Neurology Asia 2014; 19(1) : 19 – 25

Neuropsychological profiles and their correlation to motor symptoms in newly diagnosed Parkinson disease patients with mild cognitive impairment

[1]Eun Joo Chung, [2]Jae-Hyeok Lee, [3]Kyngha Seok, [1]Sang Jin Kim

[1]Department of Neurology, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea; [2]Department of Neurology, Pusan National University Yangsan Hospital, Yangsan, Korea; [3]Institute of Statistical Information, Department of Data Science, Inje University, Kimhae, Korea

Abstract

Background & Objectives: Frontal executive dysfunction, which is hypothesized to reflect dorsolateral prefrontal function, predominates in Parkinson's disease (PD). Visuospatial dysfunction and episodic memory deficit, which are associated with the posterior cortical area, are critical symptoms of mild cognitive impairment in PD (PD-MCI). The first aim of this study is to investigate whether dominant cognitive deficits are caused by posterior cortical dysfunction in drug naïve, de novo PD-MCI patients. The second aim is to analyze the relationship between parkinsonian motor symptoms and the cognitive domain in these patients. *Methods:* Newly diagnosed PD patients who had not received treatment were divided into two subgroups as follows: PD-MCI (n=39) and PD patients with normal cognition (PD-NC) (n=39). Various neuropsychological tests were performed in all of the patients. The parkinsonian motor subscores were divided into tremor, rigidity, axial impairment, bulbar dysfunction and bradykinesia by the UPDRS motor scores. *Results:* Verbal episodic memory (immediate recall; $p = 0.0001$, delayed recall; $p = 0.0001$, recognition; $p = 0.003$), visual episodic memory (immediate recall; $p = 0.0001$, delayed recall; $p = 0.002$) and visuospatial function ($p = 0.046$) were lower in the PD-MCI group than in the PD-NC group. In the analysis of the correlation of the motor components to the cognitive tests, impairment in visual episodic memory correlated with axial symptoms (immediate recall; r = -0.441, p = 0.021, delayed recall; r = -0.393, p = 0.042). The contrast program test correlated with bradykinesia ($r = -0.479$, $p = 0.013$)
Conclusion: Episodic memory and visuospatial dysfunction, which reflect impairment of the posterior cortical area, are critical cognitive deficits, and memory impairment is correlated with the axial symptoms that are associated with non-dopaminergic pathways in newly diagnosed PD-MCI patients.

INTRODUCTION

Although Parkinson's disease[1] is classically defined as a motor disorder[2], non-motor symptoms (NMS) are an important part of the clinical features of PD.[3] Cognitive dysfunction is one of the NMS that could occur even in the early stages of PD[4-7], and PD patients present with a wide spectrum of cognitive dysfunction ranging from mild cognitive impairment (PD-MCI) to PD dementia (PDD).[7-10]

Despite the heterogeneous characteristics of cognitive deficit in PD[8], deficits of memory, visuospatial ability and executive functions are consistent findings, regardless of the presence or absence of dementia.[5,11,12] Initially, some reports of cognitive impairment in PD have been focused on frontal-type dysfunction, which is associated with disconnection of the fronto-striatal circuits, particularly in newly diagnosed and non-medicated PD patients.[13-16] The frontal executive dysfunction in PD, which involves manipulation of information within the working memory, has been related to specific under activation in regions of the basal ganglia (BG) and/or frontal cortex.[17,18] The executive and working memory deficits in the early stage of PD is similar to those observed in frontal lobe-damaged patients.[19] A process leading to dementia such as PDD is associated with more posterior cortical deficits resulting in aphasia, apraxia and agnosia, which resemble deficits observed in patients with temporal lobe damage and cortical dementia.[19]

Different patterns of cognitive impairments that are associated with the various PD motor types have been reported.[20,21] Bradykinesia and rigidity, which are controlled by the dopaminergic

Address correspondence to: Sang Jin Kim, Department of Neurology, Busan Paik Hospital, Inje University College of Medicine, Gaegeum-2 dong, Jin-gu, Busan, 614-735, South Korea. Tel: +82 51 890 6425; Fax: +82 51 895 6367; E-mail: jsk502@hotmail.com

networks, were associated with frontal executive dysfunction.[20] Whereas axial impairment such as postural instability, gait disturbances and/or bulbar dysfunction are associated with visuospatial function and episodic memory, which indicate dysfunction of the posterior region.[20] Posterior cortical deficits are associated with the axial motor symptoms of PD, such as postural and gait dysfunction, that reflect a non-dopaminergic pathology.[19] Prominent axial impairment in PD patients could be related to the faster conversion of cognitive decline in PDD.[20]

The first aim of this study is to investigate whether the cognitive deficits in newly diagnosed, drug naive PD patients with MCI are associated with temporoparietal dysfunction or frontal dysfunction. The second aim is to analyze the correlation between motor signs and cognition domains.

METHODS

Patients

One hundred and ten patients were newly diagnosed with PD according to the clinical criteria of the UK Parkinson's Disease Society Brain Bank.[22] The patients had received no treatment with anti-Parkinson's drugs such as dopaminergic agents, anticholinergics, amantadine or MAO-B inhibitors. The motor severity of PD was determined by the motor scale (part III) of the United Parkinson's Disease Rating Scale.[1] All of the PD patients were evaluated with the Hoehn-Yahr (H-Y) scale. Seventy-eight of the 110 patients were included by the propensity score matching method adjusting for age and education. We diagnosed the patients into the PD-MCI group (n = 39) according to the Movement Disorder Society Task Force (MDS-TF) guidelines[7], which specify that PD-MCI patients should not show evidence of abnormality in the activities of daily living (ADL), judged by an ADL scale.[23] The PD patients with normal cognition (PD-NC) (n = 39) did not meet the criteria for PD-MCI or PDD.[7,10] We divided the patients into three motor subtypes: akinetic-rigid (ART), mixed (MT) and tremor dominant (TDT)[24], according to the previous classification based on the UPDRS motor score. The UPDRS scores were divided into subscores for tremor, rigidity, bradykinesia, axial impairment (postural instability and gait disturbances) and bulbar dysfunction. The divisions were based specifically on the following UPDRS items: the sum of 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 a chair, posture, gait and postural stability); and the sum of items 18 and 19 for the bulbar score (speech and facial expression).[20,25] The patients were excluded for presentation of atypical features, secondary causes of Parkinsonism, evidence of focal brain lesions, diffuse white matter hyperintensities or multiple lacunes in the BG by MRI. Possible medical comorbidities were excluded by laboratory tests including a thyroid function test, vitamin B12 and folic acid levels and a serological test of syphilis.

The protocol was approved by the Institutional Review Board of the Busan Paik Hospital of the Inje University Medical School. We obtained written informed consent from all of the subjects participating of this study.

Neuropsychological assessment

For the diagnosis of PD-MCI and PD-NC, we used the Seoul Neuropsychological Screening Battery (SNSB).[26,27] The SNSB covers the following cognitive subsets: attention (forward and backward digit span and letter-cancellation tests); language and related functions (the Korean version of the Boston Naming Test [K-BNT][28] and calculation); visuospatial function (drawing an interlocking pentagon and the Rey Complex Figure Test [RCFT]); verbal memory (3-word registration and recall and the Seoul Verbal Learning Test [SVLT]); visual memory (the RCFT, immediate recall, 20-minute delayed recall and recognition); and frontal executive function (motor impersistence, the contrasting program, the go-no-go test, fist-edge-palm, alternating hand movement, alternating square and triangle, the Luria loop, the phonemic and semantic Controlled Oral Word Association Test [COWAT] and the Stroop test).[26,29,30] Cognitive dysfunction was defined as a score below the 16th percentile of the norm for the language, memory and visuospatial domains. The frontal/executive function tests were classified into three groups as follows: motor executive function, COWAT and the Stroop test. We considered attention and frontal executive function to be abnormal if at least two tests or groups were abnormal.

All of the patients were administered the Korean version of the Mini Mental State Examination (K-MMSE), the clinical dementia rating (CDR), the global deterioration scale (GDS), the Korean

version of the Montreal Cognitive Assessment (MoCA-K) and the Frontal Assessment Battery (FAB).[31-37]

A neuropsychologist administered all of the neuropsychological assessments.

Statistical analysis

The statistical comparison of the parametric clinical items between the PD-MCI and PD-NC groups was performed with the chi square test and the *t*-test. The nonparametric variables were analyzed by Fisher's exact test and the Wilcoxon signed-rank test. The SNSB scores were adjusted for age and education. The relationship between the cognitive subsets and the parkinsonian motor symptoms was evaluated with Pearson's correlation and/or Spearman's correlation test after controlling for age, sex, education and depression. $P < 0.05$ was considered statistically significant.

RESULTS

There were no significant differences in the gender, age, age at onset, disease duration, education, UPDRS motor scores, H-Y stage, parkinsonian motor subscores and motor subtypes between the PD-NC and PD-MCI patients (Table 1). There were no statistical differences in the K-MMSE, FAB and depression between the PD-NC and PD-MCI patients. The MoCA-K (20.9 ± 4.7) of the PD-MCI patients showed a significantly lower score than that (24.2 ± 3.8) of the PD-NC ($p = 0.005$) (Table 1). The CDR and GDS showed worse scores for the PD-MCI patients compared with the PD-NC patients ($p = 0.003$ and 0.0001, respectively) (Table 1).

Neuropsychological profiles

In the SNSB, all of the variables for attention, the K-BNT for language, recognition of visual episodic memory, and all of the tests for frontal

Table 1: The demographic characteristics of the Parkinson disease with mild cognitive impairment (PD-MCI) and Parkinson disease with normal cognition (PD-NC) patients

	PD-MCI (n = 39)	PD-NC (n = 39)	p-value
Sex (male, %)	46.2	43.6	1.0
Age (y, mean ± SD)	68.15 ± 7.6	67.2 ± 8.9	0.603
Age at onset (y, mean ± SD)	66.4 ± 7.5	65.5 ± 9.0	0.634
Disease duration (m, mean ± SD)	18.8 ± 23.1	19.2 ± 20.3	0.941
Education (y, mean ± SD)	8.6 ± 4.6	7.5 ± 4.4	0.989
UPDRS III motor score (mean ± SD)	22.8 ± 11.0	20.6 ± 8.6	0.333
Motor subscores (mean ± SD)			
rigidity	5.1 ± 3.4	3.9 ± 2.7	0.091
tremor	2.8 ± 2.7	3.4 ± 2.6	0.15
bradykinesia	7.4 ± 4.0	6.9 ± 3.5	0.599
axial impairment sign	3.3 ± 2.4	2.6 ± 2.2	0.13
bulbar sign	1.9 ± 1.1	2.0 ± 1.2	0.806
H & Y stage (mean ± SD)	2.4 ± 0.5	2.3 ± 0.6	0.538
Motor subtypes (%)			
Akinetic-rigid	47.1	30.8	
Mixed	35.3	46.2	
Tremor dominant	17.6	23.1	
K-MMSE	26.2 ± 3.1	26.8 ± 3.3	0.198
CDR	0.47 ± 0.11	0.33 ± 0.24	**0.003**
GDS	2.9 ± 0.5	2.1 ± 0.8	**0.0001**
MoCA-K	20.9 ± 4.7	24.2 ± 3.8	**0.005**
FAB	14.1 ± 3.2	14.6 ± 2.5	0.672
Geriatric depression score	17.3 ± 8.7	17.4 ± 7.6	0.969

K-MMSE, Korean version of the Mini Mental State Examination; MoCA-K, Korean version of the Montreal Cognitive Assessment; CDR, Clinical dementia rating; GDS, Global deterioration scale; FAB, Frontal assessment battery

executive function except the Luria loop were not significantly different between the PD-NC and PD-MCI patients (Table 2). Verbal episodic memory (immediate recall; $p = 0.0001$, delayed recall; $p = 0.0001$, recognition; $p = 0.003$), some variables of visual episodic memory (immediate recall; $p = 0.0001$, delayed recall; $p = 0.002$) and visuospatial function ($p = 0.046$) in the PD-MCI patients were less than those of the PD-NC patients (Table 2). There were higher abnormal percentages of calculation and drawing of the Luria loop ($p = 0.013$ and $p = 0.029$, respectively) in the PD-MCI group compared with the PD-NC group (Table 2).

Correlation between the cognitive subsets and motor symptoms in the PD-MCI patients

After age, sex, education and depression were controlled, the immediate and delayed recall of visual episodic memory ($r = -0.441$, $p = 0.021$ and $r = -0.393$, $p = 0.042$, respectively) correlated with the axial symptoms, and the contrast program test correlated with bradykinesia ($r = -0.479$, $p = 0.013$) (Table 3).

DISCUSSION

Neuropsychological features between PD-MCI and PD-NC

The MMSE[38] and MoCA[32] tests are the most commonly used brief screening instruments in patients with cognitive impairment. The MoCA test is a screening tool for PD-MCI[39,40], and the FAB is a useful tool for the screening of

Table 2: The characteristics of the neuropsychological profiles in the Parkinson's disease patients with mild cognitive impairment (PD-MCI) and Parkinson disease with normal cognition (PD-NC) groups

	PD-MCI (n = 39)	PD-NC (n = 39)	p-value
forward digit span	5.1 ± 1.6	5.5 ± 1.4	0.339
backward digit span	3.2 ± 0.8	3.5 ± 1.0	0.204
abnormal letter cancellation (%)	12.8	2.6	0.2
K-BNT	41.8 ± 9.1	44.9 ± 11.8	0.19
abnormal calculation (%)	28.2	5.1	**0.013**
RCFT	27.0 ± 9.6	30.8 ± 6.5	**0.046**
verbal immediate recall	14.9 ± 4.6	20.7 ± 8.1	**0.0001**
verbal delay recall	3.3 ± 2.2	6.4 ± 3.0	**0.0001**
verbal recognition	19.5 ± 1.8	20.5 ± 2.8	**0.003**
visual immediate recall	8.8 ± 6.1	14.1 ± 6.9	**0.0001**
visual delay recall	8.8 ± 6.3	13.5 ± 6.7	**0.002**
visual recognition	18.4 ± 2.4	19.4 ± 2.2	0.071
abnormal contrasting program (%)	20.5	2.6	0.29
abnormal go-no-go test (%)	12.8	7.7	0.711
contrast program score	18.2 ± 4.9	19.5 ± 3.3	0.18
go no go test score	17.9 ± 5.4	19.2 ± 3.6	0.055
abnormal fist-edge-palm (%)	46.2	35.9	0.49
abnormal AHM (%)	17.9	12.8	0.755
abnormal AST (%)	28.2	10.3	0.083
abnormal Luria loop (%)	20.5	2.6	**0.029**
COWAT; fluency			
semantic animal	12.7 ± 3.4	14.1 ± 5.2	0.234
semantic supermarket	13.9 ± 4.8	15.7 ± 5.8	0.147
phonemic, sum	17.7 ± 11.5	21.6 ± 12.7	0.168
Stroop color reading	67.4 ± 27.8	78.3 ± 24.8	0.088

K-BNT, Korean-Boston Naming test; RCFT, Rey complex figure test; SVLT, Seoul verbal learning test; AHM, alternating hand movement; AST, alternating square and triangle; COWAT, controlled oral word association test
The clinical variables expressed as the mean±mea indicate that a higher score indicates better performance. An abnormal frequency of clinical parameters indicates that a higher score indicates worse performance.

Table 3: The relationship between the cognitive subtests and parkinsonian motor symptoms in the Parkinson disease with mild cognitive impairment (PD-MCI) patients

	tremor	rigidity	axial	bulbar	bradykinesia
digit forwards	r = 0.103	r = -0.09	r = 0.126	r = 0.088	r = -0.102
	p = 0.608	p = 0.654	p = 0.531	p = 0.664	p = 0.611
digit backwards	r = -0.007	r = 0.205	r = -0.007	r = 0.062	r = 0.038
	p = 0.973	p = 0.304	p = 0.972	p = 0.76	p = 0.852
K-BNT	r = 0.026	r = 0.109	r = 0.055	r = 0.031	r = 0.169
	p = 0.898	p = 0.59	p = 0.784	p = 0.877	p = 0.4
calculation	r = 0.103	r = -0.125	**r = -0.373**	r = -0.151	r = -0.196
	p = 0.61	p = 0.534	**p = 0.059**	p = 0.451	p = 0.328
RCFT	r = 0.063	r = -0.238	r = -0.064	r = -0.12	r = -0.182
	p = 0.756	p = 0.232	p = 0.752	p = 0.552	p = 0.363
visual memory					
immediate recall	r = -0.113	r = -0.324	**r = -0.441**	r = -0.224	r = -0.243
	p = 0.575	p = 0.099	**p = 0.021**	p = 0.26	p = 0.222
delayed recall	r = -0.183	r = -0.361	**r = -0.393**	r = -0.244	r = -0.278
	p = 0.36	p = 0.064	**p = 0.042**	p = 0.219	p = 0.161
recognition	r = -0.301	r = 0.063	r = -0.197	r = -0.037	r = -0.087
	p = 0.126	p = 0.756	p = 0.325	p = 0.854	p = 0.666
verbal memory,					
immediate recall	r = 0.002	r = -0.206	r = -0.111	r = -0.31	r = -0.074
	p = 0.992	p = 0.304	p = 0.582	p = 0.116	p = 0.715
delayed recall	r = -0.237	r = 0.211	r = 0.09	r = -0.044	r = 0.168
	p = 0.234	p = 0.291	p = 0.656	p = 0.828	p = 0.403
recognition	r = -0.192	r = 0.001	r = 0.093	r = -0.155	r = 0.083
	p = 0.337	p = 0.996	p = 0.644	p = 0.441	p 0.68
contrasting program	r = 0.183	r = 0.369	r = 0.315	r = 0.327	**r = 0.479**
	p = 0.371	p = 0.064	p = 0.117	p = 0.103	**p = 0.013**
go-no-go	r = 0.024	r = 0.179	r = 0.261	r = 0.199	r = 0.351
	p = 0.906	p = 0.381	p = 0.198	p = 0.329	p = 0.079
semantic fluency					
animal	r = -0.083	r = -0.339	r = -0.069	r = -0.074	r = -0.058
	p = 0.682	p = 0.083	p = 0.731	p = 0.714	p = 0.774
supermarket	r = -0.116	r = -0.205	r = 0.058	r = -0.032	r = -0.003
	p = 0.564	p = 0.304	p = 0.773	p = 0.873	p = 0.988
phonemic fluency	r = 0.035	r = -0.232	r = -0.081	r = -0.156	r = -0.044
	p = 0.861	p = 0.243	p = 0.688	p = 0.437	p = 0.826
Stroop color reading	r = -0.022	r = -0.34	r = -0.088	r = -0.384	r = -0.353
	p = 0.922	p = 0.112	p = 0.69	p = 0.071	p = 0.099

K-BNT, Korean-Boston Naming test; RCFT, Rey Complex Figure Test

executive dysfunction in PD.[41] The CDR and GDS demonstrate the severity of cognition loss, the activities of daily living and the abnormal behaviors of patients with dementia to testers and are not affected by the educational level of the patients.[34-36] MoCA-K in this study showed a significant difference between the PD-MCI and the PD-NC patients, in contrast to the K-MMSE and FAB scores. As a result of a previous study[42], our study shows a significant difference in the CDR and GDS between the PD-MCI and the PD-NC patients.

The neuropsychological profiles showed significantly lower scores for the visuospatial and memory function of the PD-MCI patients than those of PD-NC patients. Because memory function and visuospatial function were generally associated with the temporoparietal section of brain, this result suggests the early involvement of posterior cortical regions as dominant lesions of cognition in PD-MCI patients, even in the de novo stage. These findings are supported by a [^{18}F]-fluorodeoxyglucose positron emission tomography study.[42] A high frequency of abnormal

calculation in PD-MCI patients is typically associated with lesions of the posterior brain such as the Brodmann area 40 and angular gyrus at the junction between the temporoparietal cortex.[43,44]

This result suggests a probability that PD-MCI, which can be progress to dementia, could be associated with a posterior cortical deficit[19], although general cognitive impairment of early PD is associated with frontal executive dysfunction.[5]

Correlations between the cognitive tests and motor signs in the PD-MCI patients

We recognized that axial symptoms are correlated with immediate and delayed recall for visual episodic memory. These findings agreed with results of a previous report, in which axial dysfunctions such as postural instability and gait disturbances were associated with visual episodic memory.[20] Our result is supported by a reduction of cerebral glucose uptake in extensive posterior cortical areas, particularly in the occipitoparietal junction and temporal cortex of patients with PD-MCI.[45]

Bradykinesia is correlated with contrasting program measures mental flexibility and working memory, and a contrast program test is considered to require executive demand.[20] Our results suggest that memory impairment correlates with the axial symptoms that reflect the non-dopaminergic pathways, whereas executive dysfunction is associated with bradykinesia, which is connected with the dopaminergic pathways. Episodic memory impairment and visuospatial dysfunction are major cognitive problems in patients with untreated, newly diagnosed PD-MCI, which reflects posterior cortical dysfunction. Memory impairment correlates with axial symptoms, and each motor symptom associated with PD-MCI could be connected to various cognitive domains.

ACKNOWLEDGEMENT

This work was supported by grant from Inje University in 2013.

DISCLOSURE

Conflict of interest: None

REFERENCES

1. Fahn S, Elton ER, Members of the UPDRS Development Committee. The United Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Golstein M, eds. Recent development in Parkinson's disease. New York: Macmillan Health Care Information; 1987: 153-63.
2. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol* 1999; 56(1):33-9.
3. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol* 2006; 5(3): 235-45.
4. Erro R, Picillo M, Vitale C, *et al*. Non-motor symptoms in early Parkinson's disease: a 2-year follow-up study on previously untreated patients. *J Neurol Neurosurg Psychiatry* 2013; 84(1):14-7.
5. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology* 2005; 65(8):1239-45.
6. Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain* 2004; 127(Pt 3):550-60.
7. Litvan I, Goldman JG, Troster AI, *et al*. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord* 2012; 27(3):349-56.
8. McKinlay A, Grace RC, Dalrymple-Alford JC, Roger D. Cognitive characteristics associated with mild cognitive impairment in Parkinson's disease. *Dement Geriatr Cogn Disord* 2009; 28(2):121-9.
9. Barton B, Grabli D, Bernard B, *et al*. Clinical validation of Movement Disorder Society-recommended diagnostic criteria for Parkinson's disease with dementia. *Mov Disord* 2012; 27(2):248-53.
10. Dubois B, Burn D, Goetz C, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. *Mov Disord* 2007; 22(16):2314-24.
11. Dubois B, Pillon B. Cognitive deficits in Parkinson's disease. *J Neurol* 1997; 244(1): 2-8.
12. Janvin C, Aarsland D, Larsen JP, Hugdahl K. Neuropsychological profile of patients with Parkinson's disease without dementia. *Dement Geriatr Cogn Disord* 2003; 15(3):126-31.
13. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 1986; 9:357-81.
14. Owen AM, James M, Leigh PN, *et al*. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain* 1992; 115 (Pt 6):1727-51.
15. Lees AJ, Smith E. Cognitive deficits in the early stages of Parkinson's disease. *Brain* 1983; 106 (Pt 2):257-70.
16. Zgaljardic DJ, Borod JC, Foldi NS, Mattis P. A review of the cognitive and behavioral sequelae of Parkinson's disease: relationship to frontostriatal circuitry. *Cogn Behav Neurol* 2003; 16(4):193-210.
17. 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(Pt 2):336-46.
18. Lewis SJ, 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(15):6351-6.
19. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 2007; 130(Pt 7): 1787-98.
20. Domellof ME, Elgh E, Forsgren L. The relation between cognition and motor dysfunction in drug-naive newly diagnosed patients with Parkinson's disease. *Mov Disord* 2011; 26(12):2183-9.
21. Burn DJ, Rowan EN, Allan LM, Molloy S, O'Brien JT, 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(5):585-9.
22. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992; 55(3):181-4.
23. Cho H YD, Shon YM, *et al*. Abnormal integrity of corticocortical tracts in mild cognitive impairment: a diffusion tensor imaging study. *J Korean Med Sci* 2008; 23: 477-83.
24. Jankovic J, McDermott M, Carter J, *et al*. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. *Neurology* 1990; 40(10):1529-34.
25. 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(18):1469-77.
26. Kang Y ND. Seoul Neuropsychological Screening Battery. Incheon: Human Brain Research & Consulting Co.; 2003.
27. Lee JE, Park HJ, Park B, *et al*. A comparative analysis of cognitive profiles and white-matter alterations using voxel-based diffusion tensor imaging between patients with Parkinson's disease dementia and dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry*. 2010; 81(3):320-6.
28. Kim H, Na DL. Normative data on the Korean version of the Boston Naming Test. *J Clin Exp Neuropsychol* 1999; 21(1):127-33.
29. Lee JE, Park HJ, Song SK, Sohn YH, Lee JD, Lee PH. Neuroanatomic basis of amnestic MCI differs in patients with and without Parkinson disease. *Neurology* 2010; 75(22):2009-16.
30. Stroop J. Studies of interference in serial verbal reactions. *J Exp Psychol* 1935; 18: 643-62.
31. Kang K, Na DL, Hahn S. The Validity study on the Korean Mini-Mental State Examination (K-MMSE) in dementai patients. *J Korean Neurol Assoc* 1997;15:300-7.
32. Nasreddine ZS, Phillips NA, Bedirian V, *et al*. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; 53(4):695-9.
33. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology* 2000; 55(11):1621-6.
34. Fillenbaum GG, Peterson B, Morris JC. Estimating the validity of the clinical Dementia Rating Scale: the CERAD experience. Consortium to Establish a Registry for Alzheimer's Disease. *Aging (Milano)* 1996; 8(6):379-85.
35. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993; 43(11):2412-4.
36. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982; 139(9):1136-9.
37. Lee JY, Dong Woo L, *et al*. Brief screening for mild cognitive impairment in elderly outpatient clinic: validation of the Korean version of the Montreal Cognitive Assessment. *J Geriatr Psychiatry Neurol* 2008; 21(2):104-10.
38. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12(3):189-98.
39. Gill DJ, Freshman A, Blender JA, Ravina B. The Montreal cognitive assessment as a screening tool for cognitive impairment in Parkinson's disease. *Mov Disord* 2008; 23(7): 1043-6.
40. Hoops S, Nazem S, Siderowf AD, *et al*. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. *Neurology* 2009; 73(21):1738-45.
41. Lima CF, Meireles LP, Fonseca R, Castro SL, Garrett C. The Frontal Assessment Battery (FAB) in Parkinson's disease and correlations with formal measures of executive functioning. *J Neurol* 2008; 255(11):1756-61.
42. Hosokai Y, Nishio Y, Hirayama K, *et al*. Distinct patterns of regional cerebral glucose metabolism in Parkinson's disease with and without mild cognitive impairment. *Mov Disord* 2009; 24(6):854-62.
43. Levy LM, Reis IL, Grafman J. Metabolic abnormalities detected by 1H-MRS in dyscalculia and dysgraphia. *Neurology* 1999; 53(3):639-41.
44. Mayer E, Martory MD, Pegna AJ, Landis T, Delavelle J, Annoni JM. A pure case of Gerstmann syndrome with a subangular lesion. *Brain* 1999; 122(6):1107-20.
45. Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *Lancet Neurol* 2010; 9(12):1200-13.