ORIGINAL ARTICLE

Clinical relevance of amnestic versus non-amnestic mild cognitive impairment subtyping in Parkinson's disease

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Background and purpose: To clarify whether subtyping of amnestic and non-amnestic mild cognitive impairment (MCI) is clinically relevant in Parkinson's disease (PD) by analyzing patterns of neuroimaging and longitudinal cognitive changes.

Methods: We performed comparative analyses of cortical thickness, hippocampal volume, white matter integrity and resting-state functional connectivity between the patients with *de-novo* PD with amnestic MCI (PD-aMCI) (n = 50) and non-amnestic MCI (PD-naMCI) (n = 50) subtypes. Additionally, we assessed the longitudinal rate of cognitive decline in each cognitive domain over time and the rate of dementia conversion in patients with *de-novo* PD-aMCI (n = 125) and PD-naMCI (n = 61).

Results: The demographic data showed that scores in memory domains were lower in the PD-aMCI group compared with the PD-naMCI group. There were no significant differences in cortical thickness, hippocampal volume and white matter integrity between the two groups, although the PD-aMCI group exhibited more cortical thinning and hippocampal atrophy relative to the control group. The PD-aMCI group exhibited increased functional connectivity in the left posterior parietal region with the salience network relative to the PD-naMCI group. The longitudinal cognitive assessment demonstrated that patients with PD-aMCI exhibited a more rapid cognitive decline in frontal/executive function than those with PD-naMCI (P = 0.022). In addition, the PD-aMCI group had a higher risk of dementia conversion than the PD-naMCI group.

Conclusions: This study suggests that the designation of PD-MCI subtypes based on memory function would highlight the heterogeneity of functional correlates as well as the longitudinal cognitive prognosis.

Introduction

Cognitive impairment is one of the most disabling non-motor symptoms of Parkinson's disease (PD). Cognitive dysfunction occurs in the early stages of PD; approximately 25% of patients have mild cognitive impairment (MCI) and 30% have dementia [1]. The clinical significance of PD with MCI (PD-MCI) has been growing as it increases the risk of progression to dementia [2,3].

In non-PD populations, the classification of MCI subtypes using amnestic or non-amnestic terminology is a well-established concept for the prediction of disease etiology and prognosis [4]. Recently, a guideline of MCI diagnostic criteria recommended classifying PD-MCI into single-domain or multiple-domain subtypes with a specification of the affected domains [2]. Some evidence has suggested that the categorization of PD-MCI into a

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posterior cortical- or frontostriatal-based cognitive deficit is invaluable for prognosis or pathophysiology [5]. Although new diagnostic criteria have been proposed for PD-MCI, they do not specifically address the distinction between amnestic and non-amnestic PD-MCI, a subdivision that clearly reflects the Alzheimer's disease-centric methodology toward the definition of MCI. It remains unclear whether this categorization can represent the clinicopathological heterogeneity in PD-MCI. Thus, the aim of this study was to investigate the patterns of structural change and functional connectivity of patients with PD-MCI, in relation to the presence of memory dysfunction. Additionally, we assessed longitudinal changes in cognitive performances using detailed neuropsychological tests and compared the rate of dementia conversion between the groups.

Methods

Subjects

The present study included 100 patients with PD-MCI for neuroimaging analyses [50 patients with PD with amnestic MCI (PD-aMCI) and 50 patients with PD with non-amnestic MCI (PD-naMCI)] who were consecutively recruited from the outpatient clinic from January 2011 to June 2015. PD was diagnosed according to the clinical diagnostic criteria of the UK Parkinson's Disease Society Brain Bank. All subjects showed decreased dopamine transporter availability in the posterior putamen on ^{18}F-fluorinated N-3-fluoropropyl-2-beta-carboxymethoxy-3-beta-(4-iodophenyl) nortropane (^{18}F-FP-CIT) positron emission tomography (PET) scans. Each subject underwent a neuropsychological assessment and brain MRI within a 1-year period. PD-MCI was diagnosed according to the Movement Disorder Society Task Force guidelines [2]. A total of 30 healthy subjects with no history of neurological disease were also included as a control group. In addition, we reviewed the medical records of 186 patients with *de-novo* PD-MCI who underwent the serial neuropsychological assessment between twice and five times with intervals of 1–4 years to measure longitudinal cognitive decline (Appendix S1). This study was approved by Yonsei University Severance Hospital institutional review board and the need for informed consent was waived because of the retrospective nature of the study.

Neuropsychological assessment and subtype classification of Parkinson's disease with mild cognitive impairment

All subjects were administered the Seoul Neuropsychological Screening Battery (SNSB) [6], which covers five cognitive domains. The scores on each cognitive domain were classified as abnormal when they were below the 16th percentile of the age-, sex- and education-specific norms of 447 normal subjects. A diagnosis of PD-MCI was made if impairments on at least two tests were demonstrated either within a single cognitive domain or across different cognitive domains [2,7] (Appendix S1).

We classified patients with PD-MCI into two subtypes according to the presence of memory impairment: subjects with MCI who demonstrated a normal cognitive performance in memory function (PD-naMCI) and those with deficits in delayed recall using the Seoul Verbal Learning Test [6] and/or Rey Complex Figure Test [8] who met the diagnostic criteria for PD-MCI of the Movement Disorder Society Task Force guidelines [2] (PD-aMCI).

Neuroimaging analyses

We performed comparative analyses of cortical thickness, hippocampal volume, white matter integrity (tract-based spatial statistics) and resting-state functional connectivity [regions of interest: default mode network (DMN), central executive network (CEN), dorsal attention network (DAN), and salience network (SN)] between patients with *de-novo* PD-aMCI and PD-naMCI. We also compared the differences in dopamine transporter availability in the caudate and anterior/posterior putamen between the PD-MCI groups (Appendix S1) [9].

Comparison of longitudinal cognitive decline between the *de-novo* Parkinson's disease groups

Differences in the cognitive decline rate of five cognitive domains between the PD-aMCI ($n = 125$) and PD-naMCI ($n = 61$) groups were analyzed using the linear mixed model. We also compared the risk of PD with dementia (PDD) conversion between the PD-aMCI and PD-naMCI groups (Appendix S1).

Statistical analyses

Student's *t*-test and Pearson's chi-squared test were conducted to compare the baseline demographic characteristics. To compare the subscores of the neuropsychological test, an ANCOVA was performed adjusting for age, sex and years of education as covariates, and the Bonferroni–Holm method was used for multiple comparisons correction. The statistical analyses were performed with SPSS software (version 23.0; IBM Corp., Armonk, NY, USA) and a two-tailed $P < 0.05$ was considered significant.

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Results

Demographic characteristics

Table 1 shows that there were no significant differences in the baseline demographic characteristics between patients with PD-aMCI and those with PD-naMCI included in the neuroimaging analyses. A total of 91 (91.0%) patients were identified as having multiple-domain PD-MCI. As expected, scores in the verbal and visual memory domains were lower in patients with PD-aMCI when compared with patients with PD-naMCI. The cognitive performance in other domains was similar between the PD-aMCI and PD-naMCI groups (Table S1).

Table S2 shows the baseline demographic characteristics and detailed neuropsychological data of subjects included in the longitudinal assessment of cognitive decline ($n = 186$; 93.5% had multiple-domain PD-MCI). There was a significantly higher frequency of female patients with PD-naMCI than PD-aMCI. Patients with PD-aMCI had poorer performances in verbal and visual memory function tests when compared with patients with PD-naMCI. No significant differences were observed in other demographic characteristics and cognitive performances.

Table 1 Baseline demographic characteristics of patients with Parkinson's disease with mild cognitive impairment (MCI) for neuroimaging analyses

	PD-aMCI ($n = 50$)	PD-naMCI ($n = 50$)	*P*-value
Age (years)	69.12 ± 7.88	69.52 ± 7.46	0.795
Gender, female	22 (44.0)	30 (60.0)	0.109
Education (years)	8.42 ± 4.70	8.83 ± 4.69	0.663
PD duration (months)	31.48 ± 40.29	31.00 ± 31.28	0.947
UPDRS-III score	27.89 ± 10.73	25.53 ± 10.90	0.299
CCSIT score	5.70 ± 2.24	6.10 ± 2.27	0.419
K-MMSE score	25.40 ± 2.37	26.00 ± 2.49	0.220
Vascular risk factors			
Hypertension	18 (36.0)	21 (42.0)	0.539
Diabetes mellitus	10 (20.0)	7 (14.0)	0.424
Dyslipidemia	4 (8.0)	9 (18.0)	0.137
Cardiac disease	6 (12.0)	8 (16.0)	0.564
DAT availability			
Right posterior putamen	2.26 ± 0.62	2.28 ± 0.48	0.870
Left posterior putamen	2.27 ± 0.68	2.25 ± 0.56	0.931
Right anterior putamen	3.06 ± 0.83	2.98 ± 0.72	0.703
Left anterior putamen	3.06 ± 0.88	3.00 ± 0.79	0.909
Right caudate	2.12 ± 0.66	2.20 ± 0.65	0.592
Left caudate	2.08 ± 0.58	2.20 ± 0.66	0.399

Data are expressed as mean ± SD or *n* (%). CCSIT, cross-cultural smell identification test; DAT, dopamine transporter; K-MMSE, Korean version of the Mini-Mental State Examination; PD, Parkinson's disease; PD-aMCI, Parkinson's disease with amnestic MCI; PD-naMCI, Parkinson's disease with non-amnestic MCI; UPDRS-III, Unified Parkinson's disease Rating Scale Part III.

Analysis of cortical thickness

Controls exhibited greater cortical thickness in the left frontotemporal regions relative to patients with PD-aMCI (random field theory-corrected $P < 0.05$; Fig. 1I-a); however, no regions of different cortical thickness were observed in patients with PD-naMCI relative to controls. There were no regions of different cortical thickness between patients with PD-aMCI and PD-naMCI.

Hippocampal volume analysis

Post hoc analyses revealed that controls [estimated mean (standard error), 6442.6 (134.1) mm^3] had a tendency towards a larger hippocampal volume when compared with patients with PD-aMCI [6106.1 (102.2) mm^3, $P = 0.052$], whereas the hippocampal volume in the control group was similar to that in the PD-naMCI group [6174.0 (101.1) mm^3, $P = 0.114$]. No significant difference in hippocampal volume was found between the groups of PD-MCI ($P = 0.639$; Fig. S1).

Tract-based spatial statistics analysis

Controls exhibited significantly higher fractional anisotropy (FA) values in the frontoparietotemporal and corpus callosal white matter than either the PD-aMCI or PD-naMCI group (family-wise error-corrected $P < 0.05$; Fig. 1II-a and b). The PD-MCI groups did not have areas with higher FA values compared with controls. There was no significant difference between the PD-aMCI and PD-naMCI groups in either FA or mean diffusivity values.

Resting-state functional connectivity analysis

Compared with healthy controls, patients with PD-MCI exhibited decreased functional connectivity in the bilateral frontal, parietal, temporal and occipital cortices with the DMN (Fig. 2I-a and b); in the bilateral parietal cortices with the CEN (Fig. 2II-a and b); and in the bilateral parietal, temporal and occipital cortices and cerebellum with the DAN (Fig. 2III-a and b). There were no significant differences between the PD-MCI groups in cortical functional connectivity with the DMN, CEN and DAN.

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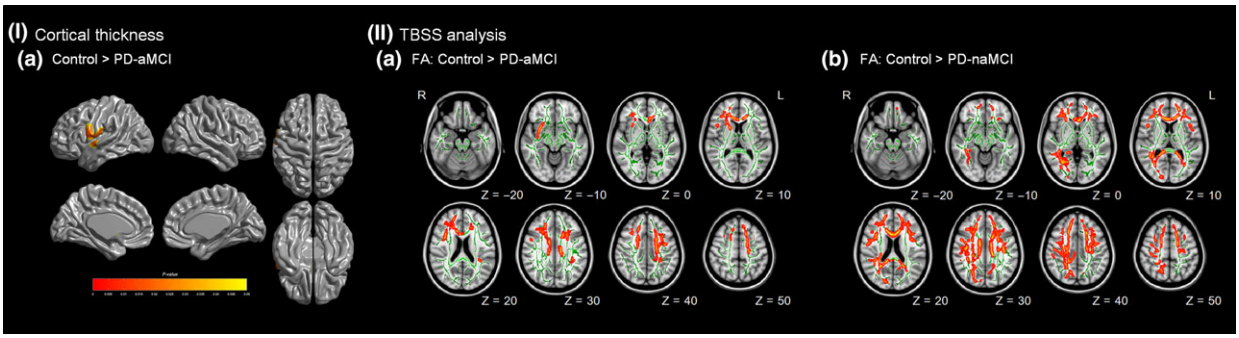

Figure 1 Cortical thickness and tract-based spatial statistics (TBSS) analyses. (I) Cortical thickness analysis. (a) Controls exhibited greater cortical thickness in the left frontotemporal regions relative to patients with Parkinson's disease with amnestic mild cognitive impairment (PD-aMCI) (random field theory-corrected $P < 0.05$). (II) TBSS analysis. Controls exhibited significantly higher fractional anisotropy (FA) values in the frontoparietotemporal and corpus callosal white matter than either the (a) PD-aMCI or (b) Parkinson's disease with non-amnestic mild cognitive impairment (PD-naMCI) group (family-wise error-corrected $P < 0.05$). L, left; R, right. [Color figure can be viewed at wileyonlinelibrary.com]

The patients with PD-aMCI exhibited increased functional connectivity in the left posterior parietal cortex from the SN relative to healthy controls, whereas the PD-naMCI group did not exhibit any significant difference in cortical functional connectivity from the SN relative to healthy controls (Fig. 2IV-a and b). The PD-aMCI group also exhibited increased functional connectivity in the left posterior parietal cortex from the SN compared with the PD-naMCI group (Fig. 2IV-c). No areas were observed where cortical functional connectivity was significantly increased in patients with PD-naMCI relative to patients with PD-aMCI. The anatomical locations of the significant peaks based on seed regions of interest are listed in Table S3.

Quantitation of the ^{18}F-FP-CIT PET

There were no significant differences in striatal dopamine transporter availability between the PD-aMCI and PD-naMCI groups (Table 1).

Longitudinal cognitive decline

The comparisons of estimated change of cognitive decline between the groups using the linear mixed model are shown in Table 2. The patients with PD-aMCI exhibited a more rapid cognitive decline in frontal/executive ($P = 0.022$) and attention/working memory function ($P = 0.066$) domains relative to the patients with PD-naMCI. There were no significant differences in the rate of cognitive decline in language ($P = 0.565$), visuospatial ($P = 0.535$) and memory function ($P = 0.646$) domains between the PD-MCI groups.

During the follow-up period, 44 out of 125 patients with PD-aMCI and 9 out of 61 patients with PD-naMCI converted to PDD (Fig. 3). The Kaplan–Meier analysis revealed that the PD-aMCI group had higher risk of PDD conversion than the PD-naMCI group ($P_{\text{Log-rank}} = 0.036$). The Cox proportional hazard model also revealed that the risk of PDD conversion in the PD-aMCI group was higher than that in the PD-naMCI group [hazard ratio, 2.291; 95% confidence interval, 1.100–4.774; $P = 0.027$; Table 3].

Discussion

The present study investigated the clinical significance of the designation of PD-MCI subtypes based on amnestic or non-amnestic terminology. The major findings were as follows. (i) Patients with PD-aMCI exhibited increased functional connectivity in the left parietal cortex with the SN compared with those with PD-naMCI. (ii) Baseline demographic characteristics and cognitive profiles were similar between the PD-MCI groups, except for the cognitive performance in the verbal and visual memory domains. (iii) There were no significant differences in cortical thickness, hippocampal volume, white matter integrity and striatal dopamine nerve terminal integrity between the PD-MCI groups. (iv) The PD-aMCI group exhibited a faster rate of cognitive decline in frontal/executive function domain compared with the PD-naMCI group using a linear mixed model. (v) The PD-aMCI group also had a higher risk of PDD conversion relative to the PD-naMCI group. These data suggest that patients with PD-aMCI would have different functional correlates of the SN without concomitant structural abnormalities and this difference would affect the cognitive prognosis in frontal/executive functions as well as the risk of PDD conversion.

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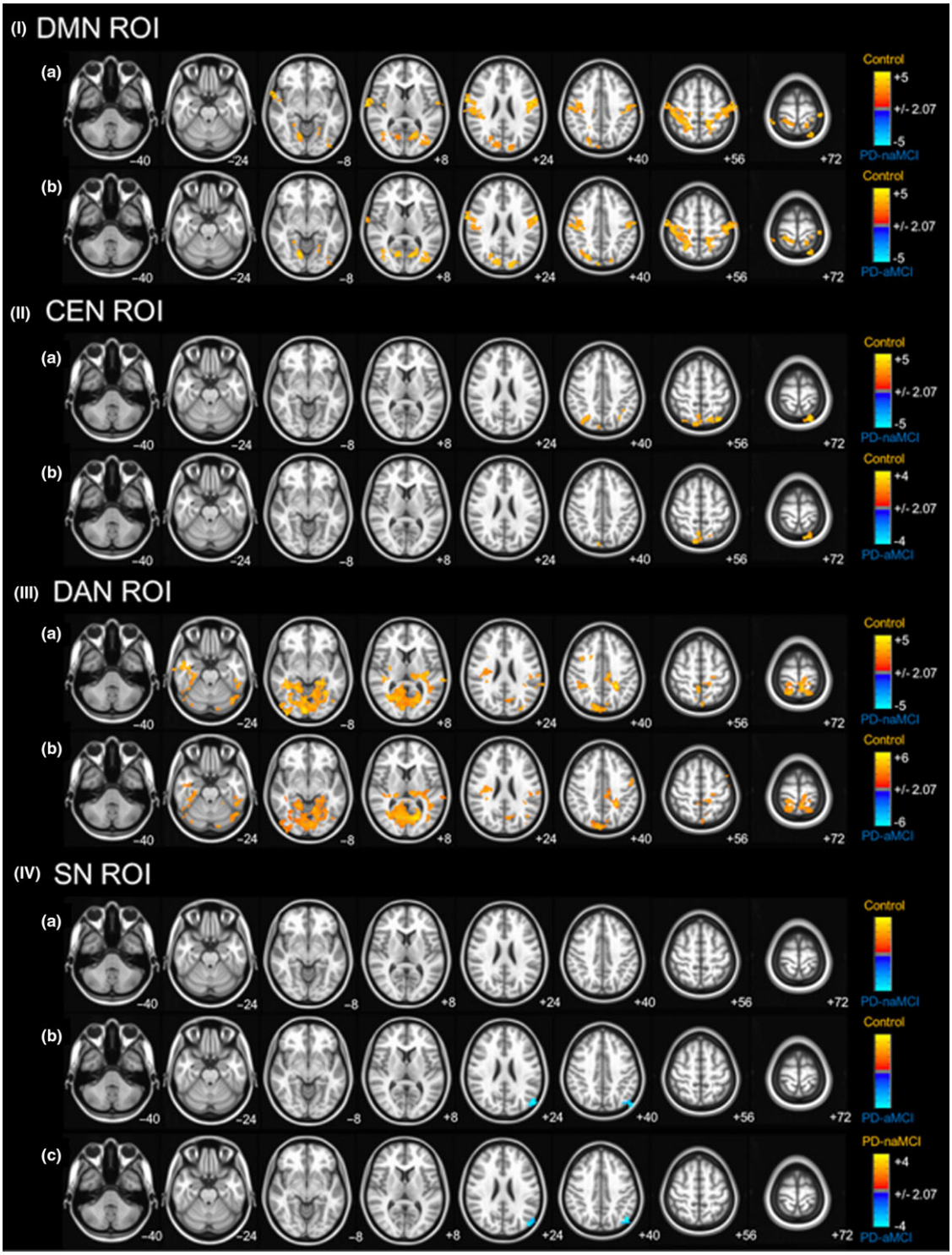

Figure 2 Comparison of resting-state functional connectivity with regions of interest (ROIs). ROIs in the (I) default mode network (DMN), (II) central executive network (CEN), (III) dorsal attention network (DAN) and (IV) salience network (SN). Group-wise comparisons between (a) Parkinson's disease with amnestic mild cognitive impairment (PD-aMCI) and controls, (b) Parkinson's disease with non-amnestic mild cognitive impairment (PD-naMCI) and controls and (c) PD-aMCI and PD-naMCI (only the SN showed significant differences in a direct comparison) are shown. [Color figure can be viewed at wileyonlinelibrary.com]

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Table 2 Comparisons of cognitive decline rate between the Parkinson's disease (PD) with mild cognitive impairment (MCI) groups

	Estimated slope (standard error)					
	PD-naMCI	*P*-value	PD-aMCI	*P*-value	Difference	*P*-value
K-MMSE score	−0.0718 (0.0905)	0.428	−0.1324 (0.0515)	0.011	−0.0606 (0.1035)	0.558
Attention	0.0098 (0.0468)	0.834	−0.0889 (0.0267)	0.001	−0.0987 (0.0536)	0.066
Language	−0.0143 (0.0732)	0.845	−0.0625 (0.0417)	0.135	−0.0482 (0.0837)	0.565
Visuospatial	−0.1783 (0.1102)	0.106	−0.2564 (0.0628)	< 0.001	−0.0782 (0.1260)	0.535
Memory	0.0199 (0.0497)	0.690	−0.0063 (0.0283)	0.825	−0.0262 (0.0569)	0.646
Verbal memory	0.0708 (0.0777)	0.363	−0.0226 (0.0442)	0.611	−0.0933 (0.0888)	0.294
Visual memory	−0.0311 (0.0471)	0.509	0.0125 (0.0268)	0.641	0.0436 (0.0539)	0.418
Frontal/executive	0.0842 (0.0467)	0.072	−0.0387 (0.0266)	0.146	−0.1229 (0.0534)	0.022

The negative value of estimated slope of the PD with MCI groups indicates cognitive decline in the follow-up assessment. The difference of estimated slopes between the groups has a negative value if the PD with amnestic MCI (PD-aMCI) group had a steep slope of cognitive decline compared with the PD with non-amnestic MCI (PD-naMCI) group. K-MMSE, Korean version of the Mini-Mental State.

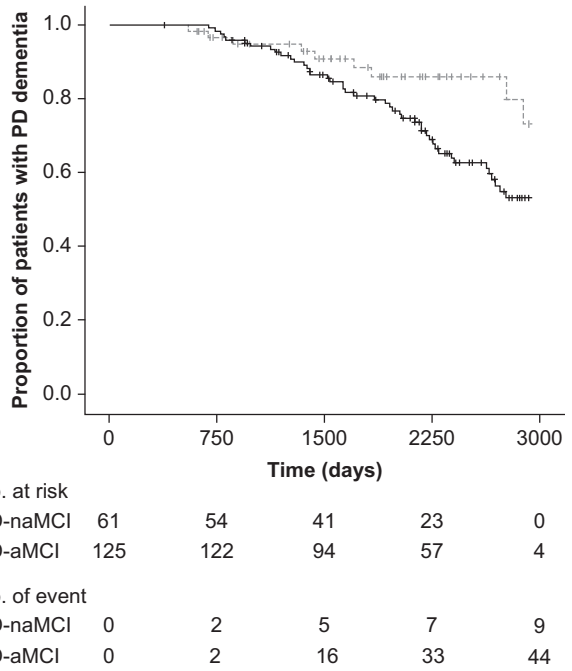

Figure 3 Curves showing the conversion to dementia in the Parkinson's disease with mild cognitive impairment (MCI) groups according to the presence of memory impairment based on Kaplan–Meier estimates. The Parkinson's disease with amnestic MCI (PD-aMCI) group (solid black line) had a higher risk of Parkinson's disease with dementia conversion than the Parkinson's disease with non-amnestic MCI (PD-naMCI) group (dashed grey line) ($P_{\text{Log-rank}} = 0.036$). The crosses in the graphs indicate censored data.

Table 3 Cox regression analysis for the conversion of dementia

Factor	Hazard ratio (95% CI)	*P*-value
Group (PD-aMCI versus PD-naMCI)	2.291 (1.100–4.774)	0.027
Age	1.068 (1.022–1.115)	0.003
Sex	1.002 (0.560–1.795)	0.994
Years of education	0.997 (0.935–1.062)	0.918

CI, confidence interval; PD-aMCI, Parkinson's disease with amnestic mild cognitive impairment; PD-naMCI, Parkinson's disease with non-amnestic mild cognitive impairment.

Neuroimaging analyses

The SN (anterior insula and anterior cingulate cortex) is known to play a critical role in switching between the CEN and DMN (i.e. consistent activation of the SN modulates the activation of the CEN and deactivation of the DMN during cognitively demanding tasks) [10]. Both the CEN and DMN are important for multiple cognitive functions and also seem to be related to memory function in patients with PD-MCI [11,12]. In this regard, the results of our study suggest that the altered functional connectivity from the SN to the left posterior parietal cortex or a part of the CEN would affect the modulation of the CEN and DMN activities, and thus have an impact on memory dysfunction in patients with PD-aMCI without direct involvement in the DMN and CEN. More increased functional connectivity from the SN in the PD-aMCI group compared with the other groups can be interpreted as a compensatory mechanism against the selective SN dysfunction.

The exact pathomechanism of the selective SN involvement in the PD-aMCI group remains uncertain. Recently, Christopher *et al*. reported a significant reduction in D2 receptor availability in the regions of the SN in patients with PD-aMCI relative to patients with PD-naMCI without any difference in the CEN [13] and explained that this distinct D2 receptor expression may be ascribed to different vulnerability to Lewy body deposition [13,14]. Moreover, as the insula is one of the earliest and most affected cortical

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regions according to Braak's staging of brain pathology in PD [15], the burden of other coexistent neuropathologies, such as β-amyloid in the SN, would be important for memory dysfunction in the PD-MCI groups [16]. Alternatively, the degeneration of neurotransmitter systems could affect the functional integrity of the SN [14]. Further investigations are needed to determine whether other pathological changes or neurotransmitter systems in the SN could influence memory function in patients with PD-MCI preceding the structural changes.

Longitudinal cognitive assessment

The current study demonstrated that the PD-aMCI group exhibited a faster cognitive decline in attention/working memory and frontal/executive function domains and had a higher rate of PDD conversion relative to those with PD-naMCI. These results suggest that functional alterations in the susceptible SN are associated with the cognitive prognosis, particularly executive function in patients with PD-MCI [17]. However, contrary to our expectations, there was no significant difference in the rate of cognitive decline in the memory function domain between the PD-aMCI and PD-naMCI groups. This might be ascribed to different baseline levels of cognitive performance of the groups, i.e. the floor effect of memory dysfunction in the PD-aMCI group may not allow a further memory decline in the follow-up assessment. Indeed, caution should be exercised when assessing the course of cognitive decline in PD-MCI. It is widely accepted that cognitive impairment in PD can be categorized into two distinct cognitive syndromes with potentially different prognoses: cognitive deficits with a posterior cortical basis are related to rapid cognitive decline and incident dementia in PD, whereas deficits with a frontostriatal origin are not [5]. In this study, nearly 80% of patients in both the PD-aMCI and PD-naMCI groups exhibited various posterior cortical deficits without significant between-group differences.

Limitations

Our study had some limitations. First, the subgroups for the neuroimaging analyses and longitudinal cognitive assessment were not identical; however, there were no significant differences in demographic characteristics except for gender between the subgroups. Secondly, the possible effect of dopamine replacement therapy on longitudinal cognitive changes in PD was not considered in this study. Thirdly, the interval and number of follow-up neuropsychological assessments were not consistent for each subject. Consequently, we used the linear mixed model to analyze the cognitive decline, but were unable to reflect the inflection point of the cognitive course in PD [1]. Fourthly, the SNSB has not yet been specifically validated for PD. However, most of the subtests comprising the SNSB are recommended by the Movement Disorder Society Task Force guidelines [2]. Finally, although PD pathology was identified in the present study with a clinical diagnosis as well as with dopamine transporter imaging, we did not consider the effect of Alzheimer's disease pathology in this group.

In conclusion, our data suggest that the designation of PD-MCI subtypes based on amnestic or non-amnestic terminology highlights the heterogeneity of functional correlates in these patients. The vulnerability of the SN would affect the memory function in patients with PD-MCI in the absence of structural abnormalities, as well as the longitudinal cognitive prognosis.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Comparisons of the hippocampal volume between the groups.
Table S1. Neuropsychological data in patients with Parkinson's disease with mild cognitive impairment for neuroimaging analyses
Table S2. Baseline demographic characteristics and neuropsychological data of patients with Parkinson's disease with mild cognitive impairment for the longitudinal cognitive assessment
Table S3. Anatomical locations displaying significant group differences from the seed regions of interest in the default mode network, central executive network, dorsal attention network and salience network
Appendix S1. Methods.

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References

1. Svenningsson P, Westman E, Ballard C, Aarsland D. Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. *Lancet Neurol* 2012; **11:** 697–707.
2. Litvan I, Goldman JG, Troster AI, *et al*. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord* 2012; **27:** 349–356.
3. Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. *Mov Disord* 2006; **21:** 1343–1349.
4. Busse A, Hensel A, Guhne U, Angermeyer MC, Riedel-Heller SG. Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology* 2006; **67:** 2176–2185.
5. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. *Brain* 2007; **130:** 1787–1798.
6. Kang Y, Na DL. *Seoul Neuropsychological Screening Battery (SNSB)*. Incheon: Human Brain Research & Consulting Co., 2003.
7. Chung SJ, Yoo HS, Oh JS, *et al*. Effect of striatal dopamine depletion on cognition in *de novo* Parkinson's disease. *Parkinsonism Relat Disord* 2018; **51:** 43–48.
8. Meyers JE, Meyers KR. *Rey Complex Figure Test and Recognition Trial: Professional Manual*. Lutz, FL: Psychological Assessment Resources, 1995.
9. Chung SJ, Choi YH, Kwon H, *et al*. Sleep disturbance may alter white matter and resting state functional connectivities in Parkinson's disease. *Sleep* 2017; **40:** https://doi.org/10.1093/sleep/zsx009
10. Goulden N, Khusnulina A, Davis NJ, *et al*. The salience network is responsible for switching between the default mode network and the central executive network: replication from DCM. *NeuroImage* 2014; **99:** 180–190.
11. Blumenfeld RS, Ranganath C. Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. *J Neurosci* 2006; **26:** 916–925.
12. Huijbers W, Pennartz CM, Cabeza R, Daselaar SM. The hippocampus is coupled with the default network during memory retrieval but not during memory encoding. *PLoS ONE* 2011; **6:** e17463.
13. Christopher L, Duff-Canning S, Koshimori Y, *et al*. Salience network and parahippocampal dopamine dysfunction in memory-impaired Parkinson disease. *Ann Neurol* 2015; **77:** 269–280.
14. Christopher L, Koshimori Y, Lang AE, Criaud M, Strafella AP. Uncovering the role of the insula in non-motor symptoms of Parkinson's disease. *Brain* 2014; **137:** 2143–2154.
15. Braak H, Bohl JR, Muller CM, Rub U, de Vos RA, Del Tredici K. Stanley Fahn Lecture 2005: the staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. *Mov Disord* 2006; **21:** 2042–2051.
16. Compta Y, Parkkinen L, O'Sullivan SS, *et al*. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? *Brain* 2011; **134:** 1493–1505.
17. Christopher L, Marras C, Duff-Canning S, *et al*. Combined insular and striatal dopamine dysfunction are associated with executive deficits in Parkinson's disease with mild cognitive impairment. *Brain* 2014; **137:** 565–575.

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