incompletely recovered (more on the left), and he developed involuntary, irregular, synchronous, bilateral facial movements approximately 4 months later. Facial movements became more frequent and intense over the following 9 months. They remained unchanged for the following twenty six years. Though facial movements were worse with stress and better at rest, he could not voluntarily suppress them. They were not preceded by inner tension or anxiety. On examination irregular clonic symmetric contractions affecting the orbicularis oculi, zygomaticus complex, and buccinator were present. The intensity of the movements was higher on the right. Mentalis muscle was only involved on the right side. Smiling provoked clonic contractions of bilateral orbicularis oculi and forced eye closure triggered clonic spasms in bilateral zygomaticus muscles, buccinator and right mentalis. Electromyography of the facial muscles (i.e., orbicularis oculi, etc) revealed bilateral irregular synchronous bursts of muscle activity lasting for less than 200 ms, that when compared between symmetrical muscles had higher amplitude on the right. Imaging studies revealed no signs of neurovascular compression. His movements were successfully controlled with botulinum toxin injections.

Conclusions: We present the first case of simultaneous onset of bilateral HFS characterized by synchronous contractions. Synchronous ectopic activation of facial nerve fibers damaged by previous bilateral BP is the most likely cause of the bilateral HFS.

TREMOR

Mo-362

Cognitive impairment in persons with essential tremor: Preliminary results from Carmel cohort study of essential tremor

S. Badarny, G. Sinoff, S. Honigman (Haifa, Israel)

Objective: This study is a prospective follow-up over a period of two-years of a cohort of persons suffering from Essential Tremor (ET). The aim of this study is to evaluate in the recruited subjects cognitive function at baseline and over time. This poster will describe the cognitive evaluation and the possible areas of cognitive impairment found in the subjects at baseline.

Background: ET is considered a pure motor disease of CNS system. However, it has been reported in the literature that patients with ET have possible cognitive decline with time and the working hypotheses for this study were that at baseline, many of these subjects would have cognitive impairment and also that at follow-up there will be a decline.

Methods: Recruited to this study were 25 subjects from the Movement Disorder Clinic of Carmel Medical Center during 2008 and 11 of these were retested after 6 months. The study is an ongoing study and recruitment is still being carried out. All patients underwent cognitive assessment in the Cognitive Clinic of Carmel Medical Center testing cognition by both screening and neuropsychological instruments.

Results: The mean age were 67 and were highly educated (mean of 13 years). The average age of the start of the tremor was 53 with a mean duration of 14 years. The subjects scored 28 points on MMSE, with normal clock drawing. However by means of the SLUMS (mean 23.2) and COGNISTAT (mean 66.5) instruments, they showed evidence of Mild Cognitive Impairment (MCI). On neuropsychological testing there was evidence of semantic memory disturbances in verbal fluency, disturbance in executive function, logical memory and concentration. By means of Clinical Dementia Rating Scale, over 50% of the subjects had MCI or early dementia. On examination at time T_2 (6 months), there is a trend for worsening of the cognitive status of these patients.

Conclusions: The preliminary results of this study show that even though the subjects recruited were not demented at time T_1 by means of MMSE, they already were showing signs of cognitive impairment. Over 50% were with enough cognitive decline to define them as suffering from MCI or early dementia. This cohort will be followed up longitudinally for the next two years for future cognitive assessment.

Mo-363

Spirography in essential tremor and parkinsonism

M. Knoebel, P.G. Bain (London, United Kingdom)

Objective: To examine the characteristics of spirals drawn by patients with essential tremor (ET) or parkinsonism (PSM), in order to identify any distinguishing features in the spirals drawn by these 2 groups of tremulous patients.

Background: Spirography has been shown to be a simple practical method for recording tremor severity (Bain & Findley. Assessing Tremor Severity 1993) and distinguishing proximal from distal arm tremors (Liu & Bain, Movement Disorders 2006; 21: 2032).

Methods: We examined the spirals drawn by 103 PSM patients and compared them with those drawn by 41 patients with ET. The following data was abstracted from the spirals: 1. Tremor severity (0-10 rating scale) at first consultation, 2. Spiral 3- and 5-turn diameters (cm) and 3. Spiral turn density. In addition for the PSM patients the change in spiral tremor severity (at 1 year) and spiral density by first and most affected hand were analysed.

Results: Initial spiral severity was significantly worse in ET (74% graded $>$ 1) compared to PSM (22% graded $>$ 1) ($P=0.0003$). The mean spiral diameter measured at both 3 turns (3.0 v 2.6 cm, $p<0.03$) and 5 turns (4.4 v 3.6 cm, $p<0.01$) was greater and mean spiral density less (3.3 v 7.3 completed turns per dm^2, $p<0.013$) in ET than PSM. In 76% of PSM cases the tremor severity in spirals remained unchanged over 1 year, in spite of treatment. In PSM the spiral density was greater in the first affected and most affected hand compared to the contra-lateral hand ($p<0.0003$).

Conclusions: Our data indicate significant differences in spirals drawn by patients with ET compared to parkinsonism. In ET spirals tremor severity and spiral diameter are greater than PSM, whilst spiral density is less. In addition spiral density reflects the severity of parkinsonism. This data could be invaluable for clinical and epidemiological studies.

Mo-364

Post-traumatic movement disorders

E.J. Chung, H.S. Lee, C.J. Lim, B.J. Suk (Busan, Korea)

Objective: To describe 3 patients developed a movement disorder after traffic accident and analyze pathogenesis of their symptoms.

Background: In spite of theoretically advancing background of post-traumatic movement disorders and growing of the hypothesis for movement disorders following peripheral trauma, a cause-and-effect relationship between peripheral injury and subsequent movement disorder has not yet been universally accepted.

Methods: Three patients were met the following criteria: first, the trauma have been severe enough to cause local symptoms for two weeks, second, the initial symptoms of the movement disorder is anatomically associated with the site of injury, and third, the onset of the movement disorder should be within a year of the injury.

Results: An 24 year old man was a driver in his stationary car when it was hit from behind. He immediately became aware a tremor in his left hand. The EMG suggests damage to the left C5 to 8 roots. However, cervical spine and shoulder MRI were normal. A 45 year old woman was involved in a trunk on road traffic accident. Within first week after the accident she had developed jerking movements of her trunk radiating into her neck and lower limbs. Cervical and thoracic spine MRI showed no gross abnormality. A 62 year old woman was thrown forwards and hit the back of her head against the head rest and she had developed severe pain by right elbow injury and mandibular fracture. Several months after trauma she insidiously noted mild tremor in right hand and jaw.

Conclusions: As previous criteria, our cases showed severe pain of left arm and shoulder with limitation of motion and tremor was immediately occurred to our patient. In spite of no neuroradiologic related lesions, EMG supported that there was obvious connection between clinical manifestation and the site of injury. The pathogenesis for occurrence of movement disorders after peripheral trauma was that over-activity of stretch reflex loop and sensitization of primary muscle spindle input were related to peripherally induced tremor. The possibility of central reorganization in response to altered peripheral input was also referred to another pathogenesis of movement disorder by peripheral trauma. These findings suggest that peripheral nervous system-central nervous system interaction may be involved in the pathogenesis of tremor after peripheral injury.

Mo-365

Orthostatic tremor and motor cognition

M.W. Cowey, D.R. Williams (Melbourne, Victoria, Australia)

Objective: To assess the paradoxical onset of electrophysiological tremor and clinical unsteadiness in orthostatic tremor.

Background: Orthostatic tremor (OT) is a rare disorder with characteristic high frequency discharges (13-18 Hz) leading to severe unsteadiness, but rarely falls. The physiological origin of the movements is unknown. One characteristic observed in OT is a delay in onset of unsteadiness after standing, although electrophysiological tremor is recordable immediately on standing. We hypothesised that time difference between these phenomena may be informative regarding the circuits involved in generating the tremor.

Methods: Four patients who met the MDS Consensus Statement criteria for OT were studied using bipolar recordings from 10mm disk surface electrodes, placed three centimetres apart on tibialis anterior. All recordings were performed on a GRASS tremor machine, using 300-3000Hz band pass filters, and 1K gain**.** Continuous recordings were made with video and marked at the following time points: seated at rest; upon standing; when the patient first reported a feeling attributable to tremor in the legs; and finally when they felt the maximum degree of unsteadiness. The times from standing to subjective tremor, and standing to unsteadiness were measured.

Results: The mean age of patients was 68 years (range 48-79) and mean duration of OT was 4.8yrs (2-10). The mean time to awareness was 40sec (10-81). The mean time to unsteadiness was 156sec (40-365). There were no changes in tremor frequency or amplitude at any time point after standing (onset of subjective tremor and onset of maximum unsteadiness) in any patient.

Conclusions: We found that despite the tremor being present within milliseconds of standing, patients became conscious of "tremor" at

least 10 seconds later and maximum unsteadiness developed only after 40 seconds. These subjective experiences were not related to any change in the electrophysiological characteristics of the tremor. These findings lend support to a role for the cerebellum. Cerebellar motor cognition is thought to provide efficient adaptation to movements by way of sensory comparison of predicted and desired movement trajectories. These adaptations occur over seconds to minutes and may explain the observed subjective delay in unsteadiness in OT patients.

Mo-366

The smiling tremor

J. Czerny, C. Cordivari, P. Schwingenschuh, M. Esposito, K.P. Bhatia (London, United Kingdom)

Objective: To describe two patients, who present with what we describe as "smiling tremor" involving facial muscles and appearing only on smiling or other activations of the risorii muscles.

Background: Together with tremors of the jaw, tongue and pharynx, tremors involving the face are part of the spectrum of orolingual tremors. The "smiling tremor", an action-induced facial tremor involving mainly the cheeks and occurring on activation of the risorii muscles is a rare phenomenon and has been mentioned in the literature only once.

Methods: We performed a diagnostic workup including accelerometry and needle electromyography (EMG) recordings from the orbicularis oculi and risorii muscles at rest and during smiling in 2 patients who presented to us with the complaint of a facial tremor induced by smiling.

Results: Accelerometry and needle electromyography recordings from the orbicularis oculi and risorii muscles at rest were unremarkable. Recordings during smiling showed highly regular and rhythmical electrical discharges (burst duration between 50 and 70 msec). Power spectrum analysis revealed a peak tremor frequency of 9.5Hz and 9.1Hz respectively. EMG-EMG coherence analysis during smiling showed a common drive for the right and left risorius in both patients. One patient additionally suffered from young-onset Parkinson's disease, however his "smiling tremor" did not resemble classical orolingual parkinsonian tremor in that it did not occur at rest or in association with a tremor of the limbs and did not respond to antiparkinsonian medication. The second patient presented with no other neurological symptoms or signs.

Conclusions: We believe that this form of tremor should be recognized and encourage others with a similar experience to describe their findings. It would be interesting to see whether this tremor is a rare and possibly early symptom of Parkinson's disease or whether it exists as a discrete entity.

Mo-367

Late onset dystonia in essential tremor (ET)

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Objective: To further characterize the clinical spectrum of ET.

Background: The co-morbidity of ET and dystonia suggests possible shared pathogenic mechanisms, including genetic pleiotropy or digenic effects. A retrospective chart review reported that 47% of ET patients have dystonia, although this population was skewed as 12 patients had a family history of dystonia and 42 (25%) were referred to the clinic because of dystonia. Further characterization of ET patients who develop dystonia is warranted and may aid in the identification of causative genes.

Methods: All patients with a diagnosis of essential tremor who were examined in our movement disorders center in the past 2 years (2007-2008) were identified for chart review. None of the patients were referred to the clinic for dystonic symptoms. Clinical information including sex, ethnic origin, age and site of ET onset, age and site of dystonia onset, family history, and exposure to DA blocking agents were noted. Accompanying videos were reviewed, when available.

Results: Forty-one patients were identified for review; 23 (56.1%) were women. Mean age of ET onset was 40.2 yrs and mean disease duration was 24.4 yrs. Twenty patients (48.7%) were AJ. Although a family history of ET was seen in 56.1% of the total population, only 8 (40%) of the AJs had a family history compared to 15 (71.4%) of the non-Jews (NJ), p=.04. Five patients (12.2%) were identified with both ET and late onset dystonia, 1 NJ man and 4 AJ women. All had a family history of ET and no exposure to DA blockers. The NJ man had a paternal inheritance and writer's cramp. Three of the AJ women had maternal inheritance. Patient 1 developed ET in both hands at age 22 and cervical dystonia at 51. Patient 2 developed ET in both hands at age 29 and cervical dystonia at 50. Patient 3 had neck tremor at 52 that was responsive to alcohol and significantly improved on primidone. She developed neck dystonia at 60. Unilateral brachial dystonia appeared in late adulthood; exact age of onset was uncertain.

Conclusions: We have identified a subpopulation of AJ women with ET and late onset dystonia. Family history suggests a genetic origin with sex influences on expression. Further clinical characterization of this population including family studies may aid in elucidating the genetic origins in this clinical-ethnic group.

Mo-368

Lower limb rest tremor – A red flag for the diagnosis of Parkinson's disease

M. Hellmann, A. Shteinmetz, E. Melamed, R. Djaldetti (Petah Tiqva, Israel)

Objective: To describe characteristics and follow up of consecutive patients that presented to the Movement Disorders Clinic with lower limb rest tremor.

Background: Most patient who present with an isolated asymmetrical upper limb rest tremor go on to develop Parkinson's disease (PD). Lower limb rest tremor at disease presentation is an unusual phenomenon. It may represent a rare presentation of PD or may herald the start of another degenerative neurological disease.

Methods: Patients who presented consecutively to the Movement Disorders Clinic between 2000 and 2009 with lower limb rest tremor were selected. Patients without a definite clinical diagnosis underwent cardiac MIBG SPECT.

Results: 16 patients presented to our clinic with a lower limb rest tremor. Mean age was 56±16 years and mean disease duration 5.7±9 years. Six of the patients were diagnosed as PD on grounds of the clinical symptoms and response to levodopa therapy. They subsequently developed levodopa side effects including motor fluctuations, dyskinesias and visual hallucinations. Four patients met clinical criteria for MSA according to the Second Consensus Statement on the diagnosis of multiple system atrophy (MSA). Three other patients without a definite diagnosis of PD or MSA underwent MIBG scan which did not show cardiac denervation in two. One patient had drug-induced tremor. The last 2 patients had fluctuating tremors that ultimately disappeared and were diagnosed as psychogenic tremor.

Conclusions: Lower limb rest tremor is an unusual presentation of PD and should raise the suspicion of MSA, other neurodegenerative diseases or psychogenic tremor.

Mo-369

Are patients with psychogenic movement disorders and psychogenic non-epileptic seizures one and the same?

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Objective: To compare PNES and PMD patient demographics, clinical features, symptomatology, risk factors for developing a psychogenic disorder, psychiatric and neuropsychological profiles, and the standard diagnostic approach in the two groups.

Background: Psychogenic non-epileptic seizures (PNES) and psychogenic movement disorders (PMDs) are common in neurology

practice, yet it is not established whether clinically relevant differences between these two groups exist. No previous studies have directly compared them.

Methods: Following IRB approval, clinical data was obtained in a retrospective chart review study of patients diagnosed with PNES and PMD at Mayo Clinic Arizona (MCA) department of neurology from January 2005 through December 2007. Statistical comparisons were performed using chi-square tests for categorical variables and t-tests for continuous variables with a two-tailed test of significance. A p-value of <0.01 was considered statistically significant throughout, given the number of statistical comparisons. In some cases, a small sample size precluded comparison and descriptive information is provided in those cases.

Results: 172 patients were identified (PNES n=116, PMD n=56). Both groups were characterized by female gender (82%), abuse history (45%), chronic pain (70%), depression (42%), subjective fatigue (47%), subjective cognitive impairment (55%), and referral for psychiatric evaluation (54%). Statistically significant differences ($p<.01$) were found for age, education, frequency of symptoms, altered consciousness, developmental abuse, and coexisting anxiety. PMD diagnosis relied on head MRI and neurologic history and physical exam, while PNES evaluation also including video-EEG monitoring (100%) and neuropsychological evaluation (82%).

Conclusions: This comparison study revealed more similarities between PMD and PNES patients than differences suggesting they are manifestations of the same psychopathology. Observed differences may largely be explained by false sub-classification as seizure or a movement disorder. Future studies focusing more globally on somatoform disorders are needed to improve clinical care and outcomes.

Mo-370

Transcranial sonography in patients with essential tremor

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Objective: To compare the echogenicity of the Substantia nigra (SN) in patients with pure Essential tremor (ET) and Essential Tremor and Parkinson's disease (PD).

Background: ET is the most common adult movement disorder with a prevalence between 2,8% and 4% in individuals aged older than 40 years. Several studies have found ET patients to carry an increased risk for PD compared with the general population. A SN hyperechogenicity is a characteristic ultrasound finding in more than 90 % of patients with PD. In ET patients typically a normoechogenic SN is found.

Methods: The transcranial sonography (TCS) was performed by using a phased-array ultrasound system equipped with a 2.5 MHz transducer (Sonoline Elegra, Siemens). The examination was performed through a preauricular acoustic bone window according to Berg, SN echogenic sizes of less than 0,20 cm^2 were classified as normal, sizes of 0,20 cm^2 and above as hyperechogenic. Consecutive patients with the clinical diagnosis of Essential tremor according to MDS consensus criteria and Essential tremor with Parkinson's disease according UK Brain Bank criteria were included in this case series. The ultrasound investigator was blinded to the clinical diagnosis.

Results: 15 patients with pure ET and 11 patients with ET and PD, admitted as inpatients in the Paracelsus-Elena Klinik from March 2006 to November 2008 were examined. In 11 of 15 patients with pure ET the SN was normal (mean 0,12 cm^2), in 4 patients the acoustic bone window was inadequate. In 5 of 11 patients with ET and PD a hyperechogenic SN was found, a normoechogenic SN was found in 3 patients (mean 0,21cm^2), in 3 the acoustic bone window was inadequate.

Conclusions: Recent studies (Stockner et al., Movement disorders 2007; Budisic et al., Acta Neurol Scand. 2008) showed an SN hyperechogenicity in ET patients between 13 and 16 %, which is more frequent compared to healthy controls, as approximately 9% of the the healthy population exhibit a hyperechogenic ultrasound signal. Our data confirm the results of Stockner et al. (Movement disorders 2007) and suggest that SN hyperechogenicity in ET patients may be a biomarker for developing PD.

Mo-371

Case of orthostatic tremor responsive to bilateral thalamic deep brain stimulation

V.G.H. Evidente, J.N. Caviness, B. Falk, R. Hillman, M.K. Lyons (Scottsdale, Arizona)

Objective: Describe a case of Orthostatic Tremor (OT) responsive to bilateral thalamic deep brain stimulation (DBS).

Background: There are only 3 reported cases of OT that have undergone DBS surgery. Two underwent bilateral thalamic DBS with a sustained response of 1.5 and 4 years so far. One had unilateral thalamic DBS with only a 3 month benefit. We report a patient with medically refractory OT who underwent bilateral thalamic DBS.

Methods: Case report

Results: A 75 yo man has had a 10-year history of progressive OT. Before surgery, he had to use a portable stool/cane anytime he had to stand in place. He had tried unsuccessfully clonazepam, valproate, gabapentin, topiramate, and acetazolamide. Before DBS, he would have immediate onset of fine tremors of both legs upon standing. He could only stand in place for 20 seconds at most before needing to sit, lean, or hold on to something. Surface EMG showed 10-12Hz tremors of the lower extremities upon standing, which spread upwards to his paraspinal muscles, truncal muscles, and upper limb muscles. He underwent bilateral thalamic VIM DBS surgery using Medtronic® 3389 DBS electrodes and Kinetra pulse generator. Intraoperative mapping was assisted by surface EMG recordings of the legs, asking the patient to push down on each leg against resistance. Final electrode placement per side was determined based on stimulation side effects and improvement of the contralateral leg tremor on surface EMG with macrostimulation. Initial programming settings post-DBS for the left IPG were contacts 0 & 1(-), contact 2(+), 2.8 volts, 90microseconds, & 185Hz. For the right IPG, settings were contact 0(-), contact 1(+), 2volts, 90microseconds, & 185Hz. At these settings, he had a subjective 75% improvement of his orthostatic leg tremor in the left, and 50% in the right. He was able to stand in place for 5 minutes. On last follow-up 1 month post-DBS, he reports a subjective 80% improvement of his orthostatic leg tremor in the left, and 50% in the right. He was able to stand in place for 7 minutes. He had stopped using his portable stool/cane by then.

Conclusions: Bilateral thalamic DBS may be a viable option for medically refractory OT. As with arm tremor, the effect of bilateral thalamic DBS on OT can be different in either leg. Longterm response needs to be monitored and more cases need to be observed.

Mo-372

Use of Nintendo Wiimote(R) to evaluate postural tremor after DBS

J.Y. Fang, T.L. Davis (Nashville, Tennessee)

Objective: To develop a simple recording method to evaluate the efficacy of deep brain stimulation (DBS) in essential tremor (ET) patients

Background: Programming DBS stimulators can be a time-consuming process due to the need to trial multiple settings in a systematic fashion. In this study, ET patients who had previously undergone DBS were evaluated using the Nintendo Wiimote (R) at various settings of their DBS pulse generator. Analysis of the acceleration data was compared to previously determined DBS settings.

Methods: Patients who had undergone DBS for ET were asked to participate in this study. After informed consent, each subject was asked to hold the Wiimote(R) with each arm extended for at least ten seconds. Postural tremor was measured by recording the accelera-

tion measured by the Wiimote(R) on a Windows-based PC. The DBS voltage was adjusted to 0%, 25%, 50%, 75%, and 100% (default) of the previously determined optimal settings in random order. Total acceleration was compared for each of the settings.

Results: Total acceleration as measured by the Wiimote(R) correlated inversely with the voltage of DBS settings.

Conclusions: Our data show that the Wiimote(R) is a useful device to measure postural tremor in patients with essential tremor who have undergone bilateral DBS. This technology can be useful in programming DBS patients. Interestingly, there was a voltage-dependent efficacy response curve, supporting the view that DBS effectiveness can be titrated by adjusting the DBS output strength.

Mo-373

Tremor associated with chronic inflamatory demyelinating peripheral neuropathy

M. Gallardo, A. Soto (Caracas, Venezuela)

Objective: To report a case of a patient seen in our institution with tremor associated with chronic inflamatory demyelinating neuropathy.

Background: Neuropathies may cause abnormal movements including tremor. The tremor reported in this condition is mostly of postural and action type. The pathophysiology of this tremor is believed to be due to abnormal interaction of peripheral and central factors.

Methods: We studied a patient with tremor who developed unsteady gait **of lower limbs gradually**. Detailed history was taken and physical examination and routine laboratory test were performed. Magnetic resonance imaging of the brain, nerve conduction studies and nerve biopsy were also performed on the affected patient.

Results: We report on a 57 year-old woman with distal demyelinating symmetric neuropathy who complained of gradually increased weakness and clumsiness in her lower limbs. A disabiling postural and kinetic tremor in both hands was present since one year ago. Voice tremor was also observed 6 months ago. No medical history of familial neuropathy, central nervous system disorder or essential tremor was reorted. Neurological examination revealed mild distal muscle weakness, decreased deep tendón reflexes and glove-stocking distribution of sensory déficits. Romberg sign was positive. She could stand well but she had unsteady gait because of impaired proprioception. Postural and action tremor were observed in distal upper extrremities. No lower limbs tremor or signs of Parkinson's disease was observed. Electrophysiological studies revealed mixed motor-sensory demielynating polyneuropathy. Sural nerve biopsy demonstrated loss of myelinated fibers. Routine laboratory and Brain RMI were normal. Serum protein electrophoresis was also normal. Inmunological analysis was reported normal.

Conclusions: Findings in a previous reports support the neurogenic mechanism in generation of tremor in demyelinating neuropathy. An abnormal resting of central oscillator due to the distortion of sensory input caused by peripheral conduction abnormalities may cause tremor. These observations imply the important role of sensory inputs in the pathogenesis of tremor and another movement disorders.

Mo-374

The Glass-scale: A simple tool to determine severity and stage in essential tremor

A. Gironell, M. Martínez-Corral, J. Pagonabarraga, J. Kulisevsky (Barcelona, Catalonia, Spain)

Objective: We have developed a new scale, termed "the Glass-scale", which is subjective, easy to use and quick to perform for ET patients with upper limbs involvement (95 % of patients).

Background: In clinical practice, there is a need for a simple measurement tool to help stage disease and disability severity in essential tremor (ET), such as the Hoehn & Yahr scale for Parkinson's disease.

Methods: The scale is based on asking the patient one question: "Over the last week, when you are seated at the table, how do you drink water from a glass?" Scores: I- I have no difficulties. II- I can drink with one hand, but I have to fill the glass with less liquid to avoid spills. III- I can not drink with one hand, I need both hands. IV- I can not drink with my hands, I need a straw. If tremor only involves upper limbs, the Glass-scale score is followed by "A", and if tremor involves other areas such as head, trunk and voice, the score is followed by "B". The scale was validated in 40 ET patients (10 patients for each scale score). Construct validity of the Glass-scale (ranging from I to IV) was examined against the Tremor Clinical Rating Scale (TCRS) and the Bain subjective disability scale. A second neurologist blinded to the Glass-scale score assessed inter-rater reliability.

Results: The scale displayed strong construct validity compared to TCRS (w. kappa = 0.90) and to the Bain scale (w. kappa = 0.87). High inter-rater validity was also observed (w. kappa = 0.98).

Conclusions: The Glass-scale appeared to be a reliable and valid tool to indicate tremor severity in ET. The simplicity of the scale makes it appropriate for use in routine clinical practice. Future prospective studies would determine its utility as a marker of disease stage.

Tu-362

Differential neuroscientific analyses of the pathological tremor

M.I. Gospodinov (Sofia, Bulgaria)

Objective: To examine the problem of differential neuroscientific analyses of the pathological tremor to a sertain degree.

Background: Still the problem of differential neuroscientific analyses of the pathological tremor is less investigated.

Methods: The methodical standard for investigation includes a comlex statokinesimetry. 75 patients with pathological tremor (mean age 60.56 ± 12.10 years, range 12 – 89 years) and 19 healthy control subjects (mean age 27.05 ± 9.12 years, range 17 – 37 years) have been investigated. We applied non-parametrical statistical analyses, esp. Statistics 7.

Results: The research established statistically significant difference between tremor frequencies of the both hands in rightist females ($p< 0.001$) and rightist males ($p< 0.001$) and did not establish statistically significant difference between tremor frequencies of the right hands of rightist females ($p> 0.05$) and rightist males ($p> 0.05$). The results exhibit group tendencies ($p<0.05$) and interindividual differences ($p<0.001$) for energetic-and-informative ($p<0.002$) and time-space ($p<0.001$) parameters of the motor activity in parkinsonian ($p<0.001$), like-parkinsonian($p<0.001$) and non-parkinsonian patients ($p<0.001$).

Conclusions: The results we obtained showed that differential neuroscientific analyses serve for early diagnosis ($p<0.05$) as well as for monitoring ($p<0.001$) the treatment of Parkinson's disease.

Tu-363

Case report of tremor and deep brain nuclei hyperintensities in Kabuki syndrome

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Objective: To describe the neurological and imaging findings in a patient with Kabuki syndrome.

Background: Kabuki make-up syndrome (KMS) is a rare congenital disorder first described in 1981. Case reports have indicated multiple congenital abnormalities; skeletal anomalies, mental retardation, characteristic facial appearance, and peculiar dermatoglyphic pat-

terns. While multiple CNS structural abnormalities and exam findings have been reported previously, the findings observed in our patient have not yet been described.

Methods: We evaluated a patient with Kabuki syndrome while on the neurology consult service at our institution. A complete history and neurological exam were performed. Relevant laboratory investigations, electroencephalography, CT, and MRI were collected and interpreted. We also obtained video imaging of our patient's tremor.

Results: While our patient had the characteristic morphological features of Kabuki syndrome, she was also found to have physiological tremor in her distal upper extremities. MRI revealed symmetric T2-hyperintense lesions with mildly restricted diffusion in the lentiform nuclei, red nuclei, and dentate nuclei bilaterally. There was also subtle T2-hyperintensity in the corpus callosum. EEG showed no seizure discharges, and the jerking movements that occurred during the study were not associated with any epileptiform activity.

Conclusions: We report the finding of physiological tremor and multiple deep brain nuclei T2-hyperintensities in a patient with Kabuki syndrome. While multiple CNS abnormalities have been reported previously, this is the first case in which a patient was found to have the findings we observed. The significance of these features in the setting of KMS is unknown, but may suggest the presence of a metabolic disturbance preferentially affecting the deep brain nuclei.

Tu-364

Audiogenic startle response in patients with orthostatic tremor

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Objective: We aimed to investigate the functional role of brainstem and presence of similar generator in brainstem through the evaluation of Audiogenic startle response (ASR)and blink reflex (BR) in primary OT patients.

Background: Primary orthostatic tremor (OT) is defined as a clinical syndrome with high frequency tremor predominantly on calf muscles while standing. It is thought to be driven by a supraspinal generator. This generator is hypothesized to be brainstem since brainstem comprises bilaterally projecting centers regulating stance or tone such as reticulospinal tract and pedinculopontine nucleus. ASR is a brainstem reflex and is mediated by reticulospinal tract, especially the caudal pontine reticular nucleus in conjunction with vestibulospinal tracts.

Methods: We investigated ASR and BR in consecutive 2 male and 5 female OT patients with mean age 68.5±10.5 years and compared the results with those of age and sex-matched 9 healthy volunteers. Surface electromyography and reflex recordings from certain muscles of lower and upper extremity and paraspinal region were performed during sitting, standing and standing with different gravity centers. Comparisons were made by t test or Fisher exact test for quantitative data and by chi-square test for qualitative data.

Results: Frequency of leg tremor was 14 Hz in one patient, 15 Hz in two patients, 17 Hz in three patients and and 18 Hz in one patient. In all patients, paraspinal involvement accompanied. In 2 patients, OT also emerged on arms and in 3 patients postural arm tremor accompanied. ASR was not obtained in two patients with OT even over O.oc muscle and mean probability rates of ASR in O.oc were lower in OT group (68.8% vs 100%, $p=0.022$). Amplitudes of responses in O.oc were also lower in OT group compared to controls, however this was statistically insignificant (235.0±144.8 vs 313.5±161.7, $p= 0.433$). Patients with OT had similar ASR onset latencies in O.oc in comparison to controls (38.1 vs.41.6 msec; $p=0.652$). In OT group, no difference is observed between investigations upon sitting and standing. ASR Responses over other muscles or BR responses didnot show significant difference.

Conclusions: Intact R1 and R2 responses together with decreased probability ASR may reflect dysfunction of pontomedullary reticulospinal tract.

Tu-365

High-dose 1-Octanol in essential tremor: Further evidence for mechanism of action mediated through octanoic acid

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Objective: To characterize clinical and pharmacokinetic properties of oral high-dose 1-octanol (128mg/kg) in adults with essential tremor (ET).

Background: As previously demonstrated, 1-octanol is effective in reducing tremor in doses up to 64mg/kg. Pharmacokinetic data suggest a rapid conversion to octanoic acid (OA), while 1-octanol is only detectable at low levels (Nahab, 2008). The goal of this study extension was to investigate the mechanism of action of 1-octanol and its metabolism by further dose escalation to 128mg/kg.

Methods: Two subjects (1f, 1m), who participated in the 64mg/kg fixed dose study-phase, received oral 1-octanol at a dose of 128mg/kg. Plasma samples were collected 5, 20, 45, 70, 100, 130, 160, 210, and 360min post dose and analyzed using high-performance liquid chromatography and mass spectrometry to measure 1-octanol and OA. Efficacy measures included digitizing-tablet based Archimedes spirals drawn by subjects at multiple time-points after administration and washout, as well as long-term bilateral uniaxial accelerometry, wrist-worn throughout the entire study.

Results: The subjects tolerated the dose well. OA plasma levels were detectable 5min after administration and persisted until 6 hours post dose with a peak at 100min (Cmax 444.5 ng/ml/kg). 1-octanol was only detectable at low levels lacking a dose-response relation. Calculated OA plasma half-life was 88.9min. Spirography revealed a 56% peak reduction of tremor intensity (amplitude of velocity signal at tremor spectral peak frequency), mean accelerometric tremor severity, calculated based on published algorithms (Van Someren, 2006; Nahab, 2007), showed a reduction of 49% over a 5 hour period after administration.

Conclusions: After the oral administration of 1-octanol, a rapid rise in OA plasma levels was detectable, demonstrating a pharmacokinetic profile as seen at lower doses, however with higher Cmax values than observed after 64mg/kg. Overall OA plasma responses across doses (1–128mg/kg) describe an exponential relationship, while no consistent dose-response relation was seen for 1-octanol levels. Clinical measures of tremor intensity improved considerably after administration of 1-octanol. These data provide further evidence for OA as the potential active metabolite of 1-octanol.

Tu-366

Clustering of dystonia in some pedigrees with autosomal dominant (AD) essential tremor (ET) suggests the existence of a distinct genetic subtype of ET

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Objective: To analyze the frequency and distribution of dystonia in kindreds with AD ET.

Background: There is an ongoing discussion whether ET represents a monosymptomatic disorder or other neurologic signs are compatible with the diagnosis of ET. Many patients with ET develop dystonia. Cervical dystonia, blepharospasm and spasmodic dysphonia are the most common types of dystonia in ET. It remains unknown whether tremor associated with dystonia represent a subtype of ET or is unrelated to ET.

Methods: We studied patients diagnosed with either ET or dystonia if their first-degree relatives met diagnostic criteria for clinically definite ET. Furthermore, we included only individuals from the pedigrees containing at least two living individuals with ET, defined as

bilateral postural and action tremor without any additional neurologic abnormalities, and the mode of inheritance was consistent with AD. This cohort was ascertained for the presence of focal or segmental dystonia. We did not include patients with isolated spasmodic dysphonia as a sole manifestation of dystonia, and also excluded patients with generalized dystonia and dystonic tremor.

Results: The studied cohort consisted of 457 individuals from 136 kindreds. Dystonia was diagnosed in 78 patients (30 men and 48 women); 68 had a motor phenotype consistent with ET associated with dystonia, and 10 had an isolated dystonia without any tremor. Blepharospasm was present in 15 patients (19%), cervical dystonia in 42 (54%), Meige syndrome in 16 (21%), and a limb dystonia in 5 (6%). Within the subgroup of 10 patients with an isolated dystonia, 3 had blepharospasm and 7 had cervical dystonia. Overall, all 78 patients with associated dystonia were from 21 pedigrees (15% of all included pedigrees), and only seven families had a single individual with dystonia. Each family with a single dystonia patient consisted of only three affected individuals.

Conclusions: We did not observe a random distribution of dystonia in AD ET pedigrees but it rather clustered in a small number of kindreds. Our results suggest that ET associated with dystonia may represent a distinct subtype of ET. The coexistence of clinically definite ET and ET with dystonia in these families also indicates that tremor with dystonia is related to ET.

Tu-367

Double-blind, randomized, placebo-controlled, cross-over trial of pregabalin in essential tremor

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Objective: To assess the tolerability and efficacy of pregabalin (PGB) in patients with essential tremor (ET).

Background: PGB is an amino acid derivative of gamma-amino butyric acid with antiepileptic, analgesic, and anxiolytic properties. Preliminary studies suggest that PGB also has tremorlytic effects; however, data regarding the drug's efficacy and tolerability in ET is limited.

Methods: In this double-blind, crossover-design study, 20 patients with moderate-to-severe ET (11 women, mean age 62.2±12.7 years, mean ET duration 25.5±14.9 years) were randomized to treatment with PGB (150-600 mg/day) or placebo, titrated over 6 weeks. Assessments with the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) (primary endpoint), Clinical Global Impression Change (CGI-C), Quality of Life in Essential Tremor Questionnaire (QUEST), Hamilton Anxiety Scale (HAM-A), and a sleep hygiene questionnaire (HD-16) were made at baseline, at the end of treatment periods for both drug and placebo, and following the 2-week washout period preceding crossover. Adverse effects were monitored at weeks 3 and 6 after initiating PGB or placebo. Sixteen of 20 patients completed the study and were included in analysis of drug efficacy. Outcome was assessed via ANOVA models using a 2 x 2 Latin-square crossover design including sequence, period, and treatment effects.

Results: The mean percent change in TRS summary score from baseline was -3.9 (±9.4) for PGB and -4.9 (±15.5) for placebo ($p=0.6$). There were no statistically significant differences in the secondary outcome measures including CGI-C between PGB and placebo. Adverse events were generally mild and were similar in incidence to previously published studies of PGB, the most common being drowsiness and dizziness.

Conclusions: This pilot, placebo-controlled trial fails to provide evidence for a tremorlytic effect of PGB in patients with moderate-to-severe ET. A larger sample size and parallel-design study is needed before it can be concluded that PGB is not effective in ET.

Tu-368

Impairment of rapid repetitive finger movements and visual reaction time in patients with essential tremor

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Objective: To analyze motor performance in a large series of patients with ET and in healthy matched controls.

Background: The question whether patients with ET have also slowed movements as part of their clinical manifestations, is still a matter of controversy. To date, only a few studies tried to approach to this issue. However, most of them had a low sample size and/or assessed only one or two tasks; and none of them tried to establish the possible relationship between motor impairment and clinical scales of tremor severity.

Methods: We studied 61 patients with ET and 122 age and sex matched controls. Evaluation included four timed tests (pronation-supination, finger tapping and movement between two points, all with both hands, and walking test); and three tests performed on a personal computer (speed for pressing repetitively a key –frequency-, visual reaction time, and movement time, all with both hands). We assessed tremor severity with the Fahn-Tolosa Marin and Louis Tremor Rating Scales. Statistical analyses included the t-test, the Mann-Whitney Rank Sum test, Bonferroni's test, bakcward logistic, and Pearson's or Spearman's correlation coefficients when appropriate.

Results: In an univariate study, the total group of ET patients showed higher mean values for right and left finger taping, left movement between two points; and with right and left frequency and reaction time. In the multivariate study, the total group of ET patients showed significantly higher values than controls for right and left finger tapping; mean, standard deviation, maximum and rank values of right and left frequency; and mean, standard deviation, minimum, maximum and rank values of right and left visual reaction time. Tremor severity was not correlated with the altered values.

Conclusions: Patients with ET showed impairment in rapid repetitive finger movements (finger tapping and frequency) and in visual reaction time (impairment was not related with tremor severity); while performance of alternating pronation-supination movements, movement between two points, movement time, and walking test, was similar to those of age- and sex-matched controls.

Tu-369

Dystonic tremor as the initial manifestation of brain tumor

J. Kim, S. Ahn, H. Kim (Gwangju, Korea)

Objective: To report a case of leg tremor as the initial manifestation of brain tumor.

Background: Sudden involuntary movement among the old age is not uncommon. Various etiologies such as stroke, drug, toxin, epilepsy and infection cause involuntary movements. Among them, brain tumor is a very rare event. We recently experienced a case of focal involuntary movement associated with malignant parasagital frontal tumor.

Methods: A 67-year-old woman came to the hospital because of suddenly developed painful cramping and tremulous movements of the right leg persisting several minutes starting 1 week ago. The frequency and duration of the patient's symptoms increased. Right knee and ankle extension with toe dorsiflexion was followed by 6-7Hz tremor which persisted for 2–3 minutes. The frequency was 2-3 times an hour and it was not affected by a certain position or action and decreased but not disappeared during sleep. On admission, neurologic examination showed neither focal motor or sensory deficit nor pathologic reflex.

Results: MRI showed high intensity lesion of left parasagital area in FLAIR and T2 weighted images with minimal gadolium enhancement. EEG revealed frequent bifrontal but left dominant theta-range

slowing. During involuntary movement, surface EEG polygraphy of leg muscle showed continuous contraction of right tibialis anterior, gastrocnemius and vastus muscle with later 6-7Hz semirhythmic contraction reflecting tremor. Follow up EEG and video EEG monitoring showed no epileptic evidence and anticonvulsant medications were ineffective, so dystonic tremor associated with subacute anterior cerebral artery infarction was considered. Clonazepam was substituted and involuntary movements were decreased. MRI followed up 1 month after the onset showed no significant changes. Involuntary movement disappeared after 2 months of the onset. At 7 months after the onset, dysarthria and right hemiparesis developed. Follow up MRI showed much increased lesion with prominent enhancement and surrounding cerebral edema. PET-CT scan displayed hypermetabolic mass lesion suggesting high malignant potential. Cerebral biopsy and aggressive therapy were refused.

Conclusions: Focal involuntary movement is strongly suggestive of focal cerebral lesion. Brain tumor should be a diagnostic consideration.

Tu-370

Is there white matter pathology in essential tremor? An optimised diffusion tensor imaging study

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Objective: To determine if there is white matter pathology in Essential Tremor detectable by DTI.

Background: Despite being the most common movement disorder, there are only few neuropathologic studies investigating the cause of Essential Tremor. Its progressive nature suggests a degenerative disease, and previous studies have tried to analyse its impact on white matter pathways in the human brain using non-invasive DTI MRI. These studies, however, have been inconclusive so far with conflicting results published by different groups. Here, we aim to study a larger set of ET patients using an MRI protocol optimised for high signal to noise and low distortion. We report interim results on the subjects acquired so far.

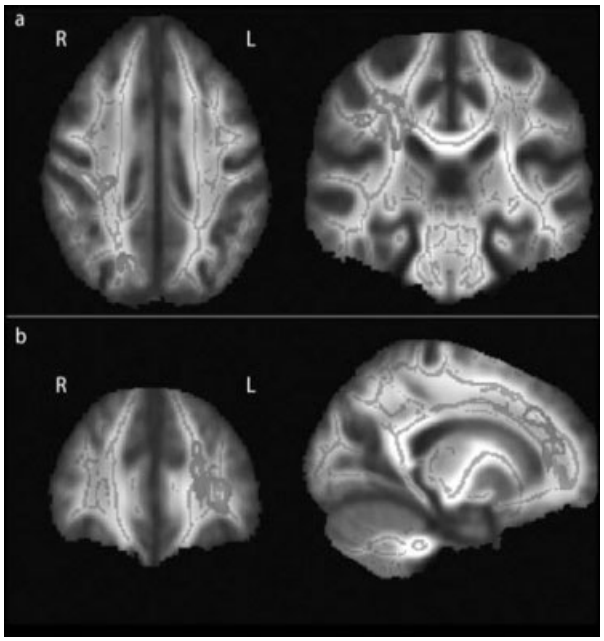

FIG. 1 (Tu-370).

Methods: 10 patients with ET (67.7 ± 4.2 yrs) and 9 control subjects (61.8 ± 8.8 yrs) underwent diffusion MRI (Siemens Trio 3T, 60 directions, $b=1000\times mm^2$, 70 axial slices, $2\times2\times2$ mm^3, SENSE 2, TE 95ms, 3 repeats). Data were analysed using FMRIB's software library (FSL), including motion and eddy-current correction, averaging and fitting of the diffusion tensor model. FA images were registered non-linearly, and a tract skeleton for FA>0.2 was derived (TBSS). Individual FA were projected onto this skeleton using maximum FA values found perpendicularly to the planes defined by the skeleton. Non-parametric statistics were computed using permutation-based testing and threshold-free cluster formation, corrected for age.

Results: We did not find statistically significant differences between patients and control subjects. There was a trend for reduced FA in white matter underlying right somatosensory cortex (Fig. 1a) and left premotor cortex (Fig. 1b, $p\approx0.15$).

Conclusions: While we did not detect significant differences in FA, there was a trend for reduced FA in projections within the cerebral motor system. Cortico-thalamic motor loops are part of the hypothetical network thought to generate the tremor in ET, effectively targetted by deep brain stimulation and lesional techniques. We plan to enhance our statistical power by acquiring more subjects, and if our findings are confirmed in a larger group of patients, they would be compatible with involvement of both somatosensory and somatomotor projections in the pathologenesis of ET.

Tu-371

Delayed-onset parkinsonian tremor after a mesencephalic lesion

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Objective: To report an isolated parkinsonian tremor associated with a cerebral peduncular lesion.

Background: The topography of the lesions associated with secondary parkinsonian tremors can provide relevant information for the physiopathology of idiopathic parkinsonian symptoms.

Methods: The patient was assessed by a movement disorder specialist. Ancillary exams comprised brain MRI and EMG of upper limbs.

Results: This 63 years-old woman complaint of a left hand tremor, which had started at the age of 43. It was present at rest and while holding postures, regressing during movements. Her medical history was significant for an acute episode of vomit, diplopia and weakness of her left body at the age of 6, the aetiology of which we could not ascertain. She recovered almost completely. There was neither neuroleptic exposure nor tremor history in her family. The neurological examination showed a left upper limb, slow, rest tremor, with a "pill-rolling" pattern, which re-emerged during postures. There was no rigidity or bradykinesia and her gait was normal. There were slight pyramidal signs in her left body. EMG showed a 4-5 Hz rest and postural tremor with an alternating pattern. MRI showed a right peduncular residual lesion, comprising the dorsal area of the sustantia nigra (SN) and prerubric area. She was started on levodopa/carbidopa 100/25mg TID and her tremor improved.

Conclusions: Our patient presented with an isolated typical parkinsonian tremor, possibly related to destruction of the dorsal SN region and pre-rubric area. While suggesting a separate topography for parkinsonian symptoms on SN, this also supports the involvement of other neuronal circuits in the pathogenesis of classic parkinsonian tremor. It seems that both SN and rubro-olivo-cerebellar/cerebello-thalamic pathways involvement is needed to produce this symptom. The influence of Vim nucleus stimulation on the latter circuit could explain its restricted benefit on tremor in Parkinson' disease patients. Late onset could be explained by the adding effects of natural, age-related depletion of dopaminergic neurons on an already damaged SN.

Tu-372

Changes in physiological tremor induced by acute hypoxia

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Objective: To quantify and characterize the effects of one hour of acute hypoxia on human physiological tremor and finger tracking performance.

Background: Human physiological tremor is a complex phenomenon modulated by numerous neurophysiological and environmental conditions. It has been suggested that an increase of tremor amplitude can result from acute hypoxia. Based on the results of prior studies, we hypothesized that human participants exposed to a simulated altitude of 4,500 m would display an increased tremor amplitude within the 7 – 12 Hz frequency range.

Methods: Altitude stress was induced using two digitally-controlled air units simulating 4,500 m altitude inside a transparent tent (normobaric chamber with a 14.8% O_2 gas mixture). Postural and kinetic tremors were recorded at the tip of the dominant index finger with a laser system for twenty-three healthy male participants before, during, and after one hour of induced hypoxia.

Results: Acute hypoxia (blood saturation in oxygen = 80.9 %) increased tremor amplitude between 7 and 12 Hz during both postural and kinetic tremor tasks ($p<0.005$, $F=6.47$, $eta^2=0.24$ and $p<0.01$, $F=6.69$, $eta^2=0.23$ respectively). No significant effects were observed on the tracking performance (timing and precision).

Conclusions: This study confirms that changes in human physiological tremor can be detected at low hypoxemic levels. These changes are concentrated in the 7-12 Hz frequency range which suggests an effect of acute hypoxia at the central nervous system level.

Tu-373

Focal task-specific hand tremor with using scissors

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Objective: To evaluate the clinical features in a case of task specific focal hand tremor with using scissors.

Background: Task-specific tremors are a rare form of tremor that involves skilled, highly learned motor acts. Focal, task specific tremors are most commonly found in the hand and arm. The most common form is writing tremor and in most of these cases, other manual tasks are unaffected. Focal task-specific tremors besides primary writing tremor have rarely been reported.

Methods: A 51-year-old right –handed tailor had a 8-year history of shaking of his right hand in particular circumstances that interfered with his work. On using scissors, when his hand got into a certain position, he developed a severe tremor of his right hand. The problem gradually worsened, and he visited the hospital for the further evaluation and treatment. In family history, his father had an arm tremor. We took video-taping with performing multiple tasks.

Results: On examination, he had no resting or postural tremor. There was a slight terminal tremor on finger-to-nose testing. There was a 5-6Hz flexion-extension tremor of his right wrist, that occurred only when he used scissors with his right hand. The tremor was worse when starting the scissoring, and especially supinated posture; the heavier the scissors and the greater the required accuracy, the tremor increased. Whereas, the tremor decreased when he posed his wrist more pronated. He could write normally, with his right hand, but he complained of discomfort when writing a long sentence. He had no problem with other manual tasks. He could hold a cup and hold a scissor without tremor in various positions. There was a minimal response to propranolol.

Conclusions: In this case, the tremor was absent at rest and during the manual tasks including writing, holding a cup, holding scissors, only appeared when shearing off cloth on the right hand. Whether this is the pure task-specific tremor, or it is related to essential tremor or focal dystonia is unclear. Most focal task-specific tremors are known to be worsened in particular position, especially pronation. However in this case, the tremor worsened at supinated posture. We report a rare case of task-specific isolated hand tremor in usage of scissors.

Tu-374

Associated neurological diagnosis in orthostatic tremor: A case series

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Objective: To characterize neurological abnormalities associated with Orthostatic tremor (OT).

Background: OT is a unique tremor syndrome characterized by subjective unsteadiness during stance relieved by sitting or walking and confirmed neurophysiologically by the recording of a fast coherent 13-18-Hz tremor in the legs, trunk, and sometimes arm muscles. In addition, OT has been reported concominantly with other neurological diagnosis such as Parkinson's disease, vascular parkinsonism, primary gait ignition failure, progressive supranuclear palsy, restless legs syndrome, orofacial dyskinesia, cerebellar ataxia and muscle hypertrophy of the lower limbs. Those cases have been suggested to be "OT plus" syndromes.

Methods: All subjects with the diagnosis of OT according to the criteria proposed by the consensus of The *Movement* Disorder Society were selected. We searched through the medical record and video databases of the Toronto Western Hospital Movement Disorders Center between 1988-2008. Medical records were retrospectively analyzed for demographic and clinical features of OT. Ethical approval was obtained.

Results: We identified 15 cases of OT. 8 were women. The median age of onset was 61 (range: 82–31 years) with a median diagnostic delay of 3 years (range: 0–41 years). OT was the single feature in 2 (13.3%) cases and in 4 (26.7%) a postural arm tremor was present. In the remaining cases, the following neurological features/conditions were identified: parkinsonism (3), progressive supranuclear palsy + restless legs syndrome (1), restless legs syndrome (1), Dementia with Lewy Bodies (1), task-specific arm dystonia (1), foot dystonia (1) and phenytoin-induced cerebellar ataxia (1). Clonazepam produced mild benefit in 4/14 (28.5%) cases. 12 additional drugs were used such as primidone, levodopa, gabapentin and propranolol. From a total of 38 therapeutic trials (median number of trials per patient–4), only 4 produced some benefit in 2 patients previously treated with clonazepam.

Conclusions: The present case series expands knowledge about the neurological conditions associated with OT. The presence of focal dystonia and Dementia with Lewy Bodies has not been previously described. A referral bias may contribute for the increased proportion of "OT plus" syndromes. In line with current literature, the treatment response was generally poor.

We-358

Correlation between Kinesia™ system assessments and clinical TETRAS scores in patients with essential tremor

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Objective: To correlate scores on the Tremor Research Group (TRG) Essential Tremor Rating Assessment Scale (TETRAS) with quantitative assessments using the Kinesia™ (CleveMed) tool in patients with essential tremor (ET).

Background: Kinesia™ motor assessment system integrates three orthogonal accelerometers and three orthogonal gyroscopes to monitor three-dimensional motion. It has already been used to quantify tremor in Parkinson's disease, but the automated scores given by the tool have not been compared with clinical rating scales of ET, such as the TETRAS.

Methods: We enrolled 20 patients with ET from the Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine who satisfied the ET standardized diagnostic criteria formulated by the Tremor Research and Investigation Group. The Kinesia™ device was attached to the wrist and the patients were instructed to hold their arms in an outstretched position in front of them and then touch their nose while data were wirelessly transmitted to a computer. Subjects were videotaped in a standardized manner during the recording and rated on the same arm where the system was placed using the TETRAS items for arm tremor. A linear regression model was constructed for both tasks using the clinical scores, the root-mean square amplitude and the peak-power spectrum density of detected signals.

Results: The mean age of enrolled patients was 62.03 ± 12.95 years. The mean scores of TETRAS items for postural and kinetic tremor were 1.90 ± 0.82 and 1.95 ± 0.78, respectively. TETRAS clinical scores correlated with predicted Kinesia™ scores for postural ($r = 0.747$; $p < 0.001$) and kinetic ($r = 0.617$; $p = 0.004$) tremor.

Conclusions: Data captured with Kinesia™ correlated well with clinical rating scores and may be used in the quantitative assessments of tremor in patients with ET and possibly with other forms of tremor. **Acknowledgments:** We thank the CleveMed and the National Parkinson Foundation (NPF) for their support of the NPF Center of Excellence at Baylor College of Medicine.

We-359

Tremor in a cohort of patients with Inflammatory Bowel disease (IBD)

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Objective: To quantify tremor in patients with Crohn's disease (CD), ulcerative colitis (UC) and gastritis/dyspepsia (controls).

Background: Central and peripheral nervous system disorders are common in patients with inflammatory bowel disease (IBD) (Oliveira et al., 2008). We hypothesized that enhanced physiological tremor, detectable by Archimedes spirals, would be more severe in patients with IBD than controls.

Methods: We studied the prevalence of neurological disorders and tremor in a cohort of patients with IBD and controls who were seen at the IBD Clinic at the Hospital Walter Cantdio (city of Fortaleza, Brazil). Participants were evaluated with a neurological examination and nerve conduction studies. Each participant was asked to draw an Archimedes spirals with each hand using a standardized procedure (Hafeman et al., 2006). Tremor in each Archimedes spiral was blindly rated by a senior neurologist specialized in movement disorders (E.D.L.), who used a semi-quantiative rating scale (0-3). Differences among the groups were evaluated using Mann-Whitney test and Spearman correlation coefficients.

Results: We enrolled 31 patients with CD, 63 with UC and 41 with gastritis/dyspepsia. Patients with gastritis/dyspepsia were younger than those with CD and UC (34.9 ± 2.4 vs. 41.1 ± 2.4 and 44.7 ± 1.9 years, respectively, $P<0.05$). Mean tremor scores for the right hand were higher ($P<0.05$) in controls than CD or UC (0.49 ± 0.06 vs. 0.39 ± 0.08 and 0.41 ± 0.05, respectively). This effect was due to decreased caffeine intake in the IBD group. However, mean tremor scores for the left hand did not differ ($P>0.05$). In CD patients, there was a significant correlation between tremor score, use of medications with CNS effects, use and amount of caffeine intake and presence of other neurological conditions (carpal tunnel syndrome, epilepsy, myasthenia gravis, neuropathies, strokes). In patients with UC, there was a significant correlation between tremor score, age, and use and the amount of caffeine intake.

Conclusions: Despite the presence of several neurological disorders in IBD patients, these preliminary findings do not support the hypothesis that enhanced physiological tremor (detectable by Archimedes spirals) is more severe in patients with IBD than controls.

We-360

Task specific writing tremor: Series and outcomes

W.G. Ondo, P. Satija, M. Ummat (Houston, Texas)

Objective: To describe a large series of subjects with task specific writing tremor.

Background: Task specific tremors remain a controversial area, possessing some features similar to essential tremor and some similar to dystonia. Task specific tremor can occur with many occupational and repetitive tasks but writing tremor is probably the best to study because the majority of people write.

Methods: We evaluated 36 subjects seen in the past 3 years for task specific writing tremor. The diagnosis was made by observing tremor only elicited by writing, without more than trace postural tremor, or by a robust history of tremor only during writing for at least three years before tremor in any other setting. Patients in whom the major feature was dystonia (abnormal posturing of the hand) were not included.

Results: The age of tremor onset was highly variable, 45(18) years, and 24 (68%) were male; 25 were Caucasian, 7 were African-American, 2 were Asian, and 2 were Hispanic. A family history of some tremor was reported in 19: 7 non-specific action tremor, 6 task specific writing tremor, 6 Parkinson's disease. No patient reported a family history of dystonia. In subjects that later developed tremor with other actions the subsequent action was: eating/drinking (5), grooming (3), occupation specific (2), holding a phone (1). Interestingly, 6 developed rest tremor and 2 more developed tremor of postural repose without a true rest tremor. Three of these rest tremors first occurred in the contralateral hand. Pharmacologic treatments of writing tremor, including alcohol, were generally poor, whereas botulinum toxin and VIM DBS were relatively successful.

Conclusions: Compared to patients with "classic" essential tremor in our clinic, writing tremor patients were more likely African, more refractory to tremor medications, and more likely to develop rest tremor without other overt parkinsonian signs.

We-361

The cognitive profile of Essential Tremor-Parkinson's disease (ET-PD) group

B. Ozen, D.I. Gunal, C. Turkmen, A. Mollahasanoglu, H. Ankarali (Istanbul, Turkey)

Objective: To compare the cognitive profile and some clinical features of patients with a diagnosis of essential tremor (ET), Parkinson's disease (PD) and Essential Tremor – Parkinson's disease (ET-PD).

Background: Although both PD and ET are distinct clinical entities sometimes their co-occurance cause diagnostic problems. Several studies in literature discuss the relationship between PD and ET but whether the co-occurance of ET and PD might occur by chance or are these patients belonging to a separate or an overlap syndrome, are still under question.

Methods: Nine patients with both ET and PD, fullfilling both MDS Tremor Inv. Group and PD Society Brain Bank criterias were selected. Nine ET and ten PD patients were also recruited to the study as control groups. There was no significant difference among demographic features (age, sex, education,). Family history, clinical features and cognitive functions (attention, memory, visuospatial functions, language and executive functions) were the main domains studied by appropriate statistical tests.

Results: The family history of a tremor disorder was more common in ET-PD patients compared to PD patients. PD severity, and duration was similar between ET-PD and PD patients. However, pure PD patients had more akinetic rigid type parkinsonism and their levodopa response was better. ET symptoms were more severe in ET-PD group compared to pure ET patients. Constipation and REM Behavioural disorders (RBD) was significantly more common in ET-PD patients than ET patients. Some cognitive tests were significantly

worse in ET-PD patients including Animal counting, Benton line orientation, Aduituar verbal learning test, digit order tests and Stroop tests. In all these tests except stroop time difference, ET patients had significantly better results.

Conclusions: ET+PD patients were different from ET patients in terms of tremor intensity, some cognitive functions, RBD and constipation story. These patients had more tendency of having family history than PD patients. Although both ET-PD patients and PD patients had levodopa response, response degree was better in PD patients. This is a small sample sized study and these features should be cofirmed with larger population studies to comprehend the clinical features of ET-PD group.

We-362

Holmes tremor may be a treatment challenge
A.Q. Rana (Toronto, Canada)

Objective: To discuss resistance of Holmes tremor to phamacological treatments as shown by this interesting case of a Holmes tremor which did not respond well to the medications.

Background: Holmes tremor, also called rubral tremor is a 2-5 Hz rest, postural and kinetic tremor of an upper extremity and is caused by lesion in the vicinity of red nucleus resulting in demage to the cerebellothalamic, cerebello-olivary and nigrostriatal fibers. It has also been called midbrain tremor because isolated lesions of red nucleus may not cause tremor. Holmes tremor may be resistant to pharmacological treatments. Holmes tremor may only partially respond to levodopa and dopamine agonists but responds better to stereotactic thalamatomy and DBS in ventralis intermedius.

Methods: We report a case of 75 year old male who suffered from an ischemic stroke involving left thalamus and left midbrain region. Soon after he developed a moderate to severe amplitude, 5 Hz resting, postural and action tremor of right upper extremity. He was tried on levodopa, pramipexole, benztropin, amantadine without any significant improvement. He declined surgical options.

Results: MRI showed a small left thalamic and midbrain ischemic infarct.

Conclusions: Holmes tremor is a treatment challenge and surgical options should be considered without delay.

We-363

Task specific tremor type B, with more difficulty writing numbers than letters
A.Q. Rana (Toronto, Ontario, Canada)

Objective: To report a case of task specific tremor type B, with more difficulty writing numbers than letters.

Background: Task specific tremors are rare form of tremor that involve highly learned and skilled motor tasks. Tremor occurs only during the specific activity and no other signs and symptoms are present during other activities. Primary writing tremor is the most common form of task specific tremor that occurs during writing and not during other hand tasks.

Methods: We present a 58 year old, right handed male with tremor of right hand only during writing and not during any other hand tasks. The tremor started gradually about a year ago and got worse with time. His hand writing became very sloppy over the course of year. Unusually he had more difficulty writing numbers than letters and interestingly the tremor would increase during writing numbers than letters and sentences. The tremor would disappear when he would stop writing. He would also develop tremor on assuming a writing posture of the hand. There were no features of any other movement disorders in other body parts.

Results: MRI brain was unremarkable.

Conclusions: Most task specific writing tremors described so far affect both number and letter writing, but this is an interesting case of task specific writing tremor type B which aggravates more with writing numbers than letters.

We-364

Multiple sclerosis associated with a midline truncal tremor
A.Q. Rana (Toronto, Canada)

Objective: To discuss association of multiple sclerosis with midline truncal tremor in addition to limb tremor.

Background: Multiple sclerosis causes formation of demyelinating plaques in the central nervous system. Involvement of the cerebellere hemispheres results in ipsilateral limb tremor which is not uncommon in MS patients. Truncal tremor due to midline cerebellar involvement is quite infrequently seen in multiple sclerosis and is very resistant to treatment.

Methods: We report a 62 year female with history of multiple sclerosis for last 16 years. Two years ago she developed an intention tremor of upper extremities but later she developed the postural and kinetic tremor of upper extremities as well. She was reffered to our movement disorder clinic for assessment of the tremor of her arms. On examination she was not only found to have intention, postural and kinetic tremor of both upper extremities but also a significant truncal tremor which was being conducted to her head. The truncal tremor was causing difficulty sitting for prolonged time. She had tried Propranolol without any success. Primadone was initiated.

Results: She did not notice any significant improvement of tremor of upper extrimities and trunk with primadone but objectively amplitude of tremor was noticed to be slightly decreased.

Conclusions: Multiple sclerosis could be associated with turncal tremor in addition to the tremor of limbs and carfull assessement is necessary as shown by this interesting case of an MS patient with midline tremor of trunk in addition to tremor of limbs.

We-365

Isolated facial tremor could be diagnostic chellange
A.Q. Rana (Toronto, Canada)

Objective: To discuss how an isolated facial tremor could be diagnostic chellange as shown by this interesting case of isolated facial tremor, which is an essential tremor variant and required multiple assessments before diagnosis was reached.

Background: Isolated facial tremor is an essential tremor variant which is not frequently seen even in the movement disorders clinic. Patients usually report a bilateral facial tremor with half hearted smile. Isolated facial tremor may be mistaken as bilateral hemifacial spasm, tics or post Bell's palsy synkinesis and may lead to unnecessary imaging of brain and treatments. Isolated facial tremor usually responds to alcohol intake. Treatments includes propranolol, primadone and other drugs which are helpful in the essential tremor syndrome affecting limbs.

Methods: We present a case of 37 year old male who developed bilateral facial tremor on half hearted smile. The tremor was very responsive to alcohol intake. There was no tremor of head, voice, tongue, upper or lower extrimities. The tremor was very bothersome especially in social setting and at his work. He was seen by first neurologist and a diagnosis of bilateral hemifacial spasm was entertained and patient was injected Botox without any significant relief. Second neurologist did not conclude a diagnosis. He was referred the movement disorders clinic where propranolol was initiated with a good response.

Results: Patient responded to propranolol.

Conclusions: Isolated facial tremor in the absence of trmor of upper extrimities, head, voice, tongue or lower extirimities could be a diagnostic challenge and history of alcohol response should be asked carefully. It is a treatable condition and responds well to phamacological therapy used for essential tremor syndrome.

We-366

The electrophysiological confirmation of simple bent and locked knee manoeuvres for clinical diagnosis and management of orthostatic tremor

W.A. Robert, J.D. O'Sullivan, S.A. Peter, C.H. Michael, M. Steven, K.K. Graham (Brisbane, QLD, Australia)

Objective: To define whether postural manoeuvres are valuable in the clinical assessment of orthostatic tremor (OT).

Background: OT is uncommon and is characterised by its fast 14-18 Hz frequency with high bilateral intermuscular coherence. OT occurs predominantly in the legs on standing, associated with often disabling unsteadiness that can usually be aborted by walking, sitting and lying. We have observed OT patients whose tremor and symptoms were exacerbated or relieved by simply changing their standing posture, and we have sought to confirm this observation with electrophysiological tremor analysis.

Methods: Six patients with primary OT were studied, both on and off medication treatment. Patients were studied with surface EMG and accelerometry standing normally and with two postural manoeuvres; bent knees and locked knees. Tremor amplitude, frequency and coherence were analysed.

Results: Tremor amplitude characteristics changed between postural manoeuvres on and off medication therapy. The electrophysiological changes correlated with exacerbation (bent knees) or relief (locked knees) experienced by the patient.

Conclusions: Postural manoeuvres are a useful tool for bedside assessment of OT. Postural maneuvers also markedly change the characteristics of OT in patients on and off medicine. The implications of these findings may broaden our understanding of OT.

We-367

Gradual disappearance of essential tremor due to a cerebellar tumour

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Objective: Several lines of evidence from animal and functional imaging studies point to an involvement of the cerebellum in the pathogenesis of essential tremor (ET). Additionally, subtle cerebellar signs can be found in ET. However, the pathophysiological relevance of cerebellar (dys-) function to ET generation is still a matter of conjecture.

Background: Complementary information based on human lesion data is limited to two case studies. Hence, we would like to report on a 57-year-old gentleman suffering from hereditary ET since adolescence.

Methods: Case report.

Results: Over the past years, however, the decades-long tremor in this gentelman's right arm gradually disappeared. When he presented to our hospital for headache, clinical examination revealed a high-frequency, low-amplitude postural and action tremor of the left arm only. A mild-to-moderate ataxia was present on both arms, but more pronounced on the right side. Computer Tomography revealed a tumour in the right cerebellar hemisphere with accompanying occlusion-hydrocephalus. The cerebellar tumour was surgically removed and diagnosed as a heamangioblastoma based on neuropathology. Neurological status including the tremor characteristics was not altered post-operatively.

Conclusions: This case adds to the notion of cerebellar dysfunction as a pathophysiological feature in ET. It should be noted, that growth of the tumour, i.e., damage to cerebellar structures and pathways, resulted in a gradual amelioration of the tremor. On the other hand, as ET has been associated with a loss of (inhibitory) Purkinje cells, we would hypothesise, that the remission caused by the tumour may be attributable to its lesioning of potentially dis-inhibited olivocerebellar pathways. Crucially, these putative alterations may involve isolated circuits and not cerebellar function per se, as demonstrated by the congruent aggravation of ataxia in the arm controlled by the affected cerebellar hemisphere.

We-368

Deep brain stimulation in the treatment of essential tremor – An evaluation of 61 cases

U. Sandvik, A. Fytagoridis, G.-M. Hariz, L.-O. Koskinen, P. Blomstedt (Umea, Sweden)

Objective: To evaluate deep brain stimulation (DBS) in the he Nucleus Ventralis Intermedius Thalami (Vim) and the Posterior Subthalamic Area (PSA) in the treatment of Essential Tremor (ET).

Background: DBS is an established treatment for ET. At present the Vim is the target of choice, but promising results regarding the PSA have been presented in 3 studies (18 patients).

Methods: 61 patients (34 Vim/27 PSA) with ET were included in this non-randomized sequential study. 69% were males and the mean age being 61±16 years. Evaluation, using the Essential Tremor Rating Scale (ETRS), was done before, and one year after surgery concerning PSA, and after a mean time of 28±24 months concerning Vim.

Results: Total ETRS for the whole group was before surgery 49.5±15.3, which was reduced to 23.1±14.7 (53%) on unilateral stimulation. Total ETRS was reduced by 49% from 54.1±16.2 in the Vim group and by 60% from 43.8±11.8 in the PSA group. Tremor in the treated hand, when tested with item 5/6 (hand tremor) and item 11-14 (hand function) was before surgery 16.7±5.2 and on stimulation 3.6±4.4 (78%). This score was slightly higher in the Vim than in the PSA, 17.9±5.3 and 15.2±4.7 ($p<0.05$), respectively, and the reduction on stimulation was 71% and 90% ($p<0.005$), respectively. When evaluating factors that might contribute to differences in tremor reduction between the two groups, no significant differences were found regarding sex and age. Concerning the difference in tremor severity it was found, that even though the level of postoperative tremor, and the absolute reduction of tremor on stimulation was positively correlated to the preoperative level of tremor ($p<0.01$), the relative reduction of tremor was not significantly correlated to preoperative tremor.

Conclusions: DBS provided a marked reduction of tremor, the effect being more pronounced in the PSA than in the Vim. It is possible that the PSA is a more efficient target than the Vim for ET. The two groups in this non randomized sequential study are however not directly comparable. It is possible that differences in time to evaluation, or other unknown factors, might affect the result. A randomized study comparing these targets is warranted.

We-369

Objective quantification of lower limb tremor characteristics in Parkinson's disease

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Objective: To define characteristics of resting/postural lower limb movement in Parkinson's disease (PD) patients and healthy volunteers (HV).

Background: The characteristics of clinically detectable, sub-clinical and physiological tremor have been extensively studied in the upper limbs with electrophysiological measures such as accelerometry. However, only a few studies have attempted to characterize lower limb rest and postural tremor features in PD patients and HV.

Methods: Patients with or without clinically detectable lower limb rest tremor (N=16; age M=63.6; disease duration M=9.7) who met UK PD Society Brain Bank criteria for PD and HV (N=8) were recruited from outpatient clinics of our department. Tremor was recorded with bi-axial accelerometry using CATSYS® (Danish Product Development Ltd., Denmark) at rest and with the lower limb extended.

Results: The standard deviation of resting movement center frequency (f50), a measure of discoordination, was significantly higher in both the dexterity dominant (DD) and non-dominant (nD) foot of HV compared to PD patients. The standard deviation of postural movement f50 did not differ between groups in the nD foot, but was significantly different in the DD foot. The upper and lower limbs most affected by resting movement in the PD group also demonstrated significantly different f50.

Conclusions: These findings indicate that movement at rest in both lower limbs and postural movement in the DD lower limb presents with less rhythmicity in healthy adults than in those diagnosed with PD. Therefore, pathological oscillators generating rhythmic movements may be detectable with accelerometry in the lower limbs of PD patients with clinical and subclinical tremor. PD rest tremor frequency is discrepant between upper and lower limbs, which points to multiple oscillator involvement in tremorgenesis. Objective measurement tools may aid in developing a better understanding of motor dysfunction in PD. Furthermore, while continued research is necessary, accelerometry may provide diagnostic utility in early detection of Parkinson's disease and related disorders.

We-370

Holmes tremor: Clinical and neuroimaging study

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Objective: To present and compeare neuroimaging, clinical and demographic data and to evaluate functioning of nigrostriatal system in the group of patients with Holmes Tremor (HT).

Background: Holmes Tremor is an unusual kind of symptomatic tremor related to lesions of brainstem, cerebellum and thalamus. It is combination of rest, postural and kinetic tremor. The functional deficits of two systems, the dopaminergic nigrostriatal system and the cerebellothalamic system must come together to produce this specific form of tremor according to pathoanatomical and PET data.

Methods: From 4 different Neurology Departments in Poland we selected 11 patients with HT (5 women, 6 men) according to diagnostic critria proposed in Consensus Statement On Tremor. Age range at onset of symptom 10-68 years. All patients underwent MRI or CT. The following data were collected from each patient and analyzed: gender, distribution of tremor, types of tremor, cause of brain lesion, delay between lesion and occurrance of tremor, age at symptom onset, tried treatment and response, neurological state and concomitant diseases. For 6 patients who underwent SPECT(DATSCAN) indices of asymmetry of uptake (IA) for each striatum structure were calculated as the ratio of the appropriate indices for ipsilateral and contralateral hemispheres to the clinical symptoms.

Results: All demographic nad clinical informations was collected nad compared as it is shown in table 1.

For 6 patients who underwent SPECT(DATSCAN) We found lower uptake in the part of nigrostriatal system (striatum) contralateral to the tremor.

Conclusions: In all patients who correctly passed diagnostc criteria for HT typical lesions of brainstem, cerebellum or thalamus were found. This structural deficits come together with lower activity of nigrostriatal system contralateral to the tremor as it was shown in SPECT studies. We confirmed hypothesis that functional deficits of two systems, the dopaminergic nigrstriatal system and the cerebellolthalamic must come together to produce HT.

Table (We-370). Clinical and demographic data of patients

Subject	Gender	Distribution of tremor	Cause of brain lesion	Delay lesion to tremor (months)	Age at tremor onset (years)	Treatment trials	Clinical state
LP	M	Left upper limb (more distal)	SICH (malformation)	3	25	Propranolo (NI) amantadin (NI) baclofen (NI)	Left hemiparesis, paresis of right oculomotor nerve, supranuclear paralysis, right-sided pyramidal syndrom;
RM	M	Left upper limb (mixed)	SICH (cavernoma)	4	25	L-dopa (MI) Piribedil (MI, AE)	Bilateral paresis of oculomotor nerve; bilateral ataxia much more
RJ	F	Right upper limb (more proximal)	PICH	6	68	Clorazepate (NI) biperiden (NI) sulpirid (NI)	Right hemiparesis,
KS	M	Right upper limb (more proximal)	stroke	3	63	Propranolol (MI) L-dopa (MI)	Right hemiparesis, dysarthria, ataxia of lower extremities,
JG	F	Right upper and lower limbs (more proximal)	stroke	3	15	Haloperidol (NI) trihexyphenidyl (NI) diazepam (NI)	Right hemiparesis, ataxia of right lower extremity, right-sided Babinski sign;
AH	F	Left upper limb (more proximal)	stroke	4	27	none	Paresis of left facial nerve, greater deep reflexes of left lower extremity;
SO	M	Right upper and lower limbs (mixed)	PICH	24	37	Levetiracetam (NI) biperiden (NI) pridinol (NI) L-dopa (NI)	Right hemiparesis, dysarthria, horizontal-rotatory nystagmus, i
JS	F	Right upper limb (more proximal)	trauma	3	20	Levetiracetam (NI) propranolol (NI) clonazepam (NI)	Hypomimic face, supranuclear palsy, paresis of right facial and sublingual nerve,
KP	M	Left upper limb (more distal)	trauma	4	12	tiapridal (MI)	Scanned speech, internuclear paralysis, right pupil fixed; central paresis of right facial nerve; deep reflexes of left limbs greater; ataxia of left limbs; bilateral Marinesco-Radovici sign;
PW	M	Right upper limb (more proximal)	trauma	1	10	Diazepam (NI) valproate (NI) tiapridal (NI) L-dopa (NI)	Atrophy of right hand short muscles;
ZP	F	Left upper limb (mixed)	stroke	12	42	None	Left lower extremity paresis, left-sided hemihypoesthesia, ataxia of left extremities;

SICH-secondary intracranial haemorhagia; PICH-primary intracranial haemorhagia; NI-no improvement; MI-mild improvement; AE-adverse effect; HA-hypertension arterialis.

Th-364

Tremor in immune-mediated neuropathies

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Objective: To evaluate frequency and clinical characteristics of tremor in immune-mediated neuropathies.

Background: Neuropathic tremor is diagnosed if a patient develops tremor in association with a peripheral neuropathy and there is no other cause for tremor. Some forms of peripheral neuropathy, especially demyelinating neuropathies tend to be more often associated with tremor than others. The pathophysiology of neuropathic tremor remains unclear.

Methods: We investigated 43 consecutive patients (30 men/13 women) with immune-mediated neuropathies. 28 fulfilled recognised criteria for chronic inflammatory demyelinating polyneuropathy (CIDP), 9 for multifocal motor neuropathy with conduction block (MMNCB), and 6 for IgM paraproteinemic neuropathy (IgM-PN). We performed a review of medical records, and clinical assessment including Fahn–Tolosa–Marin (FTM) tremor rating scale, Medical Research Council (MRC) sum score as motor outcome measure, and Overall Neuropathy Limitations Scale (ONLS).

Results: Mean age at onset of neuropathy was 49.5 years (SD 12.9), mean disease duration 12.9 years (SD 8.9). Tremor was present in 67% of all patients (63% CIDP, 56% MMNCB, 100% IgM-PN). Tremor started on average 6.0 years (SD 7.4) after the neuropathy, but 19% of patients had the onset of tremor from the onset of the neuropathy. Tremor was present on action (82%), posture (74%), and less commonly at rest (44%). FTM score was on average 16.7 (SD 15.6). Patients with tremor had a significantly lower (i.e. better) MRC score but similar ONLS score compared to patients without tremor ($p=0.018$), suggesting a degree of disability being caused by tremor. The course of tremor was rated as stable in 50% and progressive in 32%. Tremor did not respond to immune mediating drugs with only 2 patients each with CIDP and MMN-CB having a clear response on IVIG, while 2 others with IgM-PN had a clear benefit from CHOP-R and Rituximab. Classical anti-tremor treatment was unsuccessful in all patients tried.

Conclusions: Tremor is a common and underrecognized feature in patients with immune-mediated neuropathies that adds to their global

disability. As expected, patients with IgM-PN most frequently have a tremor, but also half of our patients with a pure motor neuropathy were affected. Further work is needed with regard to pathophysiology and treatment of neuropathic tremors.

Th-365

Membrane mechanisms for essential tremor

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Objective: We hypothesize that increased excitability of central motor neurons has a key role in the pathogenesis of ET.

Background: We propose that the neural circuit controlling ballistic movements is inherently unstable due to an underlying reciprocal innervation (Figure 1A). Adequate external inhibition normally prevents oscillations in this circuit. However, instability is enhanced by pathologically increased neural membrane excitability that reduces the effects of external inhibition. The circuit begins to oscillate (Figure 1B). The oscillations manifest as ET.

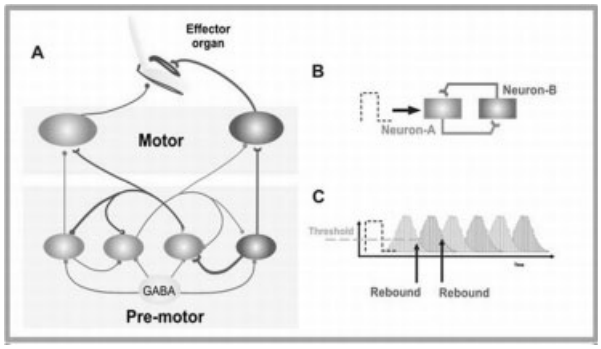

FIG. 1 (Th-365). (A) The circuit of reciprocally innervated neurons for controlling ballistic movements. The excitatory premotor neurons send excitatory projections to the motor neurons innervating the agoinst muscle group. At the same time this neuron also sends an excitatory projection to the inhibitory neuron innervating the motor neuron for the antagonist muscle group. In addition, mutual inhibitory connections exist between premotor neurons. These mutually inhibitory connections predispose the neural circuit to instability and oscillations. (B, C) Demonstration of oscillations in a two-neuron circuit. Neuron-A inhibits neuron-B and *vice-versa*. A small pulse to neuron-A increases its discharge and thus inhibits neuron-B. Once the discharge of the neuron drops inhibition from neuron-B is removed. This results in a rebound increase in the neuron-B firing rate. Since neuron-B also inhibits neuron-A, the same phenomenon of post-inhibitory rebound repeats for neuron-A. In the panel 'C' response of neuron A is schematized with red bars, while the green trace is response from neuron B.

Methods: We tested this hypothesis by recording postural limb tremor in 22 ET patients and simulating the phenotype with a conductance-based neuromimetic model of ballistic limb movements. The model featured a reciprocally innervated circuit of neurons that project to agonist and antagonist muscle pairs. The model neuron was Hodgkin-Huxley type with hyperpolarization activated cation current (I_h), low threshold calcium current (I_T), and GABA and glycine mediated chloride currents (Figure 2A). The neurons also featured rebound excitation after release from sustained inhibition (post-inhibitory rebound; PIR).

Results: Neural excitability was modulated by depolarizing the membrane by increasing I_h and/or I_T (Figure 2B). The increase in these currents resulted in alternating bursts of action potentials in the neurons innervating the sets of agonist and antagonist muscles (Figure 2C). The alternating burst of discharge correlated with the simulated oscillations (grey trace, Figure 2D). The black trace in Figure 2D illustrates a representative postural limb tremor recorded from one ET patient. Increases in I_h and I_T determined the frequency and amplitude of the simulated oscillations.

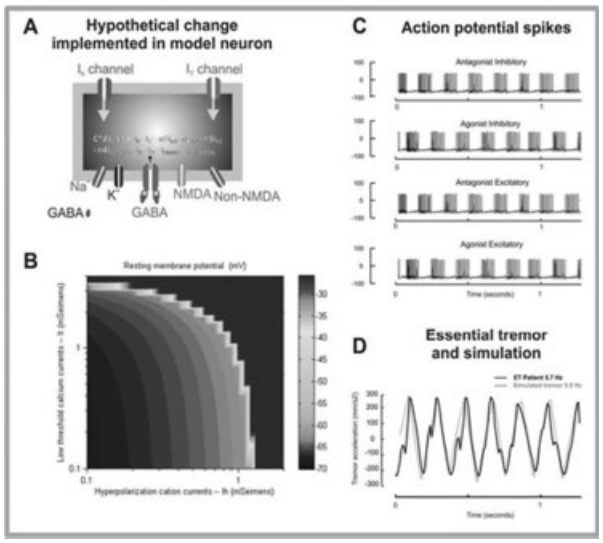

FIG. 2 (Th-365). (A) A traditional Hodgkin-Huxley model of cell membranes with multiple ion channels was used to generate the action potential. In order to simulate physiologically realistic neural behavior, ion channels such as hyperpolarization activated cation currents (I_n) and low threshold calcium current (I_T) were also included. NMDA and non-NMDA excitatory glutamatergic channels as well as GABA sensitive inhibitory channels were also included. The grey box schematizes the burst neuron, while its grey outline schematizes the cell membrane. The ion channels span the membrane thickness. dV is the rate of change in the membrane potential over period 'dt'. C is the membrane capacitance (1μF/cm2) and n1-n4 is a rate scaling factor determining the ion channel expression profile in the neuron. I_L, I_T, $I_{n1\text{-}4}$, I_{Na}. and I_k, denote the leak current, low-threshold calcium current, hyperpolarization activated current (carried by HCN1-4), fast sodium current and delayed rectifier potassium current, respectively. I_a is the synaptic current mediated by glycinergic and GABAergic neurotransmitters. I_{NMDA} and $I_{nonNMDA}$ are synaptic currents mediated by NMDA and non-NMDA sensitive glutamate receptors. (B) The effects of changing I_h (x-axis) and I_T (y-axis) on the resting membrane potential (color coded) in the simulated neuron. As expected, increases in I_n and I_T further depolarize the neuron. A depolarizing shift in the resting membrane potential reflects increased neural excitability. (C) Illustration of bursts of action potential spikes from the agonist and antagonist burst neurons. The alternate spiking behavior of these neurons is evident when they are plotted along the same time scale (x-axis). (D) Simulation (grey trace) of essential tremor (black trace) is shown. The tremor amplitude (y-axis) is plotted against time (x-axis). The time scale for simulated essential tremor is the same as the time scale for the traces representing the spiking behavior of the burst neurons. The frequency of tremor recorded from the patient is 5.7 Hz, which is closely simulated by the neuromimetic model (5.9 Hz). The amplitude of the simulated tremor also resembles the one recorded from the ET patient.

Conclusions: These simulations support the hypothesis that increased membrane excitability in unstable, reciprocally innervated circuits can produce oscillations that resemble ET. Neural excitability could be increased in a number of ways. In this study membrane excitability was increased by up-regulating I_h and I_T. This approach

suggests new experimental and clinical ways to understand and treat common tremor disorders.

Th-366

Pseudo-nystagmus – Clinical presentation and quantitative features

A.G. Shaikh, D.S. Zee (Baltimore, Maryland)

Objective: Describing quantitative characteristics of 'pseudo-nystagmus' in a patient with head tremor and vestibular hypofunction.

Background: The vestibulo-ocular reflex (VOR) facilitates clear vision during head movement. Patients with an unusual combination of head tremor and vestibular loss present with oscillopsia due to the absence of VOR driven, compensatory eye movements. When their optic fundus is examined the instability of the eyes will appear as a 'pseudo-nystagmus' because their head tremor remains uncompensated.

Methods: A 60 year old woman, with multiple sclerosis, was referred for the evaluation of oscillopsia, imbalance, and head tremor. Eye and head movements were measured when the head was passively stabilized or when it was free to move.

Results: Downbeat nystagmus was noticed during fixation in primary gaze when the head was stabilized (Figure 1A). The slow-phase velocity was 7.4 ± 3.4 degrees/second. Downbeat nystagmus is consistent with the demyelinating changes in vestibulocerebellar-brainstem connections. When the head was free to move, pendular horizontal eye and head oscillations were noticed (Figure 1B). Superimposed on the downbeat nystagmus were subtle vertical pendular eye oscillations, coherent with the head tremor. The mean frequency of the head tremor was 4.65±0.86 Hz. The amplitude but not the frequency changed with the head position (Figure 1C,D). VOR (black traces, sign inverted) was diminished (gain: 0.4±0.1) and peak

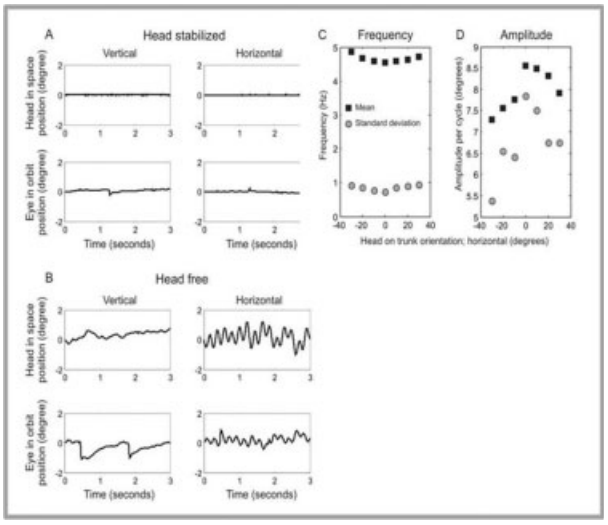

FIG. 1 (Th-366). An example of gaze fixation when head was passively stabilized (A) and was free (B). Coherent eye and head pendular oscillations are seen during head free condition. These oscillations are larger in horizontal direction as compared to vertical. Pendular eye head oscillations are not seen during head fixed condition. Vertical down-beating nystagmus was seen during both head fixed and head free conditions. Head positions were recorded during various head-on-trunk orientations. (C) Mean and standard deviations of the frequency of head tremor (during various head-on-trunk orientations) are plotted. The frequency of head tremor was unchanged during various head-on-trunk orientations. (D) The amplitude head tremor, however, was affected by head on trunk orientation.

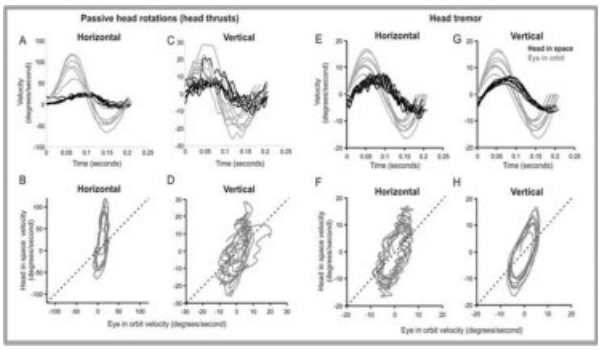

FIG. 2 (Th-366). VOR responses to horizontal and vertical head thrusts. (A,C) Head velocity during horizontal and vertical head thrusts are plotted versus time. Grey traces represent superimposed head velocities from several trials of head thrusts. Corresponding eye velocity is plotted with black trace. Normally the head rotation transients are accurately tracked by compensatory eye movements of equal amplitude. Therefore, grey and black traces in the figure should normally overlap. There is a remarkable reduction and delay in the peak eye velocity suggestive of diminished VOR responses. (B,D) Head velocity is plotted versus corresponding eye velocity. Normal response is characterized by traces falling along the dashed equality line. However, the resultant trace here is elliptical, suggestive of delay in the peak eye velocity. The long axes of the elliptical trace are not parallel to the equality line suggesting reduced peak velocity of the compensatory eye movements during head thrusts. (E,G) Head velocity of each cycles of head tremor is plotted versus time. Grey traces represent superimposed head velocities from several cycles of head tremor. Corresponding eye velocity is plotted with black trace. There is a remarkable reduction and delay in the peak eye velocity suggestive of diminished VOR responses. (F,H) Head velocity is plotted versus corresponding eye velocity. The resultant elliptical trace is suggestive of delay in the peak eye velocity. The long axes of the elliptical trace are not parallel to the equality line suggesting reduced peak velocity of the compensatory eye movements during head thrusts. Collectively these features of elliptical traces are consistent with the diminished VOR function during head tremor.

response was delayed by 56 ± 15 ms during high velocity head impulses (grey traces; Figure 2A-D). Similar phenomenon was noticed during head tremor. Head velocities during each tremor cycle are superimposed in Figure 2E,G (grey trace). Black traces are corresponding eye velocities (sign inverted). The eye velocities were smaller and delayed as compared to head – comparable to the abnormal head impulse response of the VOR (Figure 2F,H).

Conclusions: Attempted gaze fixation in patient with VOR hypofunction and head tremor may give a false appearance of nystagmus–'pseudo-nystagmus'–when looking at the position of the eye relative to the torso as opposed to relative to the head. *This study underlines the importance of eye examination when the patient's head is stabilized.* Treatment of pseudo-nystagmus should be guided by etiology and is a two step process, pharmacological treatment of head tremor and vestibular rehabilitation to diminish oscillopsia.

Th-367

Synchronous inferior olive discharge and superimposed cerebellar learning explain irregular eye oscillations in oculopalatal tremor

A.G. Shaikh, S. Hong, K. Liao, J. Tian, D. Solomon, D.S. Zee, R.J. Leigh, L.M. Optican (Baltimore, Maryland)

Objective: To explain mechanisms underlying irregular eye oscillations in oculopalatal tremor (OPT).

Background: Inter- and intra-subject variability and irregularity of eye oscillations is common in OPT. We hypothesized that a synchronous inferior olive (IO) discharge and superimposed cerebellar learning is the source of irregular oscillations in OPT.

Methods: Binocular, 3D eye movements were recorded in 10 OPT patients. Independence of the six waveforms along the three axes recorded from each eyes was evaluated in each patient with an Independent Component Analysis (ICA).

Results: Figure 1 shows the irregularity of waveforms observed in ten patients. The waveforms in each patient must arise from one or more neural oscillators, with or without subsequent mixing and filtering. If there are fewer than six independent oscillators, the waveforms of some of the six signals can not be mathematically independent. The ICA uses this property to reveal how many independent oscillators underlie the six signals. Surprisingly, the ICA indicated that there were at least six independent oscillators in all patients. Figure 2 shows how our model of OPT can explain the large number of independent oscillators seen in each patient. IO hypertrophy in OPT increases electrotonic coupling between IO neurons (indicated as large colored dots in Figure 2), causing them to oscillate. This pulsatile oscillation is then smoothed by cerebellar learning (Figure 2A). We hypothesize that the different sources of OPT oscillators identified in the patients are located in the IO as groups of electrotonically coupled neurons (Figure 2B). The variation of OPT pattern may arise due to different combinations of these independent oscillators projecting to the motor system.

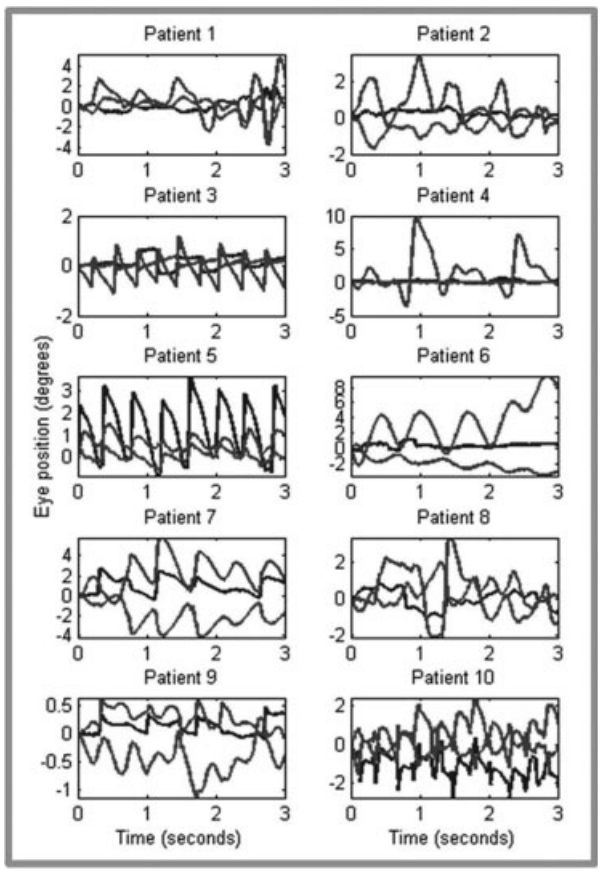

FIG. 1 (Th-367). Horizontal (green), vertical (blue), and torsional (red) eye positions are plotted versus time. Each panel depicts one patient. Oscillatory waveforms are irregular and have remarkable intra- and inter-subject variability.

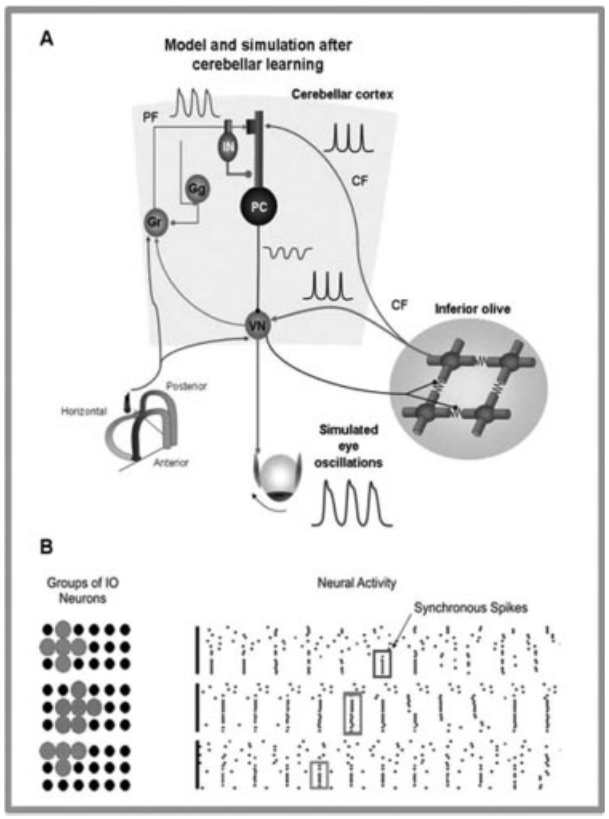

FIG. 2 (Th-367). (A) Schematic representation of our physiologically realistic model that features anatomical connections among inferior olive (10), brainstem vestibular nuclei (VN) and cerebellar cortex. Synchronous IO discharge results in small, jerky oscillations (simulated jerky oscillations are plotted in black color). IO projects to the VN and to the cerebellar cortex. Cerebellar learning evoked by the synchronous discharge results in sinusoidal waveforms (simulated learned oscillations are plotted as green sinusoids). VN, a projection site of cerebellar Purkinje neurons, thus receives jerky IO oscillations and smoothened, cerebellar oscillations from the cerebellar cortex. Irregular waveforms are thus simulated. The simulated waveforms feature the irregularity and variability that is noticed in eye oscillations in patients with OPT. (B) We hypothesize that the different sources of OPT oscillators identified in the patients are located in the IO as groups of electrotonically coupled (color coded circles) neurons. Synchronous discharge for given set of oscillators is shown as the clusters of dots.

Conclusions: Each patient with OPT presents with a unique set of coupled IO neurons, thus leading to a unique set of oscillations. Thus, waveform variability in OPT can arise without invoking anatomically distinct lesions.

Th-368

Further theory on the mechanism of DBS in tremor control

J.E. Arle, J.L. Shils (Burlington, Massachusetts)

Objective: Investigate the effect of a non-regular firing rate on the control of parkinsonian tremor in patients with STN DBS.

Background: It has been suggested that DBS might work in controlling PD tremor mainly by supplanting the tremor bursts of so-called 'tremor-cells' with a regular, faster output of action potentials at the frequency of the stimulator (typically 130-185Hz).

Methods: Parkinsonian patient's with 0 in their UPDRS III tremor scores during DBS treatment of the there PD symptoms were studied. These studies were performed at the time of the DBS battery replacement, due to battery depletion. The patient's extension wire was connected to a grass S-88 biphasic stimulator through SIU-7 constant current isolators. Other than amplitude the stimulus was controlled using spike 2e software with a special "jitter" stimulus signal that was outputted via a CED micro1401 interface. Simulation signals were sent through the patient therapeutic electrodes while using the patients best stimulation amplitude and pulse width. The stimulator frequencies used included a pure frequency (that replicated the exact shape of the Medtronic Synergy IPG) and stimulation signals with ISI that deviated by +/- 20 %, 50%, and either 80% or 100% from the pure frequency. Jitter percent was determined by calculating the deviation percent from the center frequency (both + and -) and randomly setting the ISI for the stimulator spikes to a value inside this range. The mean of the stimulation frequency was always kept constant. Tremor power was recorded using a 3 axis accelerometer placed on the patient's wrist and arm.

Results: We have now tested 3 patients. Findings consistently show that tremor is eliminated quite well (using power spectral analysis at the tremor frequency) as long as the average frequency is high, noisy or not. Tremor power was reduced by 95.0–99.9% at the baseline therapeutic setting. Tremor power was statistically reduced by the same amount, at all three jitter levels. Computational modeling using our previously published representation of STN DBS in the basal ganglia also corroborates this finding with a similar prediction.

Conclusions: Thus, we conclude that the typical 'tremor' pattern of firing is replaced by a higher frequency stimulus, regular or not, and this is the basis of tremor control in DBS.

Th-369

Are there clinical features associated with the development of Parkinson's disease in essential tremor?

R.M. Simoes, A. Constantino, D. Houghton, E. Louis, I. Litvan (Amadora, Portugal)

Objective: To characterize motor and nonmotor features of patients with Essential Tremor (ET) that later develop Parkinson's disease (PD).

Background: Clinical, imaging and neuropathological studies suggests that ET is a heterogeneous group of disorders. There is a specific subset of ET patients that has higher risk of developing PD and that has not yet been clinically characterized.

Methods: Retrospective review of charts of patients with ET, PD and ET that later developed PD (ET→PD).

Results: Eighteen ET→PD, 20 age-matched ET and 30 PD patients matched for age and disease duration, with similar gender distribution, were included. ET and ET→PD patients had similar age at onset, duration and family history of ET. Tremor was restricted to the upper extremities in 80% of ET→PD and only 35.3% of ET ($p=0.01$). ET patients more frequently needed >1 medication to control tremor (66.7% vs. 13.3%, $p=0.008$). Both groups with PD had similar UPDRS, Hoehn and Yahr and Schwab and England scores ($p=0.14$; $p=0.22$; $p=0.15$). There were no differences between nonmotor symptoms except for decreased olfaction ($p=0.06$), constipation ($p=0.002$) and vivid dreaming ($p=0.009$) which were more frequent in the ET→PD than in ET group, and similar to PD. A regression model identified constipation and restriction of tremor to upper extremities as independently associated with the development of PD in ET patients ($p=0.004$; $p=0.02$).

Conclusions: Constipation, vivid dreams, decreased olfaction and tremor restricted to the upper limbs and requiring less aggressive treatment, differentiated the clinical subset of ET patients who developed PD. For the same disease duration, PD with and without a previous history of ET, was similarly severe. Our findings support the emergence of a distinct ET-like disorder that physiopathologically overlaps with PD and suggest potential clinical predictors of the development of PD in ET patients.

Th-370

Solitary parkinsonian signs in essential tremor may herald the eventual appearance of Parkinson's disease

A.G. Guevara Salcedo, A. Pandey, F. Nahab, C. Sengun, S. Papapetropoulos, A. Russell, C. Singer (Miami, Florida)

Objective: To characterize features of parkinsonism in a cohort of patients with essential tremor (ET).

Background: ET has been recognized as a predisposing factor for development of Parkinson's disease (PD) [1]. Certain cases of ET have isolated features of parkinsonism. We refer to these cases as ET-Plus since they may herald the eventual appearance of PD.

Methods: We conducted a retrospective chart review of ET patients seen at the Movement Disorders Clinic by one of our neurologists (CS) between 1997-2007. Our criteria required patients with upper limb predominant tremor (ET-UE) [2] and additional subtle signs of parkinsonism which would not otherwise allow for a diagnosis of PD. We excluded patients with only axial tremor (head, voice), or with additional dystonic features.

Results: We identified 25 patients with ET-UE and subtle signs of parkinsonism (mean age: 69.4 years, mean disease duration 13.6 years, M/F: 11/14). 18 patients had upper limb bradykinesia (72%), 19 patients had lower limb bradykinesia (76%) and 14 patients had rigidity, rest tremor, decreased arm swing and/or postural instability (56%). In 11 patients, with a unilateral predominant upper limb tremor, we found ipsilateral bradykinesia in 7 and symmetric features in 3. Twelve subjects received follow up (mean:4.08 years). Nine of the subjects showed no symptom progression, while 3 subjects fulfilled criteria for PD on follow up.

Conclusions: The presence of subtle signs of parkinsonism may commonly be noted in subjects with limb-predominant ET. Based on this retrospective analysis, the presence of these isolated features of parkinsonism did not predict the eventual diagnosis of PD in 75% of cases during a 4-year follow-up. Future prospective studies are needed to characterize the incidence of isolated features of parkinsonism and their ability to predict future neurodegeneration. This cohort may represent an interesting group for future observational, imaging, and neuroprotective studies. 1. Shahed, J and J Jankovic, Exploring the relationship between essential tremor and Parkinson's disease. Parkinsonism Relat Disord, 2007. 13(2): p. 67-76 2. Brin MF and W Koller, Epidemiology and genetics of essential tremor. Mov Disord, 1998. 13 Suppl 3: p. 55-63.

Th-371

Chopstick-induced task specific tremor: A case report

K.Y. Tay, E.C. Pica, L.C.S. Tan (Singapore, Singapore)

Objective: We report a case of a patient who developed task-specific tremor whenever chopsticks were used.

Background: Focal task-specific tremor besides primary writing tremor have rarely been described in the literature. Chopsticks are commonly used as utensils by Chinese during meals from a young age. To the best of our knowledge, chopstick-induced task specific tremor has not been previously reported. Herein, we report a case of a 62 year old man who complained of tremor only when using chopsticks.

Methods: A case report.

Results: A 62 year old right handed man presented to our clinic with complaints of upper limb tremor while holding chopsticks with his dominant hand. He first noted deterioration in his ability to manoeuvre chopsticks 3 years prior to his consultation and it has remained the same since. His tremor is more evident when the pair

of chopsticks are heavy. This has caused him difficulty in handling food during meals. In contrast, tremors were not observed when he performed other activities such as writing or holding a spoon or fork. He did not have any significant family history, history of trauma and any symptoms to suggest peripheral neuropathy in his right hand. There is no history of thyrotoxicosis. He denied drinking alcohol and was not on any medication. Clinically, there was no resting tremor or any postural and kinetic tremor. Examination of the upper limbs was unremarkable besides a low frequency 2-3Hz flexion and extension tremor of the 4th and 5th fingers while he was holding a pair of chopsticks and this was aggravated when the chopsticks were used to pick up food or objects. There was no associated dystonia. No tremor was noted when he wrote or when he was holding a spoon. Assuming a posture to hold chopsticks without having actual chopsticks in his hand did not induce the tremor. Nerve conduction studies were normal. A brain MRI done showed an acute hemorrhage on the right basal ganglia which did not corresponds to the side of the tremor. Furthermore, the temporal sequence of the hemorrhage did not correspond to that of the tremor. A diagnosis of task-specific tremor was made and he was started on propranolol.

Conclusions: Chopstick use may be associated with a task-specific tremor.

Th-372

The computer-based tremor analyzer for clinic

E.M. Timanin, E.V. Eremin, A.V. Gustov, M.A. Ustimkina
(Nizhny Novgorod, Russian Federation)

Objective: To study a validity of developed tremor analyzer for Parkinson's disease diagnostics.

Background: The computer-based system is designed for tremor registration and analysis in clinic. This system includes two accelerometers, an electronic unit with the USB output and a managing program. The electronic unit includes amplifiers and an ADC module. The program provides a record of two signals on computer hard disk, reading and displaying the records, marking an analysis window, calculating and displaying Fourier spectra, finding a set of quantitative parameters of signals and of their spectra, entering from the keyboard a patient data, a test title and a textual commentary (doctor opinion). It provides also the final protocol saving as one page A4 in PDF form.

Methods: A patient examination consisted of tremor registration of both hands or of both foots simultaneously at different body positions, ensuring registration the rest tremor, the postural tremor and the kinetic tremor (8 tests for a person, each in 15–30 seconds). Tremor records of 11 healthy individuals are obtained by now as well as of 42 neurological patients of Nizhny Novgorod regional hospital, including 13 patients with Parkinson's disease (6 with akinetico-rigid form (PDR-group) and 7 with trembling form (PDT-group)), 5 patients with essential tremor, 9 patients with multiple sclerosis, 8 patients with vegetative dysfunction (VD-group) and 7 patients with diskogenic radiculopathy. Processing of all records has been performed and protocols of tremor analysis have been obtained for each person.

Results: A few possible diagnostic criterions have been formulated and their sensitivity and specificity have been examined on the basis of studying the tremor protocols. In particular for the Parkinson's disease the best results have been shown by the criterion "Asymmetric maximum existence in the rest tremor of hands". Its sensitivity is 85.7% in the PDT-group and 16.7% in the PDR-group. The specificity of this criterion is 100% relating to all groups of individuals excepting only the VD-group. The specificity relating to this group is 75%.

Conclusions: The developed tremor analyzer ensures obtaining data being in agreement with known concepts of tremor character at Parkinson's disease and ensures high sensitivity and specificity of diagnostics.

Th-373

Dystonic tremor and essential tremor differ by width of the tremor frequency peak

K.G. Tuck, M.W. Cowey, D.R. Williams
(Melbourne, Victoria, Australia)

Objective: To compare the variability in tremor frequency between patients with dystonic tremor (DysT) and essential tremor (ET). We hypothesized analysis of the width of the frequency power spectrum derived from the accelerometer trace of tremor studies in these patients would spearate DysT and ET.

Background: DysT and ET are often difficult to separate clinically and their frequencies overlap between 4 and 8Hz. Clinically DysT is characterised by the presence of dystonia and often appears irregular, but there are no diagnostic electrophysiological characteristics. The width of the electrophysiologically recorded frequency spectrum is one objective measure of tremor regularity that may separate these conditions.

Methods: Eleven dystonic tremor patients and nine essential tremor patients were studied. DysT was defined by the presence of dystonia in the tremulous limb (n=5) or task specific tremor with dystonia (n=6). Surface EMG of bilateral forearm flexor and extensor muscles was recorded and an accelerometer trace was recorded from the dorsum of the hand. Digital recordings were made with the arms at rest, holding postures (arms held outstretched and wing-beating position) and during spiral drawing. A fast fourier transform of

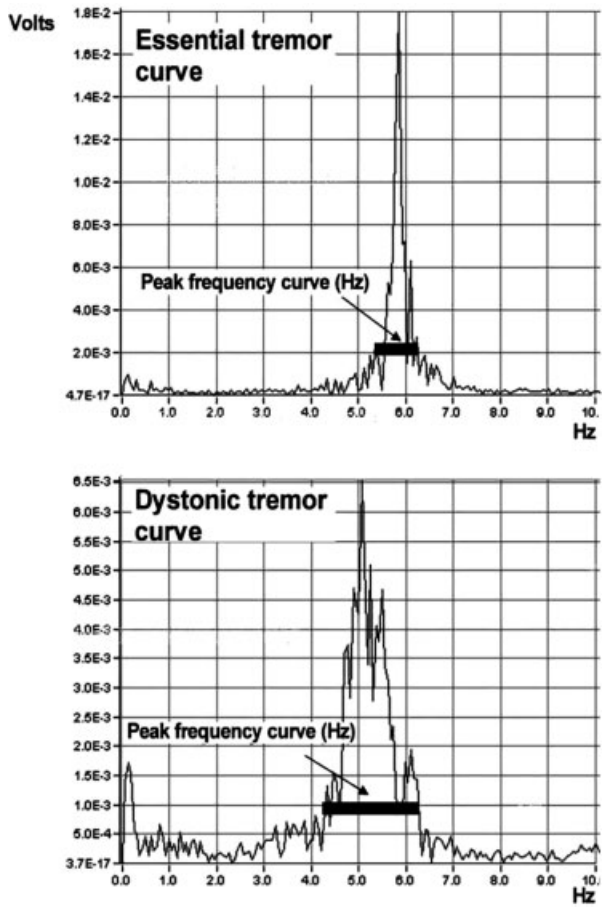

FIG. 1 (Th-373).

the accelerometer trace was performed to give frequency power spectrum. The peak frequency curve (PFC) was measured from frequencies indicated by a sustained increase above 3 SD of the baseline mean.

Results: Eight DysT patients and 9 ET patients had a tremor with arms held in the wing-beating posture. Analysis of the frequency spectrum showed the DysT group (mean 1.6Hz) had a significantly wider PFC than the ET group (mean 0.8Hz, Mann WhitneyU, $p=0.001$). No patient with DysT had PFC less than 1.0Hz. Analysis of the EMG mean muscle burst duration during wing-beating posture (DysT 79ms vs. mean ET 76ms) and PFC during spiral drawing (DysT 1.8Hz vs. mean ET 1.9Hz) did not separate the groups. We noted that in ET the PFC was significantly wider during spiral drawing than wing-beating posture ($p<0.001$).

Conclusions: Peak frequncy curve measurement separated DysT from ET patients during wing beating posture only. These findings suggest that accelerometry recording may be a useful clinical tool to differentiate these tremors (e.g DysT= wingbeating PFC>1.0Hz, ET=wingbeatingPFC<1.0Hz).

Th-374

The cerebellar signs and saccades abnormalities in essentials tremor

M. Wójcik, M. Rudzinska, M. Dec, A. Szczudlik (Krakow, Poland)

Objective: To investigate the relation between the occurrence of cerebellar signs and the visually-guided and volitional saccades abnormalities in ET patients.

Background: Essential tremor (ET) is characterized by postural and/or kinetic tremor. However, in some cases mild cerebellar signs so as intention tremor, dysmetria and tandem gait disturbances may also occurre. Previous studies of the eye movements in ET patients revealed certain abnormalities of saccade latency.

Methods: 42 ET patients (mean age: 59 ± 19 years; mean disease duration: 15 ± 10 years) were included to the study. The diagnosis of ET was estabilished according to the Tremor Research Investigatory Group (TRIG) criteria. Visually-guided and volitional saccades were recorded using the Saccadometer Advanced device. The parameters of saccades: amplitude, duration, latency and velocity were compared among ET with vs. without cerebellar signs.

Results: Mean volitional saccades latency was significantly longer in ET patients with vs. without cerebellar signs (901 ± 280 vs. 667± 169 ms, $p=0.003$). There were no significant differences between mean visually-guided saccades latency and the other parameters so as amplitude, duration and velocity of visually guided and volitional saccades between ET patients with vs. without cerebellar signs.

Conclusions: The latency of volitional saccades in ET is related to the cerebellum involvement.

Th-375

Botulinum toxin treatment of a drug resistant head tremor induced by a pontomesencephalic stroke

B. Wuschitz, G. Kranz, G. Kasprian, E. Auff, B. Voller (Vienna, Austria)

Objective: We report a case of a 69-year-old female patient who developed Holmes' tremor with horizontal head tremor four days after a stroke in the paramedian pontomesencephalic region. Our patient showed Holmes' tremor of the upper extremities and severe rest and postural tremor of the head. Her head tremor was increased by turning the head to the left side and was decreased by turning the head to the right side.

Background: A few drugs have been reported to give some benefit to the patients.

Methods: Our patient did not benefit from levodopa, propranolol, primidon, levetiracetam and tiaprid. We injected botulinum toxin typ A into the patient's neck muscles.

Results: Administration of botulinum toxin into the neck muscles led to a significant reduction of tremor severity.

Conclusions: We suggest botulinum toxin injections as effective treatment option for head tremor secondary to stroke as shown in this case.

Th-376

Cardiac MIBG SPECT in essential tremor

M. Yamamoto, Y. Kageyama, M. Sakai, T. Nakayma (Takamatsu, Japan)

Objective: We performed cardiac MIBG SPECT in patients with ET to investigate cardiac sympathetic function. We also follow up the clinical course of patients with ET for 3-6 years after diagnosis.

Background: Patients with Essential tremor (ET) and Parkinson's disease (PD) sometimes have both resting and postural tremor. ET may also be a risk factor of PD. Dysfunction of cardiac MIBG is a sensitive biomarker for Lewy body disease including PD and Dementia with Lewy Body. Cardiac MIBG SPECT in patients with PD showed decreased uptake of MIBG, but ET has not been well investigated.

Methods: Using cardiac MIBG SPECT, we investigated 35 consecutive patients with ET and 45 normal controls between 2002 and 2006. Dystonic type of writer's cramp and patients under 40 years old were not enrolled in the ET group. Statistical analysis was performed by Analysis of Covariance (ANCOVA).

Results: Age, early Heart/ Mediastium (H/M) ratio and late H/M ratio did not show significant differences between the two groups as the following Early H/R:control=2.4(0.03):ET=2.14(0.03), Late H/M:control=2.35(0.04):ET=2.24(0.05). (values:mean(SED). Three of 35 patients with ET showed relatively low uptakes of MIBG at early and late imagings reaching the lower limit of those in the normal control group. None of patients with ET developed PD during 3-6 year observation.

Conclusions: Some reports have shown that about 20% of ET patients develop parkinsonism. Our series of ET patients showed normal cardiac sympathetic function on MIBG SPECT and did not develop PD during the 3-6 year following up period. Three patients showed relatively decreased uptake of MIBG, but did not develop PD. Conclusions: Cardiac MIBG SPECT may be useful examination to differentiate ET from PD when patients have both resting and postural tremor. The long-term observation is also useful for this purpose. A small number of patients showing decreased MIBG uptake might comprise a subgroup of ET complicated by Lewy body disease.

PARKINSON'S DISEASE: PHENOMENOLOGY

Mo-375

New unified staging system for Lewy body disorders

C.H. Adler, J.N. Caviness, H.A. Shill, M.N. Sabbagh, D.J. Connor, D. Walker, L.F. Lue, L. Sue, L. Vedders, J.G. Hentz, T.G. Beach, Arizona PD Consortium (Scottsdale, Arizona)

Objective: Describe clinical findings and compare a new staging system for Lewy body disorders with previous staging systems for cases of incidental Lewy body disease (ILBD) and Parkinson's disease (PD).

Background: Current Lewy body staging systems do not categorize all subjects with Lewy bodies, especially olfactory bulb only or limbic predominant cases. We propose a new staging system and correlate clinical and path findings in cases of PD and ILBD.

Methods: We reviewed motor and cognitive findings from 191 autopsied subjects (97 controls, 68 PD, 26 ILBD) in the Sun Health Research Institute Brain/Body Donation Program. Dementia with

Lewy bodies (DLB) and Alzheimer's disease (AD) with Lewy body cases are not included in this presentation. Standard neuropathological methods were used, including immunohistochemical analysis with α-synuclein antibodies for Lewy bodies and Lewy-related neurites, and staging for neuritic plaques and neurofibrillary tangles. All subjects were classified using the Braak PD staging and DLB Consortium III staging as well as our proposed new staging system: I. Olfactory Bulb Only; IIa Brainstem Predominant; IIb Limbic Predominant; III Brainstem and Limbic; IV Neocortical.

Results: Groups differed in age (Control 84.8 yrs; ILBD 86.6; PD 79.2) and gender (Control 51.7% male; ILBD 61.5; PD 69.1). The PD group had lower MMSE (Control 28.6; ILBD 27.8; PD 19.4) and higher UPDRS motor scores (Control 9.8; ILBD 7.8; PD 42.0). Groups differed in nigral neuron loss (Control 0.39; ILBD 0.72; PD 2.69) and striatal tyrosine hydroxylase activity (Control 90.4; ILBD 45.9; PD 10.6) but not in neuritic plaque density or Braak neurofibrillary tangle stage. Using the newly proposed staging system cases are classified in Table 1. Lewy body stage correlated with UPDRS motor scores and inversely correlated with MMSE in PD cases.

Table (Mo-375). Classification of subjects by new Lewy body staging system

Diagnosis (N)	I. Olfactory bulb only	Brainstem predominant	Limbic predominant	Brainstem/Limbic	Neocortical
ILBD (26)	15%	55%	11%	15%	4%
PD-all cases (66)	0	18%	4%	44%	34%
PD-CogNL (23)	0	30%	13%	44%	13%
PDD w/o AD (15)	0	13%	7%	66%	14%
PDD w/AD (28)	0	7%	7%	54%	32%

Conclusions: The newly proposed Lewy body staging system allows for classification of Lewy body cases including olfactory bulb only cases. Clinical findings correlated with severity of Lewy body stages in subjects with PD. Further validation of the proposed staging system, including classification of DLB and AD cases with Lewy bodies is underway.

Mo-377

The accuracy of clinical diagnosis of tremor dominant Parkinson's disease in a specialist hospital setting: A blinded videotape study

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Objective: To examine the ability of experienced movement disorder specialists to distinguish clinical TDPD from SWEDDs.

Background: There have been few studies concentrating on the accuracy of clinical diagnosis in tremor dominant PD patients (TDPD). The main differential diagnoses are atypical tremor and dystonic tremor, which are subjects without evidence of dopaminergic deficit on dopamine transporter SPECT imaging (SWEDDs).

Methods: Two blinded experienced movement disorder specialists were asked to distinguish clinical TDPD from SWEDDs(as assessed by ^{123}I-/V-cu-fluoro-propyl- 2ß-carbomethoxy-3ß-(4-iodophenyl) nortropane ([^{123}I] FP-CIT) SPECT) by video analysis of 38 patients. All patients were rated according to fulfilment of step 1 of the Queens Square Brain Bank criteria for PD as well as the clinical features of dystonic tremor (1) and criteria for essential tremor (2). This reviewer diagnosis was compared to the operational diagnosis by reference to the SPECT scan result, the historical knowledge of the case and in some cases the known response to dopaminergic medications. This comparison allowed a calculation for false positive and false negative rate of diagnosis of PD in this study.

Results: Comparison of the blinded reviewer diagnosis to the operational diagnosis in this study revealed a sensitivity of diagnosis of PD between 72 and 93% and a specificity of 79 to 85%.

Conclusions: The study found a surprisingly high false positive (up to 26%) and negative rate (up to 20%) for the diagnosis of PD. This compares to similarly high error rates in community studies for the diagnosis of PD, where benign tremor is a frequent confounding diagnosis. Dystonia was noted in a number of drug naïve PD cases which limited the specificity of clinical distinguishing features of dystonic tremor in this study. Bradykinesia with fatiguable motor decrement was the most frequent cause of false positive diagnosis of PD in cases of SWEDD. This study highlights the difficulty of differentiation of some cases of SWEDD from PD.

Mo-378

Prevalence and phenomenology of olfactory hallucinations in Parkinson's disease

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Objective: To determine the prevalence and to describe the clinical characteristics of olfactory hallucinations in a Parkinson's disease (PD) population associated with an evaluation of smell abilities (detection, identification).

Background: Hallucinations are frequent in the course of PD, especially minor forms and visual hallucinations. Olfactory hallucinations (OH) have been mentionned in a few reports but there is no transversal study looking specifically toward these phenomena.

Methods: consecutive patients with idiopathic PD, aged 40 to 80, without cognitive impairment (MMSE⟩26) were examined for the presence of OH. Disease duration, age of onset, severity of the disease (Hoehn and Yahr) and antiparkinsonian treatment were recorded. Then, patients answered a semi stuctured questionnary to determine OH frequency, duration, insight, kind of odor. Smell abilities (detection, identification of odors) were also evaluated. PD patients were compared with healthy subjects.

Results: 87 patients were examined: 48 women and 39 men aged 65.4 ± 0.9 years with a disease duration of 6.7 ± 0.6 years. 9 PD patients among the 87 PD patients described OH compared to none of the 40 controls, that is an estimated prevalence of 10.3 %. Patients with OH were not different from patients without OH in terms of age, disease duration and severity. OH frequency is rather rare (once or twice a month), they generally last few seconds to few minutes. Most of time they are made of unpleasant odors but they are not frightening, they have few impact on life quality. In our study, we found that smell abilities were significantly impaired for PD patients compared to controls but there was no difference between PD patients with and without OH.

Conclusions: This study is the first to specifically focus on OH in PD. We think olfactory hallucination may be of multifactorial origin. The impairement of smell abilities, a non motor symptom generally occuring in PD before motor signs, is probably involved in olfactory hallucinations genesis just like abnormality of the visual system may be related to visual hallucinations in PD.

Mo-379

Impaired sense of smell as early indicator of Parkinson's disease

I. Bilic (Split, Croatia)

Objective: The aim of the study was to evaluate impaired sense of smell as possible early indicator of Parkinson's disease (PD).

Background: Nowadays, we know that an odor identification deficit can predate the development of PD by at least four years. Decreased odor identification is associated with older age, smoking, more coffee consumption, less frequent bowel movements, lower cognitive function and excessive daytime sleepiness. Detecting impaired sense of smell can be like diagnosing coronary artery disease before the heart attack, and neurologists in practice should be aware of this early non motor symptom of PD.

Methods: PD patients were asked for 2 questions: if they ever had impaired sense of smell in last 10 years and if they ever had been asked about smell difficulties by their neurologists.

Results: 23 individuals with PD was included in the study. The mean age was 65.1±12.4 years, the mean disease duration was 6.4±3.1 years, the median stage was 2.5 (1-3) in Hoehn-Yahr scale. 6 (26%) patients reported impaired sense of smell in last 10 years,

and only 1 patient (4%) said he had been asked about smell difficulties by his neurologist throughout the period since diagnosed as having PD.

Conclusions: Smell disorders can have many other causes than PD, most frequent, upper respiratory infections and allergies but in this cases disorders are often transient and in PD impaired sense of smell often deteriorates through time. The pathophysiology of smell impairment in PD is yet not completely understood. Olfactory testing along with screening for other potential early indicators of PD such as constipation or sleep disturbances could provide a simple and relatively economic means of identifying individuals at high risk for developing PD. Many individuals with Parkinson's disease are able to recall losing their sense of smell well before the onset of more commonly recognized symptoms such as tremors, impaired dexterity, speech problems, memory loss and decreased cognitive ability. In the future, early detection combined with neuroprotective therapy may be important for interventions that slow the progression or even prevent the onset of Parkinson's disease.

Mo-380

Falls and freezing of gait in Parkinson's disease

I. Bilic (Split, Croatia)

Objective: To assess episodes of falls and freezing of gait in patients with Parkinson's disease (PD).

Background: Falls and freezing of gait (FOG) are generally thought to be closely intertwined. They are most common in advanced PD and often respond poorly to the therapy. Falls and FOG can cause distress and discomfort and impact quality of life and it is important to be aware of these symptoms.

Methods: 43 patients were included in this study. Parkinsonian symptoms were scored using UPDRS. The mean age was 67.5±10.9 years and the mean disease duration was 8.5±4.1 years. Quality of life was measured with EQ-5D scale. Patients were asked about falls and episodes of FOG in the previous 12 months. Episodes of FOG were assessed according to Freezing of Gait questionnaire (FOG-Q).

Results: Episodes of FOG were found in 24 (55.8%) of patients and falls in 27 (62.8%), and all of patients who reported episodes of falls and FOG had reduced quality of life compared with patients who did not experienced such symptoms.

Conclusions: The underlying pathophysiology of falls and FOG in PD is rather complex. It is most important to ask patient and caregiver about these symptoms. Falls in PD can be caused by postural instability, orthostatic or postural hypotension, dopaminergic drugs and many other causes. Most falls in PD occur indoors. Falls are common during transfers, such as rising from a chair or bed. PD patients fall mostly forward. FOG is much more common in the advanced stage of PD and in the off state. The mobility problems related to falls and FOG have marked impact on the patients' lives. The reduced and impaired mobility causes depression, poor sleep quality, hip fractures and other "minor" injuries, restriction of daily activities, and finally also an increased mortality risk. Nowadays, there are many treatment options to reduce falls and FOG in PD which include: pharmacotherapy, sterotactic neurosurgery and physiotherapy. Multidisciplinary team approach is recommended.

Mo-381

Disturbances in gait and interlimb coordination in Parkinson's disease patients with freezing of gait

S.W. Mahabier, A.H. Snijders, A. Delval, S. Overeem, B.R. Bloem (Nijmegen, Netherlands)

Objective: To examine whether Parkinson's disease (PD) patients with freezing of gait (FOG) exhibit disturbances in arm swing, stride length regulation and interlimb coordination between the upper and lower limbs more than PD patients without FOG and control subjects.

Background: FOG is a common gait disturbance in PD, characterized by a sudden inability to start walking or to continue moving forward. Previous studies have found a higher asymmetry and variability of gait in PD patients with FOG compared to those without FOG. Arm movements and coordination between the upper and lower limbs were not examined in these studies, but it is known that these features are disturbed for PD patients in general.

Methods: We included 13 PD patients with FOG (PD+FOG), 15 PD patients without FOG (PD-FOG), and 15 healthy controls. Subjects walked over ground (at preferred speed and as fast as possible) and on a treadmill (at 1.5 km/h, 2 km/h, 3 km/h, and at preferred speed). Kinematic gait parameters were measured with a motion analysis system. Outcome measures were duration, length, asymmetry in length, and variability (coefficient of variation) of arm swing and strides. Interlimb coordination was the delay in time between heel strike on one side and maximal forward arm swing on the contralateral side.

Results: There were no group differences in duration and asymmetry of arm swing and strides. During both over ground and treadmill walking, arm swing amplitude and stride length were smaller in PD patients than in controls, and variability of arm swing and strides was higher. Stride length was smaller for PD+FOG compared to PD-FOG in the treadmill conditions, and stride length variability was higher. E.g. stride length was 14 cm smaller ($p=0.047$) and stride length variability was 17% higher ($p=0.046$) in PD+FOG at the 3 km/h. Interlimb coordination between upper and lower limbs was less synchronized in patients compared to controls. When the coordination between the affected arm and the less affected leg was observed during fast over ground walking, it was 2.16 times worse in PD+FOG compared to PD-FOG ($p=0.03$).

Conclusions: FOG appears to be caused by a defect in regulation of leg movements (stride length and stride length variability), but not in arm movement regulation or the coordination between upper and lower limbs.

Mo-382

Auditory cueing and obstacle avoidance in Parkinson's disease patients

S.W. Mahabier, A. Delval, S. Overeem, V. Weerdesteyn, B.R. Bloem (Nijmegen, Netherlands)

Objective: To examine the interaction between walking with an obstacle avoidance task and the ability of Parkinson's disease (PD) patients to synchronize their heel strikes to an auditory cue, and how both tasks affect each other when executed at the same time.

Background: PD patients suffer from gait disturbances with e.g. a decreased stride length or freezing of gait (FOG). Rhythmic auditory cueing may facilitate walking in PD by increasing stride length and reducing FOG. However, improper cueing frequencies may also aggravate gait disturbances. In daily life, cueing might interfere as a dual task, when other tasks have to be executed simultaneously.

Methods: 17 PD patients (6 with FOG) and 15 healthy controls were examined in 4 conditions: normal walking, walking with a metronome (-10% of preferred cadence for patients, +10% for controls), walking with an obstacle avoidance task, and walking with both a metronome and an obstacle avoidance task. These conditions were recorded during over ground walking and during walking on a treadmill. Outcome measures were foot clearance, metronome synchronization (delay between heel strikes and metronome), and kinematic gait parameters (walking speed, stride length, stride time and cadence). All patients were tested in 'off' state.

Results: There were no differences in foot clearance between both groups and the several conditions. Freezers and non-freezers showed the same results. Controls adhered best to metronome synchronization during over ground walking ($p=0.009$). On the treadmill, metronome synchronization was worse compared to over ground walking for both groups. During obstacle avoidance tasks on the treadmill, metronome synchronization was better in controls.

Conclusions: Patients had more difficulties to synchronize their heel strikes to the metronome than controls. Auditory cueing did not affect obstacle avoidance performance in either group. The obstacle avoidance task also did not affect the performance on the metronome task in both groups. However, on the treadmill, controls performed better on the metronome task than patients. This suggests that PD patients were able to prioritize prevention of stumbling above the metronome task, at the expense of less accurate adherence to the metronome task.

Mo-383

Non-motor symptoms in Parkinson's disease

R. Borgohain, N.K. Venigalla, R. Mridula, S.A. Jabeen, M.A. Kanikannan (Hyderabad, AP, India)

Objective: To identify the most common NMS in PD and to determine the influence of demographic details on the presence of NMS.

Background: It has been recognized that non dopaminergic and non motor symptoms are sometimes present prior to diagnosis of Parkinson's disease (PD) and inevitably emerge with disease progression with worsening morbidity, quality of life and mortality. Non motor symptoms (NMS) are poorly recognized and inadequately treated.

Methods: We report the common non motor symptoms identified in Parkinson's disease patients using the questionnaire (NMS Quest) developed and validated by International PD Nonmotor Group. Non-demented patients of all ages and all stages of the disease were included in the study. Patients were divided in to groups based on onset, severity and duration of disease. Significance of group comparison was determined by Mann-Whitney or Kruskall Wallis tests.

Results: Sixty PD patients were evaluated with the nonmotor symptoms questionnaire, which is a 30 item screening questionnaire. Mean age of the patients was 58.2±3.8 years. Patients had nonmotor scores ranging from 3 to 20. Most of the patients had nonmotor scores between 8-12. The mean nonmotor score was 10±4.24. Mean duration of disease was 7.86±4.83years. The most common nonmotor symptoms identified in this cohort were dribbling of saliva (55%), swallowing difficulty (51%), constipation (58%), urinary urgency (51%), sexual disturbances (33%), unexplained pains (75%), frightening dreams (62%), insomnia (76%), and excessive sweating (55%). The occurrence of NMS significantly increased as severity and duration of disease increased ($p < 0.05$). No statistically significant difference was noted in scores between groups less than and more than 50 years age.

Conclusions: Nonmotor symptoms are common across all stages of Parkinson's disease and become more prominent as the disease advances. Bodyaches, sleep disturbances, urinary and gastrointestinal disturbances were the commonest problems. Early recognition and attention to these symptoms is of utmost importance.

Mo-384

Upper extremity freezing in two patients with Parkinson's disease

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Objective: To report two patients with Parkinson's disease and upper extremity freezing.

Background: Freezing is a phenomenon often reported in patients with Parkinson's disease. It is often present in the lower extremities while walking or at gait initiation, hence the term, freezing of gait. It can cause morbidity and mortality if gait freezing results in falls. Freezing in the upper extremities has rarely been reported. We have previously reported two patients with upper extremity freezing occurring exclusively while eating.

Methods: A retrospective chart review identified two patients with upper extremity freezing.

Results: Case 1: A 51-year old male with Parkinson's disease for 10 years, on rasagiline, carbidopa/levodopa/entacapone, and pramipexole, had fair control of motor symptoms and no complaint of gait freezing. He is right-handed and complained of freezing of his right hand while walking. His hand would swing to his back and remain there as if "stuck to his back". His hand froze while doing various tasks such as eating or drinking and reaching for an object. He had to consciously and with great effort bring his right hand forward and clap his hands to stop the freezing. Case 2: 47 year-old male with Parkinson's disease for 12 years, was doing well on ropinirole, selegiline, and carbidopa/levodopa. He is right-handed and complained of freezing of his right hand while eating, shaving, and brushing his teeth. This happened frequently and occurred whether he was on or off his medications. He used his left hand to bring his right forearm down. Recently, he had been using his left hand more often to do the same tasks. Since he was not very adept at using his left hand, he had a couple of small accidents while shaving.

Conclusions: Freezing of the upper extremities has been rarely reported. Freezing of the upper extremities is a unique phenomenon occurring separately from freezing of gait. It is similar to freezing of gait in that it can occur as an "on" or "off" phenomenon. It may also cause significant morbidity due to freezing occurring while eating, writing or using a tool. Besides medication adjustment to improve on time, visual and auditory cues have been reported to help with lower extremity freezing. We need further studies to explore treatment strategies to help with upper extremity freezing.

Mo-385

Long-term effects of high frequency stimulation (HFS) on tremor in Parkinson's disease (PD): A case study

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Objective: To demonstrate a durable effect of HFS by describing a case of sustained tremor control in Parkinson's disease after discontinuing HFS for 3 months.

Background: The durable effects of HFS are not well-understood. A decrease in responsiveness of levodopa with long-term HFS of the STN for PD has been described, but medication reduction and disease progression were confouners (Piboolnurak P, et al. Mov Disord 2007). Sustained motor benefit was described in a case of cranial dystonia after HFS was discontinued (Hebb M, et al. Mov Disord 2006). Long-term potentiation (LTP) and long-term depression (LTD) are possible mechanisms for the durable effects observed with prolonged HFS.

Methods: A 61-year-old man with a 13-year history of idiopathic PD underwent frame-based, MRI-guided stereotactic placement of bilateral STN DBS leads (model 3387; Medtronic, Minneapolis, MN) for refractory tremor. Tremor analysis was performed 6 months prior to surgery. Several adjustments were required because of refractory dysphonia that developed a few hours after the second day of programming. Final settings were 3-C+, 3.0V, 60 microseconds, and 185 Hz bilaterally with impedance of 1056 on the left and 942 on the right. MRI was repeated six weeks after initial programming. After 10 months, HFS was discontinued. Three months after HFS discontinuation, tremor was re-evaluated, Archimedean spirals were recorded, and comparisons were made with pre-operative samples.

Results: Tremor analysis demonstrated a rest tremor with a narrow peak at 5 Hz. Tremor in the upper and lower extremities were well controlled after initial programming. Baseline rest tremor scores were 4 bilaterally with and without medication (figure 1) and was reduced to 0 with stimulation. MRI revealed no enhancement, lead migration, or abnormal signal intensities. Tremor benefit was reversible during for the first 4 months after initial programming. After 3 months without HFS, rest tremor was maintained at 0 in the upper extremities.

Conclusions: Prolonged HFS resulted in durable benefits on tremor in the upper extremity. Possible mechanisms include direct and indirect

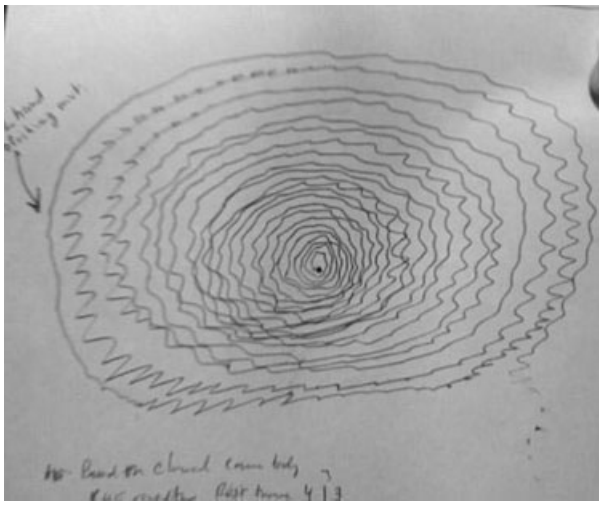

FIG. 1 (Mo-385).

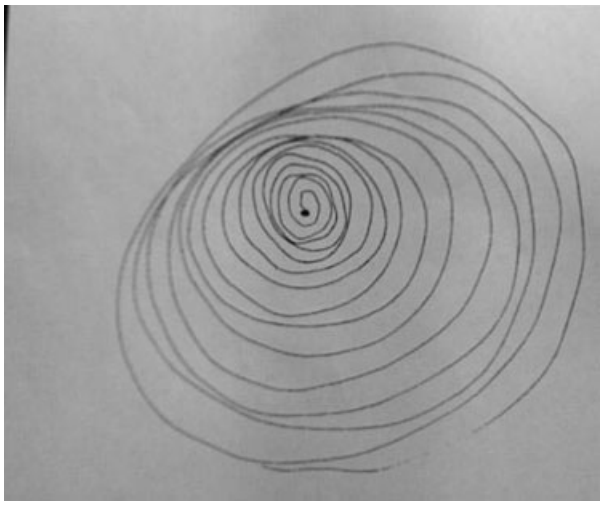

FIG. 2 (Mo-385).

synaptic changes from LTP and LDP as a result of HFS, but alternative post-operative processes like scarring cannot be excluded.

Mo-386

Segmental progression scores in PD and cross-sectional team results in movement disorders office-based work-up

S.G. Echebarria (Las Arenas, Spain)

Objective: Comprehensive sizing and grouping sampling may be derived in Segmental Score Progression applied to recent-onset PD. This methodics may be described in motor subscores, post-hoc samples, symmetry grades and associated movements.

Background: Comprehensive perspectives in PD diagnostics and neurologic sampling have been extended in recent years considering new evolutive hints, based on exploratory -signs distribution and focal-segmental-areal extension and diagnoses correlation. New developments in such sense have been established according to segmental progression findings. Scores in such series were related to akinesia, rigidity and tremor, with sign severity ranging from 0 to 5. Such segmental progression may be concreted (in rest tremor) as 0.5 to 0.33 coefficients and 0.67 to 0.17 coeffcients in lower limbs. Sequential r may be obtained too between akinesia and rest tremor. Longitudinal projection in initail tools and variables may be observed: UPDRS subscores, H&Y and S-E scores, age, sex and BDI.

Methods: PCA as method applied to Segmental Signs progression/ Functional samples. -Qualitative methods, applied to motor /descriptors and diagnostic scores Spearman r between QLS-MD and cross-sectional samples. -Applicability of Movement Disorders QLS-MD to recent-onset PD (pre-DBS).

Results: Correlation between UPDRS III and Segmental Rigidity Progression at 12 months is described as significant $r = 0.67$ (based on median UPDRS III results in ON/OFF series (recent-onset PD): 20.2-21.1) -UPDRS III and Segmental Rest Tremor Progression at 6 months is described as significant $r = 0.60$. -Akinesia scores and quality -functional scores (Handipark) in PD patients series with less than 5 years of evolution are related with a $r = 0.52$(distributional results in Handipark with $x = 3.9$). -QLS-MD and Segmental Rigidity Progression show a linear correlation $r = 0.14$.

Conclusions: -Pre-diagnostic evolution and comorbidity series previous to sampling and sensibility in diagnostic work-up described in 3ry Movements Disorders Services may be significantly related to akinesia/tremor Segmental Scores Progression. -Rest tremor and akinesia onset in pre-diagnostic indexes application (motor subscores and minor signs) have positive correlation ranks.

Mo-387

Motor response in Parkinson's disease patients treated with continuous infusion of apomorphine or of duodopa or with STN deep brain stimulation

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Objective: To compare motor response in Parkinson's disease (PD) treated with continuous infusion of apomorphine or of duodopa or with subthalamic deep brain stimulation (DBS).

Background: Three different strategies are available to reduce motor complications that cannot be controlled by oral therapies in PD patients: DBS, continuous infusion of duodopa or of apomorphine, but no direct comparison of these therapies is available.

Methods: We recruited a series of consecutive PD patients with stable antiparkinsonian medication during the last three months. The patients were evaluated after overnight drug withdrawal under three different experimental conditions with timed motor tests, the UPDRS-III and the AIMS dyskinesia scale, that were administered every 30 minutes. During the first day the patients had their current home regimen. During the second day they were in monotherapy (with duodopa, apomorphine or DBS). On the third day an acute levodopa challenge (levodopa/carbidopa 250/25 mg) was added to the patients' monotherapy. The mean area under the curve was compared by univariate ANOVA analysis between the three groups and with a post-hoc analysis with Tukey or Dunnet test.

Results: Thirty patients (ten for each treatment group) were enrolled in the study. Mean age at disease onset was 46.9 ± 9.1 years (range 31-68). Mean clinical follow up was 21.9 ± 18.9 months for DBS, 52.2 ± 64.9 months for apomorphine and 3.9 ± 3.3 months for duodopa. Duodopa and DBS were more effective than apomorphine in reducing UPDRS-III during home therapy observation (respectively $p=0.037$ and $p=0.011$), monotherapy ($p=0.003$ for both comparisons) and acute levodopa challenge (respectively $p=0.048$ and $p=0.017$). Treatment with duodopa was related to higher dyskinesia score than DBS during home therapy observation ($p < 0.001$), monotherapy ($p < 0.001$) and acute levodopa challenge ($p=0.011$). Treatment with duodopa was related to higher dyskinesia score than treatment with apomorphine during observation with monotherapy ($p=0.001$).

Conclusions: These results indicate that DBS is associated with better motor performance whereas duodopa is associated with more

severe dyskinesias. Further studies with longer clinical follow up are needed to evaluate long term effect of duodopa.

Mo-388

Prodromal non-motor symptoms of Parkinson's disease, long-term uneffective non-dopaminergic treatment and subsequent response to dopaminergic medication: A retrospective study

K. Farnikova, P. Kanovsky (Olomouc, Czech Republic)

Objective: The aim of this study were to review the prevalence of NMS as presenting complaints in cases of PD that approved the most often as musculoskeletal problems.

Background: Parkinson's disease (PD) in many patients will in hindsight recall a prodromal phase including non-motor symptoms (NMS).

Methods: A retrospective review of cases of patients suffering from PD has been performed. There were 82 cases, 52 men and 30 women. The mean age was 61,5 years in men and 66,2 years in women. The mean age in disease onset (diagnostic made and treatment initiation) was 57,4 years in men and 61,5 years in women. The mean disease duration was 5,3 years in men and 6,1 years in women. The hospital inpatient notes and emergency room admission notes were reviewed. The initial presenting complain prompting patients to attend medical services was noted and early diagnoses made were documented. The included symptoms were considered retrospectively to be associated with PD.

Results: NMS as prodromal PD symptoms were present in personal history in 27 (33%) cases, 14 men and 13 women), which were initially diagnosed with the osteoarthritis, degenerative spinal disease and frozen shoulder. The mean time from appearance of first signs to dopaminergic treatment initiation was 6.6 years in NMS group and 2.3 years in group with typical PD signs. Significant improvement of NMS after dopaminergic treatment initiation was present in 23 (85%) cases, 12 men and 11 women.

Conclusions: 33% of PD population assessed in this study who went on to develop motor features of PD, descibed their initial symptoms in exclusively NMS terms. NMS presentations of PD were frequently misdiagnosed, leading to a high proportion of potentially inappropriate specialist referrals and treatments including long-term ineffective physiotherapy, steroid injections to frozen shoulders and surgical interventions for degenerative spinal disease or carpal tunnel syndromes. A good response to L-DOPA therapy was seen in 85% cases with presenting NMS. Our findings suggest that NMS may be significant features in earlier PD stages and that an increased awareness of such a manifestation of PD is also required at a primary care level.

Mo-389

Modulation of gait symmetry by subthalamic stimulation improves intractable freezing of gait

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Objective: To study how modulation of symmetry between both legs by subthalamic deep brain stimulation (STN-DBS) impacts on freezing of gait (FOG) in patients with Parkinson's disease (PD).

Background: Gait is a complex multi-component motor process which amongst others requires precise coordination between both body sides. It has therefore been hypothesized that dysfunction in rhythmicity, symmetry or coordination between both legs might be an important risk factor for FOG. It is yet unclear whether change of these variables by STN-DBS influences the gait performance of PD patients.

Methods: We enrolled 22 PD patients (13 FOG+) with STN-DBS. At time of examination mean age was 63.2 ± 7.7, disease duration 15.2 ± 4.3 years, and follow-up after surgery 35.9 ± 32.2 months. Patients were evaluated in the following four conditions: STN-DBS on (DBS ON), STN-DBS off (DBS OFF), 50% reduction of stimulation voltage contralateral to the slower leg (worse side reduction, WSR), 50% reduction voltage contralateral to the faster leg (better side reduction, BSR). Gait analysis was performed on a motor-driven treadmill and recorded by three-dimensional opto-electronic analysis system. We measured the frequency and duration of FOG-episodes during 40 sec of recording. The bilateral coordination of gait was assessed by the Phase Coordination Index (PCI) quantifying the phase between the left and right leg with lower values indicating more symmetric gait.

Results: In FOG+ patients, during DBS OFF, there were 2.0 ± 0.37 FOG episodes lasting for 12.19 ± 2.63 sec. During DBS ON, FOG significantly improved with reduction of episodes (1.38 ± 0.46) and duration (2.58 ± 0.81 sec) ($P=0.005$). During WSR, FOG worsened with increase of episodes (1.31 ± 0.41) and duration (5.23 ± 2.10 sec). Remarkably, BSR further improved FOG with significantly lesser FOG episodes (0.23 ± 0.23) and duration (0.21 ± 0.21 sec) compared to DBS ON ($P=0.03$). During BSR, FOG reduction was accompanied by normalisation of symmetry as measured by PCI (16.5±6.0%) which was significantly lower than in the other three conditions.

Conclusions: In FOG+ patients, change of symmetry by STN-DBS significantly improves limb coordination and reduces FOG. This identifies poor leg coordination as a major risk factor for FOG which just be considered during adjustment of stimulation parameters.

Mo-390

Parkinson's disease patients with freezing of gait: Evidence for a specific impairment at the beginning of the single-support phase of the gait cycle

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Objective: We used force-sensitive insoles that localize the center of pressure (COP) under each foot to test for abnormalities in COP dynamics in PD patients with and without FOG during normal walking.

Background: Freezing of gait (FOG) is a phenomenon that occurs in advanced PD, characterized by an involuntary inability to move forward. The underyling mechanisms are yet unclear.

Methods: PD patients (N=29, age 66±7 yrs; mean UPDRS motor score of 20±7) with motor fluctuations were tested during their "on" state of medication. They completed three 2-minute walks along a 20m corridor at their comfortable walking pace. Two walks involved an additional cognitive task (serial subtraction of 3 or 7). Subjects wore capacitive force sensitive insoles (Pedar-X, Novel, Germany) that measure the COP under each foot in the medio-lateral (ML) and anterior-posterior (AP) axes of the foot (sampled at 100 Hz). To assess presence and severity of FOG, patients completed a six-question FOG questionnaire (FOG-Q) [1], with higher scores indicating more severe FOG. Mean FOG-Q scores were 9.9 ± 5.3 (range 1-21).

Results: FOG-Q scores were significantly correlated with occurrence of backwards or lateral COP movements at times between 20%-25% into stance, when single support starts (Spearman's rho=0.50, 0.53, 0.60 for the three walks for backwards COP displacements, $p<0.01$; rho=0.55, 0.65 and 0.68 with $p<0.003$ for the corresponding lateral COP displacements). During other phases of stance, there were only weak, usually insignificant correlations with the FOG-Q score. Replacing the FOG-Q score with a sub-score that sums only the 3 questions related specifically to FOG duration gave essentially the same results, as did a replacement of the correlations with t-tests comparing those with lower and higher FOG-Q scores. Dual tasking exacerbated these observed abnormalities.

Conclusions: Our findings suggest that FOG severity is associated with a specific abnormality at the beginning of the single-support phase of gait. It remains to be determined whether this phenomenon reflects the disease process, is an adaptive compensatory strategy that

subserves normal walking, or contributes to FOG itself. References: 1. Giladi N. et al. parkinsonism Relat Disord. 6(3):165-170, 2000.

Mo-431

Pregnancy in a patient with Parkin-positive, juvenile-onset Parkinson's disease

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Objective: To describe pregnancy in a Parkin-positive, juvenile-onset Parkinson's patient.

Background: Pregnancy in Parkinson's disease (PD) is rarely reported. There is one French-language report of pregnancy in a Parkin-positive patient. L-dopa crosses the blood-brain barrier, but teratogenicity has not been demonstrated either in animal studies or human case reports. Ropinirole increased fetal mortality and and digit malformations in rabbits; no other teratogenicity has been demonstrated in animal studies of other dopamine agonists. Amantadine has been linked to cardiac malformations in humans. The effect of pregnancy on PD symptom control is not well characterized. Some reports note worsening of motor symptoms during pregnancy.

Methods: Retrospective chart review revealed one patient with Parkin-positive, juvenile-onset PD.

Results: 23-year old female with juvenile-onset PD, Parkin-positive. Symptom onset was at age 12, with prominent dystonia. Her symptoms progressed to include motor fluctuations with painful "off" dystonia and dyskinesia. She also had prominent non-motor symptoms including pain, depression and emotional lability which led to repeated emergency room visits. She was taking carbidopa/levodopa, pramipexole, amantadine, and subcutaneous apomorphine. At 4 weeks gestation, all medications except carbidopa/levodopa were discontinued because of teratogenicity concerns. Despite repeated adjustment of levodopa dose, and reintroduction of pramipexole, the patient's symptoms could not be controlled. In consultation with high-risk obstetrician, at 10 weeks' gestation, the patient restarted amantadine and apomorphine, with reasonable symptom control. The patient vaginally delivered a healthy baby girl with no fetal malformations at 41 weeks gestation. Notably, patient's non-motor symptoms have improved since delivery. Rather than experiencing severe anxiety associated with her "off" symptoms, she states that she just "deals with it and takes care of the baby."

FIG. 1 (Mo-431).

Conclusions: This is, to our knowledge, the second case report of pregnancy in a juvenile-onset parkinson's patient, and the first English-language report. Despite use of amantadine, no cardiac or other fetal malformations were noted. Discontinuing PD medications in the setting of pregnancy may adversely affect patients' symptom control, despite meticulous dose adjustment.

Tu-375

A timeline for Parkinson's disease

C.H. Hawkes, K. Del Tredici, H. Braak (London, United Kingdom)

Objective: To provide a consensus view of the evolution of classic Parkinson's disease (PD) by combining what is known of clinical, epidemiologic, imaging and neuropathologic findings.

Background: Classic PD has a fairly consistent clinical and neuropathologic profile with a lengthy 'prodromal' or 'premotor' phase. The duration of the prodrome is not known with certainty and correlation of Braak staging with clinical features is not straightforward. Several prodromal features are suggested but many are not substantiated by prospective studies.

Methods: Relevant literature was reviewed including publications by the current authors. Information concerning studies from imaging, neuropathology, clinical and epidemiologic sources were combined to synthesize a model of disease onset and progression incorporating the more robust features that appear before typical disease onset.

Results: The best established premotor features, based on long-term, prospective studies supplemented by pathological verification are: hyposmia, constipation, obesity, sleep and autonomic (sympathetic) disorder. We suggest there is a lengthy prodromal period for PD lasting approximately 20 years, followed by a clinical stage of 15- 20 years. There is inevitably considerable variability for both estimates, but an overall 40 year disease course would constitute a reasonable estimate.

FIG. 1 (Tu-375).

Conclusions: If PD starts 20 or more years before clinical presentation, this provides a reasonably long period for intervention. We suggest that measurement of olfaction, bowel habit, weight and sleep pattern would be an appropriate way to assess at-risk subjects who may be in the prodromal phase of PD. For neuroprotective measures to be of benefit, patients in this phase need to be identified even though they may be healthy outwardly. Initially this goal may be achieved by identifying those at risk in families with mutations

known to be associated with PD. For the vast majority who have no such mutations, population screening will be required.

Tu-376

Positive family history of essential tremor influences the motor phenotype of Parkinson's disease

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Objective: To analyze motor phenotype in patients with Parkinson's disease (PD) whose first degree relatives have essential tremor (ET). We hypothesized that the presence of a positive family history of ET affects the degree of tremor in these PD patients.

Background: Recent reports have suggested that ET represents a significant risk factor for the development of PD. Patients with a long-standing ET who develop PD tend to have a tremor-predominant subtype. These patients typically display a prolonged course of isolated tremor before exhibiting rigidity or bradykinesia and in these cases there is no question about the coexistence of ET and PD. The possible relationship between ET and PD is less certain in patients with probable PD who developed action tremor or have a prominent postural tremor that is clearly distinct from a re-emergent rest tremor.

Methods: We examined patients who had signs of isolated PD but did not meet criteria for overlapping ET. They were from kindreds in which at least two individuals were classified as having definite ET. We required evidence for vertical transmission of ET, consistent with an autosomal dominant mode of inheritance, in these pedigrees. Motor deficit was quantified using UPDRS-II scale and tremor was quantified using the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) scale.

Results: The studied cohort consisted of 543 individuals affected by definite ET or probable PD from 158 kindreds. We identified 22 patients with PD meeting these diagnostic criteria and 90% (20/22) had tremor-predominant subtype of PD. Four patients had Hoehn/Yahr stage I, 10 stage II, and 8 stage III. Unilateral rest tremor was the presenting symptom in 15/22 of patients, bradykinesia or rigidity in 5/22 and gait problems in 2/22. Postural tremor was relatively mild and the severity of action tremor tightly correlated with rest tremor ($r=0.83$, $p<0.001$). Patients with tremor-predominant PD also developed additional cardinal signs of PD, and bradykinesia was present in 20 patients (91%), rigidity in 21 (95%), gait disturbance in 6 (27%) and postural instability in 4/22 (18%).

Conclusions: Tremor dominant subtype of PD in patients with a positive family history of ET suggests that these patients have inherited a genetic susceptibility factor for tremor, which affects the motor phenotype of PD.

Tu-377

Parkinson's disease and falls in means of public transport

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Objective: The aim of this study is to ascertain prevalence and sequels of falls of PD patients in the specific situation present in means of public transport.

Background: To maintain mobility, independence and a high level of quality of life, patients with Parkinson's disease (PD) largely depend upon the use of public transport. It is well established that particularly the elderly are prone to falls in busses, trams and trains and that PD is associated with a high risk of falling even on solid ground.

Methods: Two-hundred-thirteen PD patients (101 men, 112 women; mean age 71,03±11,17 years; mean Hoehn and Yahr stage 2,62±0,90; mean UPDRS motor score 31,62±15,04) and 108 age-, sex- and regionally-matched healthy control subjects (36 men, 72 women; mean age 70,15±7,19 years) were included in the study. The data was collected with the help of a self-designed questionnaire.

Results: PD patients were found to fall significantly more frequent in public transports ($p=0{,}013$) than healthy controls. PD patients at older age ($p=0{,}001$), advanced stages of the disease (UPDRS motor score: $p=0{,}004$; Hoehn and Yahr staging: $p=0{,}019$; Schwab and England scale: $p=0{,}029$; retropulsion-test: $p=0{,}001$), with hallucinations ($p=0{,}010$) or fear of falling in means of public transport ($p<0{,}001$) were at particular risk. In PD patients organic sequels of falls were neither more frequent nor more serious as compared to healthy controls.

Conclusions: Our results should serve as a base to develop and initiate fall-preventing measures in public transport for the PD population. Because of the importance of public transports for this patient group further prospective studies are needed to gain a more detailed insight into the complexity of PD-related fall-events in public transport.

Tu-378

Serum uric acid concentrations in patients with Parkinson's disease

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Objective: To determine whether there is a relationship between uric acid(UA) level and Parkinson's disease(PD).

Background: Oxidative stress contributes to degeneration of nigral neurons in PD. UA is an endogenous antioxidant and acts as a scavenger of free radicals. It has been reported that high serum level of UA are associated with a decreased risk of PD.

Methods: A total of 50 PD patients participated. Secondary parkinsonism were excluded. The cardinal parkinsonian signs were divided into the groups according to severity from 1 to 3, in which one is mild and 3 indicates severe. The control group consisted of 50 healthy people. The patients with other diseases known to affect uric acid concentrations were excluded from this study.

Results: There were no statistically different for serum UA levels between PD and control groups. Correlation coefficient in the PD patients showed no significant relationship among variable age, sex duration and the severity of caridinal parkinson features.

Conclusions: The present study indicates no significant differences of serum UA between PD and controls. Serial changes or CSF levels of UA are further needed for evaluation in PD. Considering the hypothesis that oxidative stress is involved the pathogenesis of PD and that UA may reduce the risk of PD via antioxidant. Treatment with UA or its precursor inosnic acid in PD remains to be warranted.

Tu-379

Clinical characteristics of Parkinson's disease patients with headache

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Objective: The aims of this study were first to determine the clinical spectrum and the frequency of headache in Parkinson's disease (PD) patients, and secondly to investigate the characteristics of PD patients with headache (PDwH), with emphasis on motor and nonmotor fluctuations (MF & NMF).

Background: Pain has been recognized as an important feature of PD since the first description of the disease. Although recent studies have revealed the clinical features of pain in PD, there have been few studies focused on headache in PD. Some reports have suggested a possible relationship between the presence of headache and nuchal rigidity in PD. However, the characteristics of nonmotor symptoms in PDwH have not been well investigated.

Methods: Our inclusion criteria were as follows: idiopathic PD according to the diagnostic criteria of the UK PD Society Brain Bank; age at onset >40 years; responsiveness to levodopa; and levodopa therapy continued for more than 3 years. Patients with signifi-

cant cognitive impairment defined by a MMSE score <24 were excluded. We evaluated the frequency, duration, characteristics and severity of headache by interview, and motor symptoms by clinical examination. We also employed the Beck Depression Inventory (BDI) and the wearing-off questionnaire of 19 symptoms (WOQ-19: Stacy et al., 2007).

Results: A total of 35 men and 52 women with PD were included in the present study. Twenty patients (23%) had chronic headache. The mean PD duration in the PDwH group was 9.5 ±5.0 years (mean ± SD), which was not significantly different from that in the PD patients without headache (PDwoH; 8.6 ± 4.0 years). There was no correlation between the severity of neck rigidity and headache. Three of the 20 PDwH patients suffered from depression (BDI >13). PDwH patients tended to have more pronounced fluctuations in symptoms, but the difference was not statistically significant (MF: 4.9 ± 2.3 symptoms in PDwH (n=10) vs. 3.5 ± 2.3 in PDwoH (n=28); NMF: 2.2 ± 2.0 in PDwoH vs. 1.3 ± 1.6 in PDwoH). The most frequent NMF symptom in PDwH was "mood change" (60%) followed by "anxiety" (30%). On the other hand, patients of the PDwoH group experienced significantly less NMF (mood change: 7.1%; anxiety: 7.1%).

Conclusions: This study suggested that the psychiatric category of NMF may affect the incidence of headache in PD.

Tu-380

Brisk tendon reflexes in idiopathic Parkinson's disease – Is it worth neuroimaging?

H.M. Raghig, H. Kumar, M.S. Jog (London, Ontario, Canada)

Objective: To examine the prevalence of brisk deep tendon reflexes in patients with Idiopathic Parkinsons disease and to look for a structural correlate, if any.

Background: Parkinson's disease (PD) is not considered to be a disorder of pyramidal tract. However, isolated hyper-reflexia (brisk tendon reflexes, not associated with other signs of pyramidal tract lesion) is frequently seen in patients with Parkinson's disease. There is no guideline available whether the isolated hyper-reflexia in Parkinson's disease should be considered significant enough to warrant neuro-imaging and further investigation.

Methods: 43 randomly selected patients that met the UK Brain bank criteria for PD were examined and graded by H & Y scale. Patients with brisk tendon reflexes (grade 3+ or more over at least two sites) were subjected to cranio-spinal MR imaging.

Results: Nine patients (21%) had isolated brisk tendon reflexes (BTR group) while 34 (NBTR) did not. Seven of these patients had generalized hyper-reflexia and two had asymmetrically brisk reflexes with more active reflex on the side with greater parkinsonian signs. None of the hyper-reflexic patient revealed any significant structural abnormality on cranio-spinal MRI. The other characteristics for the BTR vs NBTR groups were: H & Y stage 2.5 vs 2.2; disease duration 5.44 vs 8.73 yrs; age 66.6 vs 66.2 yrs).

Conclusions: The figure of 21% is much higher than the estimated 5% prevalence of brisk tendon reflex in non-parkinsonian population. Brisk deep tendon reflexes are common in PD, are more generalized than asymmetrical, more common in those with relatively shorter duration of disease and unassociated with structural cranio-cervical abnormalities. Asymmetrical hyper-reflexia, with more active reflexes over the side with greater parkinsonian signs lacks a structural correlate. Isolated hyper-reflexia is part of PD and is not worth imaging.

Tu-381

Chewing gum significantly improves swallow frequency in patients with Parkinson's disease – A pilot study

A. South, S. Somers, M.S. Jog (London, Ontario, Canada)

Objective: 1) establish a reliable methodology for measuring swallow frequency and latency across swallowing tasks in patients with PD, 2) study the frequency of swallow at baseline and during a saliva producing task (gum chewing) for patients with PD who were non-symptomatic for dysphagia complaints.

Background: Deficits of swallowing postulated to affect management of oral secretions in patients with PD include reduced frequency of swallow, impaired oral function, and impaired pharyngeal function. Studies of normal swallow function indicate that there is an average volume of saliva that is sufficient for initiating a swallow response. Gum chewing has been demonstrated to increase saliva volume/production.

Methods: Respiratory and laryngeal signals, captured by an expanding bellows positioned at the levels of the larynx and chest, were continuously recorded using a PowerLab (v 4.1.1 ADI Instruments, Castle Hill, Australia). The instructing examiner and patients were blinded to the PowerLab recordings. Nine patients (stage 2.5) were studied across three tasks each of 5 min duration: baseline resting, gum chewing, and post gum chewing resting. Frequency/timing of swallow (indicated by peaks in the laryngeal wave coinciding with flattening/lengthening of the respiratory wave -- apnea period) from PowerLab recordings was determined and agreed upon by two trained examiners.

Results: The methodology used appears to be reliable for recording swallow frequency and latency even during the task requiring mastication. Significant differences between tasks were found for frequency ($p<.0001$) and latency ($p<001$) of swallow. All patients demonstrated significantly more swallows in the gum chewing task (mean=16.89±2.74) than during the initial baseline (mean= 2.77±1.55) and post gum chewing tasks (mean=5.22± 1.722). Latency between swallows decreased significantly during the gum chewing (mean=23.47±6.64 sec.) and was longer during the baseline resting (mean=175.53±41.23 sec) and post gum chewing (mean=74.62±17.58).

Conclusions: Chewing gum alters frequency of saliva swallows and may be an effective and easy way to help patients improve secretion management by increasing swallow frequency.

Tu-382

Prevalence of speech impairments in Parkinson's disease: A systematic review

J.G. Kalf, B.J.M. de Swart, B.R. Bloem, M. Munneke (Nijmegen, Netherlands)

Objective: The aim of this study is to systematically review the prevalence of speech impairments in patients with Parkinson's disease (PD).

Background: Speech impairments and voice problems are frequently reported problems in PD patients which can be treated successfully, but the estimated prevalence rates of these complaints seem various.

Methods: A systematic PubMed and CINAHL search was done to find studies published between 1965 and December 2008 using ("Parkinson's disease"[Mesh] OR "parkinsonian Disorders"[Mesh]) and ("Speech Intelligibility"[Mesh] OR "Speech Impairment" OR Voice disorders) as search terms.

Results: Four eligible studies could be included from which 3 patient-rated outcomes were calculated and 3 clinician-rated outcomes. The patient-rated items were formulated like "difficulty making myself heard or understood by strangers" or "my voice is not as good as it used to be". For the clinician-rated outcomes, listeners (trained listeners and everyday listeners) scored intelligibility from standardized speech samples. Prevalence of speech impairments ranged from 46% to 76%. The pooled prevalence estimate weighted by sample size was 68% (95% CI 63.8-72.7) for the patient-rated scores and 71% (95% CI 66.7-75.9) for the clinician-rated scores. One study reported that 29% of PD patients perceived their speech and voice problems as one of their greatest concerns. In another study 38% of PD patients placed 'speech' among their top four concerns and 10% rated speech and voice changes as their number one concern.

Conclusions: Speech impairments are prevalent in about 70% of the community-dwelling PD population. Patient-rated and clinician-rated score are remarkably comparable and for a third of the PD patients this impairment is a major concern. Modern successful therapies like the Lee Silverman Voice Treatment (LSVT) and the Pitch Limiting Voice Treatment (PLVT) are available to alleviate these complaints.

Tu-383

Prevalence of drooling in Parkinson's disease: A matter of definition

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Objective: The aim of this study is to systematically review the prevalence of drooling in patients with Parkinson's disease (PD).

Background: Drooling (involuntary saliva loss) is a frequently reported symptom in patients with Parkinson's disease (PD), ranging from 30% tot 74%, but an accurate estimate of the prevalence of drooling is lacking.

Methods: A systematic PubMed and CINAHL search was done to find studies published between 1965 and December 2008 using ("Parkinson's disease"[Mesh] OR "parkinsonian Disorders"[Mesh]) and "Sialorrhea"[Mesh] OR "Drooling") as search terms.

Results: Seven eligible studies were found, only two as a result from the search strategy and five via reference tracing. Prevalence of drooling was based on subjective responses of PD patients on one question in questionnaires concerning gastrointestinal, autonomic or nonmotor complaints. The pooled prevalence estimate weighted by sample size was 50.2% (95% CI 48.2-52.2). But two studies revealed that only 22% to 26% of patients experience drooling more frequent than 'seldom' of 'sometimes'. The pooled relative risk to have drooling complaints in comparison with age-matched controls is 4.75 (3.69-6.23). The definitions of drooling in questionnaires are various, ranging from "ever dribbling of saliva" to more precise characterizations like "dribbling of saliva during the daytime, experienced during the last month". This may explain the wide range between the included studies.

Conclusions: Currently only a few studies provide useful data on the prevalence of drooling in PD. The summarized findings demonstrate that drooling in its widest definition (any change in saliva or ever dribbling of saliva) is prevalent in half of all community-dwelling PD patients. In about a quarter of PD patients drooling appears to be a frequently occurring problem. We recommend to report drooling in future studies more precise with descriptions of severity, frequency and nocturnal versus diurnal complaints.

Tu-384

Drooling in Parkinson's disease is a motor disorder

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Objective: The purpose of this study is to uncover the factors than contribute to drooling in patients with Parkinson's disease (PD).

Background: While there is evidence that drooling in PD patients is not caused by hypersalivation, the true pathophysiology of drooling in PD is not fully understood.

Methods: We selected 30 PD patients from our Parkinson Centre Nijmegen (ParC): 15 with confirmed complaints about saliva loss (droolers) and 15 without any complaint relating to saliva (non-droolers). We compared the two groups concerning (1) hypomimia (UPDRS subscale for facial expression), (2) swallowing capacity (maximum volume in ml per swallow), (3) stooped posture (UPDRS subscale for posture), (5) saliva production (swab method in ml/sec) and (4) swallowing frequency during 45 minutes (sEMG and video, while watching TV), all measured during ON phase.

Results: The droolers were 9.4 years older than the non-droolers ($p = 0.01$) and had more advanced PD according to UPDRS III ($p = 0.02$) and Hoehn & Yahr stage ($p = 0.01$). The mean differences between droolers and non-droolers, adjusted for age, UPDRS III score and Hoehn & Yahr stage were 1.6 point worse (95% CI 1.12-2.16) for facial expression, 18.3 ml less (95% CI 35.2- 1.4) for swallowing capacity and 0.65 point worse (95% CI 0.09-1.22) for stooped posture. Saliva production and swallowing frequency did not differ significantly between groups ($p = 0.33$ and $p = 0.43$).

Conclusions: Hypomimia, reduced swallowing capacity and stooped posture are very likely to contribute to drooling in PD, clarifying drooling in PD as a motor disorder. Reduced swallowing frequency is another reasonable cause, but typical in PD, not observed when patients are paying attention and aware of assessment.

Tu-385

Pulmonary function and relative factors in Parkinson's disease

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Objective: To evaluate the pulmonary function and the effects of exercise, singing, and rehabilitation by the blowgun in patients with Parkinson's disease (PD) by using the Japan lung age index.

Background: Pneumonia is the important complication of the patients with advanced PD. To prevent it, the estimations of patients' pulmonary function and risk-benefit factors are needed. The intervention in improvement of pulmonary function might be connected with better ADL of the patients with advanced PD.

Methods: We conducted several questions about self exercise and singing, the pulmonary function test and the Unified PD rating scale (UPDRS) for patients with PD. Changes of pulmonary function by rehabilitation by blowgun were evaluated a month after. We applied the formula of Japanese lung age as the index of pulmonary function. The method of rehabilitation by blowgun was according to the Japan Sports Fukiya Association; a deep abdominal breathing was required before firing each dart. The statistical analyses were performed by Student's t-test or Pearson correlation coefficient.

Results: 209 patients (male 104) were included. The mean age was 71.1 (SD 7.7) years and the mean disease duration was 7.8 (SD 6.4) years. The mean modified Hoehn and Yahr was 2.5 (SD 0.7) on time/3.0 (SD 0.9) off time and 110 patients (52.6 %) had wearing off. The mean lung age was 72.0 (SD 16.7) years. The delta lung age (= the actual measurement – the predicted value) was + 5.30 years in male and -3.71 years in female ($t = 4.78$, $p < 0.01$). The patients with the singing habit had the more decreased delta lung age than those without that (-4.88 versus +2.27, $t = 2.89$, $p < 0.01$). The delta lung age was correlated weakly with falling ($r = 0.24$, $p < 0.01$), freezing when walking ($r = 0.23$), speech ($r = 0.22$) and posture ($r=0.20$) of UPDRS items. 15 patients performed the rehabilitation by blowgun for a month which was not effective for improvement of the lung age.

Conclusions: Our data suggest that the singing habit is effective for improvement of the lung age. Although the rehabilitation by blowgun might make the deep abdominal breathing and hold it easily and lead to younger lung age in patients with PD, the short term trial was unsuccessful. Further investigations such as long term rehabilitation by blowgun are warranted.

Tu-386

Dissociation of cardinal motor signs in Parkinson's disease patients

S.-B. Koh, D.-Y. Kwon, S.-H. Lee, S. Hong, K.-W. Park, D.-H. Lee (Seoul, Korea)

Objective: The aims of our study are to determine the frequency of dissociation of motor signs and to study the clinical characteristics of dissociation group.

Background: Most of cardinal motor signs are pronounced on the same side in Parkinson's disease (PD). Unusually we can find one

type of cardinal motor sign that is pronounced in one side and other motor signs are pronounced in contralateral side.

Methods: Clinical characteristics for each patient during each follow-up visit were analyzed based on the Unified Parkinson's Disease Rating Scale, Mini Mental Status Examination, non-motor symptom questionnaire and Frontal lobe Assessment Battery.

Results: The dissociation was noted in 29 (7.06%) of the 411 patients. The dissociation of tremor and rigidity-bradykinesia was the most common type (17/29). There was no significant difference in demographic factors and clinical profiles.

Table (Tu-386). Changes of clinical profiles of the non-dissociation group and dissociation group

Changes of scores (during 6-months follow-up), mean(SD)	Non-Dissociation Group (n=382)	Dissociation Group	p-value
H-Y stage	0.17 (0.04)	0.18 (0.07)	ns
UPDRS-3	1.7 (1.5)	1.9 (1.4)	ns
MMSE	0.6 (0.7)	0.5 (1.2)	ns
NMS	4.5 (4.3)	5.2 (3.8)	ns
FAB	0.9 (0.4)	0.8 (0.3)	ns

H-Y stage, Hoehn-Yahr stage; UPDRS, Unified Parkinson's Disease Raing Scale; MMSE, Mini mental status examination; NMSQ, Non-motor symptoms questionnaires; FAB, Frontal Lobe Assessment Battery.

Conclusions: We thought each cardinal motor signs have different pathogenesis. The presence of dissociation did not affect the natural history of PD.

Tu-387

Age of Parkinson's disease onset as a predictor for the development of dyskinesias

S. Ku, G.A. Glass (San Francisco, California)

Objective: Examine the relationship between age of Parkinson's disease onset and future risk of developing dyskinesias.

Background: In Parkinson's disease (PD), the initial use of dopamine agonist therapy is advocated with the hope of delaying levodopa-associated dyskinesias. However, it is not clear that initial medication choice is the most important predictor of future dyskinesia onset. Two studies have recently shown an inverse association between age of PD onset and risk of developing dyskinesias [1,2].

Methods: We performed a retrospective chart review of 100 PD patients seen at the Parkinson's Disease Research, Education and Clinical Center of the San Francisco Veterans Affairs Medical Center. Age of PD onset was defined as the year in which a cardinal sign of PD was first noted by the patient, family, or provider. Age of first dyskinesia was defined as the year in which a dyskinesia of any severity was first noted by a neurologist or commented upon by the patient.

Results:

Table (Tu-387). Dyskinesia Risk by Age of PD Onset

Age of PD onset (years)	5-year DysR after LD onset (n)	10-year DysR after LD onset (n)	5-year DysR after PD onset (n)	10-year DysR after PD onset (n)
<50	66.7% (6)	100% (5)	25% (8)	42.9% (7)
50-59	44.4% (18)	82.4% (17)	20.8% (24)	57.1% (21)
60-69	36.8% (19)	100% (11)	9.5% (21)	62.5% (16)
70-79	33.3% (18)	80% (10)	8.7% (23)	72.7% (11)
>79	0% (2)	n/a	0% (3)	0% (1)

DysR = dyskinesia risk; LD = levodopa.

Conclusions: Our results agree with previous findings of an inverse relationship between age of PD onset and risk of developing dyskinesias within 5 years of beginning levodopa therapy [2]. However, the differences in dyskinesia risk are not as large as previously reported, particularly between ages 60-79. Moreover, after 10 years of levodopa therapy, dyskinesia risks are uniformly high (80-100%) across all age categories. This suggests that while age of PD onset may be an important predictor of dyskinesia risk in the early stages of levodopa therapy, longer durations of exposure to levodopa may render age of disease onset insignificant as a risk factor. **References:**

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Tu-388

How common is the postural instability and gait difficulty (PIGD) subtype in patients with newly diagnosed Parkinson's disease?

J. Linder, M. Edström, L. Forsgren (Umea, Sweden)

Objective: To assess the frequency of the PIGD subtype in patients with newly diagnosed Parkinson's disease in a population based incidence cohort.

Background: The PIGD subtype is associated with development of dementia. Many tremor-dominant (TD) patients change subtype to the PIGD subtype during the course of the disease. The risk of developing dementia is very low in the tremor-dominant patients. It is not known how common the PIGD subtype is in de novo PD patients.

Methods: The incident patients (2004-2007) who fulfilled the clinical criteria for definite Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank criteria i.e. bradykinesia plus one other feature (rigidity, tremor or postural instability) and three or more supportive criteria, or probable PD (one to two supportive criteria), were included. Excluded were patients with Mini Mental State Examination <24/30, patients with drug induced parkinsonism and patients with vascular parkinsonism. The patients were classified into three groups: TD, PIGD and indeterminate (ID) (Alves et al, Mov Disord 2006;21:1123-1130).

Results: 111 patients fulfilled the criteria for PD (definite and probable). 60 (54 %) were of the PIGD subtype and 38 (34 %) were of the TD subtype and 13 (12 %) were indeterminate. The PIGD subtype was more common in the probable PD group (n=17/23, 74 %) than the group with definite PD (n=43/88, 49 %), (p=0.039, Fishers exact test). The PIGD subtype patients had higher scoring on the Unified Parkinson's Disease Rating Scale (UPDRS) part II (activities of daily living) (median=10) than the TD (median=6) and ID group (median=7) suggesting a more severe form of disease (p<0.001, Kruskal-Wallis exact test). There was no significant influence of gender, age at diagnosis or duration of symptoms regarding the subtype classification.

Conclusions: The PIGD subtype is the most common subtype in patients with newly diagnosed PD. The finding in our incidence cohort that the PIGD subtype was more common in patients with probable PD than in patients with definite PD could reflect that the diagnosis of probable PD is more uncertain and in this group some patients eventually will develop an atypical parkinsonian syndrome which is associated with early postural instability and falls i. e. progressive supranuclear palsy or multiple system atrophy.

Tu-389

Autonomic nervous system in Parkinson's disease: New evidence on the relationship to freezing of gait

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Objective: To investigate heart rate variability (HRV) and heart rate average (HRA) in Parkinson's disease (PD) patients who experi-

ence Freezing Of Gait (PD+FOG), compared to those who do not (PD-FOG), and to assess the relation of FOG to the autonomic nervous system's (ANS) activity.

Background: FOG is a disabling symptom affecting PD patients. Some evidence suggests that FOG is exaccerbated by stress. The reaction to stress is in part regulated by ANS, as reflected in measures of HRV and HRA. Studies have demonstrated decreased HRV in patients with PD, compared to age-matched controls, however, the possible contribution to FOG has not yet been examined.

Methods: 15 healthy older adults, CO (67.6±9.5 yrs), 10 PD-FOG (66.4±5.7 yrs) and 10 PD+FOG (64.9±5.4 yrs) were studied at their "off" state. HRA and HRV (beat-to-beat variability over 1 min windows) were measured using a 2 lead ECG as subjects carried out tasks used to provoke FOG. Data was analyzed in 3 conditions: standing, usual walking and fast walking. FOG episodes were analysed in intervals of 10 seconds before, during, and after FOG.

Results: HRA increased ($p<0.0001$) between conditions in all groups. The % change in HRA from one condition to another was lower in PD, especially in PD+FOG ($p=0.002$). HRV was lower ($p=0.001$) in PD patients compared to CO. HRV and HRA were not correlated with disease duration but HRA was correlated with UPDRS-motor scores($r=0.58$, $p=0.01$) and with FOG severity ($r=0.47$, $p=0.05$;) as measured by the FOG-Q. 120 FOG episodes were observed. HRA increased ($p=0.01$), by an average of 1.1 bpm, during FOG as compared to HRA measured 10 seconds before FOG. HRA increased ($p<0.001$) by an average of 17.4±2.8 bpm during usual walking and 6.6±3.6 bpm during fast walking with FOG compared to intervals without FOG.

Conclusions: To our knowledge, these findings are the first to document the possible contribution of ANS dysfunction to FOG. In patients with FOG, HRA generally follows the same pattern as seen in patients without FOG and healthy elderly adults in response to different conditions**.** Nonetheless, the decline in HRV in patients with FOG suggests that the ANS system reacts differently to changing conditions. It appears that ANS alterations may be specific to FOG and not a general by product of disease severity.

Tu-390

Presentation of Parkinson's disease in a Pakistani cohort of patients

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Objective: The aim of our study is to identify presenting symptoms in patients with Parkinson's disease and frequency of depression among these patients.

Background: Parkinson's disease is a progressive, neurodegenerative, movement disorder. Parkinson's disease is caused by the degeneration of nerve cells in the brain. The published data related to onset symptoms and prevalence of depression among PD patients is scanty from Pakistan.

Methods: We retrospectively reviewed the medical records of patients from July 2008 to December 2008 seen at Jinnah Post Graduate Medical Center, Karachi. The demographic characteristic and clinical presentation of the disease pattern were recorded. Depression was defined and identified on DSM-IV criteria. The data collected was analyzed on SPSS version 15.

Results: A total of fifty Parkinson's patients were seen. Out of these, 17 (34%) were female and 33 (66%) were male. Mean age of the patients was 55 years (range 32- 83 years) with SD ± 12.2. Mostly patients were illiterate 21 (42%) while 14 (28%) were only primary educated. The first ever body side involved right side in 29 (58%) patients, left side in 19 (38%) patients and two (4%) not remember that which side of the body first involved. The first ever body part involved upper limb in 39 (78%) patients, lower limb in nine (18%) patients and axis part two (4%). The first ever sign & symptoms were tremor in 34 (68%) patients, slowness in 12 (24%) patients and stiffness in four (8%) patients. Out of fifty patients 36 (72%) were found in depression while 14 (28%) were not in depression.

Conclusions: Tremor at onset of PD was common in our series. Seventy two percent patients had evidence of depression at the time of evaluation.

Tu-391

Defective consolidation of anticipatory balance strategy selection in Parkinson's disease (PD)

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Objective: A more forward positioning of the center of pressure (CoP) position may represent a better control strategy to face postural perturbation in healthy subjects [1]. We investigated changes in the mean CoP position during quiet standing in relation to a series of impending perturbations of the support surface in PD.

Background: Postural instability is one of the most disabling features of PD, and is considered as the main factor predisposing to falls. Patients are impaired when shifting their center of gravity to achieve a postural change. This could be related to abnormal patterns of postural responses and/or to difficulties in sequencing motor programs necessary for postural correction.

Methods: Twelve patients were clinically assessed using the Unified PD Rating Scale (UPDRS). The mean CoP position was analyzed in a sagittal plane during control quiet stance (cQS), and during anticipatory quiet stance (aQS1-4), while expecting four backward translations of the support surface. The relationship between the total UPDRS motor score and the mean CoP position was examined.

Results: Mean CoP values significantly changed ($F=9.046$, $p< 0.0001$). The mean CoP value during cQS was 1.9 ± 0.22 cm. During aQS1–4, the mean CoP values were aQS1: 2.3 ± 0.37 cm, aQS2: 2.47 ± 0.33 cm (cQS, aQS2 $p<0{,}0019$), aQS3: 2. 7 ± 0.34 cm (cQS, aQS3 $p<0{,}0001$), aQS4: 1.85 ± 0.3 cm (aQS2, aQS4 $p<0{,}0008$; aQS3, aQS4 $p<0{,}0001$). There was a positive correlation between the total UPDRS motor scores and the mean CoP values during cQS and aQS3 ($F=6.66$, $p< 0{,}029$ and $F=11.4$, $p< 0.008$, respectively).

Conclusions: The expectation of a series of impending perturbations produced a more forward leaning posture in PD; this forward shift, however, was not maintained up to the time preceding the fourth perturbation, as in the healthy population [1], but it dropped back to cQS levels. Thus, motor adaptation, as reflected by the selection of a better postural control strategy in the face of postural perturbation, was not impaired. However, consolidation of such postural strategy was defective. Due to striatal dysfunction, PD patients may not have enough "motor motivation" for maintaining the effort of updating the selected balance strategy. [1] Popa et al. Eur J Appl Physiol 2008;104:1007-1011

We-371

Fatigue in Parkinson's disease: Clinical aspects and exploring peripheral autonomic dysfunction as a mechanism using cardiac MIBG scans

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Objective: The Parkinson Fatigue Scale (PFS-16) is one of the validated scales to assess fatigue in the bedside while cardiac MIBG scans may be used to explore the possible causative role of peripheral sympathetic function and occurrence of fatigue in Parkinson's disease (PD).

Background: Fatigue is an important non motor symptom of PD and can occur independent of depression and daytime sleepiness.

Methods: In the first phase of this work, as part of data collection related to the PD non motor scale (NMSS), fatigue data was collected in 100 cases of PD with data in 97 being computable. 21

patients also underwent cardiac MIBG scans using an established protocol based on clinical need. Cardiac MIBG uptake was analysed using standard protocol using uptake values at 15 min (R1) and 3 hrs (R2) in addition to cardiac MIBI scans to exclude any perfusion defects.

Results: Data from 97 PD cases (53% males; mean age±SD: 68.75±9.7, range: 41-88yrs; duration of disease: 7.65± 5.5, range 1-35yrs; PD subtype: 30.3% akinetic, 51.5% mixed, and 17.9% tremor dominant) were analysed. 51% were at Hoehn Yahr stage 2 while stages 1 (11.3%) and 5 (2%) were also included. PFS 16 mean was 7.85±3.8 (0-15) while 54 scored over 8 on PFS 16 suggesting significant fatigue. PFS 16 scores were significantly higher in tremor dominant PD (Kruskal-Wallis test, p = 0.04). A weak correlation was observed between impairment in sleep (Spearman's rho 0.18), mood (Spearman's rho 0.16) as well as the overall Non-Motor Symptoms Scale score (NMSS, Spearman's rho=0.12) while a stronger correlation was evident with UPDRS 3 (0.32). 21 cases underwent MIBI and MIBG cardiac scans, and a weak non significant correlation was observed between the R2 values and PFS 16 scores (0.33).

Conclusions: This pilot exploratory study confirms that fatigue is a common symptom in PD although its relationship with sleep, mood, and other related NMS of PD was weak. There was a weak correlation of fatigue as measured by PFS-16 with overall non motor scores and quality of life while UPDRS 3 scores have a stronger correlation. Fatigue was commoner in those with tremor dominant PD. MIBG studies suggest that peripheral sympathetic dysfunction is unlikely to be a major pathophysiological basis of fatigue in PD.

We-372

Body mass index, abdominal circumference and the risk of falls in Parkinson's disease

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Objective: To analyze the influence of body mass index (BMI) and abdominal circumference (AC) in the risk of falls in patients with Parkinson's disease (PD).

Background: Increased BMI and AC are known risk factors for vascular disorders, including cerebrovascular disease. Subcortical white matter lesions of vascular origin are associated with worse measurements of postural instability and falls in the elderly. We hypothesized that PD patients with increased BMI and AC may be at increased risk of falls.

Methods: We assessed consecutive PD patients following a standardized protocol. The protocol included demographic and clinical data as well as anthropometric data. AC and BMI were measured and calculated by the same author using well established parameters. Risk of falls was determined the specific UPDRS part II item, and considered positive if scored > 1. BMI above 25kg/m2 and AC above 88 cm for women and 102 cm for men were considered elevated, according to established criteria. Gender stratification for AC also did not show significant correlation with falls.

Results: From a total of 76 patients included in the study, 42 (55.2%) were female, mean age was 71.2 years, mean disease duration 8.3 years. Mean MCI was 25.9kg/m2 and mean AC was 94.8cm for men and 94.1cm for women. Positive history of falls was detected in 43 (56.6%) patients. BMI > 25kg/m2 was found in 44 (57.9%) cases. Among those with increased BMI, falls were reported by 19 (43.2%) while in the group with normal BMI, only 6 (18.7%). Diference was statistically significant (p: 0.046). AC were increased in 7 (20%) men and 29 (69%) women. Falls were reported in 12 and 13 for men and women respectively, p: 0.6.

Conclusions: Patients with PD and BMI above 25kg/m2 were more likely to report falls. Increased AC was not correlated with a positive history of falls.

We-373

Homocysteinemia, postural instability and risk of falls in non-demented patients with Parkinson's disease

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Objective: To analyze the influence of plasma homocysteine (Hcy) levels and postural instability (PI) and the risk of falls in patients with Parkinson's disease (PD).

Background: Elevated plasma Hcy levels is a known risk factor for vascular disease, cognitive decline, and white matter hyperintensities on brain MRI. Elevated Hcy levels has recently been reported in PD, probably related to breakdown of L-dopa by catechol-O-methyltransferase, which increases Hcy formation. Therefore, there are reasons to suggest that treatment with L-dopa in PD may render patients at increased risk of white matter changes that are known risk factors for falls and motor disability in the elderly.

Methods: We assessed 62 consecutive nondemented PD patients following a standardized protocol. The protocol included demographic and clinical data as well as determination of fasting plasma Hcy levels. PI and risk of falls were determined using the specific UPDRS items. The PI subscore was determined by the sum of 5 different UPDRS items (PIGD subscore). Hcy levels were divided as normal (<13 μmol/L) and abnormal (>13 μmol/L).

Results: A total of 62 patients were included. 33 (53.3%) were male, mean age was 67.6 years, mean age of onset 61.6 years and mean disease duration 6 years. Mean plasma Hcy 15.3 μmol/L. In 22 cases (nHcy), Hcy levels were within normal levels (mean 10.4 μmol/L), while the remaining 40 (aHcy) were abnormal (mean 18.1 μmol/L). Differences for age, age of onset and disease duration were not statistically significant. Mean L-dopa dosage was 579 mg for the nHcy group and 635 for the aHcy group (p: 0.7). Mean H&Y scores were 2.4 for the nHcy and 2.8 for the aHcy groups (p: 0.07). Mean PIGD score were 3.8 for the nHcy group and 6.7 for the aHcy group (p: 0.005). A positive history of falls was detected in 7 (31.8%) in the nHcy group and in 23 (57.5%) in the aHcy group (p: 0.05).

Conclusions: As already shown in previous studies, elevated plasma Hcy is common in patients with PD. Elevated plasma Hcy was significantly correlated with worst postural instability and gait scores. Although history of falls was more common in the aHcy group, the difference was only marginally significant.

We-374

Prospective assessment of falls in patients with Parkinson's disease with motor fluctuations

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Objective: To investigate the characteristics of falls in relation to motor fluctuations in patients with Parkinson's disease (PD).

Background: Recurrent falls are a disabling feature of PD and have a significant negative impact on the patient's quality of life. Although there have been a number of studies on falling in PD, the characteristics of falls in relation to motor fluctuations have not been well elucidated.

Methods: Thirty-two PD patients who had wearing off phenomenon and fell at least once in the previous year participated in this prospective study. The patients were instructed to document the circumstances of all falls and to tick pre-specified options for six months by keeping a fall diary.

Results: Three patients fell more than 150 times in a month; therefore, a 6-month follow-up was not performed. Although two other patients discontinued their fall diary within two months, complete documentation of falls was obtained from all the 32 patients. Patients who completed the 6-month follow-up reported 1 to 175 falls. In many patients, the frequency of falls decreased over time during the 6-month period. Twenty-one of the 32 patients (65%) fell predominantly in the on-state (including suboptimal "on"), and 5 patients (16%) fell during the off-state. Five patients (16%) fell preferentially

in the transitional state between on and off, while 22 patients (69%) fell in the transitional state at least once. Thirteen of 21 on-fallers (62%) also fell during the transitional state. Among the 21 on-fallers, 9 (43%) reported that freezing of gait (FOG) was the most frequent cause, 10 (48%) reported falls unrelated to FOG, and 2 experienced both equally. All the five off-fallers reported FOG as the main cause. Concurrent dyskinesias were reported in 12 patients (38%), and two patients lost balance owing to severe dyskinesias.

Conclusions: Most PD patients fall predominantly in their on-states, whether they are well or only suboptimally controlled. FOG appears to be the most frequent cause of falls particularly during the off-state. Keeping a fall diary may help prevent falls in PD.

We-375

Reasons for ER consultation in a population with parkinsonism

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Objective: In order to better address our interventions towards our parkinsonian population, we investigated the reasons for consultation at the emergency room department.

Background: Parkinson's disease patients have many reasons to consult the emergency room. Identifying these reasons may help designing preventative interventions in order to help maintain patients in their environment and decrease the risks associated to hospital stay.

Methods: We used the ER medical records system to determine the number, the reasons for admission and patients' characteristics between September 2006 and September 2007.

Results: A total of 181 patients were recorded. We randomly selected 29 patients. These patients paid 53 visits to the ER in the selected period (mean of 1,8). As a mean, patients were 67,9 years of age, had their diagnosis at 59,8 and a disease duration of 7,6 years; 23/29 patients had Parkinson' disease and paid 1.57 visits per patient, whereas 6 had atypical parkinsonism and paid 4,67 visits per patient; 44 (83%) came from home where 8 lived autonomously, 11 with help (25 unknown), and 9 came from another institution. The reasons for consultations were motor complications (11), psychiatric or cognitive complications (11), falls (3), syncope (3), orthostatic hypotension (1), loss of autonomy (2), infections (4), cardiovascular (4), musculoskeletal (6), cutaneous (2), GI (2) or other (4) problems. Patients remained in hospital for a mean of 8.6 days and 47.2% required hospitalisation (16.5 day duration) whaich was complicated in 15% mainly because of delirium. 37 patients were returned to home and 16 to an institution.

Conclusions: Most of the admissions to the ERD in our population were due to motor and cognitive/psychiatric complications. Patients with atypical parkinsonian syndromes paid more visits than patients with Parkinson's disease.

We-376

Action observation and motor priming: Can we influence the rate of self-paced movements in patients with Parkinson's disease?

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Objective: To verify whether prior observation of rhythmical movements can influence the execution of finger movements in patients with Parkinson's disease (PD).

Background: Observation of actions performed by others activates neural circuits that are similar to those involved in action production and assists action planning and execution. However, there are no studies directly determining whether such type of observation produces an effect on spontaneous motor behavior.

Methods: Ten patients with idiopathic PD (age 69.3 $\pm$ 4.7 years; Hoehn & Yahr stage: 2.5 or less) entered the study. They were naïve to the purpose of the experiment and were evaluated with the motor section of the Unified Parkinson's Disease Rating Scale. Exclusion criteria were cognitive deficits (Mini-Mental State Examination: < 24) and orthopedic or rheumatologic diseases influencing normal fingers movements. Each subject wore a sensor-engineered glove and performed with the right dominant hand (eyes closed) a motor task consisting in two blocks of repetitive finger opposition movements [Bove et al. Brain Res 2007; 1153:84-91]. Baseline evaluation was performed two days before the presentation (without any instruction) of a 10 min video-clip displaying a sequence of repetitive finger opposition movements performed at 3 Hz. Patients were tested immediately after the video-clip (T0), 45 minutes after the video (T1) and two days later (T2). The following parameters were analysed with RM-ANOVA: Touch Duration (TD: contact time between thumb and another finger), Inter Tapping Interval (ITI: time between the end of the thumb contact and the beginning of the successive one); Movement Rate (MR: 1/TD+ITI) and Errors Number (EN).

Results: Observation of actions (without explicit instructions) induced a priming of the self-paced movements. MR was significantly ($P<0.001$) increased at all times (T0, T1, T2) and EN was reduced ($P<0.05$) at T1-T2 intervals.

Conclusions: These preliminary data document the possibility to influence the rate of a self-paced movement trough a vision of a video-clip. Action observation could be a way to improve learning and motor performance in patient with PD.

We-377

Cross-sectional study on non-motor symptoms in an Argentine population of Parkinson's disease patients

C.M. Peralta, J. Toibaro, O.S. Gershanik (Capital Federal, Buenos Aires, Argentina)

Objective: To assess the prevalence of non motor symptoms (NMS) in an Argentine population of Parkinson's disease (PD) patients and whether they influence the choice of pharmacological treatment by physicians.

Background: The prevalence of NMS in PD still remains unclarified and probably underecognized by patients and physicians. However, they may contribute to identify PD at earlier stages and to assess whether they are or not taken into account in the management of PD.

Methods: As part of a multicentre study on the prevalence of NMS in two countries of Latin America, general neurologists screened the records of PD patients who attended the outpatient clinic, between September 2007 to November 2008 in different provinces of Argentina: Buenos Aires, Chaco, Cordoba, Corrientes, Entre Rios, Formosa, Mendoza, San Juan and Santa Fe, and answered a questionnaire designed ad hoc.

Results: In the overall sample of 401 PD patients, age 67.5 (40-93) years, there were 227 male and 172 female patients, with a median disease duration of 2 (0.5-6) years. NMS were present in 69% of patients, however, in patients with $\geq$10 years of disease duration NMS occurred more frequently (7.7% vs 4.3%) Sleep disorders were the most commonly present in 35.1% of patients (insomnia 70.5%, excessive diurnal somnolence 22%, REM behavior disorder 17.6%), followed by depression (33%) and anxiety (28.4%). Hyposmia was present in 14.6% and restless legs syndrome in 10.7%. Dementia was diagnosed in 8% of patients, while hallucinations in 5.8%, and pain in 4.5%. Tremor dominant PD patients had absence of NMS in 51.3%, while only 20% of patients with dominant rigid-akinetic PD had no NMS. Depression was the most commonly treated symptom (58%), followed by sleep disorders (33%), hallucinations (9.2%), dementia (3%) and pain (2.3%).

Conclusions: NMS occurred in 69% of this population of PD patients, suggesting that NMS occur frequently at earlier stages of PD, although prevalences were higher with longer disease duration and with more severe symptoms. Insomnia and depression were the two most frequent NMS, and depression was the most frequently treated.

We-378

Cross-sectional study on non-motor symptoms in an Colombian population of Parkinson's disease patients

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Objective: To assess the prevalence of non motor symptoms (NMS) in a Colombian population of Parkinson's disease (PD) patients and whether they influence the choice of pharmacological treatment by physicians.

Background: Non motor symptoms may be present in PD throughout the disease, although its prevalence remains unclear. Since they are related to quality of life, knowledge on them may help to improve the care of PD patients and to evaluate whether they are or not taken into account by physicians when choosing therapeutic strategies.

Methods: As part of a multicentre study on the prevalence of NMS in two countries of Latin America, general neurologists screened the records of PD patients who attended the outpatient clinic, between March to November 2007, in different provinces of Colombia: Barranquilla, Bogota, Cali, Medellin, Cartagena and Bucaramanga, and answered a questionnaire designed ad hoc.

Results: Three hundred and sixty six PD patients, age 66,2 (26-93) years, 201 male and 165 female patients, with a mean disease duration of 12 (0.5-18) years, answered the questionnaire. Depression was the most commonly present NMS in 58,5% PD patients, followed by sleep disorders in 48,1% (insomnia 77,3%, excessive diurnal somnolence 27,8%, REM behavior disorder in 14,8%). Anxiety was observed in 42,1% patients, while hyposmia in 21.6%. restless legs syndrome was diagnosed in 20,2% and dementia in 13,4% of patients. The rate of hallucinations was 12,6%, and pain of 13,4%. PD treatment was received by 88% of patients, while less than half of patients received treatment for depression, which was anyhow the most commonly treated NMS (39,1%), followed by sleep disorders (33,1%). Moreover, pain was treated in 9.6% of patients, hallucinations in 5,7% and dementia in 2,5%.

Conclusions: In this population of Colombian PD patients, depression was the most frequent NMS, followed by sleep disorders and anxiety. Similarly, depression and sleep disorders were the most frequently treated NMS.

We-379

Dysarthria in Parkinson's disease patients: A cross-sectional survey

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Objective: We explored the prevalence of dysarthria in 450 PD patients of the Toulouse area in a cross-sectional study and compared the demographic, clinical and pharmacological features and health-related quality of life associated with the presence or absence of this symptom.

Background: Dysarthria is commonly reported by patients with Parkinson's disease (PD). However, this symptom has been rarely evaluated in large samples of patients recruited out of tertiary specialized units and its prevalence, risk factors and impact on health-related quality of life is poorly known in the general PD population.

Methods: 450 patients were recruited in different academic and non-academic outpatient neurological clinics and underwent structured standardized clinical examination (UPDRS parts I-IV, MMSE, HADS, PDQ39). The presence of dysarthria was defined as UPDRS II item 5 $\geq$ 1. Drug consumption was obtained from the clinical records.

Results: The mean age of the 450 studied patients was 69$\pm$10 years, 57% of them were males, with a mean PD duration of 6$\pm$5 years, a mean UPDRS II+III in ON condition of 28$\pm$15. They were treated with levodopa for 5$\pm$4 years with a mean daily dose of 580$\pm$360 mg/day. 212 patients (51%) reported dysarthria. Dysarthric patients had longer disease duration (7$\pm$3 vs 4$\pm$4 years, $p<0.001$), greater UPDRS II+III score (36$\pm$16 vs 21$\pm$12, $p<0.001$), lower MMSE (27.9$\pm$2.2 vs 28.3$\pm$2.1, $p=0.05$), greater depression HADS score (7.3$\pm$3.7 vs 5.9$\pm$3.8, $p<0.0003$), longer levodopa treatment (6$\pm$5 vs 4$\pm$3 years, $p<0.0001$) and daily dose (651$\pm$391 vs 498$\pm$295, $p<0.0001$), more frequent amantadine treatment (12% vs 4%, $p<0.003$) and higher PDQ39 score (30$\pm$13 vs 23$\pm$12, $p<0.0001$).

Conclusions: Dysarthria affected 1 out of 2 patients of a large sample of ambulatory PD patients recruited in various academic and non-academic neurological outpatient clinics. Dysarthria was associated with more severe indexes of parkinsonism and poorer health-related quality of life.

We-380

L-dopa induced dyskinesia in Parkinson's disease patients. Preliminary analysis from the French PARKMIP/COPARK cohort study after 24-months follow-up

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Objective: To describe the prevalence, associated factors and progression of LID in the first 329 PD patients of the PARKMIP/COPARK cohort who reached the 24-months visit.

Background: Levodopa-induced dyskinesia (LID) are common complications of Parkinson's disease (PD) treatment.

Methods: Inclusion criteria: ambulatory outpatients randomly selected by 28 neurologists (general neurologists as well as movement disorders specialists), UKPDSBB diagnostic criteria, MMSE>24, no deep brain stimulation. Data collection: demographics, UPDRS and Hoehn & Yahr, antiparkinsonian treatments, anxiety and depression symptoms (HADS) and quality of life (PDQ39). Presence of LID was defined as UPDRS IV 32 $\geq$ 1. Statistical analysis: bivariate and logistic regression analysis.

Results: Data could be analyzed in 280 (19 deceased patients and 30 patients with missing data in the UPDRS). At baseline 71/280 (25%) of the patients exhibited LID. The main factors associated at baseline with LID presence were: longer PD duration ($p<0.0002$), younger age at onset ($p<0.04$), more severe UPDRS II+III score and Hoehn&Yahr stage ($p<0.0001$ for both), greater anxiety ($p=0.08$) and depression scores ($p<0.0001$), longer duration of treatment ($p<0.0001$), higher levodopa daily dose ($p<0.004$), amantadine co-treatment ($p<0.005$) and worst PDQ39 scores ($p<0.0003$). Logistic regression showed that PD duration $>$ 5 years and amantandine treatment were independently associated with LID ($p<0.05$ for all factors). After 24-month of follow-up, 85/280 patients (30%) had LID. 51/280 patients (18%) had a worsening in UPDRS IV 32 score. Such patients had greater UPDRS II+III score at baseline ($p<0.03$), longer levodopa exposure ($p<0.05$) and higher frequency of depression symptoms ($p<0.02$) and amantadine treatment ($p<0.05$). A multivariate analysis disclosed that levodopa exposure $>$ 3 years at baseline was the only variable significantly related to worsening of LID (OR= 2.5, [1.3-5.1]).

Conclusions: In the PARKMIP/COPARK PD cohort, 25% of the patients exhibited LID at baseline. After 2 years of follow-up 18% of the patients showed deterioration in LID score, which was associated with longer levodopa exposure at baseline.

We-381

Mortality rate in Parkinson's disease. Preliminary results from the French PARKMIP/COPARK cohort after 24-months follow-up

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Objective: To compare the mortality rate after 24-months of follow up between PD patients recruited in academic as well as non-academic neurological outpatient clinics and a group of age- and

sex-matched healthy controls recruited in general practitioners' outpatient clinics. To describe the clinical characteristics of deceased and non-deceased PD patients.

Background: Little is known on mortality and cause of death in Parkinson's disease (PD). Most available studies, which showed an increased mortality as compared to the general population, do not allow comparisons with control groups and are limited to specialized tertiary centers.

Methods: 329 non-demented (MMSE >24) idiopathic PD patients and 73 non-PD patients were recruited in the PARKMIP/COPARK cohort and seen at baseline and 24 months. At both visits, PD patients underwent standardized clinical examination, performed by the neurologist to assess PD (UPDRS, H&Y). Information on drug consumption was also collected during the visit. Non-PD patients were assessed in the same way except for PD features. Information about death and its possible cause was collected through referent physician of those who did not attend their planned 24-month visit. Mortality rate was compared between these 2 groups. Clinical characteristics of deceased and non deceased PD patients were also compared and causes of death were analyzed.

Results: 19 out of the 329 patients (5.8%) and none of the non-PD patients died during the 24-months follow up period. Relative risk for mortality was 4.27 and risk difference was 5.4% (95%CI= -2.1%; -9.4%). When comparing deceased and non deceased PD patients, the former had older age at baseline (77±8 years vs 69±9 years, p=0.001), lower MMSE (26.6±2.1 vs 28.2±2.1, p=0.001), and higher UPDRS II+III (39.7±19.9 vs 27.5±14.8, p=0.001) scores. Major reported causes of mortality were "cardiovascular diseases" (32%); "cancer" (21%); "worsening of parkinsonism" (16%); Suicide (1%) and unknown (26%).

Conclusions: PD patients had significantly higher mortality rate as compared to non PD patients. Mortality rates was higher in older patients with lower MMSE score and greater PD severity.

We-382

Dysphagia and hypersalivation in Parkinson's disease: A cross-sectional survey

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Objective: We explored the frequency of dysphagia and hypersalivation in 450 PD patients of the Toulouse area in a cross-sectional survey and compared the demographic, clinical and pharmacological features associated with the presence or absence of such symptoms.

Background: Dysphagia and hypersialorrhea can affect patients with Parkinson's disease (PD). However such symptoms have been rarely evaluated in large samples of patients recruited out of tertiary specialized units and its prevalence, risk factors and impact on health-related quality of life is poorly known in the general population of PD patients.

Methods: 450 patients underwent structured standardized clinical examination (UPDRS parts I-IV, MMSE, PDQ39). Dysphagia and hypersalivation were defined as UPDRS II items 6 or 7 ≥ 1, respectively. Drug consumption was obtained from clinical records.

Results: The mean age of the 450 studied patients was 69±10 years, 57% of them were males, with a mean PD duration of 6±5 years, a mean UPDRS II+III in ON condition of 28±15. They were treated with levodopa for 5±4 years with a mean daily dose of 580±360 mg/day. 77/450 patients (18.4%) reported dysphagia and 154/450 (36.8%) hypersalivation. Patients complaining of dysphagia had longer PD duration (8±5 vs 5±4 years, p<0.0002), higher rates of hypotension (21% vs 10 p<0.001), higher UPDRS II+III score (37±15 vs 26±14 p<0.0001), more frequent depressive symptoms (60% vs 31% p<0.0001), longer duration of treatment (7±4 vs 5±4 years p<0.001), greater levodopa dose (720±417 vs 550±335 mg/day p<0.004), more frequent amantadine therapy (15% vs 6% p<0.01) and worse PDQ39 score (32.1±13.2 vs 25.5±13.3 p<0.0001) Patients complaining of hypersalivation had longer PD duration (7±5 vs 5±4 years, p<0.004), higher UPDRS II+III score (36±15 vs 24±13 p<0.0001), longer duration of treatment (6±4 vs 5±4 years p<0.001), greater levodopa dose (641±368 vs 543±350 mg/day p<0.004), less frequent benzodiazepine therapy (6% vs 14% p<0.02) and worse PDQ39 score (28.7±14.6 vs 25.7±12.8 p<0.02).

Conclusions: Dysphagia and sialorrhea affected one-third of ambulatory non-demented PD patients recruited in academic and non academic outpatient clinics. Both symptoms were associated with more severe parkinsonism and impaired health-related quality of life.

We-383

Progression and prognostic factors of motor impairment, disability and quality of life in newly diagnosed Parkinson's disease

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Objective: To determine change and prognostic factors of motor impairment, disability and quality of life (QoL) in patients with newly diagnosed Parkinson's disease.

Methods: A group of 126 patients with newly diagnosed PD recruited from outpatient clinics participated in this three year prospective cohort study. Motor impairment was rated with the Unified Parkinson Disease Rating Scale Motor-Examination (UPDRS-ME). Disability was rated using the Schwab and England Activities of Daily Living Scale (SE-ADL), the AMC Linear Disability Score (ALDS). QoL was assessed with the Parkinson's Disease Quality of Life questionnaire (PDQL). Linear mixed model analyses were conducted to identify determinants of motor impairment, disability and poor QoL.

Results: Motor impairment progressed with 3 points per year. There was a slight progression of disability and QoL during three years of follow-up. Older age at onset predicted worse motor impairment, more disability and poorer QoL. Non-dopaminergic reactive symptoms (Axial impairment) contributed to more disability and poorer QoL. Comorbidity contributed to disability, but to a lesser extent. Self-reported mood symptoms and comorbidity were associated with poorer QoL. Female sex is associated with a slower progression of motor impairment and QoL.

Conclusions: Older age at onset predicts change in motor impairment, disability and impaired QoL over time. Non-dopaminergic reactive symptoms, comorbidity, and to some extent, affective symptoms has an impact on disability and poorer QoL. Female sex is associated with a slower progression of motor impairment and less decline of QoL.

We-384

Camptocormia in Parkinson's disease

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Objective: To (1) describe epidemiological aspects of patients diagnosed with Parkinson's disease (PD) and Camptocormia in Aracaju – Sergipe – Brazil and (2) evaluate the correlation between Camptocormia and clinical stage of PD, using Hoehn-Yahr (UPDRS–V) and Schwab and England (UPDRS–VI) scales, in these patients.

Background: Camptocormia, defined by marked anteroflexion of the trunk, which appears during walking and abates in the supine position, is becoming an increasingly recognized feature of PD.

Methods: A retrospective study of four patients with PD and Camptocormia from a Movement Disorders Clinics in Aracaju – Sergipe – Brazil was conducted, in order to find common and valid characteristics. The sample was composed of males and females in equal proportion, all married (2 widowers), mean age of 77 years (range 65-91) and predominantly white color (75%).

Results: Camptocormia was found in patients with more severe PD, as clinically shown by the Hoehn–Yahr (UPDRS–V) staging (100% classified as stage IV) and Schwab-England (UPDRS–VI) score in the OFF period (30% ± 10). Mean duration of neurologic symptoms was 13 ± 8 years and mean PD onset was 64 ± 13 years. Two patients were concomitantly diagnosed with PD and Camptocormia. In the

remaining, it emerged after 10 years from PD onset. The mean levodopa equivalent dosage was 450 mg/day. None was smoker, and just one was alcoholic. Depressive symptoms were observed in all patients.

Conclusions: Our data suggest that Camptocormia was related to (1) the clinical severity of PD, (2) depression and (3) older age at onset of neurologic symptoms.

We-385

Clinical correlations of fatigue in Parkinson's disease

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Objective: This study aimed to evaluate the clinical findings and correlations of fatigue in Parkinson's disease patients.

Background: Recognition of fatigue as a common problem in Parkinson's disease has been relatively recent. The impact of fatigue in PD is generally underappreciated and its treatment is empiric.

Methods: Consecutive parkinsonian patients of both sexes were included. Patients with parkinsonism other than PD, previous surgery for PD, concomitant illness, sensorial deficit, depression, severe cognitive impairment and illiteracy were excluded. Patients were assessed using standard measures: Hoehn and Yahr classification, Schwab and England Scale, Unified PD Rating Scale, Fatigue Severity Scale and Beck Depression Inventory.

Results: The study covered 104 patients, 52 (50%) of whom were males. Mean age was 67.9 years (SD 10.5) and mean age at onset of PD was 60.7 years (SD 11.7). There was no statistically significant differences between male and female patients for age, age at onset, duration of disease, scholarship duration, disease rating scales and depression inventory, but female patients showed signicantlly higher scores on Fatigue scale (31.2 for men and 38.9 for women, $p = 0.04$). Fatigue was present in 52% of all patients. The symptom was more frequent in female patients (61.5%) than in male patients (42.3%) and also in akinetic rigid form of PD (66,7%) than those with tremor predominant form (50%) ($p=0.03$). There was an increasing frequency of fatigue according to the stage in HY classification, fatigue being more frequent in those on higher stage (27.3% in stages I-II, 66,7% in stage III and in 80% of patients in stage IV). PD patients with fatigue had a higher score on all disease rating scales and also a higher score on depression scale than patients without fatigue. There was a correlation between FSS score and all UPDRS sub scores and SES score. There were no significant differences for actual age, age at onset and duration of disease between the two groups. Predominant side of disease and treatment did not have any influence on mean fatigue score.

Conclusions: Our findings demonstrated that fatigue is present even in the initial course of disease and its frequency increases parallel with the increase in severity of disease. It was more prevalent in female patients and in akinetic rigid forms of the disease.

We-386

The clinical features of African-Brazilian patients with Parkinson's disease

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Objective: To study the clinical features of African-Brazilian PD patients and compare them with others PD patients.

Background: It has been suggested that ethnicity may influence phenotype in Parkinson's disease.

Methods: A hundred and ninety seven consecutive patients were studied from three Academic Hospitals in Rio de Janeiro, Brazil. All cases fulfilled the Queen Square Brain Bank Criteria for PD as applied by Movement Disorders specialists. We determined the ethnicity as White (European ancestry), Black (African ancestry) and Mulatto (when there were both African and European ancestries).

Results:

Table (We-386). Results of 197 PD patients

	Black	Mulatto	White
total (%)	17 (8.7)	32 (16.2)	148 (75.1)
Male/Female (%)	10/7 (58.8/41.2)	17/15 (53.1/46.9)	91/57 (61.5/38.5)
Mean age of onset (range)	58.8 (35-76.2)	52.5 (25-78.9)	53.1 (25.8-84)
1st symptom tremor (%)	11 (64.7)	21 (65.2)	86 (58.1)
1st symptom akinesia/rigidity (%)	6 (35.3)	11 (34.4)	53 (35.8)
1st symptom others (%)	0	0	11 (7.5)
1st limb affected RA (%)	11 (64.7)	17 (53.1)	70 (47.3)
1st limb affected LA (%)	4 (23.5)	12 (37.5)	51 (34.5)
1st limb affected RL (%)	1 (5.9)	1 (3.1)	9 (6.1)
1st limb affected LL (%)	1 (5.9)	5 (15.6)	8 (5.4)
Positive family history (%)	1 (5.9)	3 (9.4)	35 (23.7)
LRRK 2 positive (%)	1 (5.9)	0	3 (2.0)
History of smoking (%)	4 (23.5)	10 (31.3)	53 (35.8)
History of caffeine intake (%)	10 (58.8)	18 (56.3)	118 (79.7)

RA -right arm; LA-left arm; RA-right leg; LL-left leg.

Of the seven Black patients who were on L-dopa (mean duration of treatment of 62.6 months and mean dose of 487.5 mg/day), only 1 (14.3%) developed dyskinesia after 3 years of the PD onset and 11 months after L-dopa onset (dose of 625 mg/day); 2 (25%) (mean duration of treatment of 78 months, mean dose of 750 mg/day and mean of 90 months of PD) out of eight Mulatto patients (mean duration of treatment of 67.3 months, mean dose of 571.9 mg/day and mean of 57.3 months of PD) and 19 (41, 3%) (mean duration of treatment of 62.2 months, mean dose of 588.8 mg/day and mean of 82.9 months of PD) from 46 White (mean duration of treatment of 63.3 months, mean dose of 427.3 mg/day and mean of 85.1 months of PD).

Conclusions: Preliminary analysis has failed to reveal any clear differences in the clinical features of PD between the three groups but further analysis is underway.

Th-377

Parkinson's disease – Characteristics of disease onset in a veteran population

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Objective: A study to investigate the clinical characteristics of disease onset in veterans with Parkinson's disease.

Background: Parkinson's disease (PD) is a heterogeneous disorder with clinically distinguishable sub-types. The distinguishing features of various (age, symptom or population based) sub-types are continually being explored, but far from being fully understood. A better understanding of disease characteristics, especially at onset, with respect to a specific patient population, is likely to facilitate early disease identification and management and may offer insights with respect to disease patho-physiology.

Methods: Using a standardized chart review approach, medical records of 321 consecutively evaluated PD patients, followed in the Movement Disorders Center of the Michael E. DeBakey VA Medical Center at Houston, TX were reviewed. The selected patient records contained demographic data, description of the initial symptom (type and distribution), and a detailed clinical assessment including standardized evaluation of parkinsonism using Unified Parkinson's Disease Rating Scale (UPDRS).

Results: The sample largely consisted of right handed (90%) Caucasian (79.8%) men 97.8% (n=314). Median age of disease onset was 67 years (range 28- 88 years). Asymmetric onset was common (n= 251, 78.1%). Right hemi-body was involved almost twice as of-

ten (n= 167, 66.5%) as the left hemi-body (n= 84, 33.5%). Handedness predicted the side of asymmetric onset. ($p< 0.05$). Exclusive involvement of the upper extremities was the most common presentation (77.9%). Right upper extremity was the most common site recalled for initial symptom emergence (48.5% n=156), followed by left upper extremity (22.4% n=72). Axial onset was reported in 14.3% (n=46) and bilateral (appendicular) in 7.5% (n=24) of the patients. Tremor was the most commonly recalled initial symptom (77%, n=247), followed by bradykinesia (15.5%, n= 50). Gait and balance difficulty at onset was reported by 5.6% (n-18) patients. Amongst the cardinal symptoms of PD, stiffness (or rigidity) was the least recalled initial symptom 0.31% (n=1).

Conclusions: Veterans with Parkinson's disease appear to be older at disease onset and have a higher incidence of tremor as an initial symptom, as compared to PD patients in the general population.

Th-378

Variable expression of nonmotor fluctuations in clinical subtypes of Parkinson's disease

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Objective: The clinical manifestations of Parkinson's disease (PD) patients are heterogeneous, and two clinical subtypes have been recognized: the tremor-dominant (TD) subtype and postural instability and gait difficulty (PIGD) subtype. The aim of this study was to examine nonmotor fluctuations (NMF) in PD patients of each clinical subtype.

Background: Although NMF of PD patients are very important, they are not well recognized and tend to be underestimated. There have been only a few studies focused on the prevalence of NMF and no discussion on the subject of NMF in each clinical subtype.

Methods: We examined motor fluctuations (MF) and NMF in 72 outpatients with idiopathic PD (according to the UKPD Brain Bank diagnostic criteria). All patients were treated with L-dopa. Our investigation employed the wearing-off questionnaire of 19 symptoms (WOQ-19: Stacy et al., 2007), which is a sensitive screening tool for assessing the fluctuation of symptoms. Patients were divided into the two subtypes of TD and PIGD using the scores on parts II and III of the UPDRS. The mean tremor score was calculated as the mean of 8 items and the PIGD score was estimated as the average of 5 items, as described in the DATATOP study (Jankovic et al., 1990). Patients with a ratio of mean tremor score/mean PIGD score (TD/PIGD) greater than or equal to 1.5 were assigned to the TD group, and those with a TD/PIGD ratio less than or equal to 1.0 were assigned to the PIGD group. We examined the details of MF and NMF in each clinical subtype of PD.

Results: Twenty-nine patients who had at least one type of MF were included in the present study. Seven of these patients were classified into the TD group (63.7±9.0 years, mean±SD; TD/PIGD ratio: 2.9±0.7) and the remaining 22 (68.4±8.2 years; TD/PIGD ratio: 0.2±0.1) were classified into the PIGD group. The mean disease duration of the TD group was 6.0±2.4 years and that of the PIGD group was 6.1±1.8 years. The mean dose of L-dopa was 300 mg/day in the TD group and 339 mg/day in the PIGD group. In the TD group, 5 patients (71%) had at least one type of nonmotor symptom (non-fluctuated) and 2 (29%) had NMF. In the PIGD group, 21 patients (95%) had at least one type of nonmotor symptom (non-fluctuated) and 16 (73%) had NMF.

Conclusions: Nonmotor fluctuations were significantly more frequent in the PIGD group than in the TD group.

Th-379

Clinico-pathological study of subtypes in Parkinson's disease

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Objective: We attempted to corroborate the data-driven subgroup classification proposed by Lewis and colleagues.[1]

Background: There have been a number of attempts to study clinical heterogeneity of Parkinson's disease by sub-classification. Most PD phenotyping studies used methodologies that divide patients according to predetermined notions, leading to inherent bias in their conclusions. A data-driven analysis helps to minimize this effect. However, pathological confirmation of the diagnosis has been lacking in almost all published studies.

Methods: Case files of 242 Queen Square Brain Bank for Neurological Disorders donors with pathologically verified Parkinson's disease (PD) were reviewed. We devised a set of clinical definitions to match the four Lewis et al subtypes: young onset (YO), tremor dominant (TD), non-tremor dominant (NTD) and rapid disease progression without dementia (RDP). A semi-quantitative scale was applied to Lewy body pathology.

Results: The mean age at disease onset was 61.0 (range 29- 85) years and mean disease duration was 15.6±6.9 years. Cases were classified as YO–25%, TD–31%, NTD–36% and RDP–8%. The YO group had significantly longer disease duration, slower progression of motor disability, more motor fluctuations and dyskinesia and longer preservation of cognitive function than other groups. TD had the least motor fluctuations and the lowest mean levodopa dosage. Surprisingly, patients with TD disease at onset did not live significantly longer than NTD patients and showed no difference in mean onset of falls and hallucinations despite their lower H&Y scores in the first 5-8 years. We found a strong association between a NTD disease pattern and cognitive disability. The NTD subgroup had a significantly higher mean grade of cortical Lewy bodies ($P<0.05$) and amyloid angiopathy than YO, TD and RDP groups.

Conclusions: Lewis's YO, TD and NTD clinical subtypes retained characteristic features according to Brain Bank data, and can be distinguished clinically and used to infer likely pattern in clinical and pathological disease progression. Further data-driven clinical research in a large patient group is also needed. 1. Lewis SJ et al. Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. J. Neurol Neurosurg Psychiatry 2005; 76: 343-48.

Th-380

"Staircase" saccadic intrusions in early Parkinson's disease

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Objective: To characterize "staircase" saccadic intrusions (SSI) in early Parkinson's disease (PD).

Background: A series of hypometric saccades separated by an interval of 100-200 ms to reach a target is called a "staircase" saccade. An uncalled for saccade away from fixation, followed by a return saccade to the target is called a saccadic intrusion (SI). "Staircase" saccade can be due to weak inhibition of superior colliculus (SC) following degeneration of substantia nigra pars reticulate (SNPR). Weak inhibition to SC can truncate the ongoing saccade; a series of corrective saccade(s) must bring gaze to the target, hence, the saccadic trajectory appears like a "staircase". Inactivation of SNPR also causes SI. We describe "staircase" saccadic intrusion (SSI) in 5 patients with early PD.

Methods: Eye movements were recorded from 5 early PD patients (table 1 for clinical features). Patients made 15 degree visually-guided saccades symmetric about the midline.

Results: Figure 1 illustrates saccade abnormalities in a PD patient. Red trace illustrates horizontal eye position; black trace is the visual target. Figure 1B is a blow up of a visually-guided "staircase" saccade (VGS), comprised of a hypometric primary saccade and subsequent corrections. Figure 1C is a typical SI, Figure 1D illustrates SSI. To compare the quantitative characteristics of SSI and VGS we measured the amplitudes and velocities of the hypometric primary and corrective saccades comprising the staircase, and their intersaccadic interval comprising the horizontal portion of the "staircase" (Figure 1A). Figure 2A,D illustrates the normal amplitude-peak velocity relationship of SSI and VGS in 5 PD patients (each color

depicts one patient, each data point represents one saccade, and black lines are normal range). Figure 2B,E illustrate the distribution of intersaccadic intervals between the hypometric saccades comprising the SSI and VGS. The amplitudes of primary and corrective saccades varied from trial to trial for both, SSI and VGS. The distribution of amplitudes and intersaccadic intervals for the hypometric saccades comprising SSI and VGS were different (Figure 2 B,C,D,F).

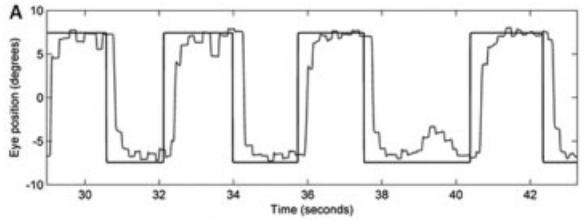

Table 1 Clinical characteristics

Patient number	Age	Duration since diagnosis	Medication (duration)	UPDRS			
				Mentation and mood	ADL	Motor score	Total
1	69 (male)	4 years	none	0	7	10	17
2	78 (male)	1 year	none	0	2	10	12
3	66 (male)	1 year	Ropinirole (1 year)	0	9	5	14
4	70 (female)	5 years	Pramipexole (5 years)	3	5	4	12
5	67 (male)	3 years	Carbidoapa/ levodopa/ entacapone (2 months)	0	5	6	11

FIG. 1 (Th-380).

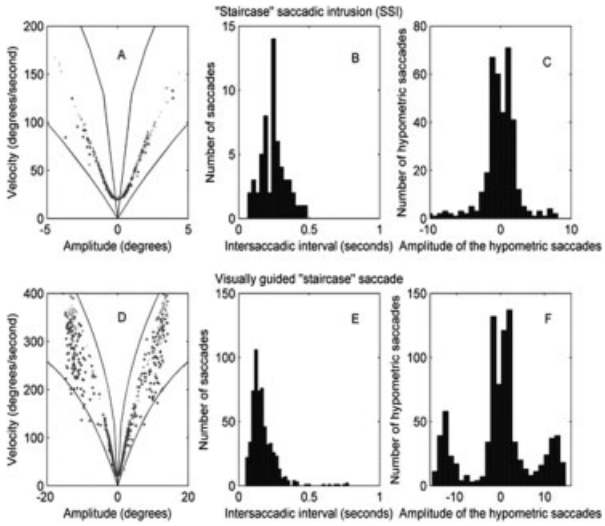

FIG. 2 (Th-380).

Conclusions: SI and "staircase" saccades in PD may have a related pathophysiology in PD. Degeneration of SNPR and relative differences in dysinhibition of different parts of SC could cause SSI.

Th-381

Clinical characteristics of weight losers in Parkinson's disease

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Objective: We have studied the differences between weight losers and non-weight losers to investigate any clues to the characteristics of weight losers.

Background: A proportion of patients with Parkinson's disease lose weight.

Methods: Three hundred and four patients with Parkinson's disease were studied for their clinical characteristics and followed up for weight measurements on a regular basis. Patients were categorised as weight losers if the final weight was lower than the initial weight.

Results: Patients were followed for a mean of 4.3±3 years. 140 of the 304 (46%) patients lost weight. Results are described between weight losers (WL) versus non-weight losers (NWL). There was no difference between WL & NWL for age of onset (67±9 vs 66±9, p=0.37), initial UPDRS (27±12 vs 28±13, p=0.29), Schwann & England score (70±14 vs 73±15,p=0.16), Hoehn & Yahr stage (3.6±1 vs 3±1, p=0.45) or MMSE (27±3 vs 27±40, p=0.17. Weight losers were older at the time of final assessment (75±8 vs 72±8, p=0.01) and had a longer disease duration (7.8±4 vs 6.4±5, p=0.01). There was no difference in the frequency of fatigue (p=0.58), dysphagia (p=0.23), anxiety (0.33), initial or final hallucinations (0.33), fluctuations (0.65), confusional episodes (0.88). Whilst there was no difference in the initial dyskinesia (p=0.43), the WL group hade higher frequency of dyskinesia at the final assessment (32% vs 21%, p=0.02). There was no gender difference (0.75). WL were more tremor predominant PD (55% vs 44%,p=0.06), no difference in the akinetic (0.58) or mixed PD (0.16) types. Drug therapy: WL patients were more often on cabergoline (18% vs 9%,p=0.04) or pergolide (31% vs 16%, p=0.005). Pramipexole was associated with higher body weight (18% vs 31%, p=0.02). No difference in ropinirole, entacapone, amantadine, selegiline, apomorphine or the highest mean daily dose of levodopa (527±270 mg vs 518±423 mg, p=0.84) therapy.

Conclusions: Weight losers were older, had longer disease duration and received more of cabergoline and pergolide. Pramipexole seems to be protective against weight loss, ropinirole was neutral. Dyskinesia may be an effect of weight loss rather than a cause. Since higher age and longer disease duration would eventually be applicable to all the patients, there is a need to investigate other reasons for weight loss in PD since only a proportion of patients lose weight.

Th-382

Progression of motor symptoms in Parkinson's disease – A community hospital-based observational study

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Objective: To efficiently utilize various therapeutic interventions now available in Parkinson's disease (PD), it is indispensible to evaluate clinical course of this invariably progressing illness.

Background: There are few longitudinally followed up data in a local community.

Methods: Medical records of the patients diagnosed and treated as PD based on the United Kingdom Brain Bank's Criteria between Apr 1995 and Oct 2008 and having more than 5 years history of motor symptoms were reviewed and their symptomatic progression was checked using modified Hoehn & Yahr stage (mHY). Patients were subdivided into 2 groups according to subjunctive intial symptoms, namely, onset with sole tremor (Group T) and onset with nontremor motor symptoms or tremor plus other motor symptoms (Group NT).

Statistical differences between means of two groups were examined by Student *t*-test.

Results: One hundred eighty-seven patients fulfilled the entry criteria. Their age at motor symptom onset (AO, years old) and disease duration (DD, years) in each mHY evaluated at latest follow up were as follows: 2.0 (n=5), 65.0±6.2, 7.4±1.6; 2.5 (n=11), 58.3±8.8, 7.0±1.9; 3.0 (n=81), 62.6±7.9, 9.3±3.5; 4.0 (n=44), 66.3±7.7, 10.4±4.0; 5.0 (n=46), 65.3±9.0, 12.2±5.7. Twenty-seven deaths were identified, of which 12 were due to non PD-related causes (DD 7.7±1.8) and 15 were due to PD-related causes (11.5±4.9). DD from onset of motor symptoms to first entry into mHY 3.0 and 5.0 were 5.9±2.9 and 9.8±3.7 in Group T (n=84, 22) and 5.7±3.3 and 11.6±6.3 in Group NT (n=87, 25), respectively. No statistical difference was obtained between the two groups (*p=0.75* for to 3.0, *p=0.24* for to 5.0). There was definite shortening of DD until first entry into mHY 5.0 among whole patients with AO older than 66 (n=26, 7.3±2.3) compared with those youger than 60 (n=12, 17.5±3.4) (*p=0.00*). Fifty-six (27/48) percent of patients with DD 10-15 years and 67% (14/21) with DD 15-20 years were severely handicapped (mHY≥4.0).

Conclusions: Still more than half proportion of PD patients has become severely handicapped in 10-15 years from motor symptom onset. Considering reduction of remaining active life span among patients with AO older than 66, aggressive therapy such as deep brain stimulation surgery should be secured for those with younger onset up to mid-sixties.

Th-383

Discordance between physician and patient recognition of motor fluctuations in Parkinson's disease

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Objective: To assess the concordance of the neurologist's assessment of the presence of motor fluctuations with patient-reported variability in daily function in PD.

Background: Accurate recognition of the presence of motor fluctuations in patients with PD is important in clinical management and trials. The accuracy of clinical recognition generally relies upon patient insight and awareness.

Methods: 775 PD patients reported their level of best and worst function on 14 daily activities on the OARS Disability Scale. At the same visit, neurologists assessed the presence or absence of motor fluctuations based on clinical history and exam. 4 patient subgroups were created: 1) nonfluctuators with low variability of function (F-/V-), 2) nonfluctuators with high variability (F-/V+), 3) fluctuators with low variability (F+/V-), and 4) fluctuators with high variability (F+/V+). Levels of PD impairment (UPDRS) and PD duration were compared across the 4 subgroups using multivariate ANOVA.

Results: 528 patients (68%) were in the two concordant groups (F-/V-; F+/V+), and 247 patients (32%) were in the two discordant groups (21% F-/V+; 11% F+/V-). ANOVA showed consistent gradations of impairment and PD duration, with less impairment in the F-/V- group, similar intermediate levels in the discordant groups (F-/V+ or F+/V-), and greatest impairment in the F+/V+ group ($p<0.001$). PD duration in the F-/V-, F-/V+, F+/V-, F+/V+ groups was respectively: 2.6(0.4), 5.5(0.8), 5.0(1.5) and 11.0(0.8) years. Total UPDRS in the 4 groups was respectively: 31.2(1.4), 51.5(2.7), 45.4(5.2) and 67.3(3.0).

Conclusions: This study shows that recognition of motor fluctuations may be inaccurate in up to one-third of PD patients. In 21% of patients assessed as nonfluctuators, the patients reported substantial variability in daily function. In 11% of patients assessed as fluctuators, patients reported little variability in function. The finding that these 2 discordant groups are similar in PD severity, and intermediate between the concordant groups suggests that these patients are in transition from nonfluctuators to fluctuators. It is likely that patients with early, mild fluctuations are more challenging to assess and are subject to miscategorization.

Th-384

Dysprosody in Parkinson's disease and correlations to UPDRS motor score

S. Skodda, U. Schlegel (Bochum, Germany)

Objective: The aim of our study was to analyse objective parameters of dysprosody with special emphasis on correlation of speech variables and aspects of motor impairment (according to UPDRS III) in patients with Parkinson's disease (PD).

Background: Parkinsonian speech results from a multidimensional impairment of phonation, articulation and prosody. The dysprosody is characterized by alterations in speech rate and pause time, speech intensity and pitch variation.

Methods: 106 PD patients (52 male, 54 female) were tested. Disease duration ranged from 1 to 19 years; UPDRS III ranged from 5 to 60 points. For further analysis, the entire UPDRS motor scale was dichotomised into subscores (axial vs. extremity symptoms and akinesia vs. rigor/tremor symptoms). The acoustical analysis was performed on a 4 sentence reading task using a commercial audio software (WaveLab). Fundamental frequency (F0) variation was measured using special phonetic software (Praat). Articulatory rate and speech to pause ratios were obtained by measurement of the length of each syllable and each pause both at the end of words and within polysyllabic words.

Results: No correlation was seen between parameters of intonation variability [F0SD, F0range] and parameters of articulatory velocity (total speech rate [TSR], net speech rate [NSR], pause ratio [PR%], fraction of intra-word pauses [Pinw%]). In the male PD patients' group, Pinw% was negatively correlated to pause ratio PR% ($p<0.01$) and mean fundamental frequency [meanF0] ($p<0.05$); furthermore, PR% was negatively correlated to TSR and NSR ($p<0.01$). MeanF0, PR% and Pinw% showed the strongest correlation to axial UPDRSIII subscore. In the female PD patients' group, TSR and NSR were negetively correlated to PR% and showed positive correlation to Pinw% ($p<0.01$). Variables of speech velocity were not correlated to UPDRSIII, whereas F0SD and F0range showed to strongest correlation to the axial and akinesia UPDRS subscore ($p<0.01$).

Conclusions: Measures of dysprosody are different in male and female PD patients possibly due to a differential impact of the disease on speech in men and women, e.g. as a result of sexual dimorphism of laryngeal size. Changes of pitch variablity in female PD patients and of speech velocity in male PD patients are strongly related to axial motor symptoms and to akinesia, whereas patients' age and disease duration have no influence on dysprosody.

Th-385

The effect of L-dopa on speech in Parkinson's disease

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Objective: The aim of our study was to analyse the effect of l-dopa on dysprosody in PD based upon a standardized l-dopa challenge.

Background: The aim of our study was to analyse the effect of l-dopa on dysprosody in PD based upon a standardized l-dopa challenge.

Methods: Motor examination according to UPDRS motor score and speech testing were performed in 21 PD patients (7 male, 14 female; median age 68 y, range 42 to 77 y) in the early morning after having abstained from dopaminergic medication overnight ("off" state) and again 40min after administration of 200mg of soluble l-dopa ("on" state). Speech examination comprised a standardized reading task which was digitally recorded (WaveLab) and analysed using a commercial software (Praat). Measurement of speech variables included first meanF0, jitter, shimmer, noise-to-harmonics ratio (nh-r) and vowel keeping time (VKT) as parameters of phonation,

second F0SD, F0range and sound pressure levels (SPL) as parameters of intonation, third articulatory rate (TSR and NSR) and speech to pause ratio (PR%) as parameters of speech velocity and last fraction of intra-word pauses (Pinw%) as parameter for articulatory precision.

Results: While UPDRS motor score showed a significant amelioration after l-dopa application (UPDRSIIIoff: mean 32.95 pts./median 31/SD 13.04/range 14 to 60 pts.; UPDRSIIIon: mean 18.76 pts./median 18/SD 8.29/range 9 to 40 pts., p=0.0001), none of the parameters of phonation, intonation, articulation and speech velocity improved significantly in the "on" state, but some positive effects on speech loudness and articulatory rate could be seen in some individual patients.

Conclusions: Our study did not show a significant beneficial effect of short-term l-dopa administration on the different dimensions of speech in PD patients. Our findings do not necessarily serve as an evidence for non-dopaminergic pathophysiology of parkinsonian speech disturbance, since an improvement of disturbed speech might necessitate long-term dopaminergic stimulation. Furthermore, as some improvement of single speech variables was evident, the preexisting speech profile of the individual patient might be responsible for the different l-dopa response.

Th-386

Side of onset of motor symptoms cannot be predicted from premorbid handedness of patients with Parkinson's disease

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Objective: To investigate the relationship between the side of onset of initial symptoms of PD and premorbid handedness of patients.

Background: Previous studies suggested that initial symptoms of Parkinson's disease (PD) occur more often on the right-sided extremities than on the left, or that there is a trend toward symptom onset on the dominant side.

Methods: A survey consisting of validated items measuring handedness and questions related to side of occurrence of initial symptoms was administered to 472 consecutive PD patients [(277 men, 195 women, mean age 66.5 (9.3), mean duration of the disease 10 (6.1) yrs]. The relationship between both parameters was studied using Spearman correlations and structural equation modeling. The ordinal character of data and the sample size substantiated the use of robust maximum likelihood model estimation.

Results: Between-items correlations of side of onset of PD symptoms and handedness items were very low (ranging from 0.02 to 0.09) and nonsignificant. The overall correlation estimated using structural equation modeling was also found very low (correlation = 0.11) and nonsignificant (p=0.14).

Conclusions: In contrast to previous studies it was shown that the side of onset of PD symptoms cannot be predicted from the premorbid handedness of patients.

Th-387

Subcellular localization of DJ-1 in the mouse brain and cultured cell lines

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Objective: The aim of the present study is to investigate subcellular distribution of DJ-1.

Background: Mutations in *DJ-1* gene cause one of autosomal recessive, early onset familial forms of Parkinson's disease (PD). It has been suggested that oxidative stress and mitochondrial dysfunction have been implicated in the pathogenesis of PD, but the molecular mechanisms involved in the degeneration of neurons remain unclear. A number of previous studies using cell lines over-expressing DJ-1 suggested that DJ-1 protein was abundantly localized within mitochondrial matrix. However, the precise localization of DJ-1 protein remains poorly understood.

Methods: We fractionated DJ-1 by immunoisolation, immunoprecipitation, and sucrose gradients using synaptosomal fraction from mouse brains. To further study this issue, we performed immunolabeling assay for endogenous DJ-1 using cultured cells as well as primary neurons from mouse brain.

Results: DJ-1 was co-purifed with synaptophysin by immunoisolation. Additionally, DJ-1 showed punctuate appearance in cytosol and plasma membrane by immunocytochemisty. DJ-1 also colocalized with synaptobrevin and Rab3A.

Conclusions: Based on its specific localization, DJ-1 appears implicated in membrane trafficking.

Th-388

Patterns of motor and non-motor features in Parkinson's disease

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Objective: To evaluate the presence and nature of patterns of coherency among the motor and non-motor domains in Parkinson's disease (PD) and to examine how clinical parameters are related to these patterns.

Background: Knowledge on the coherency of motor and non-motor domains is important because it may suggest underlying constructs that provide new insight in the contributions of the primary disease process and anti-parkinsonian medication to the broad clinical symptom profile of PD.

Methods: A cohort of 397 PD patients was randomly divided into two samples. Exploratory factor analysis (EFA) was performed on the motor and non-motor symptoms in PD in the first sample. Findings of the EFA were used to construct a model which was tested in the second sample by confirmatory factor analysis. Multiple regression analyses on the resulting factors were performed to evaluate the relation of clinical parameters upon these factors.

Results: Four factors were identified. The first and strongest factor (cognitive impairment, autonomic dysfunction, psychotic symptoms, depression, daytime sleepiness, and axial symptoms) was related to disease severity. Another factor largely reflected motor complications of therapy and was related to dopaminergic medication. The other two factors reflected sleep/depression and tremor/bradykinesia/rigidity, and were only marginally related to disease severity or medication.

Conclusions: The motor and non-motor features in PD can be characterized by four distinct patterns of coherency, which provide insight in the contributions of the primary disease process and anti-parkinsonian medication to the broad clinical spectrum of PD. One factor, consisting of predominantly non-motor symptoms together with axial features, clearly reflects disease severity and may provide a new basis for monitoring disease progression in PD.

Th-389

Slowly and fast progressing symptoms in Parkinson's disease (PD): A new approach to the early diagnosis and determination of the stage

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Objective: The assessment of rates progression of symptoms in patients with PD.

Background: Currently, the Braak et al. theory on the spread of the degenerative process to the new areas of the brain in the course of time is well recognized. But existing clinical classifications do not take into account the rate of pathological symptoms progression.

Methods: Anamnesis of progression symtoms in PD.

Results: Lately, there have been defined a number of symptoms, which precede the occurrence of motor manifestations in PD. Consensus is attained in the following symptoms: hyposmia, autonomic dysfunction, disorders of mood, sleep disturbances. The

above mentioned symptoms of the PD are relatively stable and progress slowly and at the advanced stages of the PD do not play independent role. Another group of PD symptoms has a different course, they progress much faster. First of all, it concerns the well studied motor disorders. Hypokinesia, tremor, rigidity, postural instability steadily deteriorate soon after their development. It also concerns cognitive function; visual hallucinations and memory loss are considered to be unfavorable symptoms for the future development of dementia. In contrast to other autonomic disorders heart denervation, which is manifested in heart rate stabilization and orthostatic hypotension, has an unfavorable clinical course.

Conclusions: Firstly, for early diagnosis of PD (prior to motor dysfunction development) slowly progressing symptoms should be revealed. Secondly, to define the PD stage it is advisable to use only fast progressing symptoms. Hoehn-Yahr classification should be supplemented with the evaluation of memory and also particular autonomic parameters (e.g. evidence of heart rate stabilization); this will allow using it in clinical practice not complicating it significantly. Thirdly, the evaluation of even minor PD symptoms is of utmost importance as it can help estimate the pathogenesis of different mediator systems. Thus, we suggest classifying PD symptoms taking into account the rates of their progression; this will enable the development of early diagnosis methods as well as determination of the disease stage considering nonmotor manifestation.

Th-390

Freezing of gait in patients with Parkinson's disease. Three years of follow-up

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Objective: To study freezing of gait (FOG) in a group of PD patients in 2005 and in 2008, to assess what variables can influence the appearance of freezing and to evaluate if FOG-Questionnaire (FOG-Q) is sensible enough to assess the progression of FOG.

Background: FOG is a common, poorly understood, parkinsonian symptom interfering with daily activities. The Freezing of Gait Questionnaire (FOG-Q) has been developed by Giladi to assess subjectively FOG severity. There are not many studies comparing FOG in two periods of time.

Methods: This was an observational, cross-sectional, two-points-in-time evaluation study. PD patients scoring 2 to 4 on Hoehn and Yahr (H&Y) scale were assessed in 2005 for FOG severity using the FOG-Q. Demented patients were excluded. Three years later the same patients were reappraised. The progression of H&Y, the presence of motor and no motor complications were assessed. The correlation between FOG and FOG-Q to the duration and severity of the disease were studied.

Results: 75 PD patients (40 men) with a mean age of 68.1 (9.2) years and a mean disease duration of 7.3 (6.4) years were evaluated in 2005. 26 patients (34.7%) had FOG. During the three years of follow-up 14 patients developed FOG and 7 patients reached 5 on H&Y. The presence of FOG was significantly higher in 2008 ($p<0.001$). Motor and non motor complications increased in these three years. Duration of the disease was significantly longer in FOG patients (12 years) than in those without FOG (7 years) ($p= 0.001$). Most patients with FOG (70%) were on stage III and most patients without FOG (80%) were on stage II ($p<0.0001$). FOG-Q scored higher in patients with longer PD duration ($P<0.0001$). FOG-Q scored higher in patients on stage 3 (H&Y) (11.13) than on stage 2 (2.37) ($p<0.0001$). There were not differences between FOG-Q scores in 2005 (11.76) and in 2008 (12.7) in 21 patients that were followed-up ($p=0.28$).

Conclusions: FOG is very common in patients with PD. There is a high correlation of FOG with the duration of disease and with the H&Y scale. FOG-Q allows differentiation between patients on stage II and III on H&Y. A bigger sample and longer time of evolution are needed to demonstrate if FOG-Q is sensitive enough to assess progression of FOG.

Th-391

Suppression of levodopa-induced dyskinesias by sensory stimuli

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Objective: The objective was to report on an interesting phenomenon of the influence of tactile stimuli on levodopa-induced dyskinesias (LID) in Parkinson's disease (PD).

Background: The pathophysiology of LID in advanced PD is not well understood and treatment management remains a major challenge.

Methods: Here we report on four patients with advanced PD in whom disabling LID were briefly but significantly and reproducibly decreased or stopped by applying pressure to the posterior neck muscles. In all patients the stimulus had to consist of slight to moderate pressure on the upper part of the trapezius muscle whereas light touch or pain stimuli remained without any effect.

Results: Superficially the phenomenon observed in our patients may resemble the well known "geste antagoniste" in dystonia, however, in our cases the pressure to mainly axial body parts had to be applied by another person and not the patient himself. One possible explanation of the described phenomenon might be the psychological impact of sensory stimuli as putting pressure on certain muscles in the patients described here may lead to emotional and physical relaxation. However, this seems unlikely as only pressure to special well localized trigger points lead reproducibly to beneficial effects while pressure on adjacent areas did not.

Conclusions: We conclude that the phenomenon described here for the first time rather may be explained by somatosensory system influence on LID in PD which is in keeping with previous experimental results. Further research of this phenomenon could lead to better understanding of the pathophysiology of LID and possibly lead to new therapy concepts.

Th-392

Effect of smoking on disease progression in male idiopathic Parkinson's disease patients

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Objective: To evaluate the effect of smoking on the rate of disease progression in male patients with idiopathic Parkinson's disease (IPD).

Background: While it is well known that smoking reduces risk of getting IPD, studies have failed to show that smoking can slow the progression of already established IPD. This discrepancy may be due to the fact that previous studies had included both male and female patients with significantly different smoker : non-smoker ratio, and also because they didn't take into account other factors that influence the rate of disease progression such as onset age and tremor vs. non-tremor phenotype. We therefore studied the rate of disease progression in male IPD patients while taking into account other variable factors.

Methods: We studies 74 male patients with IPD who has been treated in the movement clinic of a single university hospital. Smoking histories were taken from patients and family members and were grouped into 1) those who kept on smoking after the onset of IPD, 2) ex-smokers who quit smoking before the disease onset, and 3) never smokers. Patient age, onset age, disease duration, medication dosage (calculated as levodopa equivalent dosage), UPDRS and H&Y scores, onset type (tremor vs. akineto-rigid form) were taken into account in the analysis.

Results: Analysis showed that compared to ex-smokers and non-smokers, current smokers had younger age of onset (54.5 vs. 62.9 years old, $p=0.007$), lower UPDRS motor score (15.7 vs. 18.8,

p=0.029), and slower disease progression measured by UPDRS motor score (2.93 vs. 4.76 points per year, p=0.047) There were no significant differences when age of onset, type of disease (tremor vs. akineto-rigid form), and disease durations were taken into account.

Conclusions: Current smokers with IPD had lower age onset than ex-smokers or never smokers, which is consistent with results from previous studies. Our hypothesis is that those who develop IPD despite of a protective environmental factor (i.e. smoking) have greater genetic influence in their pathogenesis, thus developing IPD at younger ages. We also found that IPD patients who continue to smoke had lower UPDRS motor scores, as well as slower progression of the disease. But, we could not rule out the possibility that this beneficial effect may be due to the fact that they developed IPD at younger ages.

Movement Disorders
Vol. 24, Suppl. 1, 2009, pp. S543–S550

Movement Disorders, Volume 24, Supplement 1, 2009
Index of Key Words

Movement Disorders
Vol. 24, Suppl. 1, 2009, pp. S551–S653

Movement Disorders, Volume 24, Supplement 1, 2009 Author Index