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ORIGINAL ARTICLE

Neural substrates underlying distinct dual cognitive syndromes in Parkinson's disease

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Abstract

Background: A dual-syndrome hypothesis, which states the cognitive impairments in Parkinson's disease (PD) are attributable to frontostriatal dopaminergic dysregulation and cortical disturbance—each associated with attention/executive and memory/visuospatial dysfunction, respectively—has been widely accepted. This multisystem contribution also underlies highly heterogeneous progression rate to dementia.

Methods: Nondemented PD patients who underwent [^{123}I]N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane([^{123}I]FP-CIT)SPECTandneuropsychological examinations were enrolled. Patients who agreed to participate and age- and sex-matched healthy controls (HCs) also underwent 7-T MRI. Patients were classified as cognitively normal (PD-CN) or mild cognitive impairment (PD-MCI) following the level II criteria of Movement Disorder Society Guideline.

Results: A total of 155 patients (PD-CN/PD-MCI 74/81) were enrolled, whereas 76 patients (PD-CN/PD-MCI 35/41) and 56 HCs underwent 7 T-MRI. The caudate [^{123}I]FP-CIT uptake in PD was correlated with the performance of attention/working memory (trail-making test [TMT]-A and symbol digit modality test) and executive (TMT-B) domains. In contrast, the regional cortical thickness in the left frontotemporal and right frontal lobes in PD was correlated with performance of memory (Hopkins verbal learning test-revised delayed recall) and visuospatial (judgment of line orientation) domains. Moreover, compared to 37 HCs with a Montreal Cognitive Assessment score of >25, PD-CN patients showed broad occipitoparietal cortical thinning.

Conclusions: We demonstrated distinctive impairments of dopaminergic frontostriatal deficits and cortical degeneration as neural bases for the dual-syndrome hypothesis. Our findings suggest that occipitoparietal lobe thinning occurs at a cognitively normal stage, and additional frontotemporal lobe thinning underlies impairments in the memory and visuospatial domains at the PD-MCI stage.

KEYWORDS
[^{123}I]FP-CIT SPECT, 7 T-MRI, mild cognitive impairment, Parkinson's disease, surface-based morphometry

INTRODUCTION

Cognitive impairments in Parkinson's disease (PD) are heterogeneous in terms of neuropsychological profile and rate of progression to dementia, which suggests a nonuniform pathological background [1, 2]. The heterogeneity of the neuropsychological profile implies variable spatial distributions of pathological changes, whereas the difference in the rate of evolution to dementia implicates various temporal dynamics of the underlying pathology [3, 4]. Uncovering spatial and temporal multiplicity is essential for constructing effective clinical research, designing disease-modifying therapies, and managing patient symptoms [5].

The dissociation between dopaminergic dysfunction and cortical degeneration in terms of predicting dementia has been proposed as the neural basis for the spatial and temporal heterogeneity of cognitive deficits based on the observations from the CamPaIGN study (Cambridgeshire Parkinson's Incidence from GP to Neurologist), a longitudinal, population-representative, cohort investigation [6]. According to the hypothesis, frontostriatal deficits resulting from the functional vulnerability of dopaminergic system in PD are associated with executive dysfunction, which does not lead to dementia within 5 years. In contrast, more posterior cortical disturbances are linked to visuospatial cognitive dysfunction, which predicted dementia progression [7, 8]. However, the neural underpinnings of this dual-syndrome hypothesis have not been fully confirmed.

Therefore, this study aimed to investigate the neural substrates underlying multifaceted cognitive impairments in PD based on the dual-syndrome hypothesis that the deficits are attributable, at least partly, to the different contributions of frontostriatal dopaminergic dysregulation and cortical degeneration. In patients with PD who were cognitively normal (PD-CN) and those with mild cognitive impairment (PD-MCI), we assessed the caudate dopaminergic terminal degeneration using [^{123}I]N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([^{123}I]FP-CIT) single-photon emission computed tomography (SPECT) since the involvement of the caudate nucleus in cognition has been well recognized [9], and surface-based morphometry (SBM) analysis using the 7-T structural MRI. For reference, healthy controls (HCs) also underwent 7-T MRI. A correlation was computed between the performance in multiple cognitive domains and caudate dopaminergic terminal loss leading to frontostriatal dysfunction and between the cognitive performance and regional cortical thinning, resulting from cortical degeneration. Due to the lack of appropriate cognitive performance in patients with dementia, patients with MCI need to be examined to clarify neural substrates underlying cognitive deficits. Although most studies have analyzed either dopaminergic depletion with positron emission tomography or SPECT functional imaging or cortical degeneration with structural MRI, we believe uniting both functional and structural imaging in an identical population is essential to uncover the neural basis of the diverse cognitive impairments in PD.

METHODS

Participants

In this cross-sectional study, a total of 155 patients with PD were enrolled at Kyoto University Hospital between September 2016 and July 2021. All patients underwent [^{123}I]FP-CIT SPECT, while 76 patients who agreed to participate also underwent 7-T MRI within 1 year from the cognitive examination. For comparison, 7-T MRI was also performed in 56 HCs, of whom 37 had a Montreal Cognitive Assessment (MoCA) score of >25 and thus were judged as cognitively normal [10].

Clinical behavioral measures

All participants received a neuropsychological battery following the Movement Disorder Society (MDS) task force recommendations [11, 12], which categorizes cognitive functions in PD into five domains (Data S1).

In patients with PD, motor symptom severity was measured with the Hoehn and Yahr (HY) stage and MDS-unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III in a practically defined drug-off state after withdrawing all anti-Parkinsonian medications for at least 12 h [13]. We also calculated the levodopa equivalent daily dose (LEDD) [14].

[^{123}I]FP-CIT SPECT data acquisition and processing

Scanning was conducted using the Infinia GE Healthcare system (Waukesha, Wisconsin, USA) as previously described [15].

DaTQUANT™ software for Xeleris 3.1 (GE Healthcare, Waukesha, Wisconsin, USA) was used for the semi-quantification of [^{123}I]FP-CIT SPECT images. The uptake ratio was averaged across the left and right sides for statistical analysis.

7-T MRI data acquisition, preprocessing, and surface reconstruction

MRI scanning was performed using a 7 T-MR system (Magnetom 7 T, Investigational Device; Siemens Healthcare, Erlangen, Germany) and 32-channel head coil (Nova Medical, Wilmington, MA, USA).

High-resolution structural images using the magnetization prepared 2 rapid acquisition gradient echoes (MP2RAGE) [16] and $B1^+$ maps using saturation-prepared with 2 rapid gradient echoes (SA2RAGE) [17] sequences were obtained for analysis. Using preprocessed images, cortical thickness (CTh) was estimated using the Computational Anatomy Toolbox (CAT12.8, http://www.neuro.uni-jena.de/cat/) [18] in the statistical parametrical mapping (SPM12, Wellcome Trust Centre for Neuroimaging, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) implemented in MATLAB 2018b (MathWorks, Natick, MA, USA). For detailed imaging protocols and preprocessing methods, see Data S1.

Statistical analysis

Clinical behavioral measures were compared between patients with PD-CN and PD-MCI using Welch's *t*-test (continuous variables), Pearson's chi-squared test (sex), and Wilcoxon's rank sum test (HY stage). Differences among HCs and patients with PD-CN and PC-MCI were tested using analysis of variance, Tukey–Kramer's test (continuous variables), and Pearson's chi-square test (sex). The threshold for significance was set at a two-tailed *p*-value of <0.05.

In the [^{123}I]FP-CIT SPECT analysis, the caudate uptake ratio was compared between patients with PD-CN and PD-MCI using the analysis of covariance adjusted for age, sex, education, and disease duration. The associations of the uptake ratio of the caudate with each cognitive performance were evaluated in all patients with PD using multiple linear regression analysis, with age, sex, education, and disease duration as nuisance covariates. We calculated standardized regression coefficients (β) to assess the effect sizes quantitatively. For multiple comparisons, the *p* values obtained in the regression analysis were controlled for using a false discovery rate (FDR) with the Benjamini–Hochberg method [19]. The statistical evaluations of the SPECT analysis and demographic data were performed with R (4.0.5, https://cran.r-project.org/).

In the SBM analysis, the difference in CTh among HCs and patients with PD-CN and PD-MCI was assessed using a vertex-by-vertex general linear model in SPM12, including age, sex, and education as nuisance covariates. The linear relationship between the cognitive performance and CTh was also evaluated in all patients with PD, with disease duration as an additional covariate. The aforementioned statistical analyses were conducted using a nonparametric, threshold-free cluster enhancement (Data S1) [20], and the threshold for multiple comparisons was set at a family-wise error (FWE)-corrected *p* value of <0.05.

To evaluate the effect size of the relationship of CTh with each cognitive performance quantitatively, we further estimated correlation coefficients (*r* values) using vertex-wise *p* maps obtained from the permutation test with 10,000 iterations [21]. In this exploratory analysis, the threshold for significance was set at a cluster-level FWE corrected *p* value of <0.05 with an initial vertex threshold of 0.05 uncorrected.

RESULTS

Clinical behavior characteristics

Study population was presented in Table 1 and Data S1. Among the patients enrolled in the [^{123}I]FP-CIT SPECT analysis, a significantly longer disease duration, higher LEDD, and a higher MDS-UPDRS Part III score and HY stage during the drug-off state were observed in patients with PD-MCI than in those with PD-CN. Despite differences in the neural circuits associated with motor and cognitive symptoms, PD-MCI patients exhibited severe motor symptoms. Significant impairment was found in all cognitive examinations in patients with PD-MCI than in those with PD-CN, except a preserved score in CPT in both groups.

The patients who underwent 7-T MRI exhibited a similar tendency. The disease duration was longer, LEDD was higher, and MDS-UPDRS Part III score and HY were higher in patients with PD-MCI than in those with PD-CN, although the differences were not statistically significant. Lower performance was observed in all cognitive examinations in patients with PD-MCI than in those with PD-CN, except for a full score in CPT in all patients, although the difference was not statistically significant for MMSE, CDT, CFT, and similarities. We further compared clinical behavioral characteristics between the patients with PD with and without 7-T MRI data and found that only the MoCA score reached a statistically significant level (Table S1).

Demographic comparisons of the cognitively normal HC group with PD-CN and PD-MCI groups in the SBM analysis revealed that the participants in the HC group were younger than those in the PD-CN and PD-MCI groups. Lower performance was observed in all cognitive examinations in the PD-MCI group than in the HC group, except for a full score in CPT in all participants, although the difference was not statistically significant in terms of MMSE, CDT, CFT, and JLO scores. In contrast, the performance level was not different in cognitive examinations when the PD-CN group was compared with the HC group, except for SDMT.

Intergroup differences and cognitive associations of striatal dopaminergic terminal

Patients with PD-CN presented a significantly higher [^{123}I]FP-CIT uptake in the caudate than those with PD-MCI [mean (standard deviation), 1.11 (0.40) versus 0.90 (0.31); $p = 0.018$].

Multiple regression analysis revealed a significant association between the caudate [^{123}I]FP-CIT uptake ratio and attention/working memory function, with trends toward significance for memory and visuospatial domains. Significant linear relationships were observed with TMT-A ($\beta = -0.21$; 95% confidence interval [CI], −0.38 to −0.05; $p = 0.01$; FDR-corrected $p = 0.04$), SDMT ($\beta = 0.30$; 95% CI, 0.14 to 0.45; $p < 0.001$; FDR-corrected $p = 0.002$), and TMT-B ($\beta = -0.28$; 95% CI, −0.43 to −0.12; $p < 0.001$; FDR-corrected $p = 0.002$), reflecting frontal lobe-associated cognitive functions (Figure 1). Considering β, near-significant relationships were noted

TABLE 1 Clinical characteristics and cognitive performance in the study groups.

	SPECT analysis			7T-MRI analysis			
	PD-CN ($n=74$)	PD-MCI ($n=81$)	p value[a]	HCs ($n=34$)	PD-CN ($n=31$)	PD-MCI ($n=37$)	p value[b]
Age (years)	62.3 (9.4)	64.4 (9.2)	0.15	56.9 (9.1)	63.0 (8.6)	62.4 (7.6)	0.006[c]
Sex (M/F)	33/41	39/42	0.78	8/26	11/20	15/22	0.30
Education	14.3 (2.4)	13.9 (2.5)	0.34	13.9 (2.0)	14.3 (2.3)	13.7 (2.2)	0.51
Duration (years)	8.9 (5.3)	11.0 (5.2)	0.01	N/A	9.7 (4.3)	11.3 (5.5)	0.19
LEDD (mg)	662.0 (442.3)	846.4 (372.2)	0.006	N/A	806.4 (391.2)	828.1 (421.3)	0.83
UPDRS III Off	38.2 (14.9)	47.9 (16.3)	<0.001[d]	N/A	42.2 (17.0)	47.5 (19.3)	0.25[e]
HY Off	5/28/23/8/7	0/21/20/16/20	<0.001[d]	N/A	1/11/8/4/5	0/14/9/7/5	0.85[e]
MMSE	29.4 (0.9)	28.6 (1.4)	<0.001	29.4 (1.1)	29.2 (1.0)	28.9 (1.2)	0.13
MoCA	26.7 (2.3)	24.4 (3.0)	<0.001	28.2 (1.4)	26.9 (2.5)	25.5 (2.3)	<0.001[f]
TMT-A	34.0 (12.2)	52.1 (21.8)	<0.001	28.0 (8.3)	32.7 (10.6)	47.5 (16.9)	<0.001[f]
SDMT	46.4 (9.5)	34.5 (8.5)	<0.001	53.2 (8.3)	47.6 (9.2)	37.0 (7.3)	<0.001[g]
CDT	14.6 (0.9)	14.0 (2.4)	0.02	14.9 (0.3)	14.6 (1.2)	14.2 (1.9)	0.08
TMT-B	81.0 (37.2)	143.0 (73.6)	<0.001	64.3 (18.9)	79.8 (35.6)	120.5 (63.9)	<0.001[f]
CFT	20.9 (4.4)	17.5 (4.9)	<0.001	20.9 (5.4)	21.0 (4.2)	19.0 (5.3)	0.16
Similarities	24.4 (5.1)	21.0 (5.0)	<0.001	24.2 (3.8)	23.2 (6.4)	20.8 (5.0)	0.02[h]
HVLT-R delayed recall	7.8 (2.7)	5.5 (2.4)	<0.001	8.7 (2.0)	8.3 (2.5)	6.1 (2.3)	<0.001[f]
RCFT delayed recall	20.9 (6.75)	14.3 (7.5)	<0.001	20.4 (5.3)	21.0 (6.8)	16.6 (7.2)	0.009[f]
CPT	10.0 (0)	9.9 (0.3)	0.06	10.0 (0.0)	10.0 (0.0)	10.0 (0.0)	1.0
JLO	25.0 (3.21)	21.4 (4.7)	<0.001	24.2 (3.4)	25.1 (3.5)	22.5 (4.2)	0.02[i]

Note: Mean (standard deviation) is shown. In the HY classification at off period, the numbers of HY1/HY2/HY3/HY4/HY5 patients are shown.

Abbreviations: 7T, 7 tesla; CDT, clock drawing test; CFT, category fluency test; CPT, copying pentagon test; HCs, healthy controls; HVLT-R, Hopkins verbal learning test-revised; HY, Hoehn-Yahr classification; JLO, judgment of line orientation; LEDD, levodopa equivalent daily dose; MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; PD-CN, Parkinson's disease with cognitively normal; PD-MCI, Parkinson's disease with mild cognitive impairment; RCFT, Rey-Osterrich complex figure test; SDMT, symbol digit modalities test; SPECT, single–photon emission computed tomography; TMT-A, trail making test part A; TMT-B, trail making test part B; UPDRS III, unified Parkinson's disease rating scale part III.

[a]Tested using the Welch's *t*-test. Chi-squared test and Wilcoxon's rank-sum test were used for sex and HY, respectively.

[b]Tested using the analysis of variance. Chi-squared test and Wilcoxon's rank-sum test were also used for sex and HY, respectively.

[c]Significant difference ($p<0.05$) was observed between HCs and patients with PD-CN, and between HCs and those with PD-MCI using Tukey–Kramer's test.

[d]Evaluated in 148 patients (71/77 for PD-CN/PD-MCI patients, respectively).

[e]Evaluated in 64 patients (29/35 for PD-CN/PD-MCI patients, respectively).

[f]Significant difference ($p<0.05$) was observed between HCs and patients with PD-MCI, and between those with PD-CN and PD-MCI using Tukey–Kramer's test.

[g]Significant difference ($p<0.05$) was observed between HCs and patients with PD-MCI, HCs and patients with PD-CN, and patients with PD-CN and PD-MCI using Tukey–Kramer's test.

[h]Significant difference ($p<0.05$) was observed between HCs and patients with PD-MCI using Tukey–Kramer's test.

[i]Significant difference ($p<0.05$) was observed between patients with PD-CN and PD-MCI using Tukey–Kramer's test.

for RCFT delayed recall ($\beta=0.20$; 95% CI, 0.03 to 0.36; $p=0.02$; FDR-corrected $p=0.06$) and JLO ($\beta=0.13$; 95% CI, −0.04 to 0.31; $p=0.13$; FDR-corrected $p=0.25$).

Intergroup differences regarding CTh

CTh comparison analysis revealed a group effect according to disease and cognitive status (Figure 2 and Table S2). Compared with HCs, patients with PD-CN showed cortical thinning primarily in the bilateral parietal, occipital, and posterior temporal lobes. A comparison of the PD-CN and PD-MCI groups revealed significant cortical degeneration in the left-dominant bilateral frontal and anterior temporal lobes in the PD-MCI group. A significant cortical thinning was observed involving almost the entire cortex in patients with PD-MCI compared with HCs.

Because participants in the cognitively normal HC group were younger than those in the PD-MCI and PD-CN groups, we performed an additional SBM group comparison analysis with all HCs without any cognitive cutoff. In this analysis, five HCs were excluded

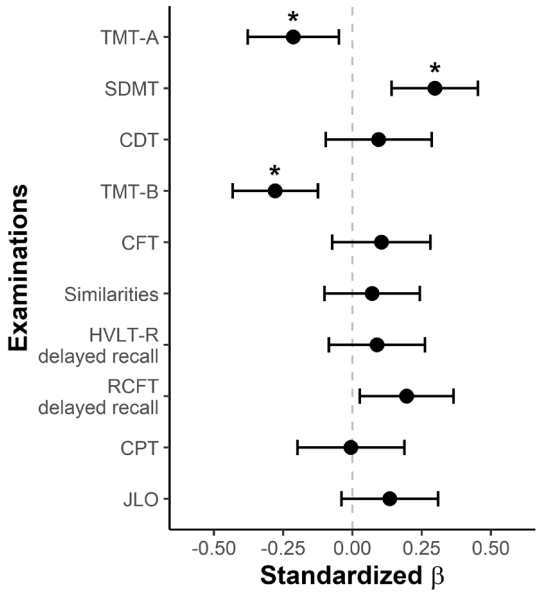

FIGURE 1 Estimated strength of correlation between caudate [^{123}I]FP-CIT uptake and cognitive performance. [^{123}I]FP-CIT uptake in the caudate shows a significant association with the performance in the TMT-A, SDMT, and TMT-B, which are used to assess the function of attention/working memory or executive domains. The error bar represents 95% confidence interval, and the asterisk (*) indicates statistical significance after FDR correction ($p < 0.05$). β, regression coefficient; CDT, clock drawing test; CFT, category fluency test; CPT, copying pentagon test; FDR, false discovery rate; HVLT-R; Hopkins verbal learning test-revised; JLO, judgment of line orientation; RCFT, Rey–Osterrieth complex figure test; SDMT, symbol digit modalities test; TMT-A, trail making test-A; TMT-B, trail making test-B.

because of the failure of surface reconstruction. Although this combined HC group composed of 51 participants was not significantly different in demographics or cognitive performance to the PD-CN group (Table S3), a similar pattern of regional cortical thinning was observed when the HC group was compared with the PD-CN and PD-MCI groups (Figure S1 and Table S4). These findings suggest that the cortical thinning demonstrated in patients with PD-CN and PD-MCI was not attributable to the difference in age compared with HCs.

Cognitive associations with CTh

Vertex-wise regression analysis elucidated the significant association between regional CTh and memory and visuospatial domains. HVLT-R delayed recall correlated with CTh primarily in the left frontal, temporal, and parietal lobes, whereas JLO scores were linked to CTh in the right frontal and parietal lobes (Figure 3 and Table S5).

These regression analysis results were supported by the vertex-wise quantitative effect size estimation using correlation coefficients (Figure S2 and Table S6). The HVLT-R delayed recall score was moderately and positively correlated with the CTh in the left frontal, bilateral temporal, left insula, bilateral parietal, and right occipital lobes, whereas the JLO score was moderately and positively correlated with the CTh in the bilateral frontal and parietal lobes. Additionally, the RCFT delayed recall score and SDMT score, which require memory and visuospatial processing, respectively, were weakly positively correlated with the CTh in the left frontal lobes. The preserved TMT-A and TMT-B scores revealed a weak association with thinner cortex in the bilateral parieto-occipital lobe, and the preserved CFT score also tended to show a weak correlation with a thinner regional CTh in the bilateral frontal and right parietal lobes.

DISCUSSION

We evaluated the comprehensive contributions of striatal dopamine dysfunction and cortical degeneration to the cognitive decline in PD using a single large cohort. The caudate dopaminergic terminal activity measured using [^{123}I]FP-CIT was significantly lower in patients with PD-MCI than in those with PD-CN, and a decline in caudate [^{123}I]FP-CIT uptake in patients with PD was paralleled by the severity of performance deficits in TMT-A, SDMT, and TMT-B scores, which evaluate the function of the attention/working memory and executive function domains operated by the fronto-striatal system. In contrast, a left-dominant bilateral frontotemporal cortical thinning, as evaluated using structural MRI, was observed in patients with PD-MCI compared with those with PD-CN, and a decrease in the left frontotemporal CTh and right frontal CTh was correlated with the degree of performance impairments in HVLT-R delayed recall and JLO scores, which were categorized as memory and visuospatial domains, respectively. The findings of this study elucidated that dopaminergically mediated frontostriatal deficits and cortical disturbance distinctively underlie cognitive impairments in PD. In addition, cognitively normal patients with PD diagnosed using the PD-MCI level II diagnostic criteria [6] showed a broad cortical thinning, especially in the occipital and parietal lobes, compared with HCs. These findings suggest that the occipital and parietal lobe thinning occurs at a cognitively normal stage, and additional frontotemporal lobe thinning, which underlies cognitive impairments in memory and visuospatial domains, was found at the MCI stage in PD.

We propose spatially independent neural dysfunction, dopaminergically mediated frontostriatal deficits, and cortical disturbances as the neural underpinnings of the cognitive dual-syndrome hypothesis in PD based on the observation of the CamPaIGN study. The present study demonstrated that the decreased uptake at the caudate dopaminergic terminal was correlated with the severity of frontal attention/working memory and executive dysfunction, whereas the degree of cortical neural degeneration was correlated with the severity of impaired performance in memory and visuospatial domains. Furthermore, caudate dopaminergic terminal loss and cortical degeneration became significantly more pronounced in patients with PD-MCI than in those with PD-CN. These findings suggest that the heterogeneity of the neuropsychological profile and severity in

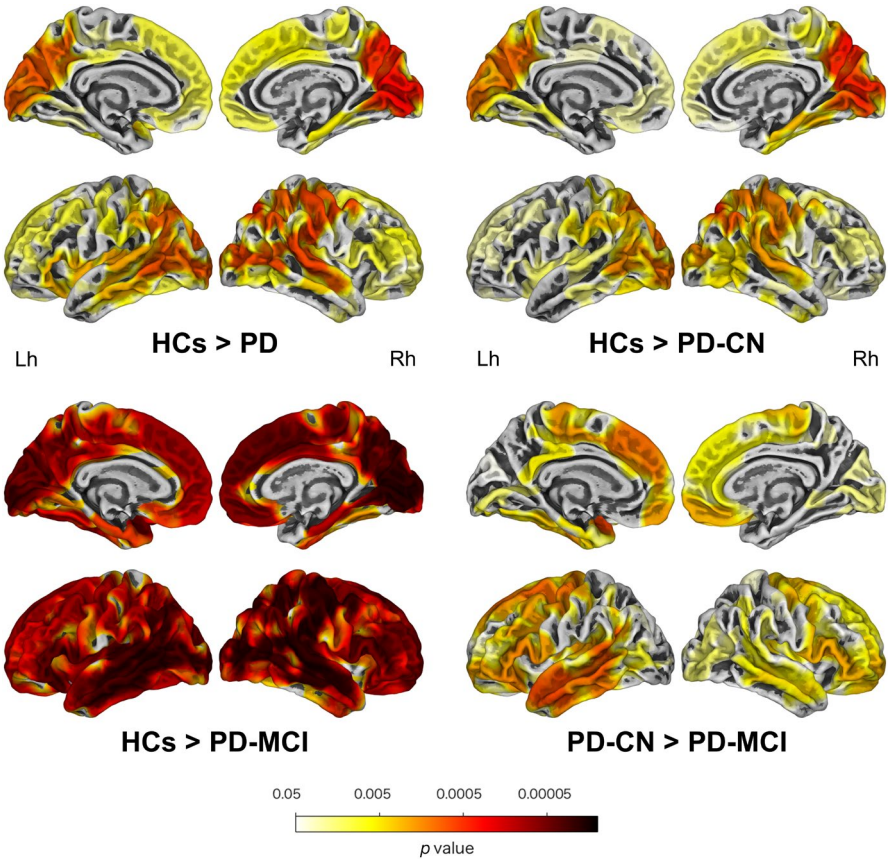

FIGURE 2 Intergroup differences in cortical thickness. Compared with cognitively normal HCs, patients with Parkinson's disease show significant global cortical thinning. Compared with HCs, patients with PD-CN exhibit cortical thinning primarily in the bilateral parietal, occipital, and posterior temporal lobes, despite a relatively preserved thickness in the frontal and anterior temporal lobes, whereas patients with PD-MCI show significant cortical thinning involving almost the entire cortex. Significant cortical thinning is found, especially in the frontal and anterior temporal lobes, in patients with PD-MCI compared with those with PD-CN. HCs, healthy controls; PD-CN, Parkinson's disease with cognitively normal; PD-MCI, Parkinson's disease with mild cognitive impairment.

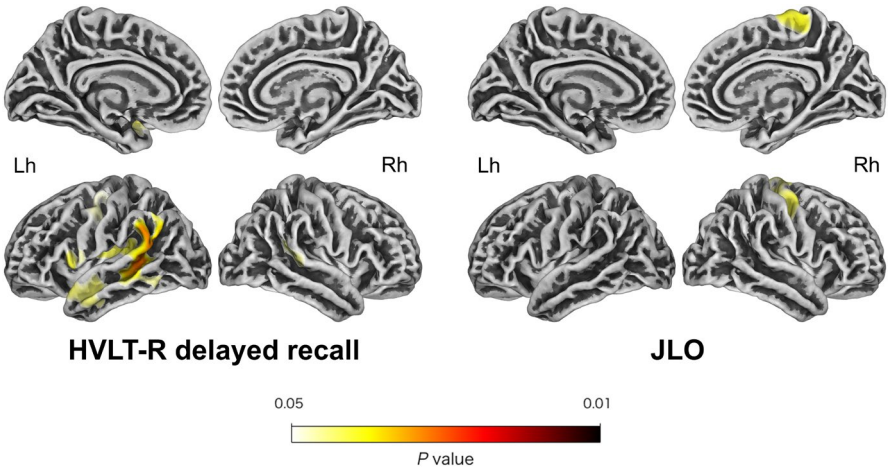

FIGURE 3 Correlation between cortical thickness and cognitive performance. In patients with Parkinson's disease, the HVLT-R delayed recall score correlates with the regional cortical thickness in the left frontal, bilateral temporal, and parietal lobes. In these patients, the JLO score correlates with the cortical thickness in the right frontal and parietal lobes. HVLT-R, Hopkins verbal learning test-revised; JLO, judgment of line orientation.

patients with PD is attributable, at least partly, to the damage to the two distinct neural systems.

Previous studies suggest that dopamine depletion in the striatum, especially in the caudate, contributes to the cognitive decline via disorganization of the frontostriatal network in PD. [9, 22, 23] In our study, patients with PD-MCI showed more severe dopaminergic damage in the caudate than those with PD-CN, suggesting a correlation between functional deterioration of the frontostriatal circuit in patients with PD-MCI and worsening of their cognitive performance. The present study also revealed a moderate correlation of dopaminergic terminal degeneration in the caudate with the impaired performance of TMT-A, SDMT, and TMT-B, which evaluate attention/working memory and executive function domains, primarily reflecting frontal lobe function [24, 25]. Additionally, the present study found a mild association between a decreased [^{123}I]FP-CIT uptake ratio in the caudate and lower RCFT delayed recall and JLO scores, which might reflect deterioration in the attentional/working memory and executive function required to perform the task [26]. The dual-syndrome hypothesis was originally proposed based on the findings of newly diagnosed patients with PD [6], whereas our findings suggest that the relationships between striatal dopaminergic loss and frontal executive dysfunction can be observed in nondemented PD patients of heterogeneous disease duration varying from de novo to more than 20 years.

This study found cortical thinning in the bilateral occipital, parietal, and posterior temporal lobes in patients with PD-CN compared with HCs. Cortical thinning in patients with PD with normal cognition compared with in HCs was previously reported in the occipital, parietal [27], and temporal cortices [28], or was reported to be nonsignificant in the whole brain [29]. Compared with the results of these previous studies, the posterior cortical thinning in patients with PD-CN in our study was broader, which was likely to be attributable to the use of 7-T MRI methodology rather than the conventional 3-T or 1.5-T MRI used in previous reports. Our findings are in line with an international multicenter analysis of over 2000 patients with PD and 1000 HCs revealing widespread cortical thinning in the occipital, parietal, and temporal cortices as demonstrated by an HY stage 2, although the preservation of cognitive function at this stage could not be fully confirmed [30]. Moreover, the cortical microstructural abnormalities assessed with T1 relaxometry imaging in patients with PD could not be explained by physiological aging alone in widespread cortical regions predominantly in the occipital, parietal, and posterior temporal cortices during the 6-year follow-up period from the baseline disease duration of 4.5 years [31]. Despite a relatively long duration of around 10 years, patients with PD-CN in our study showed almost the same cognitive performance as HCs, implying that they were in a relatively early phase of cognitive deterioration, which is almost inevitable after 20 years of follow-up in PD. [32] The present observation of relatively preserved frontal CTh in patients with PD-CN is consistent with the results of a data-driven statistical modeling study exhibiting that cortical thinning starts in the occipital and parietal cortices followed by the frontal cortex [33].

The present study showed that cortical atrophy in patients with PD-MCI was widespread, involving almost the entire cortex compared to HCs, while the atrophy in patients with PD-MCI was restricted to the left-dominant bilateral frontotemporal cortices compared with those with PD-CN. Furthermore, CTh in the left fronto-temporo-parietal and right frontal lobes were correlated with the severity of memory and visuospatial cognitive deficits, respectively. These findings suggest that additional involvement of the frontal and anterior temporal cortical degeneration plays an essential role in memory and visuospatial cognitive deterioration in patients with PD-MCI [34–36].

The CamPaIGN cohort study presented a cognitive syndrome with a poor performance in intersecting pentagon copying and verbal fluency tests implicating dopamine insensitivity, presumably more posterior cortical dysfunction involving the parietal and temporal lobes [7]. Several imaging investigations on CTh in nondemented patients with PD have shown a correlation of visuospatial dysfunction and verbal fluency deficits with degeneration, not only in the parietal and temporal regions but also in the frontal region [27, 28], suggesting cortical dysfunction in PD within a widely distributed cortical area, but not exclusive to the posterior area including the parietal lobe. Likewise, our quantitative effect size estimates suggested a relationship between poor performance in memory and visuospatial domains and reduced regional CTh involving the frontal region. Moreover, recent longitudinal imaging studies revealed cortical thinning in the frontal regions and the posterior cortical area in patients with PD-MCI who later developed dementia during the follow-up compared with those with PD-MCI who did not [37]. These findings are in line with the present observation of a coexistence of frontotemporal damage and parieto-occipital atrophy, which represents memory and visuospatial cognitive impairments in patients with PD-MCI. The temporal association between the onset of cognitive symptoms and posterior to anterior cortical atrophy extension should be investigated in a large longitudinal cohort study.

The pathological basis for heterogeneity in spatially independent neural dysfunction, dopaminergically mediated frontostriatal deficits, and cortical disturbances observed in our study may be multifactorial. Spatial spreading of α-synuclein appears to explain the clinical course, and α-synuclein may exert deleterious effects not only on dopaminergic neuronal degeneration but also on cortical neuronal degeneration [5]. The heterogeneity may be attributable to the additional contribution of abnormal proteins, such as amyloid-β and tau [38], or genetic factors related to neuronal loss [39]. Alternatively, the heterogeneity may be enhanced through cholinergic denervation since previous studies revealed an association between acetylcholine dysfunction and cognitive decline in PD [40].

Another notable implication of this study is the advantage of 7-T MRI in the SBM analysis. Possibly due to a high signal-to-noise ratio and good tissue contrast-to-noise ratio with 7-T MRI [41], the present PD cohort revealed widespread cortical thinning compared with HCs in similar topological patterns, as in a much larger cohort of over 2000 patients with PD and 1000 HCs using 3-T or 1.5-T MRI [30]. Moreover, CTh assessment has been shown to provide a more sensitive measure of the morphology of cortical gray matter than voxel-based morphology methodologies [42].

This study has some limitations. First, the CamPaIGN is a longitudinal study combining genetic methodologies and clarified temporal variations [4], whereas our cross-sectional study without genetic information provided only spatial variations of neuronal degeneration. Therefore, our findings cannot determine a temporal link between cognitive deterioration and neuronal degeneration. Second, we evaluated dopaminergic activity only in the striatum, although dopaminergic neurotransmission mediates cognitive function in the frontal cortex as well [43]. Thus, in addition to two independent neural dysfunctions, caudate dopamine-mediated frontostriatal deficits and cortical disturbances, frontal dopamine depletion is likely to contribute to frontal impairments in PD. Further, we did not examine other neurotransmitter dysfunctions, such as cholinergic or noradrenergic loss. Future studies should elucidate the link between these systems and the dual syndrome hypothesis using multimodal neuroimaging techniques. Third, our quantitative effect size estimates implicated a relationship between the preserved performance of TMT-A, TMT-B, and CFT and decreased CTh in the frontal and parietal cortices. The pathophysiological significance of this unexpected relationship should be investigated in future studies. Fourth, the floor surface of the frontal and temporal lobes was susceptible to the background noise in MP2RAGE images, which can render the accurate CTh estimation difficult in these regions.

In conclusion, our findings propose neural underpinnings for the dual-syndrome hypothesis, a widely accepted idea explaining the heterogeneity of cognitive decline in PD. Our findings also showed widespread parieto-occipital cortical degeneration, even in patients with cognitively unaffected PD. Research focusing on longitudinal progression, neurotransmitters other than dopamine, and pathological basis is needed to uncover the distinctive pathophysiological process of cognitive dysfunction in PD and to develop disease-modifying therapies.

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CONFLICT OF INTEREST STATEMENT

RT received a research grant from Nihon Medi-Physics Co., Ltd., a manufacturer of [^{123}I]FP-CIT. TO received a research grant from Siemens Healthcare KK, Japan. The remaining authors have no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

The anonymized data supporting the findings of this study are available from the corresponding author upon reasonable request after ethics clearance.

ETHICS STATEMENT

The study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (R-0494). All participants provided written informed consent to participate in the study.

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SUPPORTING INFORMATION

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