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Factor analysis-derived cognitive profile predicting early dementia conversion in PD

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Abstract

Objectives: To investigate which baseline neuropsychological profile predicts the risk of developing dementia in early-stage Parkinson's disease (PD).

Methods: We retrospectively reviewed detailed medical records of 350 drug-naïve patients with early-stage PD (follow-up > 3 years), who underwent a detailed neuropsychological test at initial assessment. Factor analysis was conducted to determine cognitive profiles which 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*). Subsequently, we assessed the effect of these cognitive function factors on the risk for dementia conversion. We also constructed a nomogram to calculate the risk for developing dementia over a 5-year follow-up period based on these cognitive profiles.

Results: Cox regression analysis demonstrated that a higher composite score of Factor 1 (hazard ratio [HR], 0.558; 95% confidence interval [CI], 0.427−0.730), Factor 2 (HR, 0.768; 95% CI, 0.596−0.991), and Factor 3 (HR, 0.425; 95% CI, 0.305−0.593) was associated with a lower risk for dementia conversion, while Factor 3 had the most predictive power. The nomogram had a fair ability (Heagerty's integrated area under the curve, 0.763) to estimate the risk for dementia conversion within 5 years. The composite scores of Factor 3 contributed more to the occurrence of dementia in PD than those of the other cognitive function factors.

Conclusions: These findings suggest that these factor analysis-derived cognitive profiles can be used to predict dementia conversion in early-stage PD. Additionally, frontal/executive dysfunction contributes most to the occurrence of dementia in PD.

Introduction

Dementia is a common and disabling comorbidity associated with advanced stages of Parkinson's disease (PD), with approximately 45% of patients affected by 10 years.[1] Early detection of patients at high risk for PD with dementia (PDD) is important for the proper and rapid implementation of supportive and therapeutic strategies,[2, 3] and several clinical and neuroimaging predictors have been proposed as markers for ongoing cognitive decline in PD.[4-6] However, the neural basis of PDD is so complex that attempts to determine the neuropsychological profiles associated with future dementia have yielded heterogeneous results, i.e., all cognitive domains including frontal/executive,[7-10] memory,[9, 11] visuospatial,[3, 8] and language function[11] have been associated with PDD conversion.

Williams-Gray et al.[3, 4] proposed the dual syndrome hypothesis suggesting that cognitive impairment in PD can be divided into two categories: fronto-striatal deficits and posterior cortical dysfunction, each associated with specific prognoses. They demonstrated that the performance on pentagon copying and semantic fluency tests, but not on phonemic fluency and other frontally based tasks, were useful predictors of dementia risk, implying that posterior cortical deficits were related to incident dementia in PD. However, most studies identified neuropsychological predictors by employing particular cognitive tests and calculating their relative risks of PDD conversion with uni- or multi-variate regression analyses. This approach can be biased depending on the neuropsychological tests selected and how well the cognitive tests represent each of the cognitive function domains. Furthermore, most cases of PD with mild cognitive impairment (PD-MCI) are affected in multiple domains,[12] creating difficulty in determining the involvement of specific cognitive domains in cognitive

prognosis. To overcome these limitations, we performed a factor analysis to collapse the 14 scorable subtests of our neuropsychological tests into four independent cognitive function factors and investigated which factor was predominantly associated with the risk of developing PDD without concerns of multi-collinearity. We also constructed a nomogram to calculate the risk of PDD conversion over a 5-year follow-up period based on these cognitive profiles.

Methods

Subjects

We reviewed the medical records of 481 consecutive drug-naïve patients with early-stage PD who visited the Movement Disorders outpatient clinic at Severance Hospital from September 2008 to August 2016 and underwent detailed neuropsychological testing upon initial assessment. PD was diagnosed according to the clinical diagnostic criteria of the United Kingdom PD Society Brain Bank. All subjects showed decreased dopamine transporter availability in the posterior putamen on ^{18}F-FP-CIT PET scans, and did not present additional atypical features (e.g., poor response to dopaminergic medications, ataxia, prominent autonomic dysfunction, vertical gaze limitation, early fall, and cortical sensory loss). Of them, 30 who were initially diagnosed with dementia, 15 who were illiterate, and 86 who were lost on follow-up within three years were excluded from the study. Finally, 350 patients with non-demented PD who were treated with PD medication for at least three 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). The white matter hyperintensities (WMHs) burden of the patients with PD was rated using the Scheltens scale[13] by two neurologists (YHS and LYH) unaware of the clinical

information. Both neurologists retrospectively reviewed every scan, and determined the WMHs severity by achieving consensus for each case.

Standard Protocol Approvals, Registration, and Patient Consents

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.

Neuropsychological assessment

All subjects underwent a comprehensive neuropsychological test battery in the Korean language, i.e., the Seoul Neuropsychological Screening Battery (SNSB).[14] Among the scorable subtests of the SNSB, age- and education-specific z-scores for the following 14 items were assessed: forward digit span task, backward digit span task, the Korean version of the Boston Naming Test (K-BNT), Rey Complex Figure Test (RCFT) copy, immediate recall, delayed recall, and recognition items using the Seoul Verbal Learning Test (SVLT) for verbal memory, immediate recall, delayed recall, and recognition items using the RCFT for visual memory, Controlled Oral Word Association Test (COWAT) for animal, COWAT for supermarket, COWAT for phonemic fluency, and the Stroop color reading test. In addition, the Korean version of the Mini-Mental State Examination (K-MMSE) was used to assess general cognition.[15]

Factor analysis for determining the cognitive profiles

To reduce the redundancy of neuropsychological subtests and the possibility of overrepresenting a single cognitive function domain, a factor analysis was conducted

based on the 14 scorable subtests of the SNSB[14] using the principal components method of factor extraction and the Varimax method of rotation. The factor analysis yielded four cognitive function factors with eigenvalues > 1.0 which accounted for 63.1% of the variance in the subjects' cognitive performance. The component score coefficients were then used to calculate the composite scores of the four cognitive function factors of each subject. Additionally, using the four cognitive function factors in an integrative formula, we calculated the global cognitive composite score of each patient with PD.

Assessment of dementia conversion during follow-up according to cognitive profiles

After diagnosis of PD, patients visited the outpatient clinic at 3-month intervals. PD patients or their caregivers were asked questions about daily functioning, such as the patients' ability to manage finances, use pieces of equipment, and cope in social situations at every visit. Additionally, patients with PD underwent serial cognitive assessment using the K-MMSE and Clock Drawing Test with an interval of one year (Level I tests).[16] In case with definite cognitive decline or evidence of impairments in daily life due to cognitive changes (Level I), a detailed neuropsychological battery (i.e., the SNSB[14]) was subsequently conducted to specify the pattern of cognitive deficits and diagnose PDD at Level II in most patients.[16] The diagnosis of PDD was made by achieving consensus between two neurologists and one neuropsychologist, according to the clinical diagnostic criteria proposed by the Movement Disorder Society Task Force.[17, 18] 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 (ADL), judged by neurologists clinically

and by instrumental ADL scales (Korean Instrumental ADL [K-IADL] ≧ 0.43 and Seoul Instrumental ADL [S-IADL] ≧ 8),[19, 20] while functional disabilities merely due to parkinsonian motor symptoms were not considered to be impairment of complex ADL. None of the features which suggest other conditions as a cause of cognitive impairment (i.e., systemic disease, relevant cerebrovascular disease, and drug) were present in patients with PDD. Time from the initial neuropsychological assessment to dementia conversion was assessed with Kaplan-Meier estimates. A Cox regression model was then used to estimate hazard ratios (HRs) and 95% confidence interval (CI) of dementia conversion according to the neuropsychological profiles (i.e., composite scores of four cognitive function factors), while adjusting for age, sex, disease duration (i.e., time from symptom onset to diagnosis), baseline UPDRS-III scores, years of education, and total WMHs burden based on the Scheltens scale.[13] Effect of global cognitive composite scores on conversion to PDD was also assessed. Additionally, we developed a nomogram to calculate the risk of dementia conversion over a 5-year follow-up period based on cognitive profiles.[21] The internal discrimination ability of the nomogram was quantified using the Heagerty's iAUC.

Statistical analysis

A factor analysis for the cognitive composite scores was performed as described above. The effects of the cognitive composite scores on PDD conversion were then assessed using Cox regression models. There were no significant correlations between the composite scores of cognitive function factors, and all these factors were included as predictor variables without concerns of multi-collinearity. In addition, to demonstrate which cognitive function factor had the highest predictive power for dementia conversion, the following parameters were calculated for each Cox regression model which included each cognitive function factor: the Akaike information criterion (AIC), discriminatory ability assessed by the linear trend χ^2 test, concordance index (Harrell's C-index), and global concordance probability (integrated area under the curve [iAUC]). A smaller AIC and larger discriminatory ability, Harrell's C-index, and iAUC indicate the preferred model with better predictive accuracy. Statistical analyses were performed using the SPSS software (version 23.0; IBM Corp., Armonk, NY, USA) and R software package (version 3.4.0; http://www.r-project.org). Results with a two-tailed $P < 0.05$ were considered statistically significant.

Data Availability

For purposes of replicating procedures and results, any qualified investigator can request anonymized data after ethics clearance and approval by all authors.

Results

Demographic characteristics of the study participants

The baseline demographic characteristics of the 350 patients with non-demented PD are listed in table 1. The mean age at the time of PD diagnosis was 67.85 ± 8.31 years and the mean number of years in education was 9.62 ± 4.37 years. Among 350 patients with non-demented PD, 142 (40.6%) patients were diagnosed with PD-MCI at baseline evaluation according to the Movement Disorder Society Task Force guidelines (cut-off scores at 1.5 standard deviation below the age-, sex-, and education-specific norms).[22, 23]

Factor analysis for determining cognitive profiles

The factor analysis yielded four cognitive function factors with eigenvalues > 1.0, which accounted for 63.1% of the variance of the subjects' cognitive performance. 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

Table 3 shows the component score coefficients of the neuropsychological subtests for each factor as well as the mean and standard deviation of each neuropsychological subtest of the 350 patients with PD. The composite score of each cognitive function

factor was calculated as the sum of (component score coefficient × standardized score for the neuropsychological subtest).

The eigenvalues of the four cognitive function factors were 4.582, 1.678, 1.442, and 1.132, respectively, and the global cognitive composite score was calculated as global cognitive composite score = (4.582 × Factor 1 + 1.678 × Factor 2 + 1.442 × Factor 3 + 1.132 × Factor 4) / 14.

Effect of the cognitive composite scores on the conversion to dementia

During the follow-up period (5.59 ± 1.93 years), 78 (22.3%) patients with PD developed dementia. Cox regression analysis demonstrated that higher composite scores of Factor 1 (*visual memory/visuospatial*), Factor 2 (*verbal memory*), and Factor 3 (*frontal/executive*) were associated with a lower risk of dementia (Factor 1, HR 0.558, 95% CI [0.427−0.730]; Factor 2, HR 0.768, 95% CI [0.596−0.991]; Factor 3, HR 0.425, 95% CI [0.305−0.593]; table 4). For example, if a patients with PD had a composite score of Factor 3 (*frontal/executive*) one point higher, he or she would have an approximately 57.5% lower risk for PDD conversion. The composite scores of Factor 4 (*attention/working memory/language*) did not affect the risk for PDD conversion (HR 0.878, 95% CI [0.678−1.119]). Additionally, higher global cognitive composite scores were associated with a lower risk for conversion to dementia (HR 0.109, 95% CI [0.052−0.228]; table 4).

Predictive accuracy of the Cox regression models

We additionally performed Cox regression analyses to estimate the HRs of PDD conversion, which included each cognitive function factor as a predictor variable separately (table 5). The Cox regression model including Factor 3 (*frontal/executive*)

as a predictive variable had the smallest value of AIC (773.755) and the largest values of the discriminatory ability (51.73), Harrell's C-index (0.743), and iAUC (0.734), suggesting that the composite scores of Factor 3 (*frontal/executive*) had the highest predictive power for the dementia conversion among those of the four cognitive function factors (table 5).

Constructing a nomogram to calculate the risk of PDD within 5 years

Based on the results of the Cox regression analyses (tables 4 and 5), the following variables were included in an equation to predict the risk of dementia conversion during the 5-year follow-up period: age, sex, disease duration, and composite scores of Factor 1 (*visual memory/visuospatial*), Factor 2 (*verbal memory*), and Factor 3 (*frontal/executive*). The risk of PDD within 5 years was calculated as $1 - S_0(5)^{exp(LP)}$, where $S_0(5) = 0.89555$ was determined from the Cox regression model and Linear Predictor (LP) = $0.04771 \times (\text{age} - 67.84657) - 0.20051 \times (\text{sex} - 1.52286) + 0.00899 \times (\text{disease duration} - 18.53848) - 0.54138 \times (\text{Factor 1} + 1.142857 \times 10^{-7}) - 0.29575 \times (\text{Factor 2} + 5.71429 \times 10^{-8}) - 0.77334 \times (\text{Factor 3} - 8.57143 \times 10^{-8})$. We constructed a nomogram according to these variables, in which a corresponding probability of PDD-free survival (i.e., 1 - risk for PDD) could be estimated from the points of each variable (see figure 1 and its legend to explain how to apply the nomogram). Factor 3 (*frontal/executive*) contributed more to the points for calculating the risk for dementia than the other cognitive function factors. The nomogram had fair discrimination ability (Heagerty's iAUC, 0.763) to predict the development of PDD.

Discussion

The present study investigated which neuropsychological profiles at baseline could

predict the risk of developing dementia in patients with early-stage PD. To reduce the redundancy of neuropsychological subtests, factor analysis was performed using the neuropsychological data of 350 patients with PD. The major findings were as follows: (1) 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 their composite scores. (2) Lower composite scores (i.e., poor cognitive performance) of Factor 1 (*visual memory/visuospatial*), Factor 2 (*verbal memory*), and Factor 3 (*frontal/executive*) were associated with a higher risk for dementia conversion. In particular, Factor 3 (*frontal/executive*) had the highest predictive power for dementia conversion. (3) The nomogram was well constructed to estimate the risk for dementia conversion within 5 years, while the composite scores of Factor 3 (*frontal/executive*) contributed more to the points for calculating the risk of dementia than those of the other cognitive function factors. These findings suggest that the level of cognitive performance on each cognitive domain, particularly the frontal/executive function domain, can be used to predict the risk for dementia conversion in patients with early-stage PD.

It is now clear that cognitive decline is prevalent during the early stages of PD. A number of studies have attempted to understand the neurobiology underlying cognitive deficits in PD for early identification of at-risk individuals. Several risk factors and biomarkers for ongoing cognitive decline have been inconsistently reported, and this variation likely reflects the marked cognitive heterogeneity amongst PD patients.[24] In terms of the neuropsychological markers, it was traditionally thought that the core symptoms of preclinical dementia in PD involved executive functions, in contrast to those in Alzheimer's disease, which involve memory and language tasks.[25]

In particular, the discovery of parallel segregated circuits linking the basal ganglia and prefrontal cortex suggested that cognitive deficits in PD may be frontal/executive in nature.[26, 27] In line with this view, early studies from the late 1990s to the early 2000s found that frontal/executive dysfunction (which may be dopamine-dependent) was an important neuropsychological predictor for PDD conversion.[7-10] However, subsequent studies have revealed that some cognitive impairments in PD are dopamine-independent and dysregulation in other neurotransmitter systems such as the cholinergic system[28] also contribute to the occurrence of dementia.[29] Impairments in memory,[9, 11] visuospatial,[3, 8] and language function[11] have also been associated with PDD conversion. Furthermore, a large community-based cohort study, namely the Cambridgeshire Parkinson's Incidence from General Practitioner to Neurologist (CamPaIGN) study, demonstrated that impairments in pentagon copying and semantic fluency tests were predictive of developing PDD; the dual syndrome hypothesis was proposed from this work.[3] This states that posterior cortical dysfunction is a predictor for incident dementia in PD, whereas early fronto-striatal deficits are not. This hypothesis is now widely accepted and supported by genetic and neuroimaging studies.[4, 30-32]

However, it should be noted that there is some degree of overlap between the two cognitive syndromes, raising the possibility that cognitive deficits on a posterior cortical basis might be exacerbated by fronto-striatal deficits or vice versa.[27, 33] Thus, caution should be exercised when predicting PDD from these syndromes. Furthermore, the dual syndrome hypothesis is based on the assumption that semantic fluency, but not phonemic fluency, is a posterior cortical lobe-based task, and this has not been validated using neuroimaging data.[3] However, several lines of evidence have

suggested that verbal fluency tasks (both phonemic and semantic fluency) engage several executive processes, such as response initiation, self-monitoring, and cognitive flexibility,[34] and neural correlates of phonemic and semantic fluency are assumed to overlap in the frontal regions. The phonemic fluency task is likely to be sensitive and specific for frontal dysfunction,[35] whereas the semantic fluency task appears to require some alternative search strategies and memory processes. However, the frontal lobe still plays a crucial role in semantic fluency performance regardless of additional involvement of the temporal cortex.[35-37] Moreover, previous studies using factor analysis methods to separate cognitive subtypes in PD produced consistent results indicating that phonemic fluency and semantic fluency loaded on the same factor (i.e., these verbal fluency tasks would share the same cognitive processes or neural basis).[12, 38, 39] Our findings are in accordance with those of the previous studies,[12, 38, 39] showing that both semantic and phonemic fluency loaded heavily on the cognitive function factor which was regarded to represent the frontal/executive function domain.

Additionally, the present study demonstrated that the cognitive function factor related to frontal/executive function contributed most to the development of PDD, while other factors related to visual memory/visuospatial function and verbal memory function were also associated with the risk of dementia conversion. We also constructed a nomogram to calculate the risk for developing dementia over a 5-year follow-up period based on the cognitive profiles, which showed that the greatest impact was associated with frontal dysfunction. Considering that cognitive dysfunction occurs across multiple domains in most patients with PD-MCI,[12] factor analysis methods have the advantage of assessing the contribution of each cognitive

profile to subsequent PDD conversion without concerns of multi-collinearity by collapsing the redundant neuropsychological subtests into a few independent latent variables. Therefore, factor analysis yields cognitive function factors uncorrelated with each other, and all these factors can be simultaneously included in the statistical models. Previously, we have shown that cortical thinning in the frontal areas could serve as important markers of imminent risk for PDD conversion in patients with PD-MCI along with a posterior pattern of atrophy. The neuropsychological data in the present study support these previous observations.[6, 40] Moreover, our data are in line with a specific abnormal spatial pattern of covariance in metabolic activity related to cognitive impairment associated with PD (i.e., PD-related cognitive pattern[41]), which is characterized by metabolic reductions primarily in the medial frontal and parietal association regions. Early involvement of the frontal-subcortical pathways, which is an early predictor of PDD conversion, may affect various cognitive domains by disrupting the reciprocal cortico-cortical connections[42] or important nodes of information integration.[43] Neural substrates underlying frontal/executive dysfunction may signal the subsequent progression of cortical Lewy bodies[10] or β-amyloid and tau pathologies,[44] which likely contribute to the development of PDD.

Our neuropsychological findings (i.e., that frontal/executive dysfunction contributes most to the occurrence of PDD) appear to be inconsistent with the dual syndrome hypothesis[1, 3, 4] and its supportive data.[30-32, 45, 46] One possible explanation for these discrepant results is the different ethnic and genetic backgrounds between study cohorts. Available evidence has suggested there may be genetic susceptibility loci involved in cognitive impairment in PD. The catechol-O-methyltransferase (COMT) genotype appears to impact on executive function in PD by directly influencing

frontoparietal activation,[47] while the microtubule-associated protein tau (MAPT) haplotype modulates tau transcription[4] and parietal activation.[48] Additionally, β-glucocerebrosidase (GBA), α-synuclein (SNCA), and apolipoprotein E (APOE) genes may influence the presence or severity of cognitive deficits in PD.[49, 50] Further studies are needed to link our neuropsychological and neuroimaging data to genetic analysis. Alternatively, differences in study populations (e.g., whether cohorts were recruited from community or hospital outpatient clinics; clinical heterogeneity of PD), neuropsychological assessment, diagnostic criteria for cognitive impairment, and analysis methods also contribute to variation between the studies.

Our study had some limitations. First, the equations to estimate the composite scores of the cognitive function factors can differ according to the dataset. Moreover, it would be more appropriate to construct a nomogram using the development dataset and then test its discrimination ability using the validation dataset. In addition, the number of PD patients who were diagnosed with PDD during the follow-up period was relatively small. It could possibly reduce the predictive accuracy of the statistical model, although the Cox regression model used for constructing a nomogram had a fair predictive power (Harrell's C-index, 0.790). Further studies are needed to validate and generalize our findings. Second, for cases of incident dementia, we defined the time of dementia onset as the time to diagnose PDD at the outpatient clinic visited every three months, which could be inaccurate. However, we still obtained similar results if the time of dementia onset was assumed to be the midpoint of the interval between the outpatient clinic visits (data not shown).[3] Third, although the Movement Disorder Society Task Force guidelines recommend the use of at least two tests in each cognitive domain to diagnose PD-MCI,[23] language and visuospatial function

domains were composed of only one test (K-BNT and RCFT copy, respectively) due to lack of scorable cognitive subtests in the SNSB. However, the possibility of overrepresenting the cognitive domains by a single test may be minimized using factor analysis. Fourth, other neurodegenerative or vascular pathologies could affect the rate of cognitive decline in some patients with PD, although we included the total WMHs burden as a covariate when assessing the effect of the neuropsychological profiles on the conversion to PDD. Finally, several factors, such as the ethnic and genetic backgrounds, level of education, and female frequency, could affect the generalization of the results of this study conducted at a single center in Korea.

In conclusion, the present study suggests that neuropsychological profiles have predictive value for future dementia conversion in patients with early-stage PD. Frontal/executive dysfunction contributes most to the development of PDD, while other posterior cortical deficits are also associated with the occurrence of dementia in patients with PD.

Appendix 1: Authors

Name	Location	Contribution
Seok Jong Chung, MD	Yonsei University College of Medicine	Design and conceptualized study; analyzed data; major role in the acquisition of data; interpreted the data; drafted the manuscript for intellectual content
Hye Sun Lee, PhD	Yonsei University College of Medicine	Analyzed data; interpreted the data; revised the manuscript for intellectual content
Hang-Rai Kim, MD	Korea Advanced Institute of Science and Technology	Analyzed data; interpreted the data; revised the manuscript for intellectual content
Han Soo Yoo, MD	Yonsei University College of Medicine	Major role in the acquisition of data; analyzed data; revised the manuscript for intellectual content
Yang Hyun Lee, MD	Yonsei University College of Medicine	Major role in the acquisition of data; analyzed data; revised the manuscript for intellectual content
Jin Ho Jung, MD	Yonsei University College of Medicine	Major role in the acquisition of data; analyzed data; revised the manuscript for intellectual content
KyoungWon Baik, MD	Yonsei University College of Medicine	Major role in the acquisition of data; analyzed data; revised the manuscript for intellectual content
Byoung Seok Ye, MD,	Yonsei University	Interpreted the data; revised

PhD	College of Medicine	the manuscript for intellectual content
Young H. Sohn, MD, PhD	Yonsei University College of Medicine	Interpreted the data; revised the manuscript for intellectual content
Young H. Sohn, MD, PhD	Yonsei University College of Medicine	Design and conceptualized study; interpreted data; drafted the manuscript for intellectual content

References

1. Williams-Gray CH, Mason SL, Evans JR, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. Journal of neurology, neurosurgery, and psychiatry 2013;84:1258-1264.

2. Eberling J, Vincent L, Goldman JG, et al. Therapeutic development paths for cognitive impairment in Parkinson's disease: report of a regulatory roundtable. Journal of Parkinson's disease 2014;4:585-589.

3. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain : a journal of neurology 2007;130:1787-1798.

4. Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain : a journal of neurology 2009;132:2958-2969.

5. Firbank MJ, Yarnall AJ, Lawson RA, et al. Cerebral glucose metabolism and cognition in newly diagnosed Parkinson's disease: ICICLE-PD study. Journal of neurology, neurosurgery, and psychiatry 2017;88:310-316.

6. Chung SJ, Yoo HS, Lee YH, et al. Frontal atrophy as a marker for dementia conversion in Parkinson's disease with mild cognitive impairment. Human brain mapping 2019;40:3784-3794.

7. Jacobs DM, Marder K, Cote LJ, Sano M, Stern Y, Mayeux R. Neuropsychological characteristics of preclinical dementia in Parkinson's disease. Neurology 1995;45:1691-1696.

8. Mahieux F, Fenelon G, Flahault A, Manifacier MJ, Michelet D, Boller F. Neuropsychological prediction of dementia in Parkinson's disease. Journal of

neurology, neurosurgery, and psychiatry 1998;64:178-183.

9. Levy G, Jacobs DM, Tang MX, et al. Memory and executive function impairment predict dementia in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 2002;17:1221-1226.

10. Janvin CC, Aarsland D, Larsen JP. Cognitive predictors of dementia in Parkinson's disease: a community-based, 4-year longitudinal study. Journal of geriatric psychiatry and neurology 2005;18:149-154.

11. Hobson P, Meara J. Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. Movement disorders : official journal of the Movement Disorder Society 2004;19:1043-1049.

12. Cholerton BA, Zabetian CP, Wan JY, et al. Evaluation of mild cognitive impairment subtypes in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 2014;29:756-764.

13. Scheltens P, Barkhof F, Leys D, et al. A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. Journal of the neurological sciences 1993;114:7-12.

14. Kang Y, S. J, Na DL. Seoul Neuropsychological Screening Battery (SNSB-II), 2nd ed. Seoul: Human Brain Research & Consulting Co., 2012.

15. Kang YW, Na DL, Hahn SH. A validity study on the korean mini-mental state examination (K-MMSE) in dementia patients. J Korean Neurol Assoc 1997;15:300-308.

16. Dubois B, Burn D, Goetz C, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. Movement disorders : official journal of the Movement Disorder Society 2007;22:2314-2324.

17. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 2007;22:1689-1707; quiz 1837.

18. Yoo HS, Chung SJ, Lee PH, Sohn YH, Kang SY. The Influence of Body Mass Index at Diagnosis on Cognitive Decline in Parkinson's Disease. Journal of clinical neurology (Seoul, Korea) 2019;15:517-526.

19. Kang SJ. "The Reliability and Validity of the Korean Instrumental Activities of Daily Living (K-IADL)". J Korean Neurol Assoc 2002;20:8-14.

20. Ku HM, Kim JH, Kwon EJ, et al. A Study on the Reliability and Validity of Seoul-Instrumental Activities of Daily Living(S-IADL). J Korean Neuropsychiatr Assoc 2004;43:189-199.

21. Rouzier R, Pusztai L, Delaloge S, et al. Nomograms to predict pathologic complete response and metastasis-free survival after preoperative chemotherapy for breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2005;23:8331-8339.

22. Chung SJ, Yoo HS, Oh JS, et al. Effect of striatal dopamine depletion on cognition in de novo Parkinson's disease. Parkinsonism & related disorders 2018;51:43-48.

23. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Movement disorders : official journal of the Movement Disorder Society 2012;27:349-356.

24. Monchi O, Hanganu A, Bellec P. Markers of cognitive decline in PD: The case for heterogeneity. Parkinsonism & related disorders 2016;24:8-14.

25. Sullivan EV, Sagar HJ, Gabrieli JD, Corkin S, Growdon JH. Different

cognitive profiles on standard behavioral tests in Parkinson's disease and Alzheimer's disease. Journal of clinical and experimental neuropsychology 1989;11:799-820.

26. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annual review of neuroscience 1986;9:357-381.

27. Robbins TW, Cools R. Cognitive deficits in Parkinson's disease: a cognitive neuroscience perspective. Movement disorders : official journal of the Movement Disorder Society 2014;29:597-607.

28. Bohnen NI, Kaufer DI, Ivanco LS, et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. Archives of neurology 2003;60:1745-1748.

29. Ray NJ, Strafella AP. The neurobiology and neural circuitry of cognitive changes in Parkinson's disease revealed by functional neuroimaging. Movement disorders : official journal of the Movement Disorder Society 2012;27:1484-1492.

30. Bohnen NI, Koeppe RA, Minoshima S, et al. Cerebral glucose metabolic features of Parkinson disease and incident dementia: longitudinal study. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2011;52:848-855.

31. Tard C, Demailly F, Delval A, et al. Hypometabolism in Posterior and Temporal Areas of the Brain is Associated with Cognitive Decline in Parkinson's Disease. Journal of Parkinson's disease 2015;5:569-574.

32. Weintraub D, Dietz N, Duda JE, et al. Alzheimer's disease pattern of brain atrophy predicts cognitive decline in Parkinson's disease. Brain : a journal of neurology 2012;135:170-180.

33. Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's

disease. The Lancet Neurology 2010;9:1200-1213.

34. Schwartz S, Baldo J, Graves RE, Brugger P. Pervasive influence of semantics in letter and category fluency: a multidimensional approach. Brain and language 2003;87:400-411.

35. Robinson G, Shallice T, Bozzali M, Cipolotti L. The differing roles of the frontal cortex in fluency tests. Brain : a journal of neurology 2012;135:2202-2214.

36. Henry JD, Crawford JR. A meta-analytic review of verbal fluency performance following focal cortical lesions. Neuropsychology 2004;18:284-295.

37. Baldo JV, Schwartz S, Wilkins D, Dronkers NF. Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. Journal of the International Neuropsychological Society : JINS 2006;12:896-900.

38. Lang S, Hanganu A, Gan LS, et al. Network basis of the dysexecutive and posterior cortical cognitive profiles in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 2019;34:893-902.

39. Johnson DK, Galvin JE. Longitudinal changes in cognition in Parkinson's disease with and without dementia. Dementia and geriatric cognitive disorders 2011;31:98-108.

40. Lee JE, Cho KH, Song SK, et al. Exploratory analysis of neuropsychological and neuroanatomical correlates of progressive mild cognitive impairment in Parkinson's disease. Journal of neurology, neurosurgery, and psychiatry 2014;85:7-16.

41. Huang C, Mattis P, Tang C, Perrine K, Carbon M, Eidelberg D. Metabolic brain networks associated with cognitive function in Parkinson's disease. NeuroImage 2007;34:714-723.

42. Simons JS, Spiers HJ. Prefrontal and medial temporal lobe interactions in

long-term memory. Nature reviews Neuroscience 2003;4:637-648.

43. Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. The Journal of neuroscience : the official journal of the Society for Neuroscience 2006;26:63-72.

44. Aarsland D, Creese B, Politis M, et al. Cognitive decline in Parkinson disease. Nature reviews Neurology 2017;13:217-231.

45. Mak E, Su L, Williams GB, et al. Baseline and longitudinal grey matter changes in newly diagnosed Parkinson's disease: ICICLE-PD study. Brain : a journal of neurology 2015;138:2974-2986.

46. Tropea TF, Xie SX, Rick J, et al. APOE, thought disorder, and SPARE-AD predict cognitive decline in established Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 2018;33:289-297.

47. Williams-Gray CH, Hampshire A, Barker RA, Owen AM. Attentional control in Parkinson's disease is dependent on COMT val 158 met genotype. Brain : a journal of neurology 2008;131:397-408.

48. Nombela C, Rowe JB, Winder-Rhodes SE, et al. Genetic impact on cognition and brain function in newly diagnosed Parkinson's disease: ICICLE-PD study. Brain : a journal of neurology 2014;137:2743-2758.

49. Oeda T, Umemura A, Mori Y, et al. Impact of glucocerebrosidase mutations on motor and nonmotor complications in Parkinson's disease. Neurobiology of aging 2015;36:3306-3313.

50. Mata IF, Leverenz JB, Weintraub D, et al. APOE, MAPT, and SNCA genes and cognitive performance in Parkinson disease. JAMA neurology 2014;71:1405-1412.

Table 1. Demographic characteristics of study participants

	Patients with PD (n = 350)
Age (years)	67.85 ± 8.31
Female, No. (%)	183 (52.3%)
Onset of age (years)	66.27 ± 8.49
Time from symptom onset to diagnosis (months)	18.54 ± 16.74
Follow-up duration (years)	5.59 ± 1.93
UPDRS-III scores	22.16 ± 9.71
Education (years)	9.62 ± 4.37
K-MMSE scores	26.97 ± 2.67
Total WMHs burden	10.35 ± 7.63

Values are expressed as the mean ± standard deviation or number (percentage).

Abbreviations: PD, Parkinson's disease; UPDRS-III, the Unified Parkinson's disease Rating Scale Part III; K-MMSE, the Korean version of the Mini-Mental State Examination; WMHs, white matter hyperintensities.

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

z-scores		Factor loadings			
Cognitive subtest	**Cognitive domain**	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**
RCFT immediate recall	Visual memory	0.898	0.189	0.063	0.054
RCFT delayed recall	Visual memory	0.896	0.201	0.101	0.054
RCFT copy	Visuospatial	0.612	-0.020	0.224	0.225
RCFT recognition	Visual memory	0.538	0.139	-0.063	0.444
SVLT delayed recall	Verbal memory	0.195	0.864	0.139	0.102
SVLT recognition	Verbal memory	0.078	0.831	0.021	0.190
SVLT immediate recall	Verbal memory	0.143	0.786	0.319	0.073
COWAT supermarket	Frontal/executive	-0.079	0.093	0.730	-0.015
COWAT animal	Frontal/executive	0.062	0.157	0.726	0.076
COWAT phonemic	Frontal/executive	0.167	0.115	0.678	0.290
Stroop color reading	Frontal/executive	0.286	0.066	0.621	0.121
Forward digit span	Attention/working memory	0.031	0.086	0.025	0.811
Backward digit span	Attention/working memory	0.178	0.119	0.260	0.705
K-BNT	Language	0.309	0.199	0.223	0.455

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. Abbreviation: 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.

Table 3. Component score coefficients and mean (standard deviation) of the neuropsychological subtests

z-scores			Component score coefficients			
Cognitive subtest	**Mean**	**SD**	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**
RCFT immediate recall	-0.29	1.11	0.422	-0.016	-0.054	-0.156
RCFT delayed recall	-0.29	1.08	0.417	-0.014	-0.034	-0.163
RCFT copy	-0.04	1.28	0.259	-0.138	0.058	0.026
RCFT recognition	-0.09	1.07	0.179	-0.025	-0.149	0.227
SVLT delayed recall	-0.49	1.18	-0.033	0.436	-0.060	-0.069
SVLT recognition	-0.22	1.05	-0.098	0.437	-0.126	0.039
SVLT immediate recall	-0.19	1.15	-0.056	0.378	0.059	-0.098
COWAT supermarket	-0.35	1.03	-0.096	-0.030	0.405	-0.107
COWAT animal	-0.38	1.12	-0.048	-0.020	0.373	-0.071
COWAT phonemic	-0.25	1.15	-0.026	-0.073	0.315	0.081
Stroop color reading	-0.39	1.31	0.076	-0.090	0.305	-0.055
Forward digit span	0.25	1.02	-0.148	-0.043	-0.111	0.593
Backward digit span	-0.17	1.08	-0.072	-0.061	0.022	0.449
K-BNT	-0.25	1.10	0.034	-0.001	0.017	0.233

Standardized score for neuropsychological subtest was calculated as (raw z-score - mean) / (standard deviation). For example, if the z-score of K-BNT is -0.04, then its standardized score is calculated as (-0.04 + 0.25) / 1.10.

Then, the composite score of each cognitive function factor was calculated as the sum of (component score coefficient × standardized score for the neuropsychological subtest) as follows:

Factor 1 (*visual memory/visuospatial*) = 0.422 × RCFT (immediate recall) + 0.417 × RCFT (delayed recall) + 0.259 × RCFT copy + 0.179 × RCFT (recognition) - 0.033 × SVLT

(delayed recall) - 0.098 × SVLT (recognition) - 0.056 × SVLT (immediate recall) - 0.096 × COWAT-semantic fluency [supermarket] - 0.048 × COWAT-semantic fluency [animal] - 0.026 × COWAT-phonemic fluency + 0.076 × Color Stroop test - 0.148 × Forward digit span - 0.072 × Backward digit span + 0.034 × K-BNT

Factor 2 (*verbal memory*) = -0.016 × RCFT (immediate recall) -0.014 × RCFT (delayed recall) - 0.138 × RCFT copy - 0.025 × RCFT (recognition) + 0.436 × SVLT (delayed recall) + 0.437 × SVLT (recognition) + 0.378 × SVLT (immediate recall) - 0.030 × COWAT-semantic fluency [supermarket] - 0.020 × COWAT-semantic fluency [animal] - 0.073 × COWAT-phonemic fluency - 0.090 × Color Stroop test - 0.043 × Forward digit span - 0.061 × Backward digit span - 0.001 × K-BNT

Factor 3 (*frontal/executive*) = -0.054 × RCFT (immediate recall) - 0.034 × RCFT (delayed recall) + 0.058 × RCFT copy - 0.149 × RCFT (recognition) - 0.060 × SVLT (delayed recall) - 0.126 × SVLT (recognition) + 0.059 × SVLT (immediate recall) + 0.405 × COWAT-semantic fluency [supermarket] + 0.373 × COWAT-semantic fluency [animal] + 0.315 × COWAT-phonemic fluency + 0.305 × Color Stroop test - 0.111 × Forward digit span + 0.022 × Backward digit span + 0.017 × K-BNT

Factor 4 (*attention/working memory/language*) = -0.156 × RCFT (immediate recall) -0.163 × RCFT (delayed recall) + 0.026 × RCFT copy + 0.227 × RCFT (recognition) - 0.069 × SVLT (delayed recall) + 0.039 × SVLT (recognition) - 0.098 × SVLT (immediate recall) - 0.107 × COWAT-semantic fluency [supermarket] - 0.071 × COWAT-semantic fluency [animal] + 0.081 × COWAT-phonemic fluency - 0.055 × Color Stroop test + 0.593 × Forward digit span + 0.449 × Backward digit span + 0.233 × K-BNT

Table 4. Cox regression analyses for conversion to dementia according to factor cognitive composite scores (Model 1) and global cognitive composite scores (Model 2)

	Hazard ratio (95% CI)	*p*-value
Model 1		
Factor 1 (*visual memory/visuospatial*)	0.558 (0.427−0.730)	< 0.001
Factor 2 (*verbal memory*)	0.768 (0.596−0.991)	0.042
Factor 3 (*frontal/executive*)	0.425 (0.305−0.593)	< 0.001
Factor 4 (*attention/working memory/language*)	0.878 (0.678−1.119)	0.293
Age	1.065 (1.028−1.103)	0.001
Sex (Female vs. Male)	0.787 (0.447−1.387)	0.408
Disease duration	1.014 (0.999−1.030)	0.072
UPDRS-III scores	0.986 (0.957−1.015)	0.339
Years of education	0.982 (0.924−1.043)	0.549
Total WMHs burden	0.989 (0.958−1.022)	0.508
Model 2		
Global cognitive composite score[a]	0.109 (0.052−0.228)	< 0.001
Age	1.071 (1.032−1.111)	< 0.001
Sex (Female vs. Male)	0.604 (0.361−1.011)	0.055
Disease duration	1.081 (1.003−1.033)	0.017
UPDRS-III scores	0.999 (0.973−1.026)	0.970
Years of education	0.986 (0.930−1.044)	0.624
Total WMHs burden	0.989 (0.956−1.022)	0.499

Abbreviations: UPDRS-III, the Unified Parkinson's disease Rating Scale Part III; WMHs,

white matter hyperintensities; CI, confidence interval.

[a] Global cognitive composite score was calculated by weighting the eigenvalues of the four cognitive function factors as follows: global cognitive composite score = (4.582 × Factor 1 + 1.678 × Factor 2 + 1.442 × Factor 3 + 1.132 × Factor 4) / 14.

Table 5. Predictive accuracy of Cox regression models for the dementia conversion according to the composite scores of each cognitive function factor

	Factor 1		Factor 2		Factor 3		Factor 4	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Cox regression analyses								
Composite score	0.528 (0.401−0.695)	< 0.001	0.807 (0.626−1.042)	0.100	0.428 (0.307−0.596)	< 0.001	0.923 (0.734−1.161)	0.495
Age	1.081 (1.042−1.121)	< 0.001	1.074 (1.038−1.112)	< 0.001	1.006 (1.031−1.103)	< 0.001	1.073 (1.037−1.111)	< 0.001
Sex (Female vs. Male)	0.478 (0.282−0.808)	0.006	0.700 (0.401−1.220)	0.208	0.860 (0.501−1.474)	0.582	0.607 (0.356−1.034)	0.066
Disease duration	1.020 (1.006−1.034)	0.006	1.020 (1.005−1.035)	0.008	1.013 (0.998−1.029)	0.088	1.018 (1.004−1.033)	0.014
UPDRS-III scores	0.999 (0.974−1.024)	0.920	1.004 (0.980−1.028)	0.761	0.988 (0.963−1.014)	0.351	1.005 (0.981−1.031)	0.672
Years of education	0.975 (0.921−1.032)	0.383	0.979 (0.925−1.036)	0.457	0.969 (0.915−1.027)	0.286	0.977 (0.923−1.034)	0.428
Total WMHs burden	0.988 (0.967−1.030)	0.889	1.005 (0.974−1.037)	0.764	1.004 (0.973−1.037)	0.802	1.007 (0.976−1.040)	0.647
Predictive accuracy parameters								
AIC	780.256		798.178		773.755		802.922	
Linear Trend χ^2	48.66		32.95		51.73		27.89	
Harrell's C	0.733		0.701		0.743		0.695	
iAUC	0.718		0.680		0.734		0.670	

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

The Akaike information criterion (AIC) was calculated for each Cox regression model to demonstrate which cognitive function factor was

more explanatory for predicting the conversion to dementia (a smaller AIC indicates the preferred model). Additionally, discriminatory ability (linear trend χ^2 test), the concordance index (Harrell's C-index), and a global concordance probability (integrated area under the curve [iAUC]) were also calculated for each Cox regression model to assess the predictive accuracy (larger discriminatory ability, Harrell's C-index, and iAUC indicate better predictive ability). Abbreviations: PD, Parkinson's disease; UPDRS-III, the Unified Parkinson's disease Rating Scale Part III; WMHs, white matter hyperintensities; HR, hazard ratio; CI, confidence interval.

Figure legends

Figure 1. Nomogram to calculate the risk for dementia conversion during a 5-year follow-up period in patients with Parkinson's disease (PD). Factor 1 (*visual memory/visuospatial*); Factor 2 (*verbal memory*); Factor 3 (*frontal/executive*). For example, if a 60-year-old male PD patient with a disease duration of 40 months has a composite score of -0.5, -3.0, and 0.5 for Factor 1, Factor 2, and Factor 3, the points of each variable are calculated as 4 (sex), 26 (age), 8 (disease duration), 41 (Factor 1), 38 (Factor 2), and 50 (Factor 3), respectively; therefore, the total point is 167. The total point of 167 is translated into a probability of PDD-free survival of 80.0%. In other words, the risk of PDD within 5 years in this patient can be estimated as 20.0%.