RESEARCH ARTICLE

The Relation Between Cognition and Motor Dysfunction in Drug-Naive Newly Diagnosed Patients with Parkinson's Disease

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ABSTRACT: Recent studies have reported cognitive decline to be common in the early phase of Parkinson's disease. Imaging data connect working memory and executive functioning to the dopamine system. It has also been suggested that bradykinesia is the clinical manifestation most closely related to the nigrostriatal lesion. Exploring the relationship between motor dysfunction and cognition can help us find shared or overlapping systems serving different functions. This relationship has been sparsely investigated in population-based studies of untreated Parkinson's disease. The aim of the present study was to investigate the association between motor signs and cognitive performance in the early stages of Parkinson's disease before the intake of dopaminergic medication. Patients were identified in a population-based study of incident cases with idiopathic parkinsonism. Patients with the postural instability and gait disturbances phenotype were compared with patients with the tremor-dominant phenotype on demographics and cognitive measures. Associations between cognitive and motor scores were investigated, with age, education, and sex controlled for. Bradykinesia was associated with working memory and mental flexibility, whereas axial signs were associated with episodic memory and visuospatial functioning. No significant differences in the neuropsychological variables were found between the postural instability and gait disturbances phenotype and the tremor phenotype. Our results indicate a shared system for slow movement and inflexible thinking that may be controlled by a dopaminergic network different from dopaminergic networks involved in tremor and/or rigidity. The association between axial signs and memory and visuospatial function may point to overlapping systems or pathologies related to these abilities. © 2011 *Movement* Disorder Society

Key Words: Parkinson's disease; cognition; population based; newly diagnosed

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Cognitive changes are common in Parkinson's disease (PD). Previous studies have shown substantial decline in a wide range of cognitive functions, even at the time of diagnosis.[1,2] The course of motor and cognitive features in Parkinson's disease is heterogenic, both in its clinical manifestations and in response to medication.[3] Postural instability and other axial features respond poorly to dopaminergic treatment, whereas bradykinesia, tremor, and rigidity respond better.[4] This indicates involvement of dopaminergic networks in bradykinesia, tremor, and rigidity but not in axial features.

Cognitive deficiency in PD is related to deterioration of executive processes.[2] The executive dysfunction in PD, especially the processes that involve manipulation of information within working memory, has been related to specific underactivation in regions of the basal ganglia and/or frontal cortex.[5,6] This suggests that dopaminergic depletion also affect nonmotor symptoms. In addition to dopaminergic depletion in the

substantia nigra, other brain regions of importance for cognitive function can be damaged and are likely to be important for many nonmotor and motor symptoms in PD.[7]

Previous studies dividing patients with PD into groups based on dominant motor features, that is, tremor or postural instability gait disturbances (PIGD), suggest that belonging to the PIGD-dominant phenotype or change from tremor to the PIGD phenotype gives a higher risk of cognitive decline and the development of PD dementia (PDD).[8,9] This discrepancy in cognition between tremor and PIGD subtypes has not been shown in early stages of the disease.[10] Speech and swallowing impairments, bulbar functions that in addition to PIGD are classified as axial features, were in a recent analysis of data from the DATATOP study found to be associated with cognitive impairment as measured by the Mini–Mental State Examination (MMSE).[11]

The relation between cognition and motor dysfunction in patients treated with dopaminergic drugs is difficult to assess because the treatments both have variable influence on motor symptoms and both beneficial and detrimental effects on cognition that vary in different disease stages.[12] The association between motor signs and cognitive performance has been studied in different cohorts of various sizes.[13] Studies from well-defined cohorts in early untreated PD with an extensive cognitive test battery are rare and need to be explored further.[14,15]

We previously found bradykinesia, rigidity, and speech impairment to be more pronounced in patients with impairment in 1 or more cognitive domain in early drug-naive PD.[16] Now we want to explore which aspects of cognition are connected to different motor signs in an extended cohort from the same population. We studied patients all drug naive to dopaminergic treatment to explore the effects of the disease itself on the association between cognition and motor signs recorded by the Unified Parkinson's Disease Rating Scale (UPDRS). Further, we investigated if there is a difference in cognitive performance between the PIGD and tremor-dominant subtypes at the time of diagnosis.

Patients and Methods

Participants

Data were assembled from baseline assessments in a large community-based prospective study on idiopathic forms of parkinsonism in a defined catchment area with 142,000 inhabitants (the southeastern part of the county of Västerbotten in northern Sweden).[17] All suspected cases were referred to the only neurological department, employing all neurologists in the area of investigation. Only patients with previously undiagnosed idiopathic parkinsonism were included. Patients with dementia or cognitive dysfunction, as defined by a score below 24 on the MMSE, at baseline or onset of dementia within 12 months of the onset of parkinsonism were not included in the study. During the period January 2004–April 2009, 190 cases with idiopathic parkinsonism were identified, and 150 patients fulfilled the diagnostic criteria for PD (122 PD definite with >2 supportive criteria and 28 PD probable with 1–2 supportive criteria) according to the UK Parkinson's Disease Society Brain Bank criteria (UK PDSBB)[18] at baseline and at 12-month follow-up. One hundred and twenty-two individuals (81%) with newly diagnosed idiopathic PD agreed to the neuropsychological evaluation. Twenty-eight patients (19%) declined the neuropsychological evaluation. These patients were older (79.9 vs 68.9 yearss; $P < .001$), had higher scores on the total UPDRS (49.5 vs 34.8; $P < .001$), and had lower scores on the MMSE (27.3 vs 28.7; $P = .023$). The aim was to assess drug-naive patients at the baseline investigation. Because of ethical considerations, some patients (n = 17) had started their pharmacological treatment for PD prior to the baseline neuropsychological assessment. These patients and 2 patients with normal dopamine transporter (DAT) imaging using ^{123}I-ioflupane ([^{123}I]FP-CIT) were excluded from the study. Thus, 103 drug-naive patients were included in the present study. The study was approved by the Ethics Committee of the Faculty of Medicine at Umeå University. Written informed consent was obtained from all participants.

Procedure

Clinical Assessments

All participants were extensively examined during repeated visits the first month following the initial contact. Information about demographics and disease history was obtained. All cases with suspected idiopathic parkinsonism underwent a standardized clinical examination by a neurologist specializing in movement disorders. To confirm the presence of PD, another specialist in movement disorders (blinded to the assessment of the previous examiner) evaluated a videotape of the patient undergoing UPDRS–motor score (UPDRS-III) examination. Patients were included if both examiners judged that they had fulfilled the clinical criteria for PD according to the UK PDSBB criteria. Severity was measured by the UPDRS.[19] UPDRS scores were divided into subscores for tremor, rigidity, bradykinesia, and axial impairment divided into 2 variables based on the DATATOP factorial division (postural instability and gait disturbances and bulbar dysfunction)[11]: the sum of UPDRS items 20 and 21 for the tremor score, item 22 for the rigidity score, the sum of items 24, 25, 26, and 31 for the bradykinesia score, the sum of items 27, 28, 29, and 30 for the axial impairment score (arising from chair, posture,

gait and postural stability), and the sum of items 18 and 19 for the bulbar score (speech and facial expression). The cases were also divided into a PIGD-dominant, a tremor-dominant, and an indeterminate group based on a previously published subdivision of the UPDRS.[20] The MMSE was used as a screening instrument for dementia and to measure global cognition. DAT imaging using [^{123}I]FP-CIT was also performed within 1–2 months following inclusion. Age at symptom onset was defined as the first appearance of motor symptoms according to the patient. Duration of the disease was defined as the time between symptom onset and time of assessment.

Neuropsychological Assessment

A battery of neuropsychological tests measuring a range of cognitive functions was utilized. The participants were individually tested for 2 hours each by a trained interviewer. Verbal episodic memory was assessed with the Free and Cued Selective Reminding Test,[21] the Associative Learning Test, and the Logical Memory subtests immediate and delayed recall, both from the Wechsler Memory Scale.[22] Nonverbal episodic memory was assessed with the Brief Visuospatial Memory Test–Revised (BVMT-R).[23] Psychomotor speed and attention were tested with the Trail Making Test Part A (TMT-A).[24] Attention and rapid set shifting were tested with the Trail Making Test Part B (TMT-B).[24] Working memory was tested with WAIS-R forward and backward digit span.[25] Language function was evaluated with the Boston Naming Test (BNT)[26] and Controlled Oral Word Association (COWA)[27] with words beginning with a given letter (F, A, and S) or in a given category (animal, color, and fruit). Visuospatial abilities were measured with the Benton Judgment of Line Orientation Test.[28] Executive functions, especially the ability to shift and maintain set, were assessed with the Wisconsin Card Sorting Test–computer version 2 (WCST).[29] Sustained attention was assessed with mental control from the Wechsler Memory scale.[25]

All participants could not carry out all tests because of tiredness or technical issues. The tests with the most missing cases were the WCST (n = 15), Logical Memory (n = 9), and Logical Memory delayed (n = 11). The WCST is computerized, and computer difficulties and computer logistics were the main reasons for missing data. Missing data varied between 1 and 6 cases for the other variables. There were no difference between the PIGD, tremor, and indeterminate groups with regard to missing data.

Statistical Analyses

Differences in demographic, clinical, and cognitive characteristics between the PIGD, tremor, and indeterminate groups were analyzed. Because many variables were not normally distributed, the nonparametric Kruskal–Wallis and Fisher's exact tests were performed when appropriate. The nonparametric Spearman's rho was used to explore correlations between demographic, motor, and neuropsychological variables. Multiple linear regression analysis was performed to see if the relationships found between the motor and neuropsychological variables were unique or affected by other variables. To meet the assumptions of normality and reduce skewing and outlier influence, some variables were transformed with square-root transformation or logarithm transformation, depending on the distribution of scores. After the transformation, most variables were approximately normally distributed. Analyses were also made to ensure no violation of linearity and homeoscedasticity. This was true for most of the relationships. Assumptions were also checked by inspection of the normal probability plot (P-P) and scatter plot of the regression standardized residual.

The raw or the transformed scores from each of the neuropsychological tests were used as the dominant variable in separate multiple linear regression models. Age, years of education, and sex were used as covariates and forced into the model together with the total UPDRS score of each cardinal sign (bradykinesia, tremor, rigidity, postural instability, and axial features [postural instability, gait disturbances, and bulbar dysfunction]) that had shown a significant correlation with the dominant variable (cognitive test score) in the correlation analysis.

Because we wanted to explore any possible relation between variables and not falsely exclude possible true relationships, no adjustment for multiple comparisons were made. Therefore, P values $< .05$ were considered significant. If Bonferroni adjustment for multiple comparisons (N/27) had been applied, the P value would have been set to .00185. For all statistical analyses, we used Statistical Package SPSS version 18 (SPSS Inc., Chicago, IL).

Results

Demographic data, baseline characteristics, and neuropsychological test scores are shown in Table 1. Except for the motor scores of the UPDRS, there were no differences between the tremor-dominant and the PIGD-dominant groups in demographics or any of the neuropsychological variables (Table 1). Nonparametric correlations (Table 2) connected axial impairment and bradykinesia to a range of neuropsychological measures and rigidity to 1 measure of episodic memory. Tremor did not correlate with any cognitive measures. In the multiple linear regressions, with age, sex, education, and the other motor signs controlled for, the following cardinal signs contributed to the model (Table 3). Bradykinesia was significantly associated with WCST category completed ($\beta = -0.246$, $P = .022$), digit span ($\beta = -0.288$, $P = .002$), and

TABLE 1. Demographics, baseline characteristics, and neuropsychological test scores for 103 newly diagnosed, drug-naive patients with Parkinson's disease as a whole and divided into PIGD (56), tremor (34), and indeterminate (13) subtypes

Variable (n)	Total, mean ± SD	PIGD, mean ± SD	Tremor, mean ± SD	Indeterminate, mean ± SD	*P* value
Age	68.4 ± 9.2	69.5 ± 8.7	63.0 ± 9.9	69.3 ± 9.4	.492
Sex (female/male)	41/62	20/35	15/20	6/7	.731
Years of education	9.9 ± 4.1	10.4 ± 4.9	9.4 ± 2.9	9.3 ± 3.2	.894
Disease duration (mo)	22.1 ± 22.8	19.8 ± 16.2	27.0 ± 33.0	19.4 ± 10.9	.866
MMSE (102)	28.8 ± 1.3	28.6 ± 1.4	29.0 ± 1.1	28.9 ± 1.1	.496
UPDRS III	24.8 ± 10.6	27.5 ± 10.5	21.1 ± 9.9	23.5 ± 10.3	.020[a]
Tremor	2.6 ± 2.2	1.5 ± 1.5	4.0 ± 2.5	3.4 ± 1.4	.000[b]
Bradykinesia	9.1 ± 4.5	10.2 ± 4.6	7.5 ± 3.6	8.5 ± 5.0	.031[a]
Rigidity	5.9 ± 4.2	6.9 ± 4.0	4.6 ± 4.3	5.2 ± 3.5	.013[a]
Axial (PIGD)	2.5 ± 1.6	3.1 ± 1.6	1.4 ± 1.2	2.4 ± 1.4	.000[b]
Axial (bulbar)	2.3 ± 1.2	0.9 ± 0.9	1.3 ± 1.2	1.7 ± 1.3	.000[b]
Neuropsychology					
WCST					
—Category completed	1.8 ± 1.4	2.0 ± 1.5	2.4 ± 1.5	2.0 ± 1.4	.424
—Conceptual level	31.2 ± 14.2	30.5 ± 13.4	30.3 ± 15.8	35.9 ± 12.9	.524
—Perseverative errors	12.1 ± 6.5	11.9 ± 7.0	12.6 ± 6.6	11.4 ± 3.6	.768
—Nonperseverative errors	13.6 ± 7.9	14.7 ± 7.4	13.3 ± 9.0	10.1 ± 5.8	.084
Digit span (102)	13.7 ± 3.3	13.8 ± 3.2	13.5 ± 3.6	14.2 ± 2.7	.512
TMT A	58.2 ± 27.6	61.5 ± 30.8	51.2 ± 18	63.2 ± 33	.423
TMT B	160 ± 84	161 ± 88	157 ± 78	165 ± 87	.947
Verbal fluency (102)	38.4 ± 15.3	38.3 ± 16.5	37.0 ± 12.7	42.7 ± 17.2	.649
Category fluency (102)	38.2 ± 11.0	37.2 ± 11.6	38.7 ± 9.8	41.2 ± 11.1	.387
Mental control (100)	6.1 ± 2.0	6.0 ± 2.2	6.3 ± 1.6	6.2 ± 2.0	.940
BVMT					
—Total recall (100)	17.4 ± 6.9	17.4 ± 6.8	17.2 ± 6.3	18.2 ± 9.1	.923
—Delayed recall	7.0 ± 2.8	6.9 ± 2.7	7.1 ± 2.6	6.9 ± 4.0	.941
FCSRT					
—Free recall	24.8 ± 6.9	23.8 ± 7.2	25.5 ± 6.7	27.0 ± 6.2	.279
—Total recall	43.7 ± 4.8	42.9 ± 5.3	44.3 ± 4.5	45.3 ± 2.9	.135
Associative memory (98)	14.6 ± 3.6	15.0 ± 3.6	14.2 ± 3.5	14.4 ± 4.1	.580
Logical memory (94)	7.9 ± 2.8	7.5 ± 2.6	8.5 ± 2.7	7.4 ± 3.2	.262
Logical memory delay (92)	6.3 ± 2.7	5.9 ± 2.7	6.9 ± 2.5	6.3 ± 2.7	.283
Line orientation (101)	23.8 ± 4.1	23.6 ± 4.1	24.3 ± 4.1	23.6 ± 4.5	.715
BNT (97)	52.2 ± 5.5	52.3 ± 5.5	51.8 ± 5.8	53.2 ± 4.6	.743

[a]$P < .05$; [b]$P < .01$; disease duration, time between symptom onset and time of assessment; WCST, Wisconsin Card Sorting Test; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini–Mental State Examination; PIGD, postural instability and gait disorders; WCST, Wisconsin Card Sorting Test; TMT, Trail Making Test; BVMT, Brief Visual Memory Test; FCSRT, Free and Cued Selective Reminding Test; BNT, Boston Naming Test.

TMT B ($\beta = 0.197$, $P = .038$). Axial impairment was associated with line orientation ($\beta = -0.251$, $P = .016$) and BVMT total score ($\beta = -0.210$, $P = .022$). Bulbar score was associated with FSCRT free recognition ($\beta = -0.329$, $P = .001$), FSCRT total recognition ($\beta = -0.373$, $P = .001$), and mental control ($\beta = -0.299$, $P = .003$). Tremor and rigidity did not show any significant association with any cognitive measures in the regression analysis. Higher motor scores on the UPDRS (denoting more impairment) predicted worse cognitive performance in all significant correlations.

Discussion

We investigated the association between motor signs (bradykinesia, tremor, axial impairment, and rigidity) and cognitive performance in early stages of PD, prior to the start of dopaminergic treatment. We found that different cognitive domains were associated with different motor functions, that is, bradykinesia was associated with WCST category completed, TMT B, and digit span, tests considered to have an executive demand and to measure, among other things, mental flexibility and the ability to manipulate items in working memory. By separating axial impairment into 2 entities, we could reveal a discrepancy between bulbar dysfunction and postural and gait disturbances and their association with cognitive performance. Postural instability and gait disturbances were associated with visuospatial function and visuospatial memory, and bulbar dysfunction was associated with verbal episodic memory and sustained attention. After controlling for age, sex, and education, we found no

TABLE 2. Correlations (Spearman correlation coefficients) between demographic, motor, and cognitive variables for 103 newly diagnosed, drug-naive patients with Parkinson's disease

Variable (n)	Age	Sex	Education	Tremor	Bradykinesia	Rigidity	PIGD	Bulbar
Age	—							
Sex	.01	—						
Years of education	*−.59*[a]	−.06	—					
UPDRS								
Tremor	.04	−.02	−.16	—				
Bradykinesia	.13	.14	−.14	.02	—			
Rigidity	.08	.19	−.02	−.05	*.65*[a]	—		
Axial (PIGD)	*.41*[a]	.12	*−.31*[a]	.04	*.40*[a]	*.30*[a]	—	
Axial (bulbar)	.05	*.31*[a]	−.07	*−.30*[a]	*.55*[a]	*.45*[a]	*.43*[a]	—
Neuropsychology								
WCST								
—Category comp	*−.27*[a]	−.18	*.34*[a]	−.10	*−.33*[a]	−.20	*−.22*	−.18
—Conceptual level	−.17	−.14	*.29*	−.10	*−.27*	−.17	−.11	−.14
—Perseverative errors	.14	.10	*−.25*	.10	−.10	−.11	−.00	−.09
—Nonperseverative	.14	.12	−.19	−.10	*.23*	.14	.11	.12
Digit span	−.08	−.17	*.30*[a]	−.07	*−.28*[a]	−.15	−.11	−.16
TMT A	*.49*[a]	.17	*−.52*[a]	.08	*.26*[a]	.11	*.39*[a]	*.27*[a]
TMT B	*.53*[a]	.11	*−.58*[a]	.18	*.33*[a]	.18	*.39*[a]	*.32*[a]
Verbal fluency	*−.25*	−.15	*.48*[a]	−.07	*−.23*	−.11	−.18	*−.23*
Category fluency	*−.36*[a]	−.08	*.42*[a]	−.05	−.18	−.10	*−.25*	−.17
Mental control	−.12	−.11	*−.24*	.04	−.20	−.15	−.04	*−.32*[a]
BVMT								
—Total recall	*−.44*[a]	−.03	*.57*[a]	−.11	−.20	−.10	*−.36*[a]	−.18
—Delayed recall	*−.44*	−.03	*.59*[a]	−.11	*−.22*	−.12	*−.36*[a]	*−.21*
FCSRT								
—Free recall	*−.30*[a]	*−.28*[a]	*.48*[a]	−.03	*−.29*[a]	*−.21*	*−.31*[a]	*−.42*[a]
—Total recall	*−.23*	*−.22*	*.32*[a]	.01	−.19	−.13	*−.32*[a]	*−.37*[a]
Associative memory	*−.24*	−.19	*.43*[a]	−.18	−.14	−.05	*−.20*	*−.22*
Logical memory	*−.23*	*−.35*[a]	*.48*[a]	−.07	*−.23*	−.18	*−.28*[a]	*−.28*[a]
Logical memory delay	*−.31*[a]	*−.27*[a]	*.50*[a]	−.11	*−.21*	−.09	*−.34*[a]	*−.22*
Line orientation	−.15	.18	*.29*[a]	−.02	−.15	−.05	*−.25*	−.04
BNT	*−.22*	.02	*.43*[a]	−.02	−.00	−.11	−.03	*−.24*

Digits in italic, $P < .05$; Digits in italic plus [a]$P < .01$.
WCST, Wisconsin Card Sorting Test; TMT, Trail Making Test; BVMT, Brief Visual Memory Test; FCSRT, Free and Cued Selective Reminding Test; BNT, Boston Naming Test.

association between cognitive performance and tremor and rigidity.

According to Vingerhoets, bradykinesia represents the best clinical measure of the nigrostriatal lesion in PD.[30] Both bradykinesia and aspects of cognition involving mental flexibility[31] and working memory are improved by the intake of dopaminergic drugs.[3] Our result show significant associations between bradykinesia (in contrast to rigidity, tremor, and axial symptoms) and tests measuring mental flexibility and working memory. This extends previous studies indicating a shared system for slow movements and "inflexible thinking." This system may be controlled by a dopaminergic network different from the dopaminergic networks involved in tremor or rigidity. To date, the current model of the organization of the basal ganglia explains the bradykinetic features of PD, but not rigidity and tremor.[32] Bradykinesia was not associated with tests measuring cognitive functions related to more temporal-posterior parts of the brain, that is, episodic memory, visuospatial function, and verbal functioning, after controlling for age, education, and sex, nor were rigidity and tremor.

Dopamine does not seem to have the same effect on the amnesic features of the disease, for example, episodic memory and visuospatial abilities, indicating involvement of other transmitter systems than the dopaminergic for these functions. Compared with the effect on bradykinesia, tremor, and rigidity, the effect on the core symptoms of the PIGD phenotype—postural imbalance and falls—is small. Our findings of associations between visuospatial functioning and episodic memory and axial problems point to that the mechanisms behind these functions may stem from overlapping deterioration processes. This coincides well with previous studies showing that those with the PIGD phenotype have a greater tendency to develop dementia than those with other PD phenotypes,[8] and a history of falls in patients with PD is associated with reduced cholinergic activity.[33] Further, language and visuospatial deficits early in PD have also been

TABLE 3. Multiple regression analysis to assess motor signs' ability to predict cognitive performance in 103 newly diagnosed, drug-naive patients with Parkinson's disease, with age, sex, education, and other motor signs controlled for

	R^2	β	*P* value
Bradykinesia			
WCST category completed	0.232	−0.246	.022[a]
Digit span	0.214	−0.288	.002[b]
TMTB[d]	0.444	0.197	.038[a]
Axial impairment			
PIGD[d]			
Line orientation	0.187	−0.251	.016[a]
BVMT total	0.364	−0.210	.022[a]
Bulbar dysfunction[d]			
FSCRT recognition	0.330	−0.329	.001[b]
FSCRT total[c]	0.248	−0.373	.001[b]
Mental control	0.162	−0.299	.003[b]

[a]$P < .05$; [b]$P < .01$; [c]log transformation; [d]square root transformation; β, standardized beta; R^2 = how much of the variance in the dependent variable is explained by the independent variables.
WCST, Wisconsin Card Sorting Test; TMT, Trail Making Test; BVMT, Brief Visual Memory Test; FCSRT, Free and Cued Selective Reminding Test; BNT, Boston Naming Test.

connected to the development of dementia.[34] A recent review suggested that impairment in language and visuospatial domains in PD could indicate an early presence of Lewy bodies in the occipital-parietal and temporal cortices.[35]

Nondopaminergic systems seem to be of importance for the development of dementia in PD. We have previously shown in a smaller sample from the same study that patients with PD displayed lower test scores on a range of cognitive measures compared with a healthy control group and that 30% of the patients were impaired in at least 1 cognitive domain according to age-adjusted norms.[16] In the present study we found no differences between the PIGD and the tremor groups on neuropsychological variables in the early phase of PD. However, classifying patients into PIGD, tremor, and indeterminate groups may not be the best way to explore the relation between cognition and motor symptoms. This classification[20] is based on a quotient between tremor scores and gait/fall scores and does not describe the severity of a motor problem. If a cognitive domain is partly served by the same system as a motor function, the presence and severity of that motor problem will be of importance in revealing relationships, not which motor symptom is dominant.

Our study has several strengths, including patients belonging to an unselected study population, investigation early on in their disease prior to the intake of dopaminergic medication, and assessment of cognitive function by a more extensive battery than that used in other population-based studies of PD. A limitation is that the diagnosis has not been confirmed by autopsy. However, the diagnosis is likely to be correct in the vast majority of cases, as all patients were diagnosed by 2 independent movement disorder specialists, both at baseline and at follow-up after 12 months, when the effect of dopaminergic treatment could be evaluated. Another limitation is the assessments of motor symptoms. The measures in our study were clinical and relied solely on the investigators' judgment. More objective motor measures may give a better description of patients' disabilities. Also, some of the neuropsychological tests, particularly the TMT A and TMT B, may be directly affected by impaired motor function. On the other hand, our results show that bradykinesia explains a significant part of the variation in TMT B but not in TMT A. This discrepancy may indicate that the mental flexibility component of TMT B explains part of the association with bradykinesia. Furthermore, assessment of the relationship between these variables would benefit from a longitudinal approach to see if the motor and cognitive variables will decline or improve in parallel. Finally, there should be caution when interpreting the statistically significant findings. We made several comparisons, and because of this, some of the findings may be spurious. However, we wanted to explore any possible relation between motor and cognitive function in PD and not to falsely exclude possible true relationships by correcting for multiple comparisons. It is likely that our findings relating bradykinesia and axial features to specific cognitive functions are true given that several variables were controlled for and a relation was found with tests taxing similar cognitive functions for each of the motor features. Nevertheless other studies are needed to confirm our results.

In conclusion, our findings suggest that executive functions and bradykinesia may share common grounds and could support the idea that deterioration of these functions stem from dopamine depletion in brain networks different from those dopamine networks involved in tremor and rigidity. The association between axial signs and visuospatial function and episodic memory may indicate overlapping brain systems or deterioration processes related to these abilities that could possibly be related to development of PDD. Gaining more knowledge about these possible relationships can give us more information about the origin of different cognitive and motor symptoms. ■

References

1. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G; Norwegian ParkWest Study. Cognitive impairment in incident, untreated Parkinson disease. Neurology 2009;72:1121–1126.
2. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 2005;65:1239–1245.
3. Lewis SJG, Foltynie T, Blackwell AD, Robbins TW, Owen AM, Barker RA. Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. J Neurol Neurosurg Psychiatry 2005;76:343–348.
4. Obeso JA, Rodriguez-Oroz MC, Goetz CG, et al. Missing pieces in the Parkinson's disease puzzle. Nat Med 2010;16:653–661.

5. Lewis SJG, Dove A, Robbins TW, Barker RA, Owen AM. Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. J Neurosci 2003;23:6351–6356.
6. Marklund P, Larsson A, Elgh E, et al. Temporal dynamics of basal ganglia under-recruitment in Parkinson's disease: transient caudate abnormalities during updating of working memory. Brain 2009; 132:336–346.
7. Lang A, Obeso J. Challenges in Parkinson's disease: restoration of the nigrostriatal dopamine system is not enough. Lancet Neurol 2004:309–316.
8. Burn DJ, Rowan EN, Allan LM, Molloy S, T O'Brien J, McKeith IG. Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2006;77:585–589.
9. Alves G, Larsen JP, Emre M, Wentzel-Larsen T, Aarsland D. Changes in motor subtype and risk for incident dementia in Parkinson's disease. Mov Disord 2006;21:1123–1130.
10. Lyros E, Messinis L, Papathanasopoulos P. Does motor subtype influence neurocognitive performance in Parkinson's disease without dementia? Eur J Neurology 2008;15:262–267.
11. Uc EY, McDermott MP, Marder KS, et al. Incidence of and risk factors for cognitive impairment in an early Parkinson disease clinical trial cohort. Neurology 2009;73:1469–1477.
12. Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev 2006;30:1–23.
13. Williams LN, Seignourel P, Crucian GP, et al. Laterality, region, and type of motor dysfunction correlate with cognitive impairment in Parkinson's disease. Mov Disord 2007;22:141–145.
14. Kieburtz K, Mcdermott M, Como P, et al. The effect of deprenyl and tocopherol on cognitive performance in early untreated Parkinson's disease. Neurology 1994;44:1756–1759.
15. Cooper JA, Sagar HJ, Jordan N, Harvey NS, Sullivan EV. Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. Brain 1991;114:2095–2122.
16. Elgh E, Domellof M, Linder J, Edstrom M, Stenlund H, Forsgren L. Cognitive function in early Parkinson's disease: a population-based study. Eur J Neurology 2009;16:1278–1284.
17. Linder J, Stenlund H, Forsgren L. Incidence of Parkinson's disease and parkinsonism in northern Sweden: a population-based study. Mov Disord 2010;25:341–348.
18. Gibb WRG, Lees AJ. A comparison of clinical and pathological features of young- and old-onset Parkinson's disease. Neurology 1988;38:1402–1406.
19. Fahn S. Recent Development in Parkinson's Disease. New York: Macmillan Health Care Information; 1987:153–164.
20. Jankovic J, Mcdermott M, Carter J, et al. Variable Expression of Parkinson's disease—a base-line analysis of the DATATOP cohort. Neurology 1990;40:1529–1534.
21. Buschke H. Selective reminding analysis of memory and learning. J Verb Learn Verb Behav 1973;12:543–550.
22. Wechsler D. A Standardized memory scale for clinical use. J Psychol 1945;19:87–95.
23. Benedict R, Schretlen D, Groninger L, Dobraski M, Shpritz B. Revision of the Brief Visuospatial Memory Test: studies of normal performance, reliability, and validity. Psychol Assessment 1996;8: 145–153.
24. Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Motor Skill 1958:271–276.
25. Weschler D. Weschler Adult Intelligence Scale, 3rd edition (WAIS III): Test Manual. 3rd ed. New York: Psychological Corporation; 1997.
26. Kaplan E, Goodglass H, Weintraub S. Boston Naming Test. Philadelphia: Lea & Feiberg; 1983.
27. Spreen O, Strauss A. A Compendium of Neuropsychological Tests. 2nd ed. New York: Oxford University Press; 1998.
28. Benton A, Hamsher K, Varney N, Spreen O. Contributions to Neuropsychological Assessment. New York: Oxford University Press; 1983.
29. Heaton R. WCST: Computer version 2—research edition manual. Odessa, FL: Psychological Assessment Resources; 1993.
30. Vingerhoets FJG, Schulzer M, Caine DB, Snow BJ. Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion? Ann Neurol 1997;41:58–64.
31. Lewis SJG, Cools R, Robbins TW, Dove A, Barker RA, Owen AM. Using executive heterogeneity to explore the nature of working memory deficits in Parkinson's disease. Neuropsychologia 2003;41:645–654.
32. Obeso JA, Marin C, Rodriguez-Oroz C, et al. The basal ganglia in Parkinson's disease: current concepts and unexplained observations. Ann Neurol 2008;64:S30–S46.
33. Bohnen NI, Muller MLTM, Koeppe RA, et al. History of falls in Parkinson disease is associated with reduced cholinergic activity. Neurology 2009;73:1670–1676.
34. Williams-Gray CH, Foltynie T, Brayne CEG, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 2007;130:1787–1798.
35. Kehagia A, Barker R, Robbins T. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. Lancet Neurol 2010;9:1200–1213.