



# Baseline cognitive profile is closely associated with long-term motor prognosis in newly diagnosed Parkinson's disease

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## Abstract

**Objectives** To investigate the association between cognitive function at baseline and the progression of motor disability in Parkinson's disease (PD).

**Methods** We consecutively enrolled 257 drug-naïve patients with early-stage PD (follow-up > 2 years) who underwent a detailed neuropsychological test at initial assessment. Factor analysis was conducted to yield four cognitive function factors and composite scores thereof: Factor 1 (*visual memory/visuospatial*), Factor 2 (*verbal memory*), Factor 3 (*frontal/executive*), and Factor 4 (*attention/working memory/language*). The global cognitive composite score of each patient was calculated based on these factors. Subsequently, we assessed the effect of baseline cognitive function on long-term motor outcomes, namely levodopa-induced dyskinesia (LID), wearing-off, freezing of gait (FOG), and rate of longitudinal increases in levodopa-equivalent dose (LED).

**Results** Cox regression analysis demonstrated that higher Factor 3 (frontal/executive) composite scores (i.e., better cognitive performance) were associated with early development of LID [hazard ratio (HR), 1.507;  $p = 0.003$ ], whereas higher Factor 1 (*visual memory/visuospatial*) composite scores (i.e., better cognitive performance) were associated with a lower risk for FOG (HR 0.683;  $p = 0.017$ ). We noted that higher global cognitive composite scores were associated with a lower risk for developing FOG (HR 0.455;  $p = 0.045$ ). The linear mixed model demonstrated that higher global cognitive composite scores and better cognitive performance in *visual memory/visuospatial* function were associated with slower longitudinal increases in LED.

**Conclusions** These findings suggest that baseline cognitive profiles have prognostic implications on several motor aspects in patients with PD.

**Keywords** Cognition · Factor analysis · Parkinson's disease · Prognosis

## Introduction

Cognitive impairment frequently occurs in the early stages of Parkinson's disease (PD) [1]. The presence of early cognitive decline signals a high risk for the subsequent progression to dementia, which adversely affects the morbidity and mortality in patients with PD [2, 3]. Moreover, ample evidence suggests that cognitive impairment at baseline is a predictor of accelerated motor decline and increasing disability [4–6]. Conversely, the presence of axial motor features is associated with a faster rate of cognitive decline and an increased risk of incident dementia [7–9]. The association between cognitive dysfunction and motor deficits in PD may indicate common or parallel underlying pathological processes [8].

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However, there is little evidence of the impact of individual cognitive domain on the progression of motor disability in PD. Cognitive impairment is remarkably heterogeneous among patients with PD, and the neural basis of cognitive decline varies for each of the cognitive function domains [10]. Some research has suggested that executive dysfunction is secondary to dopamine deficiency in frontostriatal circuits [11], while deficits in memory and visuospatial function domains are related to cholinergic deficits in the posterior cortical areas: this is known as the dual syndrome hypothesis [12–14]. Deficits in attention also appear to have overlapping cholinergic correlates with memory dysfunction in PD [15]. Moreover, the progression of motor deficits in PD results from two distinct processes [6], namely gradual degeneration of nigrostriatal dopaminergic neurons (i.e., the progression of levodopa-responsive symptoms) and widespread degeneration of the extra-nigrostriatal system (i.e., the progression of levodopa-nonresponsive symptoms). The longitudinal effects of cognitive dysfunction on motor outcomes could vary depending on the affected cognitive domain and the clinical parameters measured according to the underlying pathogenic mechanisms. Accordingly, in this study, we aimed to explore the cognitive profile specifically relevant to several parameters for disease progression related to motor aspects in PD [16], including levodopa-induced dyskinesia (LID), wearing-off, freezing of gait (FOG), and longitudinal requirement of dopaminergic medications.

## Methods

### Subjects

In the patient cohort enrolled in our previous study that assessed the effect of striatal dopamine depletion on cognition in patients with drug-naïve non-demented PD ( $n=311$ ) [17], we reviewed the follow-up data of patients treated with a PD medication for at least 2 years. PD was diagnosed according to the clinical diagnostic criteria proposed by the United Kingdom Parkinson's Disease Society Brain Bank [18] and the presence of a PD drug response at follow-up. Patients ( $n=9$ ) who presented additional atypical features (e.g., ataxia, prominent autonomic dysfunction, vertical gaze limitation, early fall, cortical sensory loss, and early dementia) during follow-up were excluded. All patients showed decreased dopamine transporter (DAT) availability in the posterior putamen on [ $^{18}\text{F}$ ] N-(3-fluoropropyl)-2 $\beta$ -carbon ethoxy-3 $\beta$ -(4-iodophenyl) nortropane positron emission tomography (FP-CIT PET) scans. A detailed neuropsychological test [i.e., the Seoul Neuropsychological Screening Battery (SNSB) [19]] was administered to all patients as an initial diagnostic workup. Among all of the patients, 36 lost to follow-up within 2 years were excluded

to reduce the likelihood of including patients with atypical Parkinsonism. Nine patients with illiteracy were also excluded from the study due to many restrictions on cognitive assessment. Finally, a total of 257 patients with drug-naïve non-demented PD (follow-up > 2 years) were enrolled in the present study. Parkinsonian motor deficit severity was assessed using the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III). Depression was evaluated using the Beck Depression Inventory (BDI). The patients were classified into tremor-dominant, postural instability/gait difficulty (PIGD), and indeterminate motor subtypes based on UPDRS scores [20]. PD medication doses were calculated as levodopa-equivalent doses (LEDs) [21].

Following the diagnosis of PD, patients visited the outpatient clinic at 3-month intervals, and two movement disorders specialists (SYH and LPH) assessed the development of LID [22], wearing-off [23], or FOG [24] based on history-taking and clinical impression (see Supplementary Methods) and adjusted the dose of the PD medication for effective control of symptoms. This study was approved by the Yonsei University Severance Hospital Institutional Review Board. The need for informed consent was waived because of the retrospective nature of the study.

### Neuropsychological assessment

All subjects underwent a comprehensive neuropsychological test battery (SNSB) widely used in Korea [19], which covers five cognitive domains: attention and working memory (forward and backward digit span task), language and related functions [the Korean version of the Boston Naming Test (K-BNT), calculation, and praxis], visuospatial function [the Rey Complex Figure Test (RCFT) copy and interlocking pentagon], verbal and visual memory [immediate recall/delayed recall/recognition test using the Seoul Verbal Learning Test (SVLT) for verbal memory; immediate recall/delayed recall/recognition test using the RCFT for visual memory], and frontal/executive function [contrasting program, go/no-go test, the Controlled Oral Word Association Test (COWAT), and the Stroop test]. Among scorable subtests of the SNSB, age and education-specific  $z$ -scores for the following 14 items were automatically calculated according to the established criteria when developing the SNSB: forward digit span task; backward digit span task; K-BNT; RCFT copy; the immediate recall, delayed recall, and recognition items using the SVLT for verbal memory; the immediate recall, delayed recall, and recognition items using the RCFT for visual memory; COWAT for animal names, COWAT for supermarket items, and COWAT for phonemic fluency; and the Stroop color reading test.

## Assessment of dementia conversion during follow-up

After diagnosis of PD, patients or their caregivers were asked questions about daily functioning at every visit. Additionally, patients with PD underwent serial cognitive assessment using the Korean version of the Mini-Mental State Examination and Clock Drawing Test at an interval of 1 year (Level I tests) [25]. In cases of definite cognitive decline or evidence of impairments in daily life due to cognitive changes (Level I), a detailed neuropsychological battery (i.e., the SNSB [19]) was subsequently conducted to specify the pattern of cognitive deficits and diagnose PD with dementia (PDD) at Level II in most patients [25]. The diagnosis of PDD was made by achieving consensus between two neurologists and one neuropsychologist [26], according to the clinical diagnostic criteria proposed by the Movement Disorder Society Task Force [27, 28]. Patients who converted to PDD showed cognitive impairment in at least two of the core cognitive domains. All patients with PDD showed evidence of abnormalities in activities of daily living [29, 30].

## Quantitative analyses of <sup>18</sup>F-FP-CIT PET images

Image acquisition and processing were performed according to previously described methodology (Supplementary Methods) [17]. The volumes of interest (VOI) for the bilateral posterior putamen and one occipital VOI [i.e., calcarine fissure and surrounding cortex (V1) [31]] were drawn on the <sup>18</sup>F-FP-CIT template using MRICro version 1.37 (Chris Rorden, Columbia, SC). DAT availability in the posterior putamen was estimated using the specific/nonspecific binding ratio as a surrogate, which was defined as follows: (mean standardized uptake value of the posterior putamen VOIs—mean standardized uptake value of the occipital VOI)/(mean standardized uptake value of the occipital VOI).

## Statistical analysis

Factor analysis was conducted based on the 14 tests derived from the SNSB [19] to reduce the redundancy of neuropsychological subtests and to determine the cognitive composite cores using the principal components method of factor extraction and the Varimax method of rotation [26]. The factor analysis yielded four cognitive function factors with eigenvalues > 1.0, which accounted for 63.8% of the variance in the cognitive performance of the subjects [32]. The component score coefficients were used to calculate the composite scores of the four cognitive function factors of each subject (Supplementary Table 1). Additionally, using the four cognitive function factors in an integrative formula,

we calculated the global cognitive composite score of each patient with PD.

Subsequently, the effects of the composite scores of the four factors on the development of LID, wearing-off, and FOG were assessed using Cox regression analysis. Survival duration was defined as the time from treatment initiation to the date of the clinic visit when LID or wearing-off was first observed or reported (for patients with LID or wearing-off) or the time from parkinsonian symptom onset to the date of the clinic visit when FOG was first observed or reported (for patients with FOG) or the last clinic visit (for patients without these events). Cox regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the development of LID or wearing-off according to neuropsychological profiles (i.e., composite scores of the four cognitive function factors) while adjusting for age, sex, DAT availability in the posterior putamen, BDI scores, and LED, which are known to be major risk factors for these events. The effect of the composite scores of the four cognitive function factors on the development of FOG was also assessed using Cox regression analysis while adjusting for age, sex, DAT availability in the posterior putamen, BDI scores, motor subtype (PIGD or not [33]), and LED. A log-minus-log plot and a time-dependent covariate analysis revealed that the assumption of proportionality was reasonable. There was no significant correlation among the composite scores of the cognitive function factors, and all these factors were included as predictor variables without concerns of multi-collinearity.

A linear mixed model was used to assess the longitudinal changes in LED over time, assuming that slopes were fixed and intercepts varied across subjects (i.e., a random intercepts model). Ten fixed effects were included in the model: nine were between-subject effects (age, sex, DAT availability in the posterior putamen, UPDRS-III scores, BDI scores, and composite scores of the four cognitive function factors) and one was a within-subject effect (time). The subject factor was considered a random effect. The effects of baseline cognitive function on the changes in LED over time were tested with (time × composite score of cognitive function factor) interaction terms. A significant interaction between time and cognitive composite scores indicates that the rate of longitudinal increases in LED would be affected by the baseline cognitive composite scores, while a negative value for the effect of interaction terms would imply that the higher the composite score, the slower the LED increases. Additionally, we evaluated the effects of global cognitive composite scores on the development of LID, wearing-off, or FOG and longitudinal increases in LED using the same statistical models. The statistical analyses were performed using SPSS software (version 23.0; IBM Corp., Armonk, NY, USA), and results with a two-tailed  $p < 0.05$  were considered statistically significant.

## Results

### Demographic characteristics of the study participants

The baseline demographic characteristics of the patients with PD are listed in Table 1. The mean age at PD symptom onset was  $65.94 \pm 8.50$  years, and the mean disease duration of PD (i.e., time from symptom onset to diagnosis) was  $18.04 \pm 15.98$  months. The mean UPDRS-III score at baseline (i.e., drug-naïve status) was  $22.50 \pm 9.19$ . Approximately 40% of the patients had a PIGD clinical phenotype.

### Factor analysis for cognitive composite scores

Table 2 shows the factor loadings of the 14 scorable cognitive subtests for each factor. The four cognitive function factors were consequently named according to the cognitive subtests that constituted each factor with a heavy factor loading: Factor 1 (*visual memory/visuospatial*), Factor 2 (*verbal memory*), Factor 3 (*frontal/executive*), and Factor 4 (*attention/working memory/language*).

### Composite scores of the four cognitive function factors

The composite score of each cognitive function factor was calculated as the sum of the component score coefficient  $\times$  standardized score for the neuropsychological subtest (see Supplementary Results). The global cognitive composite score was also calculated using the eigenvalues of the four cognitive function factors as follows: global cognitive composite score =  $(4.685 \times \text{Factor 1} + 1.637 \times \text{Factor 2} + 1.443 \times \text{Factor 3} + 1.167 \times \text{Factor 4})/14$ .

### Clinical relevance of the cognitive composite scores in predicting the risk for dementia

To investigate the clinical relevance of cognitive composite scores for cognitive prognosis, Cox regression analysis was performed to assess the risk of dementia conversion according to the global cognitive composite scores after adjustment for age, sex, DAT availability in the posterior putamen, and years of education. During the follow-up period [mean  $\pm$  standard deviation,  $5.56 \pm 1.82$  years; median (minimum, maximum), 5.17 (2.19, 9.99) years], 45 (17.5%) patients developed PDD, and Cox regression analysis demonstrated that lower global cognitive composite scores were associated with a higher risk for PDD

**Table 1** Demographic characteristics of the study participants

	Patients with PD ( $n = 257$ )
Age (years)	$67.50 \pm 8.36$
Female, No. (%)	134 (52.1%)
Onset of age (years)	$65.94 \pm 8.50$
Time from symptom onset to diagnosis (months)	$18.04 \pm 15.98$
Follow-up duration (years)	$5.56 \pm 1.82$
UPDRS-III scores	$22.50 \pm 9.19$
Education (years)	$9.76 \pm 4.42$
BDI	$12.40 \pm 8.37$
Motor subtype, No. (%)	
Tremor-dominant	121 (47.1%)
PIGD	100 (38.9%)
Indeterminate	36 (14.0%)
DAT availability in the posterior putamen	$1.39 \pm 0.46$

Values are expressed as the mean  $\pm$  standard deviation or number (percentage)

PD Parkinson's disease, UPDRS-III the unified Parkinson's disease rating scale part III, BDI Beck depression inventory, PIGD postural instability/gait difficulty, DAT dopamine transporter

conversion [HR 0.151, 95% CI (0.063–0.359),  $p < 0.001$ ; Supplementary Table 2].

### Effect of cognitive function at baseline on long-term motor outcomes

#### Development of LID

During the follow-up period, LID developed in 72 (28.0%) of 257 patients with PD. Cox regression analysis demonstrated that higher Factor 3 composite scores (i.e., better cognitive performance on frontal/executive function) were associated with the early development of LID [HR 1.507, 95% CI (1.150–1.976),  $p = 0.003$ ; Table 3], while composite scores for the other factors and global cognitive composite scores were not associated with the risk for developing LID (Tables 3 and 4).

#### Development of wearing-off

During the follow-up period, wearing-off developed in 46 (17.9%) of the patients with PD. Cox regression analysis demonstrated that composite scores for each cognitive function factor or global cognitive composite scores were not associated with the risk for developing wearing-off (Tables 3 and 4).

**Table 2** Factor loadings of the scorable cognitive subtests for each factor

Cognitive subtest	Cognitive domain	Factor loadings			
		Factor 1	Factor 2	Factor 3	Factor 4
RCFT delayed recall	Visual memory	0.916	0.115	0.147	0.025
RCFT immediate recall	Visual memory	0.902	0.150	0.138	0.049
RCFT copy	Visuospatial	0.630	0.050	0.169	0.115
RCFT recognition	Visual memory	0.541	0.177	-0.066	0.402
SVLT delayed recall	Verbal memory	0.164	0.853	0.162	0.081
SVLT recognition	Verbal memory	0.082	0.843	0.003	0.159
SVLT immediate recall	Verbal memory	0.147	0.782	0.313	0.031
COWAT supermarket	Frontal/executive	0.034	0.038	0.793	-0.122
COWAT animal	Frontal/executive	0.088	0.101	0.727	0.217
COWAT phonemic	Frontal/executive	0.167	0.158	0.670	0.270
Stroop color reading	Frontal/executive	0.240	0.259	0.609	0.183
Forward digit span	Attention/working memory	0.047	0.028	0.051	0.816
Backward digit span	Attention/working memory	0.119	0.111	0.300	0.651
K-BNT	Language	0.362	0.298	0.171	0.446

Factor analyses were conducted based on the 14 scorable subtests using the principal components method of factor extraction and the varimax rotation. Factors 1, 2, 3, and 4 represent the cognitive domain of visual memory/visuospatial function, verbal memory function, frontal/executive function, and attention/working memory/language function, respectively

*RCFT* the Rey complex figure test, *SVLT*, the Seoul verbal learning test, *COWAT* the controlled oral word association test, *K-BNT* Korean version of the Boston naming test

## Development of FOG

During the follow-up period, FOG developed in 54 (21.0%) of the patients with PD. Cox regression analysis demonstrated that lower Factor 1 composite scores (i.e., poorer cognitive performance on visual memory/visuospatial function) were associated with a higher risk for FOG [HR 0.683, 95% CI (0.500–0.933),  $p=0.017$ ; Table 3]. Moreover, lower global cognitive composite scores were associated with a

higher risk for FOG [HR 0.455, 95% CI (0.211–0.982),  $p=0.045$ ; Table 4].

## Rate of longitudinal increases in doses of dopaminergic medications

The linear mixed model demonstrated significant interactions between Factor 1 composite scores or global cognitive composite scores and time ( $p=0.044$  and  $0.015$ , respectively), suggesting that higher Factor 1 composite scores

**Table 3** Cox regression analysis for the long-term motor prognosis according to the composite scores of cognitive function factors

	LID		Wearing-off		FOG	
	HR (95% CI)	$p$ -value	HR (95% CI)	$p$ -value	HR (95% CI)	$p$ -value
Factor 1	1.122 (0.871–1.446)	0.372	0.942 (0.691–1.285)	0.707	0.683 (0.500–0.933)	0.017
Factor 2	1.113 (0.874–1.419)	0.386	1.184 (0.866–1.621)	0.290	1.030 (0.777–1.364)	0.839
Factor 3	1.507 (1.150–1.976)	0.003	1.357 (0.976–1.888)	0.070	1.037 (0.755–1.425)	0.821
Factor 4	1.095 (0.845–1.418)	0.493	1.090 (0.792–1.501)	0.596	1.201 (0.890–1.622)	0.231
Age	0.981 (0.948–1.015)	0.273	0.929 (0.891–0.968)	<0.001	1.004 (0.969–1.040)	0.827
Sex (female vs. male)	1.685 (0.970–2.926)	0.064	1.208 (0.624–2.339)	0.575	0.663 (0.356–1.236)	0.196
DAT availability	0.513 (0.279–0.942)	0.031	0.477 (0.229–0.996)	0.049	0.689 (0.355–1.335)	0.269
LED	1.000 (0.999–1.001)	0.896	1.000 (0.999–1.001)	0.795	0.999 (0.998–1.000)	0.046
BDI score	1.109 (0.991–1.048)	0.175	1.050 (1.017–1.085)	0.003	0.998 (0.967–1.031)	0.921
PIGD subtype (yes vs. no)					2.595 (1.465–4.596)	0.001

Factor 1 (*visual memory/visuospatial*); Factor 2 (*verbal memory*); Factor 3 (*frontal/executive*); Factor 4 (*attention/working memory/language*)

*LID* levodopa-induced dyskinesia, *FOG* freezing of gait, *DAT* dopamine transporter, *LED* levodopa-equivalent, *BDI* Beck depression inventory, *PIGD* postural instability/gait difficulty, *HR* hazard ratio, *CI* confidence interval



**Table 4** Cox regression analysis of the long-term motor prognosis according to the global cognitive composite scores

	LID		Wearing-off		FOG	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Global composite score	1.746 (0.874–3.487)	0.114	1.188 (0.516–2.733)	0.686	0.455 (0.211–0.982)	0.045
Age	0.978 (0.948–1.010)	0.180	0.931 (0.895–0.968)	<0.001	0.999 (0.965–1.033)	0.939
Sex (female vs. male)	1.798 (1.081–2.993)	0.024	1.456 (0.789–2.685)	0.229	0.780 (0.450–1.352)	0.375
DAT availability	0.605 (0.342–1.071)	0.085	0.517 (0.253–1.057)	0.071	0.702 (0.366–1.346)	0.286
LED	1.000 (0.999–1.001)	0.961	1.000 (0.999–1.001)	0.707	0.999 (0.998–1.000)	0.057
BDI score	1.019 (0.992–1.047)	0.160	1.048 (1.015–1.082)	0.004	0.992 (0.961–1.024)	0.628
PIGD subtype (yes vs. no)					2.476 (1.396–4.390)	0.002

LID levodopa-induced dyskinesia, FOG freezing of gait, DAT dopamine transporter, LED levodopa-equivalent, BDI Beck depression inventory, PIGD postural instability/gait difficulty, HR hazard ratio, CI confidence interval

and global cognitive composite scores were associated with slower longitudinal increases in LED (Table 5).

## Discussion

The present study investigated the association between cognitive function at baseline and long-term motor outcomes in patients with early-stage PD. Factor analysis using the principal components method was conducted to determine cognitive composite scores. The main findings were as follows. (1) The factor analysis yielded four cognitive function factors (Factor 1, *visual memory/visuospatial*; Factor 2, *verbal memory*; Factor 3, *frontal/executive*; and Factor 4, *attention/working memory/language*) and global cognitive composite scores. In terms of cognitive prognosis, lower global cognitive composite scores were associated with a higher risk of conversion to dementia. (2) Higher Factor 3 composite scores were associated with the early development of LID, whereas the composite scores for each cognitive function factor or global cognitive composite scores were not associated with the risk for developing wearing-off. (3) Lower Factor 1 composite scores and global cognitive composite scores were associated with a higher risk for developing FOG. (4) Lower Factor 1 composite scores and global cognitive composite scores were associated with a more rapid rate of longitudinal increases in LED (see Fig. 1). These findings suggest that baseline cognitive profiles can predict prognosis in terms of motor aspects in patients with newly diagnosed PD.

There is increasing clinical evidence to support the potential associations between cognitive dysfunction and motor disability in patients with PD. Several prognostic models have consistently reported that the presence of cognitive decline is an important predictor of rapid motor decline [4–6]. Conversely, the motor subtypes of PD are also associated with a risk for incident dementia, and the PIGD phenotype is more relevant to rapid cognitive decline than the

tremor-dominant phenotype [7–9]. Moreover, educational attainment, one of the most representative proxies of cognitive reserve, appears to be associated with baseline motor function and motor outcomes in patients with PD [34–37]. A possible explanation for this relationship is that several motor performance measures, especially gait, depend on the level of cognitive function [38]. Alternatively, a more reasonable explanation is that both cognitive and motor function are affected by shared or parallel pathological processes related to PD [8, 39, 40]. Anatomical and physiological evidence suggests that some cognitive and motor processes are facilitated by parallel loops that link the frontal cortex to the basal ganglia and thalamus [41]. In contrast, the close temporal relationship between motor and cognitive symptoms with a distinct neural basis (e.g., the transition from tremor-dominant to PIGD phenotype and accelerated cognitive decline [8]) suggests the coincidence of different neurodegenerative processes that develop in parallel.

The underlying pathophysiology of cognitive decline and motor disability in PD is highly variable [42]. Therefore, to better understand the association between cognitive and motor function, each of the cognitive domains and motor outcomes should be separately assessed. In this study, we explored the cognitive function factor predominantly associated with the following four clinical parameters that reflect the progression of motor disability in several aspects [16]. First, a higher level of cognitive performance in the frontal/executive function domain was associated with an increased risk for developing LID. A few studies have reported the contribution of frontal areas to the development of LID, showing the overactivation of the frontal motor areas [43, 44] and increased cortical thickness of the inferior frontal gyrus [45, 46] in patients with PD with LID. Notably, thickening in the prefrontal cortex may reflect neuroplastic changes induced by using the executive circuitry to suppress involuntary movements over several years [45–47]. Furthermore, in light of our findings, we suspect that increased prefrontal volume with better frontal/executive function may be

**Table 5** Longitudinal changes in levodopa-equivalent dose (LED) according to cognitive function at baseline

	$\beta$ (SE)	<i>p</i> -value
<b>Model 1</b>		
Intercept	- 39.488 (91.232)	0.665
Age	0.401 (1.130)	0.723
Sex	- 23.505 (20.714)	0.257
DAT availability in the posterior putamen	- 15.856 (20.806)	0.446
UPDRS-III score	4.326 (1.051)	<0.001
BDI score	- 0.340 (1.124)	0.763
Factor 1 ( <i>visual memory/visuospatial</i> )	2.298 (13.510)	0.865
Factor 2 ( <i>verbal memory</i> )	11.185 (13.197)	0.397
Factor 3 ( <i>frontal/executive</i> )	10.226 (13.102)	0.436
Factor 4 ( <i>attention/working memory/language</i> )	- 17.959 (12.328)	0.146
F/U interval (months)	9.399 (0.239)	<0.001
Factor 1 × F/U interval	- 0.470 (0.233)	0.044
Factor 2 × F/U interval	- 0.390 (0.241)	0.107
Factor 3 × F/U interval	- 0.389 (0.259)	0.133
Factor 4 × F/U interval	0.398 (0.248)	0.110
<b>Model 2</b>		
Intercept	- 37.368 (89.356)	0.676
Age	0.308 (1.125)	0.784
Sex	- 19.856 (18.394)	0.281
DAT availability in the posterior putamen	- 15.709 (20.699)	0.448
UPDRS-III score	4.301 (1.032)	<0.001
BDI score	- 0.469 (1.117)	0.675
Global composite score	11.723 (34.873)	0.737
F/U interval (months)	9.421 (0.239)	<0.001
Global composite score × F/U interval	- 1.547 (0.632)	0.015

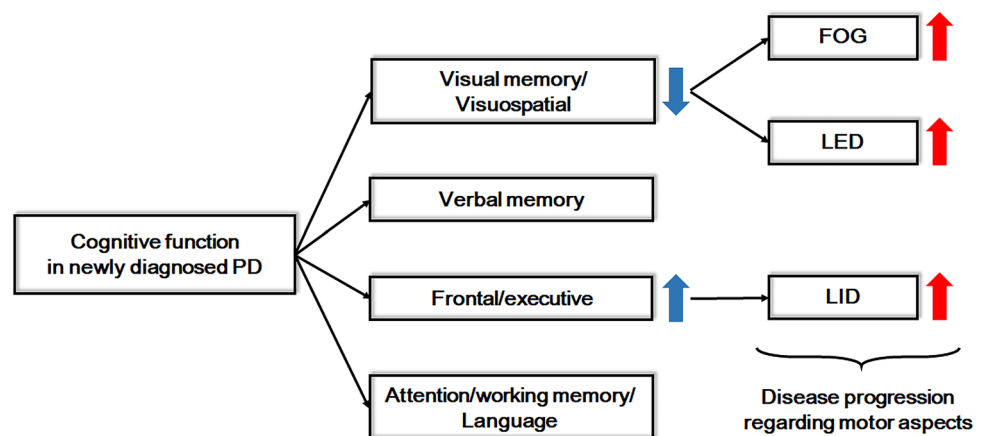
The estimate ( $\beta$ ) is the change in LED per month, i.e., positive value indicates the dose-up of Parkinson’s disease medications. There were significant interactions between global cognitive composite score and time in a mixed model

DAT dopamine transporter, UPDRS-III the unified Parkinson’s disease rating scale part III, BDI Beck depression inventory, SE standard error, F/U follow up

a characteristic of patients with PD who are vulnerable to the development of LID. In other words, a thick prefrontal cortex would have profuse interconnections with the motor cortex and basal ganglia, which consequently provide a

higher potential for neural plasticity, thereby leading to LID. We recently reported that patients with PD who experienced LID within 5 years of levodopa administration exhibited a more rapid progression of frontal/executive dysfunction than

**Fig. 1** Schematic representation of the cognitive profiles of early-stage Parkinson’s disease based on factor analysis and their prognostic relevance



those without LID [48], suggesting the parallel development of aberrant corticostriatal plasticity in the motor and cognitive loops [41]. Altogether, the potential for plastic changes in the frontal areas would be closely associated with the development of LID and frontal/executive dysfunction.

Second, baseline cognitive function was not associated with the risk of developing wearing-off. Wearing-off is generally presumed to share the same pathogenic mechanisms as LID. However, several lines of evidence have suggested that the underlying mechanisms for wearing-off and LID may be different. The two motor complications may not necessarily occur in the same individual, although the onset of either LID or wearing-off commonly signals the risk of appearance of the other. Moreover, wearing-off may be viewed as more presynaptic than postsynaptic [49, 50], whereas LID appears to be a postsynaptic phenomenon considering that presynaptic dopamine depletion is the primary predisposing factor for LID induction but not a critical determinant [49, 51]. Therefore, no association between wearing-off and cognitive subsets may imply that the contribution of postsynaptic influence on the development of motor complications may differ between LID and wearing-off.

Third, poor cognitive performance in the visual memory/visuospatial function domain and global cognitive dysfunction were associated with a higher risk for developing FOG. Previous literature has highlighted some specific cognitive domains related to FOG in PD, namely frontal/executive [52–54], attention [55, 56], and visuospatial function [54, 57–59], in addition to global cognitive dysfunction [60]. In particular, patients with PD rely heavily on visual information, during the generation of motor plans [61] and the control of balance and locomotion [62]. Thus, baseline visual memory/visuospatial dysfunction may play a critical role in the development of FOG in this study. The lack of an association between baseline frontal/executive or attention function and the development of FOG, which appears to be inconsistent with previous studies [52–56], may be because of the differences in the study design, study population, and neuropsychological assessment.

Fourth, patients with lower composite scores in visual memory/visual function factor and lower global cognitive composite scores received higher doses of dopaminergic medications throughout the follow-up period. Usually, the required LED for effective symptom control increases as the disease progresses, and it appears to be indirectly associated with parkinsonian disability [63]. Our finding is in line with that of previous studies showing that visuospatial dysfunction significantly affects disability in patients with PD through its influence on cognition and locomotion [58, 64]. However, the result must be interpreted with caution as the longitudinal changes in LED may be affected by some confounding factors, including adverse effects of PD medications and the development of LID.

Our study had some limitations. First, the development of LID, wearing-off, and FOG was determined based on history-taking and neurological examination at every visit rather than quantitative assessment. Thus, the detection of mild motor features may be delayed in some cases. Additionally, direct measures of motor deficit, such as the UPDRS-III score, were not collected in a longitudinal manner. Second, factor analysis-derived cognitive composite scores can differ according to the study population, and additional analyses on an external dataset would be needed to replicate our findings. Moreover, all cognitive domains were not equally represented in the factor analysis. For example, six tests related to memory function domain were used for the factor analysis, whereas only one test related to language function was used in this study. However, none of the tests currently used for the factor analysis were included unnecessarily to provide accurate information about the nature of each cognitive domain. Third, because cognitive dysfunction and motor deficits seem to affect each other in PD [4–9], the impact of individual cognitive function factors on long-term motor outcomes may be altered in patients who experienced cognitive decline during the follow-up period. When we additionally estimated the risk for developing PDD in each cognitive domain using the Cox regression model, better performance in all cognitive function factors except Factor 4 was associated with a lower risk of PDD (Factor 1, HR = 0.641,  $p = 0.007$ ; Factor 2, HR = 0.681,  $p = 0.014$ ; Factor 3, HR = 0.413,  $p < 0.001$ ). Therefore, the effects of visual memory/visuospatial dysfunction on the development of FOG and increases in LED would not be particularly mediated by the occurrence of PDD.

In conclusion, the present study suggests that baseline cognitive profiles may be used as a predictor of motor complications or motor disability in patients with PD. Given that coexisting cognitive dysfunction and motor impairment increase the risk of institutionalization [66], early identification of individuals at a high risk of rapid disease progression is necessary to implement appropriate therapeutic strategies.

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**Author contributions** SJC and PHL conceived the study. SJC, HSY, HSL, YHL, KWB, and JHJ acquired and analyzed the data. SJC and PHL wrote the manuscript. HSY, HSL, YHL, KWB, JHJ, BSY, and YHS revised the manuscript for important intellectual content. All authors read and approved the manuscript.



## Declarations

**Conflicts of interest** The authors declare no financial or other conflicts of interest.

**Ethical approval** This study was approved by the Institutional Review Board of Yonsei University Severance Hospital. The need for informed consent was waived because of the retrospective nature of the study.

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