“Neurophysiology and PSP: recent advances”
OVERVIEW

• Neurophysiological techniques
  – Electrophysiology
  – Kinematic analysis / Movement studies

• Neurophysiological abnormalities in PSP

• Possible pathophysiological and clinical implications
BRAINSTEM REFLEXES

Startle reflex

Auditory tone, 124 dB, 1000 Hz, 50 ms,

- Masseter
- Orbicularis oculi
- Sternocleidomastoid
- Forearm extensors
- Forearm flexors
- Abductor policis brevis
- First dorsal interosseous
- Rectus abdominis

Trigeminal blink reflex

Cruccu & Deuschl 2000

Brown et al. 1991

Berardelli et al., 1998
Noninvasive brain stimulation: from physiology to network dynamics and back

Eran Dayan1,3, Nitzan Censor1,3, Ethan R Buch1–3, Marco Sandrini1,2 & Leonardo G Cohen1

Noninvasive brain stimulation techniques have been widely used for studying the physiology of the CNS, identifying the functional role of specific brain structures and, more recently, exploring large-scale network dynamics. Here we review key findings that contribute to our understanding of the mechanisms underlying the physiological and behavioral effects of these techniques. We highlight recent innovations using noninvasive stimulation to investigate global brain network dynamics and organization. New combinations of these techniques, in conjunction with neuroimaging, will further advance the utility of their application.

Figure 1 Typical NIBS setups. (a) A standard figure-eight TMS coil placed on the scalp; here, over dorsolateral prefrontal cortex. (b) Bipolar tDCS electrode configuration, with one electrode over left dorsolateral prefrontal cortex and a reference electrode over the contralateral supraorbital region. Human head model from http://www.ir-ltd.net/. Used by Creative Commons license.
Kinematic Analysis / Movement studies

Infrared cameras
Reflective markers
Finger tapping
Experimental setting
Blinking
NEUROPHYSIOLOGICAL MEASURES: SUMMARY

• Electrophysiological studies
  – BRAINSTEM REFLEXES
    • Startle reflex
    • Trigeminal blink reflex: R1, R2 latencies, R2 recovery cycle
  – EEG recordings/ Somatosensory Evoked Potentials (SEP)
  – Transcranial Magnetic Stimulation (TMS)
    • Corticospinal/intracortical excitability, connectivity measures
    • Plasticity mechanisms

• Kinematic Analysis / Movement studies
  – Eye and eyelid movements
  – Finger tapping
OVERVIEW

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- Neurophysiological abnormalities in PSP

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STARTLE REFLEX IN PSP

Healthy subjects

PSP patients

Brown et al. 1991

Vidailhet et al., 1991; Kofler 2000
TRIGEMINAL BLINK REFLEX IN PSP

Supraorbital nerve stimulation

R1

R2

R2 recovery cycle

NORMAL R1, R2 AND LATENCY

Vidahilet et al. 1992
Valls-Solé et al. 1997

PROLONGED R2 LATENCY

Sommer et al. 2001

ENHANCED R2 RECOVERY

Valls-Solé et al. 1997
Sommer et al., 2001
Bologna et al. 2009
 BASAL GANGLIA MODULATION OF TRIGEMINAL BLINK REFLEX CIRCUITS

Basso & Evinger 1996
CORTICOSPINAL/INTRACORTICAL EXCITABILITY IN PSP

- **Measurements:** central motor conduction time (CMCT), motor thresholds (MT), input-output recruitment curve (I/O MEP), short interval intracortical inhibition (SICI), intracortical facilitation (ICF), short-latency afferent inhibition (SAI)

- **Major results:**
  - CMCT is prolonged
  - I/O MEP curve are increased
  - SICI is reduced
  - ICF and SAI are normal

*Khun et al., 2004; Nardone et al. 2005; Morita et al. 2008*
BASAL GANGLIA MODULATION OF CORTICAL CIRCUITS

Wichmann et al, 2011
INTERHEMISPHERIC INHIBITION IN PSP

• More severe reduction of interhemispheric inhibition in RS patients as compared to PSP-P and PD

• Significant correlation between reduction of interhemispheric inhibition and Addenbrooke's cognitive examination

Wittstock et al., 2013
PLASTICITY

• Activity-dependent changes in the strength of the synaptic connection.

• In animal experiments plasticity is quantified by measuring short- or long-term changes in post-synaptic responses after repetitive stimulation of pre-synaptic terminals (Cooke & Bliss, 2006), through the activation of the N-methyl-d-aspartate (NMDA) glutamatergic receptors (Collingridge et al., 1983; Cooke and Bliss, 2006).

• In human TMS studies the term plasticity commonly refers to long-term changes in the amplitude of MEPs after applying protocols of repetitive TMS (rTMS) (Berardelli et al., 2008, Zieman et al., 2008).
Abnormal Cortical Synaptic Plasticity in Primary Motor Area in Progressive Supranuclear Palsy

Antonella Conte¹², Daniele Belvisi¹, Matteo Bologna², Donatella Ottaviani¹, Giovanni Fabbrini¹², Carlo Colosimo¹, David R. Williams³ and Alfredo Berardelli¹²

Figure 1. MEPs elicited before (T₀), and at 5 (T₁), 15 (T₂), and 30 (T₃) min after iTBS in healthy subjects and in patients with PSP. x-axis: time; y-axis: MEP size expressed as percentage of MEP size at T₀. Asterisks indicate statistical significance. Note that the increase in MEP size is statistically significant at all time points in both PSP patients and healthy subjects.

Figure 3. VO curves of MEPs in patients with PSP and healthy subjects before and after iTBS. x-axis: intensity of TMS pulse expressed as percentage of the intensity able to evoke a mean MEP of about 1 mV. y-axis: MEP amplitude expressed in millivolts. Each point represents mean value; bars represent standard error. Note that the I/O curve differs significantly between PSP patients and healthy subjects before and after iTBS and that iTBS determined significant changes in the steepness of VO curve only in PSP patients.
Abnormal Cortical Synaptic Plasticity in Primary Motor Area in Progressive Supranuclear Palsy

Antonella Conte\textsuperscript{1,2}, Daniele Belvisi\textsuperscript{1}, Matteo Bologna\textsuperscript{2}, Donatella Ottaviani\textsuperscript{1}, Giovanni Fabbrini\textsuperscript{1,2}, Carlo Colosimo\textsuperscript{1}, David R. Williams\textsuperscript{3} and Alfredo Berardelli\textsuperscript{1,2}

**Figure 2.** MEPs elicited before (T\textsubscript{0}) and at 5 (T\textsubscript{1}), 15 (T\textsubscript{2}), and 30 (T\textsubscript{3}) min after iTBS in patients with PSP at baseline and at one-year follow-up session. x-axis: time; y-axis: MEP size expressed as percentage of MEP size at T\textsubscript{0}.

**Figure 5.** Correlation between the changes in the degree of post-iTBS MEP facilitation at one-year follow-up (ratios between the MEP size ratio at T\textsubscript{2}/T\textsubscript{0} at one-year follow-up and the MEP size ratio at T\textsubscript{2}/T\textsubscript{0} at baseline) and the changes in clinical severity scores (ratios between PSPRS at one-year follow-up and PSPRS values at baseline).
CORTICAL PLASTICITY IN PARKINSON’S DISEASE  
*(Studies using Theta-Burst Stimulation - TBS)*

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<thead>
<tr>
<th></th>
<th>iTBS</th>
<th>cTBS</th>
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<tbody>
<tr>
<td>Abnormally increased</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Normal</td>
<td>Huang et al., 2011</td>
<td>Kishore et al., 2012a*</td>
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<td></td>
<td>Kishore et al., 2012a*</td>
<td>Huang et al., 2011</td>
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<td></td>
<td>Zamir et al., 2012a</td>
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<tr>
<td>Abnormally reduced</td>
<td>Suppa et al. 2011</td>
<td>Eggers et al., 2010</td>
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<td>Kishore et al., 2012a</td>
<td>Kishore et al., 2012a</td>
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<td>Kishore et al., 2012b</td>
<td>Kishore et al., 2012b</td>
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*stable responders to L-dopa
STUDIES ON CORTICAL PLASTICITY IN PARKINSONIAN SYNDROME

• In PSP the facilitatory effect of iTBS is enhanced (Conte et al., 2012)

• In contrast, in patients with PD and Multiple System Atrophy (MSA) TBS-induced after-effects are anomalously reduced (Eggers et al., 2010; Suppa et al., 2011, 2013; Huang et al., 2011; Kishore et al., 2012)

• PSP is pathologically characterized by neurofibrillary tangles emerging from tau protein deposition and prominent cortical and subcortical atrophy. Thus in PSP, exaggerated TBS responses might reflect a more prominent cortical degeneration, including loss of M1 inhibitory interneurons (Halliday et al., 2005; Hoover et al., 2010; Conte et al., 2012)

• PD and MSA are pathologically characterized by deposition of alpha-synuclein (a-SYN) in cortical and subcortical brain regions, including M1 (Su et al., 2001; Ahmed et al., 2012). Given that a-SYN plays a crucial role in regulating neurotransmission and synaptic plasticity, its deposition might contribute to impaired synaptic plasticity in both PD and MSA (Cabin et al., 2002)
THE ROLE OF THE CEREBELLUM IN THE PATHOPHYSIOLOGY OF PSP

• Clinico-pathological studies

• Neurophysiology
  - reduced eyeblink classical conditioning
  - reduced cerebellar-brain inhibition

Cerebellum
CEREBELLAR INVOLVEMENT IN PSP: A CLINICOPATHOLOGICAL STUDY

- Cerebellar ataxia as the initial and principal symptom
- Neuronal loss with gliosis (A) and higher densities of coiled bodies (B) in the cerebellar dentate nucleus and cortex

Kanazawa et al. 2009
EYE-BLINK CONDITIONING

Supraorbital nerve electrical stimulation

Auditory tone 400 ms

α blink

Conditioned response
CEREBELLAR DYSFUNCTION IN PROGRESSIVE SUPRANUCLEAR PALSY: A TRANSCRANIAL MAGNETIC STIMULATION STUDY

• Cerebellar function was evaluated using suppressive effects of TMS over the cerebellum on MEPs elicited by TMS over the contralateral motor cortex, i.e. cerebellar inhibition (CBI)

• The CBI was reduced in PSP patients suggesting that Purkinje cells or the dentato-thalamo-cortical pathway assessed by CBI is involved in PSP

• The results are compatible with the pathological findings showing severe dentate nucleus degeneration in PSP patients

Shirota et al., 2010
OCULOMOTOR ABNORMALITIES IN PSP

Early stages
- Slow vertical saccadic movements
- Hypometric saccades
- Reduced blinking
- Square-wave jerks

Middle stages
- Supranuclear vertical gaze palsy
- Lid retraction with very rare blinking (<3)
- Impaired convergence
- Apraxia of eyelid opening or closing

Late stages
- Supranuclear horizontal gaze palsy
- Loss of oculocephalic reflexes
- Blepharospasm
- Disconjugate gaze

Hypothesis 1: Burst neurons in riMLF are responsible for slow saccades

Hypothesis 2: Omnipause neurons in RIP are responsible for slow saccades

Bhidayasiri et al. 2001; Garbutt et al., 2009

SPONTANEOUS BLINK RATE

Healthy subjects (~ 20 blinks/min)

PSP (1-5 blinks/min)

Karson et al., 1984; Bologna et al. 2009
Voluntary, spontaneous and reflex blinking in patients with clinically probable progressive supranuclear palsy

Matteo Bologna,¹ Rocco Agostino,¹,² Bruno Gregori,¹ Daniele Belvisi,¹ Donatella Ottaviani,¹ Carlo Colosimo,¹ Giovanni Fabbrini¹,² and Alfredo Berardelli¹,²

• Voluntary, spontaneous and reflex blinking all show abnormal kinematic parameters in patients with PSP

• Abnormal voluntary, spontaneous and reflex blinking in patients with PSP reflects the widespread cortical, subcortical and brainstem degeneration related to this disease
Abnormal switching between the closing and opening phase during voluntary blinking:

- altered basal ganglia function?
- altered cortical motor areas activity?
Voluntary, spontaneous and reflex blinking in patients with clinically probable progressive supranuclear palsy

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Opening phase abnormalities during reflex blinking: midbrain degeneration?

Graber and Straudinger 1997 Schmidtke Büttner-Ennever 1992
REVIEW

Facial bradykinesia

Matteo Bologna, 1 Giovanni Fabbri, 1,2 Luca Marsili, 2 Giovanni Defazio, 3 Philip D Thompson, 4 Alfredo Berardelli 1,2

Table 1 Synopsis of major studies on facial bradykinesia in Parkinson’s disease and atypical parkinsonism (ie, progressive supranuclear palsy, multiple system atrophy and corticobasal degeneration)

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<tr>
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<th>Spontaneous</th>
<th>Emotional</th>
<th>Voluntary</th>
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<tr>
<td>PD</td>
<td>Karson, 31</td>
<td>Rinn, 43</td>
<td>Caligiuri, 45</td>
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<td></td>
<td>Deuschl and Godde meier, 32</td>
<td>Katsikitis et al, 26</td>
<td>Connor et al, 46</td>
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<td></td>
<td>Kimber and Thompson, 35</td>
<td>Jacobs et al, 39</td>
<td>Korosc et al, 24</td>
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<td></td>
<td>Altiparmak et al, 33</td>
<td>Smith et al, 37</td>
<td>Agostino et al, 7</td>
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<td></td>
<td>Agostino et al, 7</td>
<td>Simons et al, 38</td>
<td>Bologna et al, 36</td>
</tr>
<tr>
<td>PSP</td>
<td>Altiparmak et al, 33</td>
<td>Bologna et al, 58</td>
<td>Bologna et al, 68</td>
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<tr>
<td>MSA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CBD</td>
<td>NA</td>
<td>NA</td>
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PD—the spontaneous blinking rate is reduced overall. In some cases the spontaneous blinking rate is increased, suggesting a form of ‘off period’ dystonia; emotional movements: spontaneous smiling is reduced in terms of frequency and degree of mouth opening; investigations on posed expressions in PD are contradictory; voluntary oro-facial movements are bradykinetic. Voluntary blinking is impaired in terms of switching between the closing and opening phases.

PSP—the spontaneous blinking rate is markedly reduced. Voluntary blinking is bradykinetic. Data on voluntary movements of the lower face and emotional facial movements are not available.

MSA and CBD—data on spontaneous, emotional and voluntary facial movements are not available.

CBD, corticobasal degeneration; MSA, multiple system atrophy; NA, not available; PD, Parkinson’s disease; PSP, progressive supranuclear palsy.
Repetitive finger tapping is commonly used to assess bradykinesia, i.e. 'slowness of initiation with progressive reduction in speed and amplitude of repetitive action' in Parkinson's disease.

Patients with progressive supranuclear palsy have a specific finger tap pattern of 'hypokinesia without decrement'.
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PATHOPSYCHOLOGICAL & CLINICAL IMPLICATIONS

• Comprehension of the pathophysiologica basis od sign and symptoms

• Improve diagnostic accuracy

• Enable differential diagnosis

• Individuate biomarkers of disease progression

• Objective assessment of novel therapeutic strategies
DRAWBACKS

• Limited sample size / clinical heterogeneity of PSP

• Limited number of longitudinal studies

• Lack of pathological follow up

• Selection bias / low diagnostic accuracy of clinical criteria
CONCLUSIONS

• The relationships between these neurophysiological abnormalities and the PSP symptoms is still unclear

• Future studies should investigate patients in the early stages of disease, and follow-up abnormalities over the disease course

• Given that most of the neurophysiological abnormalities present in PSP are also shared by patients with other atypical parkinsonian disorders, further effort is needed to define the specific neurophysiological changes in PSP
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Carlo Colosimo
& Alfredo Berardelli