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RESEARCH ARTICLE

Visuospatial dysfunction indicates an increased risk of rapid dementia conversion in Parkinson's disease

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Abstract

INTRODUCTION: The aim of this study was to define cognitive subtypes of early-stage Parkinson's disease (PD) based on temporal evolutionary patterns of domain-specific decline.

METHODS: We retrospectively enrolled 474 patients with early-stage PD who underwent detailed neuropsychological testing at initial assessment. Age- and education-specific *z*-scores from 13 neuropsychological subtests were used to apply Subtype and Stage Inference (SuStaIn) to identify distinct cognitive subtypes. We compared the risk of developing dementia between subtypes.

RESULTS: SuStaIn analysis delineated three pd subtypes with cognitive impairment: Subtype 1 ($n = 121$) with early verbal memory impairment; Subtype 2 ($n = 108$) with early visuospatial dysfunction; and Subtype 3 ($n = 87$) with early frontal/executive dysfunction. The remaining 158 patients were classified as a cognitively intact subtype (Subtype 0). Time-dependent Cox regression models showed that the risk of dementia after 3.5 years was highest in Subtype 2.

DISCUSSION: Visuospatial dysfunction may be a potential cognitive profile for predicting the risk of rapid dementia conversion in PD.

KEYWORDS
cognitive profile, dementia, Subtype and Stage Inference (SuStaIn), Parkinson's disease, visuospatial

Chan Wook Park and Youngseok Choi contributed equally to this work.

Seok Jong Chung is the lead contact. Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Seok Jong Chung (sjchung@yuhs.ac).

Highlights

- Cognitive profile associated with early dementia conversion in Parkinson's disease (PD) remains unclear.
- This study applied the SuStaIn algorithm to delineate three cognitive subtypes of PD.
- PD subtype with early visuospatial dysfunction had a higher risk of dementia.
- Visuospatial dysfunction indicates an imminent risk of dementia conversion in PD.

1 | BACKGROUND

Cognitive impairment is commonly observed in patients with Parkinson's disease (PD), while approximately 40% of patients develop dementia within 10 years.[1] Dementia conversion is a key milestone in the progression of non-motor disability in PD, which greatly affects morbidity and mortality. Therefore, early identification of patients at imminent risk of dementia conversion is important to facilitate closer patient monitoring and allow the rapid implementation of personalized therapeutic strategies.[2,3]

Cognitive deficits in PD have traditionally been classified as subcortical (i.e., greater impairments in executive abilities)[4]; however, recent studies have shown that the profile of cognitive impairment experienced by patients with PD is highly variable, with the vast majority of patients with PD with mild cognitive impairment (PD-MCI), having multiple cognitive domains affected.[5] Furthermore, the neurobiological basis of PD with dementia (PDD) is complex, involving multiple neurotransmitter systems, genetic factors, and coexistent Alzheimer's disease-related or vascular pathologies.[6] In this regard, several attempts to determine the cognitive profile associated with progression to PDD have yielded heterogeneous results, with all cognitive domains (i.e., frontal/executive,[7–11] memory,[9,12,13] visuospatial,[3,8,14] and language function domains[12]) reported to be associated with PDD conversion. However, prior studies were limited by methodological concerns; the majority of such studies included patients at varying disease stages and identified neuropsychological predictors by employing particular cognitive tests and calculating their relative risks of PDD conversion. The accurate determination of cognitive decline requires longitudinal follow-up of an incident PD cohort. In addition, this approach may be biased by which neuropsychological tests are chosen and how they interact with each other.[3,11,14]

To overcome these limitations, the present study enrolled newly diagnosed PD cases from two incident PD cohorts and applied the Subtype and Stage Inference (SuStaIn) algorithm[15] to identify the distinct subtypes of cognitive impairment in early-stage PD based on the temporal evolutionary patterns of domain-specific cognitive decline. We subsequently compared the risk of PDD conversion between subtypes. This approach makes it easier to determine the involvement of specific cognitive domains in the cognitive prognosis.

2 | METHODS

2.1 | Subjects

We reviewed the medical records of 474 consecutive drug-naïve patients with early-stage PD who visited the Movement Disorders outpatient clinic at Severance Hospital (n = 249, January 2015 to November 2018) and Yongin Severance Hospital (n = 225, June 2020 to September 2024) and underwent detailed neuropsychological testing upon initial assessment. PD was diagnosed according to the Movement Disorder Society (MDS) clinical diagnostic criteria.[16] All patients underwent dual-phase ^{18}F-FP-CIT positron emission tomography (PET) scans at initial diagnosis and showed appropriate decreases in striatal dopamine transporter (DAT) availability on late-phase ^{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). Parkinsonian motor deficit severity was assessed using the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III), and motor subtypes (i.e., tremor-dominant, postural instability/gait difficulty [PIGD], or indeterminate) were determined based on UPDRS scores.[17] Olfactory function was measured using the Cross-Cultural Smell Identification Test (CCSIT), and depression was evaluated using the Beck Depression Inventory (BDI). The presence of rapid eye movement sleep behavior disorder (RBD) was determined using the 13-item RBD Screening Questionnaire with a cutoff score of 5/6.[18] 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.

2.2 | Neuropsychological assessment

All subjects underwent a comprehensive neuropsychological test battery in the Korean language, that is, the Seoul Neuropsychological Screening Battery (SNSB).[19,20] Among the scorable subtests of the SNSB, age- and education-specific z-scores for the following 13 items were assessed: backward digit span task, the Korean version of the Boston Naming Test (K-BNT), Rey Complex Figure Test (RCFT) copy,

RESEARCH IN CONTEXT

1. **Systematic review**: We searched PubMed and reviewed published studies investigating the cognitive profile associated with early dementia conversion in Parkinson's disease (PD). Collectively, prior studies have failed to yield consistent results and are limited by several methodological issues.
2. **Interpretation**: Our study applied Subtype and Stage Inference (SuStaIn), a probabilistic machine-learning method, to delineate three cognitive subtypes of early-stage PD, based on the temporal evolutionary patterns of domain-specific cognitive decline. The PD subtype with early visuospatial dysfunction, along with dopamine deficits in the associative and limbic striata and posterior cortical hypoperfusion, had an increased risk of dementia conversion.
3. **Future directions**: Our results suggest that visuospatial dysfunction could be a potential cognitive profile to predict an imminent risk of dementia conversion in patients with PD. Further studies are needed to validate whether this approach can identify patients at high risk for early dementia conversion across diverse cohorts.

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) and the sum of boxes of the Clinical Dementia Rating (CDR-SB) were used to assess general cognition and function.[21,22]

2.3 | Subtyping and progression patterns modeling of PD-related cognitive impairment

The SuStaIn was used to identify distinct cognitive subtypes of PD and the temporal trajectories of their cognitive decline using the Python package (pySuStaIn; https://github.com/ucl-pond/pySuStaIn).[23] The algorithm models disease progression as the continuous accumulation of biomarker abnormalities, in which each biomarker is assumed to follow a piecewise linear trajectory over a common progression timeline. In our analysis, we applied the linear *z*-score version of the SuStaIn, which captures gradual changes in biomarker levels rather than instantaneous transitions.

For SuStaIn modeling, each of the 13 neuropsychological test scores was standardized as a *z*-score relative to cognitively unimpaired populations ($n = 1067$)[20] so that the control group had a mean of 0 and a standard deviation of 1.[24–28] To account for any potential confounding factors, we regressed out the effects of age and years of education as covariates from each cognitive domain during *z*-score calculations. As lower *z*-scored cognitive scores indicate greater impairment, we multiplied all *z*-scores by −1 so that higher values consistently represented more severe cognitive decline.[24–28] The adjusted *z*-scores were subsequently used as inputs for SuStaIn to infer any subtype-specific trajectories and stages of cognitive impairment. For modeling, we defined two *z*-score events for each cognitive score: $z = 1$ and $z = 3$, with Zmax = 5. The optimal number of subtypes was determined iteratively based on the cross-validation information criterion (CVIC) by calculating the out-of-sample likelihoods across a 10-fold cross-validation.[29] For the cross-validation, the dataset was randomly split into 10-folds, and for each candidate number of subtypes, the model was repeatedly trained on 9-folds and evaluated on the remaining fold to obtain out-of-sample log-likelihoods. These were aggregated into the CVIC, and the number of subtypes was selected as the model with the minimum CVIC across folds.

2.4 | Quantitative analyses of dual-phase 18F-FP-CIT PET images

2.4.1 | Acquisition of dual-phase ^{18}F-FP-CIT PET images

^{18}F-FP-CIT PET was performed using a Discovery 600 PET/CT scanner (GE Healthcare, Milwaukee, WI, USA). Image acquisition was performed according to the previously described methodology (Supporting Information).[30]

2.4.2 | Early-phase ^{18}F-FP-CIT PET images

Image preprocessing was conducted using the Statistical Parametric Mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm) and Advanced Normalization Tools (ANTs).[31,32] For each participant, early-phase ^{18}F-FP-CIT PET images were first rigidly aligned to the corresponding T1-weighted magnetic resonance imaging (MRI) scans using 6 degrees of freedom (DOF) registration and then nonlinearly warped to the Mayo Clinic Adult Lifespan Template (MCALT; https://www.nitrc.org/projects/mcalt) space.[33] The standardized uptake value ratio (SUVR) images were subsequently normalized to the median uptake of cerebellar gray matter as the reference.[34,35] Then, regional SUVRs were calculated by measuring the median uptake in each region of interest (ROI). ROIs were defined using an in-house version of the automated anatomic labeling atlas. The ROIs included in this analysis comprised the frontal, parietal, temporal, and occipital cortices, as well as the insula, precuneus, limbic regions, and posterior cingulate cortex.

The Parkinson's disease-related pattern (PDRP) was estimated from early-phase ^{18}F-FP-CIT PET images in an independent derivation sample of 30 individuals with PD and 30 age- and sex-matched healthy controls.[36] None of the PD participants in the derivation

cohort overlapped with the main analysis cohort; however, a subset of the healthy controls was shared between the cohorts. Spatial covariance analysis was performed using scaled subprofile modeling with principal component analysis (SSM/PCA) implemented in ScAnVP (https://feinsteinneuroscience.org/). Subject-level PDRP expression scores were computed as previously reported.[37]

2.4.3 | Late-phase ^{18}F-FP-CIT PET data

Image processing was conducted using Statistical Parametric Mapping 12 (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK) and in-house software implemented in MATLAB R2021a. T1-weighted images were first corrected for inhomogeneity and then segmented into five tissues based on tissue probability maps. Using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox and the in-house DARTEL template, T1-weighted images were spatially normalized to the Montreal Neurological Institute (MNI) template space. PET images were co-registered to their corresponding T1-weighted images and subsequently normalized to the MNI space with the flow-field normalizing MR images. The regional standardized uptake value (SUV) was measured by overlaying an in-house volume-of-interest (VOI) template for the striatal subregions. Then, the specific/nonspecific binding ratio (SNBR) was calculated for each striatal subregion as the target regional SUV divided by the cerebellar gray matter SUV (reference), by dividing the difference in uptake values between each VOI and the reference region by the uptake in the reference region. The striatum was further segmented into the anterior caudate, posterior caudate, anterior putamen, posterior putamen, ventral putamen, and ventral striatum. The DAT availability in each striatal subregion was estimated using established methodologies.[38] Additionally, the asymmetry index of the striatal SNBR was calculated using a ratio of DAT availability in the posterior putamen, as follows: (less-affected side–more-affected side)/(less-affected side + more-affected side).

2.5 | Assessment of dementia conversion during follow-up

Following the diagnosis of PD, patients visited the outpatient clinic at 3-month intervals, where movement disorders specialists (P.H.L. and Y.H.S. in Severance Hospital; S.J.C. and Y.J.K. in Yongin Severance Hospital) evaluated the conversion to dementia during follow-up (> 2 years).[11,39] At each visit, neurologists interviewed patients and caregivers regarding overall daily functioning, and all patients underwent annual cognitive screening with K-MMSE and the clock drawing test. When definite cognitive decline or functional impairment due to cognitive changes was suspected, a comprehensive neuropsychological assessment using SNSB was performed to characterize the pattern of deficits. PDD was then diagnosed by consensus between two neurologists and one neuropsychologist according to the MDS Task Force criteria, requiring impairment in at least two cognitive domains and loss of activities of daily living, after excluding other systemic, vascular, or drug-related causes of cognitive impairment (see Supporting Information for full details).[40–42] Time-to-event was defined as the time from the diagnosis of PD to the occurrence of dementia or the last clinic visit (for patients without these events).

2.6 | Statistical analysis

Baseline demographic characteristics and cognitive performance levels were compared between the identified PD subtypes using one-way analysis of variance (ANOVA) and Pearson's χ^2 tests for continuous and categorical variables, respectively. To compare striatal DAT availability and regional SUVR values on early-phase ^{18}F-FP-CIT PET images between the PD subtypes, analysis of covariance (ANCOVA) was applied, adjusting for age and sex as covariates. The Bonferroni correction was used for multiple comparisons correction following one-way ANOVA and ANCOVA. Pearson's correlation coefficient was calculated to assess the relationship between several clinical parameters (i.e., UPDRS-III scores, DAT availability in the posterior putamen, PDRP expression, K-MMSE score, and CDR-SB) and the SuStaIn stages in each PD subtype. Differences in Pearson's correlation coefficients between the two groups were assessed using Fisher's r-to-z transformation.[43] Each correlation coefficient was converted to a z-score, and the inter-group differences were tested with a standard normal approximation.

The log-rank test was applied to compare the risk of dementia conversion between PD subtypes. Before conducting Cox regression analyses, we tested the proportional-hazards assumption by including their interaction terms between subtypes and follow-up time, with a statistical significance of $p < 0.1$. The time-dependent covariate analysis results were statistically significant between Subtypes 1 and 3 [(Subtype 2 – Subtype 1) × time interaction term, $p = 0.063$], suggesting that the proportional-hazards assumption was not reasonable. Thus, we used the time-dependent Cox regression model to assess the effects of cognitive subtypes of PD on dementia conversion based on a 3.5-year time point (i.e., follow-up period within 3.5 years vs. > 3.5 years); this time point was chosen because the gap between Subtypes 1 and 2 on the Kaplan–Meier curves widened after this time point. Potential confounding factors, such as age at onset, sex, years of education, and baseline UPDRS-III scores, were included as covariates in the Cox proportional hazards models. Statistical analyses were conducted using the SPSS software (version 26.0; IBM Corp., Armonk, NY, USA) and the R software package (v4.0, http://www.r-project.org/). Results with a two-tailed $p < 0.05$ were considered statistically significant.

3 | RESULTS

3.1 | Subtyping and progression patterns of PD-related cognitive impairment

Ten-fold cross-validation revealed three subtypes as the optimal model. The CVIC reached its lowest value, and the test set

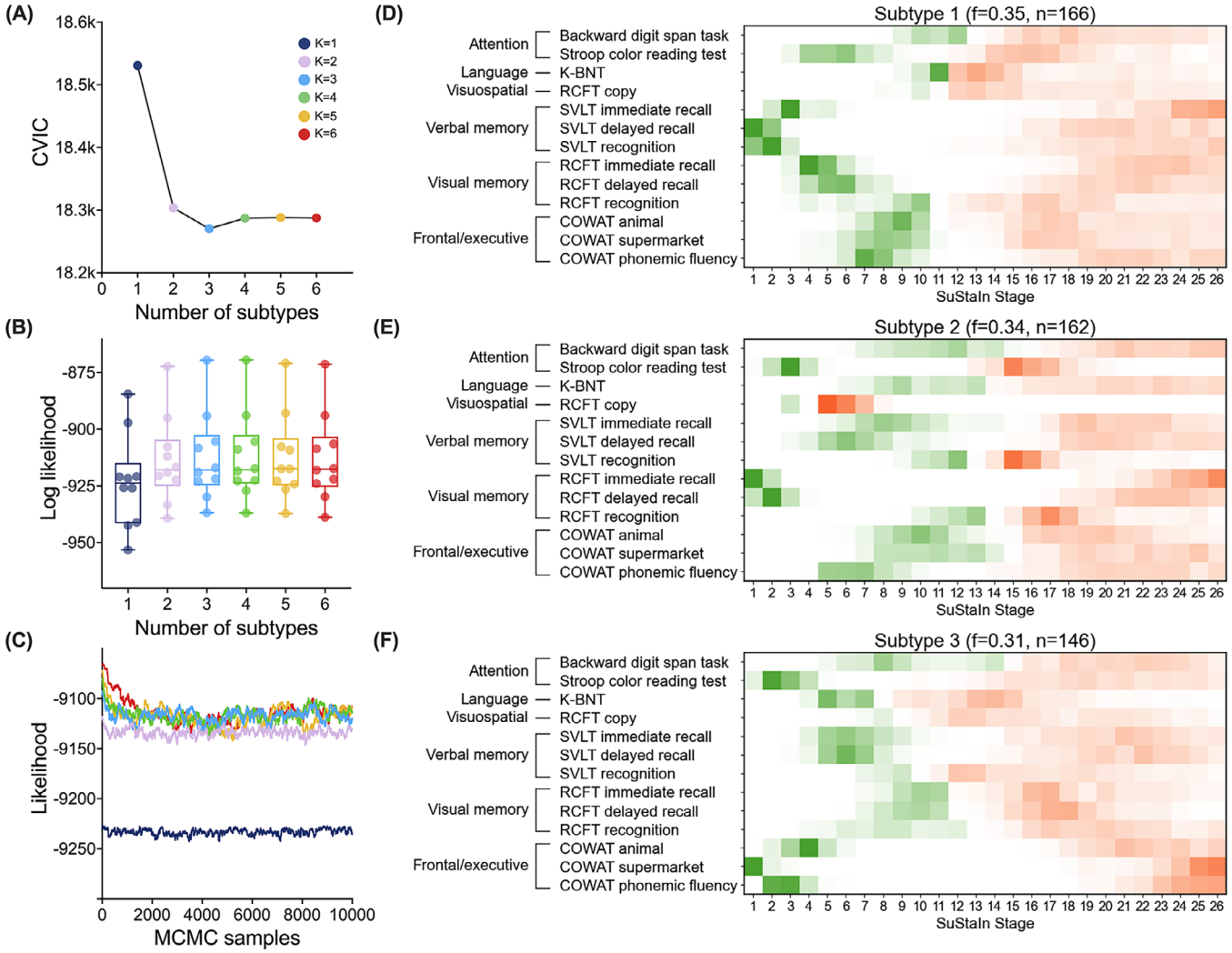


FIGURE 1 Overview of three distinct evolutionary patterns of cognitive decline observed in patients with PD. (A) The cross-validation information criterion (CVIC) from the 10-fold cross-validation shows a sharp decrease up to two splits and reaches its lowest value at two splits, indicating that the model with three subtypes provides the best summary. (B) The log-likelihood across the 10-folds increases with additional splits and begins to plateau after two splits, supporting the selection of three subtypes as the optimal solution. (C) The Markov Chain Monte Carlo (MCMC) trace demonstrates that no further improvement is observed beyond the three-subtype model. (D–F) The finalized three-subtype model assigns participants probabilistically to sequential stages, thereby delineating the subtype-specific trajectories of cognitive decline. These panels present positional variance diagrams (PVDs), in which green and orange correspond to *z*-scores of 1 and 3, respectively, with orange indicating more advanced cognitive decline than green. Color transparency reflects uncertainty in event ordering, such that solid colors indicate higher certainty, and greater transparency indicates higher uncertainty.

log-likelihood peaked when the number of splits was set to two, supporting the selection of the three subtypes as the best fit (Figure 1A, B). This conclusion was further corroborated by Markov Chain Monte Carlo (MCMC) trace analysis (Figure 1C). The finalized three-subtype model was subsequently applied to probabilistically assign participants to one of the 26 sequential stages along the corresponding subtype trajectories. Building on this modeling result, the SuStaIn model stratified patients into three cognitive subtypes of PD, each with a characteristic progression sequence (Figure 1D–F). Of the 474 patients with newly diagnosed PD, 121 (25.5%) patients were assigned to Subtype 1, which was characterized by an initial impairment in verbal memory (encoding failure, i.e., memory dysfunction with both defective encoding-retrieval strategies and impaired storage mechanisms[44]), followed by visual memory, frontal/executive dysfunction, and visuospatial dysfunction; 108 (22.8%) patients were assigned to Subtype 2, which was characterized by an initial impairment in visual memory (retrieval failure, i.e., memory dysfunction with encoding-retrieval deficits alone[44]) and visuospatial functions, followed by frontal/executive and verbal memory dysfunction; and 87 (18.4%) patients were assigned to Subtype 3, which was characterized by an initial impairment in frontal/executive function, followed by verbal memory impairments, and lastly visual memory and visuospatial dysfunctions. The remaining 158 (33.3%) patients did not show any impairments in any cognitive domain and were classified as a cognitively intact subtype (Subtype 0). Baseline demographic and clinical characteristics of Subtype 0 are presented in Table 1.

TABLE 1 Baseline clinical characteristics of PD patients designated to stage 0.

Parameter	Subtype 0 *N* = 158	Subtypes 1-3 *N* = 316	*p*-Value
Demographic characteristics			
Age (years)	69.30 ± 9.24	72.19 ± 8.50	<0.001
Onset age (year)	67.78 ± 9.28	70.37 ± 8.70	0.003
Female, No. (%)	91 (57.6%)	150 (47.5%)	0.038
PD duration (months)	18.38 ± 21.37	21.87 ± 25.06	0.067
UPDRS-III	19.70 ± 7.86	22.94 ± 9.69	<0.001
Education (years)	10.62 ± 4.01	10.70 ± 4.80	0.861
Motor subtype			0.006
Tremor dominant	64 (40.5%)	87 (27.5%)	
PIGD	70 (44.3%)	187 (59.2%)	
Indeterminate	24 (15.2%)	42 (13.3%)	
CCSIT	6.78 ± 2.31	5.90 ± 2.40	<0.001
BDI	10.68 ± 8.07	14.48 ± 9.75	<0.001
RBD	70 (44.3%)	155 (49.1%)	0.329
Vascular risk factors			
Hypertension	66 (41.8%)	180 (57.0%)	0.002
Diabetes mellitus	31 (19.6%)	100 (31.6%)	0.006
Dyslipidemia	62 (39.2%)	136 (43.0%)	0.429
Body mass index	23.47 ± 2.79	23.87 ± 3.18	0.178
Level of cognitive performance			
K-MMSE	27.74 ± 1.85	25.59 ± 3.35	<0.001
K-MMSE *z-score*	0.06 ± 0.84	−1.12 ± 1.42	<0.001
CDR	0.27 ± 0.25	0.51 ± 0.18	<0.001
CDR-SB	0.37 ± 0.38	1.70 ± 1.56	<0.001
Attention/working memory			
Digit span backward	0.25 ± 1.17	−0.49 ± 0.86	<0.001
Stroop color	0.33 ± 0.81	−1.17 ± 1.15	<0.001
Language			
K-BNT	0.31 ± 0.82	−0.61 ± 1.20	<0.001
Visuospatial			
RCFT copy	0.25 ± 0.68	−0.97 ± 1.64	<0.001
Verbal memory			
SVLT immediate recall	0.33 ± 0.83	−0.86 ± 0.81	<0.001
SVLT delayed recall	0.36 ± 0.78	−1.03 ± 0.95	<0.001
SVLT recognition	0.36 ± 0.81	−0.80 ± 1.15	<0.001
Visual memory			
RCFT immediate recall	0.22 ± 0.85	−0.88 ± 0.92	<0.001
RCFT delayed recall	0.24 ± 0.78	−0.85 ± 0.91	<0.001
RCFT recognition	0.06 ± 0.83	−0.57 ± 1.00	<0.001
Frontal/executive			
COWAT-animal	0.25 ± 0.89	−0.67 ± 1.00	<0.001
COWAT-supermarket	0.02 ± 0.90	−0.76 ± 0.88	<0.001
COWAT-phonemic	0.20 ± 0.91	−0.81 ± 0.89	<0.001
Striatal DAT availability*			
Anterior caudate	3.243 (0.066)	2.907 (0.046)	<0.001
Posterior caudate	2.073 (0.041)	1.844 (0.029)	<0.001
Anterior putamen	3.402 (0.083)	3.156 (0.058)	0.017
Posterior putamen	2.296 (0.066)	2.260 (0.047)	0.657
Ventral putamen	2.547 (0.068)	2.466 (0.048)	0.331
Ventral striatum	3.173 (0.082)	2.938 (0.058)	0.021
Asymmetry Index	0.101 ± 0.074	0.083 ± 0.068	0.008
Regional cerebral perfusion*			
PDRP	2.72 ± 3.44	4.86 ± 5.15	<0.001
Frontal cortex	0.976 (0.004)	0.972 (0.003)	0.476
Insula	0.913 (0.058)	0.894 (0.063)	0.068
Temporal cortex	0.912 (0.054)	0.900 (0.058)	0.315
Parietal cortex	0.953 (0.061)	0.939 (0.056)	0.127
Posterior cingulate cortex	1.167 (0.086)	1.131 (0.095)	0.007
Occipital cortex	1.034 (0.072)	1.009 (0.076)	0.031
Precuneus	1.018 (0.073)	0.995 (0.077)	0.054
Limbic	0.828 (0.048)	0.819 (0.057)	0.561

Note: The values are expressed as mean ± standard deviation, estimated mean (standard error), or number (percentage). Abbreviations: BDI, Beck Depression Inventory; CCSIT, the cross-cultural smell identification test; CDR, Clinical Dementia Rating; CDR-SB, sum of boxes of the Clinical Dementia Rating; COWAT, the Controlled Oral Word Association Test; DAT, dopamine transporter; K-BNT, the Korean version of the Boston Naming Test; K-MMSE, the Korean version of the Mini-Mental State Examination; PD, Parkinson's disease; PDRP, Parkinson's disease-related pattern; PIGD, postural instability/gait difficulty; RBD, rapid eye movement behavior disorder; RCFT, the Rey Complex Figure Test; SVLT, the Seoul Verbal Learning Test; UPDRS-III, Unified PD Rating Scale Part III.
*Age- and sex-adjusted.

3.2 | Demographic characteristics of the study participants

Compared to patients assigned to Subtypes 1–3 ($n = 316$), those with cognitively unimpaired PD (Subtype 0, $n = 158$) had a younger age of onset, a higher proportion of females, lower UPDRS-III scores, a higher proportion of tremor-dominant motor subtype, higher CCSIT scores, lower BDI scores, and a lower prevalence of hypertension and diabetes mellitus. There were no differences in the years of education or prevalence of RBD between Subtypes 0 and 1–3. Patients in Subtype 0 exhibited better cognitive performance in all cognitive domains than did those classified into Subtypes 1–3 (Table 1).

In direct comparisons between Subtype 1–3, Subtype 2 had a higher proportion of females and tended to be older than the other subtypes. However, there were no differences in UPDRS-III scores, years of education, motor subtypes, CCSIT scores, BDI scores, prevalence of RBD, or vascular risk factors. Subtype 1 exhibited poor cognitive performance in the verbal memory function domain, whereas Subtype

2 showed poor cognitive performance in the visuospatial and visual memory function domains, and Subtype 3 had lower scores in the frontal/executive function domain than other subtypes (Table 2).

3.3 | Correlation analyses between clinical parameters and stages in each subtype

Correlation analyses demonstrated that the stages of each subtype correlated well with the K-MMSE *z*-scores (Subtype 1, $\gamma = -0.657$, $p < 0.001$; Subtype 2, $\gamma = -0.657$, $p < 0.001$; Subtype 3, $\gamma = -0.611$, $p < 0.001$) and CDR-SB (Subtype 1, $\gamma = 0.585$, $p < 0.001$; Subtype 2, $\gamma = 0.763$, $p < 0.001$; Subtype 3, $\gamma = 0.582$, $p < 0.001$). PDRP expression showed a weak correlation with the stages of Subtype 1 ($\gamma = 0.286$, $p = 0.002$) and Subtype 2 ($\gamma = 0.224$, $p = 0.020$). The UPDRS-III scores and DAT availability in the posterior putamen did not significantly correlate with the stage of each subtype (Table 3 and Figure 2). Pairwise comparisons of the correlation coefficients showed a subtype-specific difference only for the CDR-SB (Table 3): Subtype 2 had a stronger correlation than Subtypes 1 ($p = 0.017$) and 3 ($p = 0.029$), whereas Subtypes 1 and 3 showed no difference ($p = 0.976$). No other clinical measures exhibited any significant differences between the subtypes.

3.4 | Analyses of dual-phase ^{18}F-FP-CIT PET images of subtypes

Compared with PD patients in Subtype 0, those in Subtypes 1–3 exhibited more severely decreased DAT availability in the anterior caudate, posterior caudate, anterior putamen, and ventral striatum. The DAT availability in the posterior and ventral putamen was comparable between Subtypes 0 and 1–3. However, Subtypes 1–3 exhibited more symmetric striatal dopamine depletion than did Subtype 0. Additionally, PD patients in Subtypes 1–3 had higher PDRP expression and tended to exhibit decreased uptake in the occipital, posterior cingulate, precuneus, and insular cortices on early-phase ^{18}F-FP-CIT PET images compared to those classified in Subtype 0 (Table 1).

In direct comparisons between Subtype 1–3, Subtype 2 exhibited more severely decreased DAT availability than did Subtype 1 in all striatal subregions, except for the posterior putamen. The asymmetry index of the striatal DAT availability was comparable between the subtypes. Subtype 2 further exhibited decreased uptake in the parieto-occipital cortices compared to Subtype and decreased uptake in the precuneus compared to Subtype 3. PDRP expression was comparable between the subtypes (Table 2).

3.5 | Cognitive subtypes of PD and dementia conversion

We estimated the risk of dementia conversion in patients with PD who were followed up for more than 2 years or who developed dementia within 2 years of PD diagnosis. During the follow-up period (5.17 ± 2.45 years), 24 (32.0%) of 75 patients in Subtype 1, 32 (49.2%) of 65 patients in Subtype 2, 20 (33.9%) of 59 patients in Subtype 3, and 16 (15.7%) of 102 patients in Subtype 0 developed dementia. The log-rank test demonstrated that patients in Subtype 0 had a lower risk of dementia conversion than did those in Subtypes 1–3 ($P_{\text{Log-rank}} < 0.001$; Figure 3). The Cox regression model with controlled confounding variables further demonstrated that Subtype 0 had a lower risk of developing dementia than Subtypes 1–3 (hazard ratio [HR] = 3.148, 95% confidence interval [CI] = 1.778–5.572, $p < 0.001$; Table S1).

When comparing the risk of dementia conversion between patients with low stages (stages 1–3) and those with high stages (stage > 3) for Subtype 1–3, patients in the low stages of each subtype had a lower risk of developing dementia than did those in the high stages (Subtype 1, $P_{\text{Log-rank}} = 0.004$; Subtype 2, $P_{\text{Log-rank}} < 0.001$; Subtype 3, $P_{\text{Log-rank}} = 0.003$; Figure S1).

In direct comparisons between Subtype 1–3, the Kaplan–Meier curves showed that Subtypes 1 and 3 had a comparable risk of dementia conversion ($P_{\text{Log-rank}} = 0.817$), while Subtype 2 tended to have a higher risk of dementia conversion than did Subtypes 1 ($P_{\text{Log-rank}} = 0.077$) and 3 ($P_{\text{Log-rank}} = 0.032$). Overall, these differences appeared prominent after approximately 3.5 years of follow-up (Figure 4). Next, we used the time-dependent Cox regression model (3.5-year time point) to demonstrate that the risk of dementia conversion within 3.5 years of follow-up was similar between the subtypes, while the risk of dementia conversion after 3.5 years of follow-up was significantly higher in Subtype 2 than in Subtypes 1 (HR = 7.294, 95% CI = 1.555–34.224, $p = 0.012$) and 3 (HR = 3.222, 95% CI = 1.023–10.147, $p = 0.046$; Table 4).

4 | DISCUSSION

The present study aimed to determine the cognitive profiles associated with future PDD conversion in 474 patients with early-stage PD. The major findings were as follows: (1) The SuStaIn analysis defined three PD subtypes with cognitive impairment, including Subtype 1, initially presenting with verbal memory impairment followed by frontal/executive dysfunction and visuospatial dysfunction ($n = 121$); Subtype 2, initially presenting with visuospatial and visual memory dysfunction followed by frontal/executive and verbal memory impairments ($n = 108$); and Subtype 3, initially presenting with frontal/executive dysfunction followed by verbal memory impairment and visuospatial and visual memory dysfunction ($n = 87$). The remaining one-third of patients were classified as a cognitively intact subtype (Subtype 0; $n = 158$). (2) Patients in Subtype 2 showed diffuse striatal dopamine depletion and parieto-occipital hypoperfusion compared with Subtypes 1 and 3. (3) The risk of PDD conversion after 3.5 years of follow-up was higher in Subtype 2 than in Subtypes 1 and 3. These findings indicate that all cognitive domains, including verbal memory (Subtype 1), visuospatial (Subtype 2), and frontal/executive function domains (Subtype 3), may be affected in the early stages of PD. In particular, a decline in visuospatial function could be a potential cognitive profile to predict future conversion to PDD.

TABLE 2 Baseline clinical characteristics in patients with PD.

Parameter	Subtype 1 $N = 121$	Subtype 2 $N = 108$	Subtype 3 $N = 87$	p-Value[a]	1 vs. 2[b]	1 vs. 3[b]	2 vs. 3[b]
Demographic characteristics							
Age (years)	70.92 ± 8.49	73.43 ± 7.05	72.40 ± 9.90	0.054	0.077	0.642	>0.999
Onset age (year)	68.99 ± 8.76	71.96 ± 8.4	70.42 ± 10.31	0.023	0.038	0.724	0.745
Female, no. (%)	51 (42.1%)	67 (62.0%)	32 (36.8%)	<0.001			
PD duration (months)	23.47 ± 23.55	18.25 ± 17.78	24.15 ± 33.29	0.177	0.347	>0.999	0.307
UPDRS-III	23.28 ± 9.47	22.66 ± 9.89	22.80 ± 9.84	0.879	>0.999	>0.999	>0.999
Education (years)	10.67 ± 4.64	10.09 ± 5.18	11.52 ± 4.43	0.115	>0.999	0.608	0.114
Motor subtype				0.357			
Tremor dominant	38 (31.4%)	23 (21.3%)	26 (29.9%)				
PIGD	65 (53.7%)	70 (64.8%)	52 (59.8%)				
Indeterminate	18 (14.9%)	15 (13.9%)	9 (10.3%)				
CCSIT	5.86 ± 2.66	5.73 ± 2.27	6.15 ± 2.18	0.529	>0.999	>0.999	0.800
BDI	15.62 ± 9.88	14.40 ± 9.70	13.01 ± 9.54	0.172	>0.999	0.184	0.987
RBD	59 (48.8%)	59 (54.6%)	37 (42.5%)	0.243			
Vascular risk factors							
Hypertension	68 (56.2%)	65 (60.2%)	47 (54.0%)	0.673			
Diabetes mellitus	32 (26.4%)	42 (38.9%)	26 (29.9%)	0.119			
Dyslipidemia	47 (38.8%)	56 (51.9%)	33 (37.9%)	0.074			
Body mass index	24.16 ± 3.00	23.36 ± 3.40	24.09 ± 3.09	0.127	0.180	>0.999	0.339
Level of cognitive performance							
K-MMSE	25.98 ± 3.04	25.20 ± 3.11	25.52 ± 3.97	0.208	0.238	0.966	>0.999
K-MMSE z-score	−0.94 ± 1.47	−1.34 ± 1.34	−1.10 ± 1.43	0.100	0.097	>0.999	0.736
CDR	0.51 ± 0.14	0.55 ± 0.19	0.47 ± 0.21	0.022	0.335	0.277	0.006
CDR-SB	1.62 ± 1.39	2.00 ± 1.72	1.42 ± 1.52	0.033	0.208	>0.999	0.034
Attention/working memory							
Digit span backward	−0.31 ± 0.93	−0.57 ± 0.87	−0.65 ± 0.87	0.009	0.065	0.013	>0.999
Stroop color	−0.88 ± 1.17	−1.36 ± 1.19	−1.34 ± 0.98	0.001	0.004	0.010	>0.999
Language							
K-BNT	−0.40 ± 1.06	−0.61 ± 1.18	−0.92 ± 1.35	0.011	0.553	0.005	0.196
Visuospatial							
RCFT copy	−0.29 ± 0.81	−2.23 ± 2.03	−0.36 ± 0.87	<0.001	<0.001	>0.999	<0.001
Verbal memory							
SVLT immediate recall	−1.14 ± 0.68	−0.65 ± 0.88	−0.75 ± 0.79	<0.001	<0.001	0.001	>0.999
SVLT delayed recall	−1.52 ± 0.67	−0.76 ± 1.07	−0.71 ± 0.85	<0.001	<0.001	<0.001	>0.999
SVLT recognition	−1.50 ± 0.94	−0.43 ± 1.18	−0.29 ± 0.85	<0.001	<0.001	<0.001	>0.999
Visual memory							
RCFT immediate recall	−0.94 ± 0.85	−1.40 ± 0.59	−0.16 ± 0.88	<0.001	<0.001	<0.001	<0.001
RCFT delayed recall	−0.85 ± 0.86	−1.37 ± 0.59	−0.21 ± 0.92	<0.001	<0.001	<0.001	<0.001
RCFT recognition	−0.59 ± 1.13	−0.56 ± 0.95	−0.56 ± 0.88	0.971	>0.999	>0.999	>0.999
Frontal/executive							
COWAT-animal	−0.51 ± 1.02	−0.56 ± 1.10	−1.02 ± 0.70	<0.001	>0.999	<0.001	0.003
COWAT-supermarket	−0.63 ± 0.91	−0.54 ± 0.89	−1.23 ± 0.62	<0.001	>0.999	<0.001	<0.001
COWAT-phonemic	−0.54 ± 0.86	−0.79 ± 0.99	−1.07 ± 0.72	<0.001	0.701	0.002	0.086

(Continues)

TABLE 2 (Continued)

Parameter	Subtype 1 $N = 121$	Subtype 2 $N = 108$	Subtype 3 $N = 87$	*p*-Value[a]	1 vs. 2[b]	1 vs. 3[b]	2 vs. 3[b]
Striatal DAT availability[c]							
Anterior caudate	3.030 (0.074)	2.694 (0.079)	2.872 (0.087)	0.009	0.007	0.500	0.400
Posterior caudate	1.916 (0.046)	1.712 (0.050)	1.811 (0.055)	0.012	0.009	0.419	0.557
Anterior putamen	3.332 (0.095)	2.965 (0.102)	3.125 (0.113)	0.034	0.030	0.487	0.893
Posterior putamen	2.367 (0.080)	2.157 (0.085)	2.254 (0.094)	0.204	0.228	>0.999	>0.999
Ventral putamen	2.616 (0.077)	2.326 (0.083)	2.406 (0.091)	0.033	0.036	0.241	>0.999
Ventral striatum	3.135 (0.092)	2.749 (0.099)	2.844 (0.109)	0.013	0.015	0.126	>0.999
Asymmetry Index	0.083 ± 0.071	0.082 ± 0.066	0.084 ± 0.068	0.962	>0.999	>0.999	>0.999
Regional cerebral perfusion[c]							
PDRP expression	4.69 ± 5.12	5.31 ± 5.45	4.51 ± 4.79	0.510	>0.999	>0.999	0.853
Frontal cortex	0.979 (0.005)	0.963 (0.005)	0.969 (0.006)	0.085	0.086	0.586	>0.999
Insula	0.900 (0.005)	0.890 (0.005)	0.890 (0.006)	0.340	0.613	0.668	>0.999
Temporal cortex	0.907 (0.005)	0.890 (0.005)	0.903 (0.006)	0.082	0.092	>0.999	0.341
Parietal cortex	0.948 (0.005)	0.927 (0.005)	0.941 (0.006)	0.022	0.018	>0.999	0.287
Posterior cingulate cortex	1.138 (0.008)	1.125 (0.009)	1.129 (0.010)	0.567	0.899	>0.999	>0.999
Occipital cortex	1.018 (0.007)	0.994 (0.007)	1.014 (0.008)	0.033	0.040	>0.999	0.152
Precuneus	1.002 (0.007)	0.980 (0.007)	1.006 (0.008)	0.023	0.069	>0.999	0.041
Limbic	0.822 (0.005)	0.819 (0.005)	0.815 (0.006)	0.666	>0.999	>0.999	>0.999

Note: The values are expressed as mean ± standard deviation, estimated mean (standard error), or number (percentage).
Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; BDI, Beck Depression Inventory; CCSIT, the cross-cultural smell identification test; CDR, Clinical Dementia Rating; CDR-SB, sum of boxes of the Clinical Dementia Rating; COWAT, the Controlled Oral Word Association Test; DAT, dopamine transporter; K-BNT, the Korean version of the Boston Naming Test; K-MMSE, the Korean version of the Mini-Mental State Examination; PD, Parkinson's disease; PDRP, Parkinson's disease-related pattern; PIGD, postural instability/gait difficulty; RBD, rapid eye movement behavior disorder; RCFT, the Rey Complex Figure Test; SVLT, the Seoul Verbal Learning Test; and UPDRS-III, Unified PD Rating Scale Part III.
[a]*p*-value from ANOVA or ANCOVA (age- and sex-adjusted).
[b]Bonferroni correction *p*-values of the post-hoc comparison test.
[c]Age- and sex-adjusted.

TABLE 3 Correlation analyses between clinical parameters and stages in each subtype.

Parameter	Subtype 1	Subtype 2	Subtype 3	1 vs. 2	1 vs. 3	2 vs. 3
UPDRS-III	0.126 (0.169)	0.135 (0.162)	0.147 (0.175)	0.946	0.881	0.933
ln (DAT availability)	0.013 (0.891)	−0.018 (0.856)	0.114 (0.293)	0.822	0.475	0.367
PDRP	0.286 (0.002)	0.224 (0.020)	0.170 (0.121)	0.625	0.397	0.704
K-MMSE *z-score*	−0.657 (<0.001)	−0.657 (<0.001)	−0.611 (<0.001)	1.000	0.590	0.599
CDR-SB	0.585 (<0.001)	0.763 (<0.001)	0.582 (<0.001)	0.017	0.976	0.029

Note: The values are expressed as correlation coefficients (*p*-value).
Abbreviations: CDR-SB, sum of boxes of the Clinical Dementia Rating; DAT, dopamine transporter; K-MMSE, the Korean version of the Mini-Mental State Examination; PDRP, Parkinson's disease-related pattern; and UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

Several attempts have thus far been made to identify the cognitive profile associated with early dementia conversion in patients with PD; however, they have failed to yield consistent results.[3,7–14] However, these prior studies are limited by several methodological issues, including the enrollment of patients with various disease stages, varying definitions of cognitive decline, and redundancy or overrepresentation of neuropsychological tests used in the analyses.[11,14] To overcome these methodological challenges, the present study applied the SuStaIn model to provide a data-driven classification of cognitive subtypes in early-stage PD,[15] and subsequently compared the risk of PDD between subtypes. The SuStaIn analysis delineated three distinct cognitive subtypes of PD based on the sequence and directionality of the decline in each cognitive domain (Subtypes 1–3) and one cognitively intact subtype (Subtype 0). In fact, it has traditionally been thought that the core cognitive deficits in PD involve frontal/executive function.[45] However, since the new diagnostic criteria and procedures

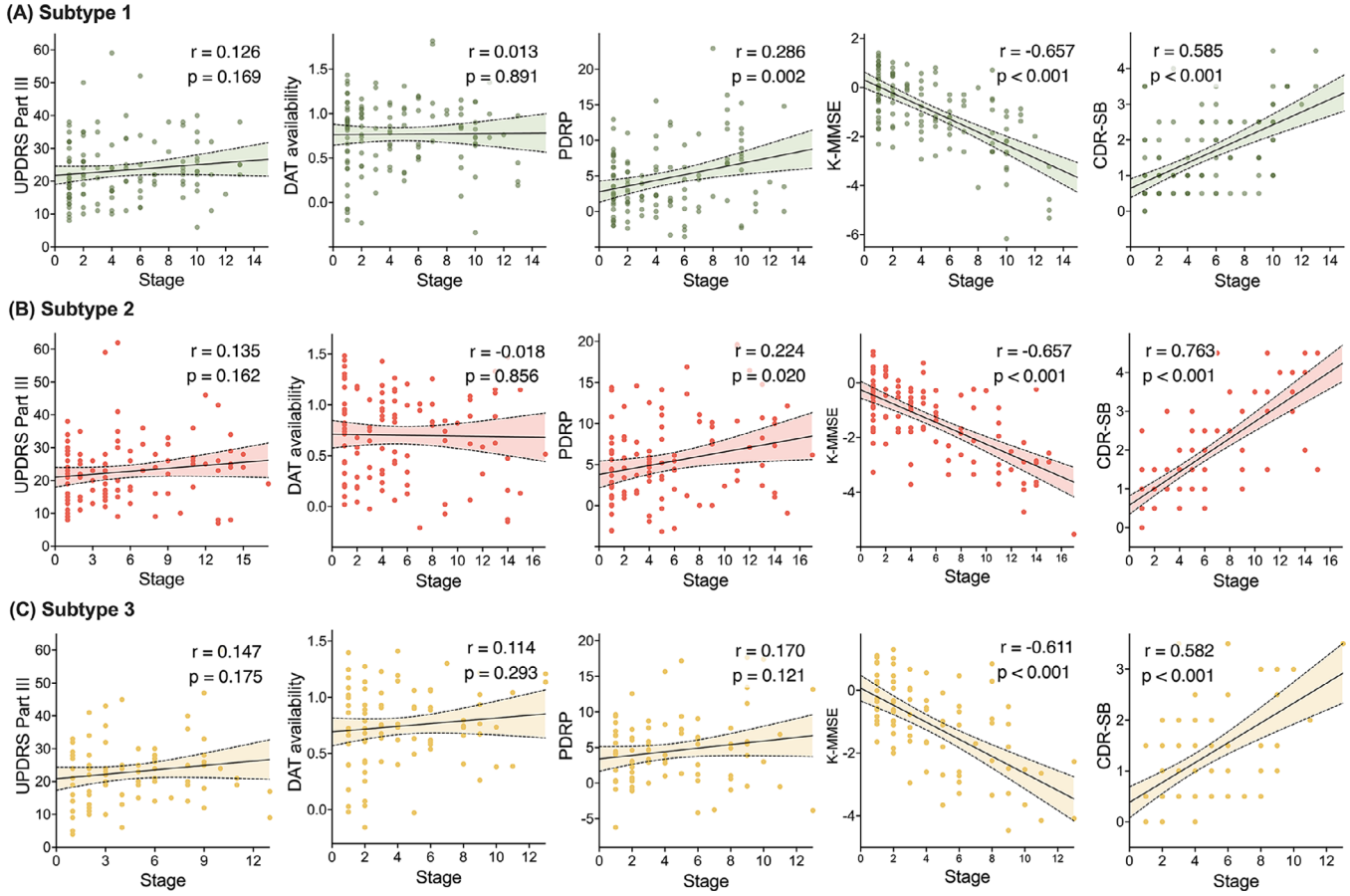
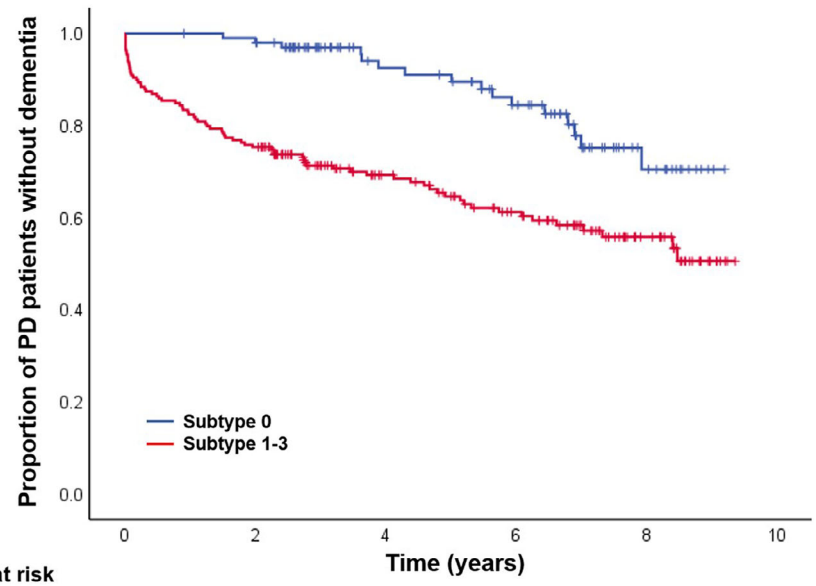


FIGURE 2 Correlation analyses between the clinical parameters and stages in each subtype. (A–C) Subtypes 1-3, respectively. Solid lines indicate linear fits; shaded bands show 95% confidence intervals. *r* denotes the Pearson's correlation coefficient, and *p* the corresponding *p*-value.



No. at risk

Subtype 0	102	99	62	48	15	0
Subtype 1-3	199	150	93	67	29	0

No. of event

Subtype 0	0	3	6	11	16	16
Subtype 1-3	0	49	59	69	74	76

FIGURE 3 Curves of Kaplan–Meier estimates of the conversion to dementia after the diagnosis of Parkinson's disease (PD). Patients with cognitively unimpaired PD (Subtype 0; $n = 102$) had a lower risk of dementia conversion than the other patients with PD (Subtype 1–3; $n = 199$; $P_{\text{Log-rank}} < 0.001$). The crosses in the graphs indicate censored data.

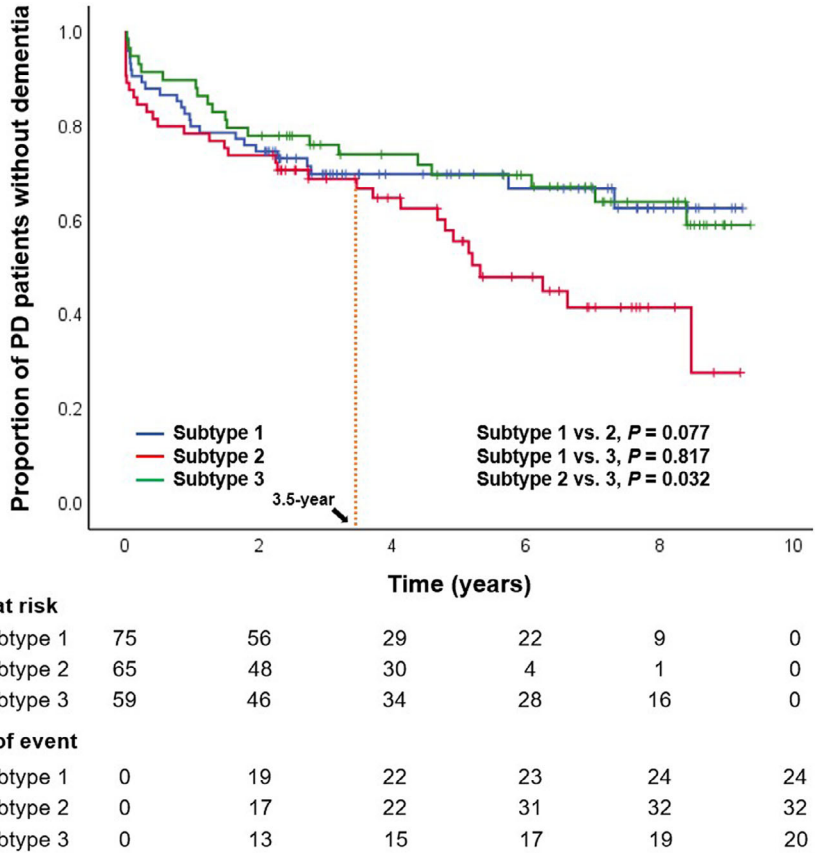


FIGURE 4 Curves of Kaplan–Meier estimates of the conversion to dementia following the diagnosis of PD. Subtype 2 tended to have a higher risk of dementia conversion than did Subtypes 1 ($P_{Log\text{-}rank} = 0.077$) and 3 ($P_{Log\text{-}rank} = 0.032$), which had a comparable risk of dementia conversion to each other ($P_{Log\text{-}rank} = 0.817$). The gap between Subtypes 1 and 2 on the Kaplan–Meier curves widened after a 3.5-year time point. Crosses in the graphs indicate censored data.

TABLE 4 Time-dependent Cox regression analysis for the conversion to dementia.

Parameter	Hazard ratio (95% CI)	*p*-Value
PD subtypes		
Follow-up period within 3.5 years		0.388
Subtype 2 vs. Subtype 1	1.084 (0.588–1.998)	0.796
Subtype 3 vs. Subtype 1	0.675 (0.337–1.351)	0.267
Subtype 2 vs. Subtype 3	1.607 (0.797–3.241)	0.185
Follow-up period after 3.5 years		0.015
Subtype 2 vs. Subtype 1	7.294 (1.555–34.224)	0.012
Subtype 3 vs. Subtype 1	2.264 (0.415–12.344)	0.345
Subtype 2 vs. Subtype 3	3.222 (1.023–10.147)	0.046
Age of onset	1.115 (1.076–1.155)	<0.001
Sex (Male vs. female)	1.676 (0.985–2.849)	0.057
Years of education	0.931 (0.884–0.980)	0.006
UPDRS-III	1.023 (1.001–1.045)	0.041

Note: We tested the proportional-hazards assumption by including an interaction term between subtypes and follow-up time with a statistical significance of $p < 0.1$. The time-dependent covariate analysis results were statistically significant between a (subtype 2 – subtype 1) × time interaction term ($p = 0.063$), suggesting that the proportional-hazards assumption was not reasonable. Thus, we used the time-dependent Cox regression model to assess the effects of cognitive subtype on dementia conversion based on a 3.5-year time point (i.e., follow-up period within 3.5 years vs. >3.5 years).
Abbreviations: CI, confidence interval; PD, Parkinson's disease; and UPDRS-III, Unified PD Rating Scale Part III.

for PD-MCI were published,[46] the profile of cognitive impairment in PD has been reported in various ways, with some studies reporting that memory impairment was the most commonly affected cognitive domain in PD.[5,47] In line with previous literature, our findings (i.e., three distinct temporal evolutionary patterns of cognitive decline) further demonstrated marked cognitive heterogeneity among patients with PD.[48]

The present study demonstrated that the risk of dementia conversion was similar across patients with three different subtypes during the first 3.5 years of follow-up; however, the risk after 3.5 years was highest in Subtype 2. As this study enrolled only patients with newly diagnosed PD, differences in the risk of dementia between subtypes are likely to become apparent only after a certain follow-up period. The results of this study are in accordance with the dual syndrome hypothesis, suggesting that cognitive deficits with a posterior cortical basis are linked to rapid cognitive decline and incident dementia in PD, whereas those with a fronto-striatal origin are not.[3,14] In fact, Subtype 2 is characterized by early involvement of visuospatial and visual memory functions, which are based on the neural substrates of the parieto-occipital circuits.[49–53] Quantitative analyses of early-phase ^{18}F-FP-CIT PET images further demonstrated that Subtype 2 was associated with more severe cerebral hypoperfusion in the parieto-occipital regions compared to other subtypes, supporting the clinical relevance of posterior cortical deficits in the risk of dementia in patients with PD.[54,55] However, some of the results of this study appear to be inconsistent with our previous studies, highlighting the contribution of

frontal/executive dysfunction and structural alterations in the frontal regions to the development of PDD.[11,39,56] This discrepancy may be attributable to methodological differences. Indeed, while the factor analysis used in a previous study simply collapsed redundant neuropsychological tests into a few independent cognitive function factors using the principal component method,[11] the SuStaIn algorithm additionally inferred subtype-specific trajectories of cognitive decline, thus demonstrating that the emergence of visuospatial dysfunction may be a sensitive indicator of impending PDD. Moreover, it should be noted that previous studies have also shown that cognitive deficits on a posterior cortical basis, as well as cortical thinning or disrupted white matter connectivity in posterior cortical regions, are associated with incident dementia in patients with PD.[11,39,56]

Additionally, Subtype 2 exhibited more severe decreases in DAT availability in the associative and limbic striata than did Subtype 1. Although it is widely accepted that the dopaminergic system is less important than the cholinergic system for future cognitive decline in PD,[57] ample evidence indicates a close relationship between nigrostriatal dopamine deficiency and cognitive dysfunction in patients with PD. A number of studies have further reported that dopaminergic deficits in the caudate are a strong candidate for cognitive impairment, mainly in the frontal/executive function domain.[58–61] The anterior putamen and ventral striatum act as an integrative hub via the convergence of multiple cortical inputs,[60,62] while a preferential dopamine loss in the anterior putamen appears to be associated with a higher risk of developing PDD.[63] Even though the exact mechanism explaining the relationship between striatal dopamine depletion and early visuospatial dysfunction in Subtype 2 remains unclear, it could be hypothesized that this relationship occurs as a secondary phenomenon to frontal system dysfunction (i.e., visuospatial impairments secondary to executive dysfunction) or a reflection of interactions between multiple neurotransmitter systems (e.g., the dopaminergic and cholinergic systems).[64,65] Accordingly, our findings indicate that the dopaminergic system is an important contributor to cognitive changes in PD.[60] Furthermore, complex interactions may exist between fronto-striatal and posterior cortical deficits.

Compared to PD patients with a cognitively normal status (i.e., Subtype 0), those within Subtypes 1–3 had a higher risk of developing PDD. In line with this clinical feature, Subtypes 1–3 exhibited more severe dopamine loss in the associative and limbic striata than did Subtype 0, as well as more symmetric striatal dopamine depletion. In addition, Subtypes 1–3 showed reductions in cerebral perfusion in the parieto-occipital regions with higher PDRP expression. Moreover, although Subtypes 1 and 3 were associated with a lower risk of dementia conversion than Subtype 2, approximately one-third of patients in Subtypes 1 and 3 still developed dementia during the follow-up period. These findings indicate that the involvement of the memory or frontal/executive function domains is also relevant to the future development of PDD,[13,56,66] even if it is not to the same extent as visuospatial dysfunction. However, it should be noted that approximately 16% of patients in Subtype 0 developed dementia during follow-up, which is consistent with previous literature showing that PD patients with normal cognition may progress to dementia over time.[60,67,68] PD itself is a neurodegenerative disorder that increases the risk of progression to dementia, and Subtype 0 also should not be considered simply a benign subtype in terms of cognitive function.

The stages of each cognitive subtype inferred through the SuStaIn analysis showed high correlations with the K-MMSE *z*-scores and CDR-SB, indicating that higher staging is associated with greater cognitive deterioration. The rate of dementia conversion also increased at higher stages across all subtypes, thus supporting the validity of the SuStaIn analysis. The stages of each cognitive subtype did not significantly correlate with the UPDRS-III scores or DAT availability in the posterior putamen. These findings are consistent with prior PET evidence that changes in PD-related cognitive metabolic pattern are not identical to those in motor-related metabolic pattern or PDRP, suggesting that the effects of disease progression vary between the motor and cognitive pathways in PD.[69]

This study had some limitations. Firstly, the SuStaIn algorithm relied primarily on cross-sectional data to reconstruct longitudinal trajectories and assumed independence between biomarkers; however, in reality, many biomarkers co-vary because of shared biological processes, thus potentially simplifying disease dynamics. Second, this study used the RCFT copy and delayed recall to assess visuospatial and visual memory functions. However, these items are not strongly recommended neuropsychological tests, and should be used cautiously in patients with PD.[70] Third, the mean age of onset of PD among study participants was quite high, likely reflecting the need for detailed neuropsychological testing for inclusion in the study. This may have influenced the results since the risk of early developing dementia increases with age at diagnosis. Finally, the possibility that Subtype 2 included some patients with dementia with Lewy bodies (DLB) cannot be completely excluded. However, we implemented a highly structured and systematic screening for core features of DLB, including fluctuating cognition and recurrent visual hallucination. This effort likely helped minimize the misclassification of prodromal DLB cases as PD cases.[16,71]

In conclusion, this study delineated three cognitive subtypes of PD with distinct temporal trajectories using the SuStaIn algorithm. These results suggest that visuospatial dysfunction, along with dopamine deficits in the associative and limbic striata and posterior cortical hypoperfusion, could be a potential cognitive profile to predict an imminent risk of dementia conversion in patients with PD.

AUTHOR CONTRIBUTIONS

Study concept and design: Jeyeon Lee and Seok Jong Chung. *Acquisition, analysis, or interpretation of data*: All authors. *Drafting of the manuscript*: Chan Wook Park, Youngseok Choi, Jeyeon Lee, and Seok Jong Chung. *Critical revision of the manuscript for important intellectual content*: All authors. *Statistical analysis*: Youngseok Choi, Hye Sun Lee, Jeyeon Lee, and Seok Jong Chung. Study supervision: Seok Jong Chung.

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CONFLICT OF INTEREST STATEMENT

No authors have conflicts of interest to disclose. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

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.

DATA AVAILABILITY STATEMENT

The anonymized data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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