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Mild cognitive impairment reverters have a favorable cognitive prognosis and cortical integrity in Parkinson's disease

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ABSTRACT

This study aimed to investigate whether reversion to cognitively normal status (CogN) is related to a favorable cognitive prognosis in Parkinson's disease with mild cognitive impairment (PD-MCI). We recruited 217 patients with PD-MCI who underwent serial neuropsychological assessments 3–5 times (mean interval, 1.84 years). Thirty-six patients reverted to CogN (reverters) during follow-up, whereas the other 181 did not (nonreverters). We assessed the risk of cognitive worsening in PD-MCI reverters, nonreverters, and patients with PD-CogN (n = 88). In addition, we performed comparative analyses of comprehensive neuroimaging studies between the PD-MCI reverter (n = 17) and nonreverter (n = 34) subgroups. PD-MCI reverters had a lower risk of dementia conversion than nonreverters. In addition, PD-MCI reverters had similar risks of cognitive worsening with patients with PD-CogN. PD-MCI reverters exhibited greater cortical thickness in the right parahippocampal gyrus and less severely decreased functional connectivity in the default mode and executive control networks relative to nonreverters. Our results suggest that PD-MCI reverters have relatively preserved structural and functional integrity and a favorable cognitive prognosis compared with nonreverters.

1. Introduction

The concept of mild cognitive impairment (MCI) is widely accepted as a transitional state between normal cognition and dementia not only in Alzheimer's disease populations (Petersen, 2004) but also in patients with Parkinson's disease (PD) (Janvin et al., 2006; Litvan et al., 2012; Pedersen et al., 2013). Early detection of MCI in PD is important because it may be helpful in identifying individuals at risk for future dementia and in developing therapeutic interventions (Eberling et al., 2014). However, not all patients with PD-MCI progress to dementia, and cognitive deterioration in PD does not always follow the normally linear involution (Martinez-Horta and Kulisevsky, 2011). Indeed, the course of PD-MCI is so variable that a large proportion of patients with PD-MCI remain clinically stable or revert to a cognitively normal status (CogN), and some of these reverters later reconvert to MCI or even progress to dementia (Pandya et al., 2016; Pedersen et al., 2017).

It remains unclear whether reverters from PD-MCI to PD with cognitively normal status (PD-CogN) require clinicians' attention similar to that given to nonreverted patients with PD-MCI based on cognitive prognosis. From 10% to 20% of newly diagnosed patients with PD-MCI return to PD-CogN during a 2–5 years of follow-up period (Broeders et al., 2013; Jones et al., 2018; Pedersen et al., 2013, 2017; Santangelo et al., 2015), with only 2 recent studies showing that these reverters continue to be at risk for subsequent cognitive decline (Jones et al., 2018; Pedersen et al., 2017), in agreement with previous studies in non-PD populations (Aerts et al., 2017; Koepsell and Monsell, 2012; Roberts et al., 2014). However, these studies were limited by a small reverter sample size (Pedersen et al., 2017) or incomprehensive cognitive test batteries (Jones et al., 2018). Therefore, the present study aimed to investigate whether reversion from PD-MCI to PD-CogN is clinically relevant for cognitive prognosis using a large sample size and a detailed neuropsychological test. In addition, we hypothesized that the reverters would have relatively preserved brain structural and/or functional integrity in the representative cognitive networks

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compared with the nonreverters and performed comprehensive neuroimaging analyses of cortical thickness, white matter (WM) integrity, and resting-state functional connectivity in patients with PD-MCI to uncover the neural correlates distinguishing the reverter and nonreverter groups.

2. Methods

2.1. Subjects

We reviewed the medical records of patients with PD who visited the Movement Disorders outpatient clinic at Severance Hospital from March 2008 to September 2016. Among 563 patients diagnosed with PD-MCI using a detailed neuropsychological test at baseline (i.e., the Seoul Neuropsychological Screening Battery; see the next section) (Litvan et al., 2012), the present study included 293 patients with PD-MCI who had undergone the serial neuropsychological assessment 2–5 times with a mean interval of 1.84 years (Supplementary Methods, Supplementary Table 1, and Fig. 1). PD and PD-MCI were diagnosed according to the clinical diagnostic criteria of the UK PD Society Brain Bank and the Movement Disorder Society Task Force guidelines (Litvan et al., 2012), respectively. To ensure clinical diagnostic accuracy, ^{18}F-fluorinated N-3-fluoropropyl-2-beta-carboxymethoxy-3-beta-(4-iodophenyl) nortropane positron emission tomography scans were performed on all subjects, and all showed decreased ^{18}F-FP-CIT binding in the posterior putamen on PET scans. Of these 293 patients, 73 had undergone brain magnetic resonance imaging (MRI) scans that were suitable for comprehensive

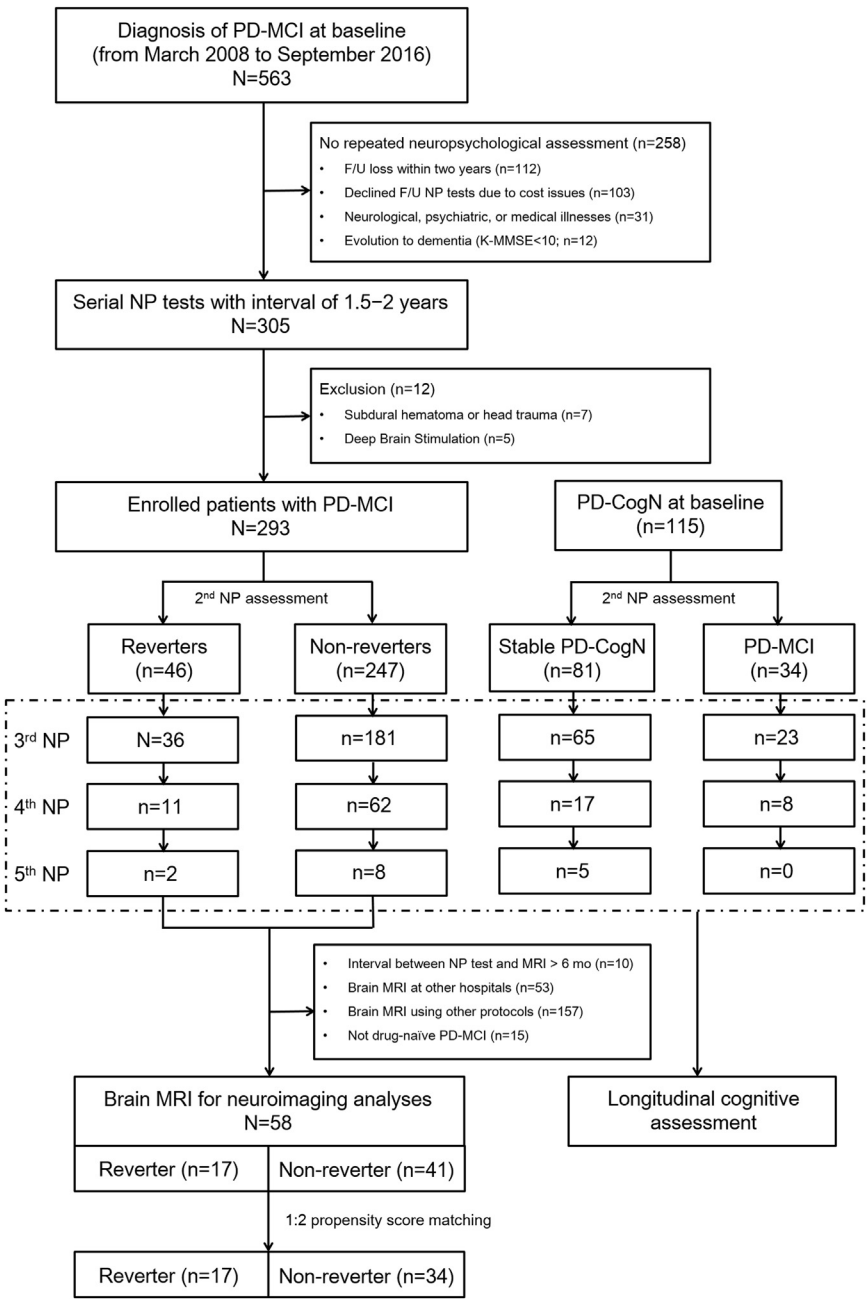

Fig. 1. Flowchart of participants and enrollment. Abbreviations: PD-MCI, Parkinson's disease with mild cognitive impairment; K-MMSE, the Korean version of the Mini-Mental State Examination; PD-CogN, Parkinson's disease with cognitively normal status; MRI, magnetic resonance imaging; NP, neuropsychological.

neuroimaging analyses at baseline evaluation (Fig. 1). Parkinsonian motor symptoms were assessed using the Unified PD Rating Scale Part III, and olfactory function was measured by the cross-cultural smell identification test. Depression was evaluated using the Beck Depression Inventory, and the PD medication doses were calculated as levodopa-equivalent doses (Tomlinson et al., 2010). This study was approved by the Yonsei University Severance Hospital institutional review board. The need for informed consent was waived because of the retrospective nature of the study.

2.2. Neuropsychological assessment

All subjects were administered the Seoul Neuropsychological Screening Battery, a comprehensive Korean language neuropsychological test battery (Ahn et al., 2010; Kang et al., 2012). To diagnose PD-MCI, 2 tests were designated to represent each of the 4 cognitive domains except language, as described in our previous work (Supplementary Methods) (Chung et al., 2018). PD-CogN was classified when a subject showed impairment on less than 2 items of the detailed neuropsychological test. PD with dementia (PDD) was diagnosed according to the clinical diagnostic criteria for probable PDD (Emre et al., 2007), and all subjects with PDD showed evidence of abnormalities in the activities of daily living, judged both clinically and on an instrumental activities of daily living scale (Kang, 2002; Ku et al., 2004).

2.3. Classification of PD-MCI into reverter and nonreverter groups

We classified the patients with PD-MCI into 2 groups according to the results of their serial neuropsychological assessment: subjects who reverted from PD-MCI at baseline to PD-CogN during follow-up (PD-MCI reverter group; n = 46) and those who did not (i.e., subjects who were still PD-MCI or progressed to PDD during follow-up; PD-MCI nonreverter group; n = 247). In addition, we reviewed our Parkinson center database entries from March 2008 to September 2016 and included 115 patients with PD-CogN at baseline to compare the risk of cognitive deterioration with that in the PD-MCI groups. Specifically, 81 of the 115 patients retained normal cognition during 3-year follow-up and were classified into a stable PD-CogN group.

2.4. Assessment of the longitudinal cognitive changes in patients with PD

2.4.1. Risk for PDD conversion in nondemented PD groups

We compared cognitive prognoses between the PD groups who underwent at least 3 assessments (i.e., 2 assessments to identify if the individuals were a reverter or not, and then additional assessments to determine the risk of cognitive deterioration; 36 in the PD-MCI reverter group, 181 in the PD-MCI nonreverter group, 88 in the PD-CogN group, and 65 in the stable PD-CogN group; see Fig. 1). We estimated the time from the baseline assessment of cognitive status to PDD conversion with Kaplan-Meier estimates. The log-rank and Breslow tests were used to compare the Kaplan-Meier plots among the PD-MCI reverter (n = 36), PD-MCI nonreverter (n = 181), and PD-CogN (n = 88) groups. A Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals while adjusting for age, sex, and years of education.

2.4.2. Comparison between PD-MCI reverters and patients with PD-CogN at baseline

We compared the risk of cognitive worsening from the baseline assessment between the PD-MCI reverter (n = 36) and PD-CogN (n = 88) groups, as described previously. Subjects were defined as cognitively worsened when they were subsequently diagnosed as having converted to a reduced cognitive status based on the results of the last neuropsychological assessment, namely to PD-MCI or PDD in patients with reverted PD-MCI or PD-CogN. We also assessed the conversion time from the cognitively normal status (i.e., reversion onset in PD-MCI or baseline assessment in PD-CogN) to the cognitively worsened status.

2.4.3. Comparison between PD-MCI reverters and stable PD-CogN patients

We also compared cognitive prognoses (i.e., cognitive worsening and PDD conversion) between PD-MCI reverters (n = 36) and stable PD-CogN patients (n = 65) using the same statistical methods.

2.5. Neuroimaging analyses

To reduce the confounding effects of advanced PD and chronic dopamine replacement on cognition, the neuroimaging analyses were performed in de novo patients with PD-MCI. Among the 73 subjects who had brain MRI scans available for neuroimaging analyses at baseline evaluation, 58 subjects (17 in the PD-MCI reverter group and 41 in the PD-MCI nonreverter group) were drug naïve. Then, the 17 patients with PD-MCI in the reverter group were matched to 34 of the 41 patients in the nonreverter group based on the propensity scores (Supplementary Methods). Thirty healthy subjects with no neurological disease history (mean age, 66.20 ± 8.41; female, 50.0%) were also included as a control group. MRI scans were acquired with the same protocol as described in our previous work (Supplementary Methods) (Chung et al., 2017).

2.5.1. Analysis of cortical thickness and tract-based spatial statistics analysis

We used a methodology similar to that used in our previous study (Supplementary Methods) (Chung et al., 2017).

2.5.2. Functional connectivity analysis

The default mode network (DMN), executive control network (ECN), dorsal attention network (DAN), and substantia innominata network were selected for the functional connectivity analyses using seed-based analysis (Chung et al., 2017; Lee et al., 2018). A detailed description is provided in Supplementary Methods.

2.6. Statistical analyses

To compare the baseline demographic characteristics and cognitive performance between the groups, Student's *t*-test and Pearson's χ^2 test were performed for continuous and categorical variables, respectively. The false discovery rate–controlling method was used for multiple comparisons correction. The log-rank test, Breslow test, and Cox proportional hazards model were used to assess the risk of cognitive worsening in the PD groups. The statistical analyses were performed with SPSS software (version 23.0; IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline clinical characteristics of patients with PD-MCI

Table 1 shows the baseline demographic characteristics and neuropsychological data of patients with PD-MCI (46 reverters and 247 nonreverters). The patients in the reverter group were younger (66.52 ± 7.35) than those in the nonreverter group (70.01 ± 6.82; $p = 0.002$). No significant differences were observed in sex, years of education, duration of PD, initial Unified PD Rating Scale Part III scores, and the presence of vascular risk factors between the groups. The reverter group had a higher cross-cultural smell identification test score and a lower Beck Depression Inventory score than the nonreverter group.

Table 1
Baseline demographic characteristics and neuropsychological data of patients with PD-MCI

Baseline clinical features	Reverter (n = 46)	Nonreverter (n = 247)	*p*-value
Age	66.52 ± 7.35	70.01 ± 6.82	0.002
Female, No. (%)	19 (41.3%)	123 (49.8%)	0.290
Education (y)	9.79 ± 3.88	9.30 ± 4.93	0.447
PD duration (mo)	39.39 ± 47.83	36.50 ± 37.91	0.650
UPDRS-III	23.57 ± 9.84	23.37 ± 10.60	0.917
CCSIT[a]	6.88 ± 2.36	5.90 ± 2.27	0.021
BDI[b]	11.67 ± 8.11	15.06 ± 9.62	0.032
LED (among treated PD)[c]	213.73 ± 357.61	210.57 ± 358.54	0.956
Vascular risk factors, No. (%)			
Hypertension	17 (37.0%)	120 (48.6%)	0.147
Diabetes mellitus	9 (19.6%)	47 (19.0%)	0.932
Dyslipidemia	9 (19.6%)	43 (17.4%)	0.725
Cardiac disease	7 (15.2%)	39 (15.8%)	0.922
MCI subtypes (1)			0.012
Nonamnestic	16 (34.8%)	75 (30.4%)	
Amnestic	30 (65.2%)	172 (69.6%)	
Retrieval failure	24 (52.2%)	87 (35.2%)	
Storage failure	6 (13.0%)	85 (34.4%)	
MCI subtypes (2)			<0.001
Single domain	19 (41.3%)	38 (15.4%)	
Multiple domain	27 (58.7%)	209 (84.6%)	
Neuropsychological data			
K-MMSE	27.50 ± 1.71	25.97 ± 2.88	<0.001
Attention and working memory	0.07 ± 0.81	−0.46 ± 0.85	<0.001[d]
Impaired, No. (%)	16 (34.8%)	168 (68.0%)	<0.001
Frontal executive function	−0.23 ± 1.00	−0.61 ± 0.78	0.007[d]
Impaired, No. (%)	27 (58.7%)	167 (67.6%)	0.240
Language and related function	−0.11 ± 1.08	−0.55 ± 1.31	0.035[d]
Impaired, No. (%)	8 (17.4%)	88 (35.6%)	0.016
Memory function	−0.24 ± 0.72	−0.62 ± 0.90	0.009[d]
Verbal memory	−0.42 ± 1.05	−0.66 ± 1.53	0.319[d]
Visual memory	−0.06 ± 0.92	−0.60 ± 0.82	<0.001[d]
Impaired, No. (%)	30 (65.2%)	172 (69.6%)	0.552
Visuospatial function	0.17 ± 1.04	−0.61 ± 0.78	0.007[d]
Impaired, No. (%)	5 (10.9%)	57 (23.1%)	0.063

The values are expressed as mean ± standard deviation or number (percentage).
Key: PD, Parkinson's disease; PD-MCI, PD with mild cognitive impairment; UPDRS-III, Unified PD Rating Scale Part III; CCSIT, the cross-cultural smell identification test; BDI, Beck Depression Inventory; LED, levodopa-equivalent dose; K-MMSE, the Korean version of the Mini-Mental State Examination.
[a] Twelve of 46 in the reverter group and 48 of 247 in the nonreverter group were not assessed with the CCSIT.
[b] Four of 46 in the reverter group and 6 of 247 in the nonreverter group were not assessed with BDI.
[c] Thirty two of 46 in the reverter group and 170 of 247 in the nonreverter group were drug-naïve PD (i.e., LED = 0).
[d] FDR-controlling method for multiple comparisons.

The frequencies of the nonamnestic and amnestic MCI types were similar between the groups. However, when we divided amnestic MCI into 2 subtypes depending on the dissociation between free recall and cued memory, the reverter group had a higher frequency (52.2%) of the retrieval failure subtype (i.e., subjects who showed free recall memory deficits that improved with cues on recognition tests), whereas the nonreverter group had a higher frequency (34.4%) of the storage failure subtype (i.e., subjects who showed abnormal performances on both delayed recall and recognition tests). In addition, the single-domain MCI type was more prevalent in the reverter group (41.3%) than in the nonreverter group (15.4%; $p < 0.001$). Scores on the K-MMSE, attention/working memory, frontal/executive, language, visual memory, and visuospatial function domains were lower in the nonreverter patients with PD-MCI when compared with the reverter patients, whereas cognitive performance in the verbal memory domain was similar in the 2 groups.

Supplementary Table 2 shows that there were no significant differences in the demographic and cognitive characteristics between the PD-MCI groups included in the neuroimaging analyses.

3.2. Risk of cognitive deterioration in patients with nondemented PD

3.2.1. Baseline clinical characteristics of patients with PD-CogN

The baseline demographic characteristics and neuropsychological data of the patients with PD-CogN are listed in Supplementary Table 3. No significant differences were observed in demographic characteristics other than disease duration between the PD-MCI reverter and PD-CogN groups. The PD-CogN group also showed better cognitive performance on the attention/working memory, frontal/executive, language, and memory function domains compared with that in the PD-MCI reverter group.

3.2.2. Risk of PDD conversion in nondemented PD groups

During the follow-up period, 2 of 36 PD-MCI reverters (follow-up duration, 5.05 ± 1.86 years), 100 of 181 PD-MCI nonreverters (4.87 ± 1.77 years), and 16 of 88 patients with PD-CogN (5.13 ± 1.84 years) converted to PDD. The PD-MCI nonreverter group had a higher risk of PDD conversion than did the other groups (PD-MCI reverter group, $p_{\text{Log rank}} < 0.001$, HR 11.113 [2.737–45.117]; PD-CogN group, $p_{\text{Log rank}} < 0.001$; HR 3.172 [1.852–5.433]), whereas the PD-MCI reverter and PD-CogN groups had similar risks of developing PDD ($p_{\text{Log rank}} = 0.109$; HR 0.285 [0.066–1.244]; Fig. 2A and Table 2A).

3.2.3. Comparison between PD-MCI reverters and patients with PD-CogN at baseline

Next, we compared the risk of cognitive worsening between the PD-MCI reverter and PD-CogN groups. During the follow-up period, 6 of 36 PD-MCI reverters and 31 of 88 patients with PD-CogN were diagnosed as having a cognitively worsened status. From the time of the baseline neuropsychological assessment, the PD-MCI

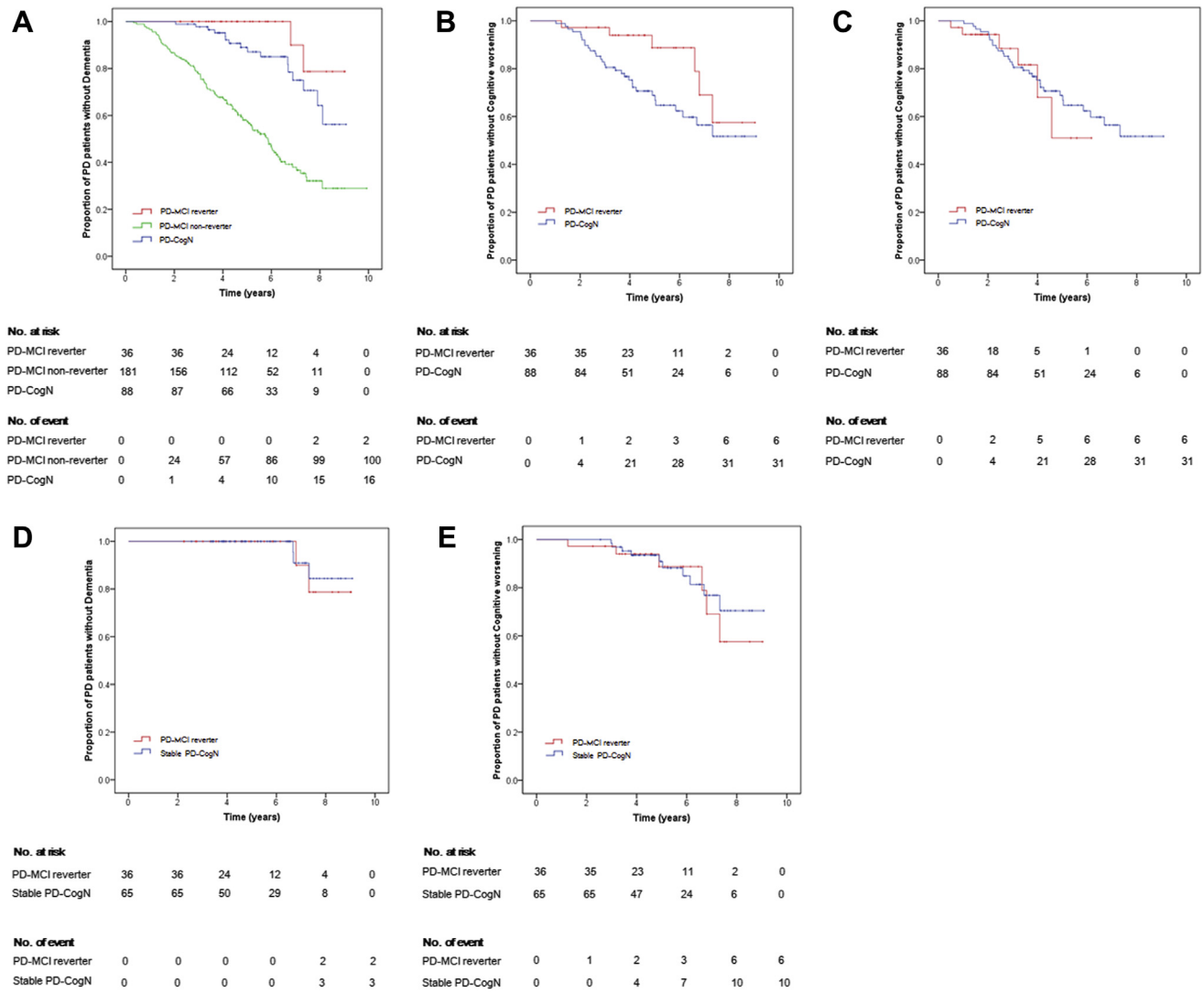

Fig. 2. (A) Dementia conversion in the PD groups from the baseline assessment (PD-MCI reverter vs. PD-MCI nonreverter, $p_{\log\ rank} < 0.001$; PD-CogN vs. PD-MCI non-reverter, $p_{\log\ rank} < 0.001$; PD-MCI reverter vs. PD-CogN, $p_{\log\ rank} = 0.109$). (B) Cognitive worsening in the PD-MCI reverter and PD-CogN groups from the baseline assessment ($p_{\log\ rank} = 0.058$; $p_{Breslow} = 0.020$). (C) Cognitive worsening in the PD-MCI reverter and PD-CogN groups from the diagnosis of cognitively normal status (i.e., from the second neuropsychological assessment in the PD-MCI reverter group and from the baseline assessment in the PD-CogN group; $p_{\log\ rank} = 0.728$). (D) Dementia conversion in the PD-MCI reverter and stable PD-CogN groups from the baseline assessment ($p_{\log\ rank} = 0.759$). (E) Cognitive worsening in the PD-MCI reverter and stable PD-CogN groups from the baseline assessment ($p_{\log\ rank} = 0.654$). Cognitive domain scores were classified as abnormal when they were 1 standard deviation below the age- and education-specific norms. Abnormalities in the activities of daily living (ADLs) were determined based on 2 standardized measures of functional impairments (Korean Instrumental ADL [K-IADL], cutoff point of 0.43; Seoul-Instrumental ADL [S-IADL], cutoff point of 8). Abbreviations: PD, Parkinson's disease; PD-MCI, Parkinson's disease with mild cognitive impairment; PD-CogN, Parkinson's disease with cognitively normal status.

reverter group had a lower risk of cognitive worsening compared with that in the PD-CogN group ($p_{\log\ rank} = 0.058$; $p_{Breslow} = 0.020$; HR 0.376 [0.155–0.913]; Fig. 2B and Table 2B). From the time of the diagnosis of cognitively normal status, the PD-MCI reverter group (follow-up duration, 2.60 ± 1.39 years) and the PD-CogN group (4.75 ± 1.97 years) had similar risks of cognitive worsening ($p_{\log\ rank} = 0.728$; $p_{Breslow} = 0.841$; HR 1.146 [0.455–2.882]; Fig. 2C and Table 2C).

3.2.4. Comparison between PD-MCI reverters and stable PD-CogN patients

During the follow-up period, 2 of 36 patients in the PD-MCI reverter group and 3 of 65 patients in the stable PD-CogN group developed dementia. From the time of the baseline assessment, the 2 groups had similar risks of PDD conversion ($p_{\log\ rank} = 0.759$; $p_{Breslow} = 0.835$; HR 1.439 [0.204–10.151]; Fig. 2D and Table 3A).

Regarding cognitive worsening, 6 of 36 patients in the PD-MCI reverter group and 10 of 65 patients in the stable PD-CogN group were subsequently diagnosed as having a cognitively worsened status. The risk of cognitive worsening did not differ between the 2 groups ($p_{\log\ rank} = 0.654$; $p_{Breslow} = 0.820$; HR 1.104 [0.387–3.147]; Fig. 2E and Table 3B).

3.3. Analysis of cortical thickness

The PD-MCI nonreverter group exhibited smaller cortical thickness in the left occipital region relative to that in the controls (random-field theory-corrected $p < 0.05$; Fig. 3I–A), whereas there were no regions with significant difference in cortical thickness between the PD-MCI reverters and controls. The PD-MCI reverter group exhibited greater cortical thickness in the right

Table 2
Cox regression analysis for the cognitive deterioration

Factors	Hazard ratio (95% CI)	*p*-value
(A) PDD conversion from initial assessment		
Group		<0.001
PD-MCI nonreverter versus PD-MCI reverter	11.113 (2.737, 45.117)	0.001
PD-MCI nonreverter versus PD-CogN	3.172 (1.852, 5.433)	<0.001
PD-MCI reverter versus PD-CogN	0.285 (0.066, 1.244)	0.095
Age	1.046 (1.018, 1.075)	0.001
Sex	1.231 (0.832, 1.822)	0.298
Education	0.981 (0.942, 1.021)	0.340
(B) Cognitive worsening from initial assessment[a]		
Group (PD-MCI reverter vs. PD-CogN)	0.376 (0.155, 0.913)	0.031
Age	1.066 (1.014, 1.122)	0.012
Sex	0.860 (0.424, 1.744)	0.676
Education	0.995 (0.931, 1.064)	0.893
(C) Cognitive worsening from CogN status[a]		
Group (PD-MCI reverter vs. PD-CogN)	1.146 (0.455, 2.882)	0.773
Age	1.074 (1.021, 1.131)	0.006
Sex	0.798 (0.389, 1.635)	0.537
Education	1.001 (0.936, 1.071)	0.974

Key: CI, confidence interval; PD-CogN, Parkinson's disease with cognitively normal status; PD-MCI, Parkinson's disease with mild cognitive impairment; PDD, Parkinson's disease with dementia.
[a] The subjects were classified into the cognitively worsened status when they were subsequently diagnosed as having an advanced cognitive status, that is, conversion to dementia from MCI or conversion to MCI or dementia from the cognitively normal status.

parahippocampal gyrus compared with that in the PD-MCI nonreverter group (random-field theory-corrected $p < 0.05$; Fig. 3I–B).

3.4. Tract-based spatial statistics analysis of PD-MCI reverters and nonreverters

The controls exhibited significantly higher fractional anisotropy (FA) values in the fronto-parieto-temporal (mainly in the frontal region) WM than did either the PD-MCI reverter or nonreverter group (familywise error-corrected $p < 0.05$). The PD-MCI nonreverter group showed higher mean diffusivity (MD) values in the similar regions compared with those in the controls. The PD-MCI reverter and nonreverter groups had no areas with higher FA or lower MD values compared with those in the controls. There was no significant difference between the reverter and nonreverter groups in either FA or MD values (Fig. 3II).

Table 3
Cox regression analysis for cognitive deterioration between PD-MCI reverters and stable PD-CogN patients

Factors	Hazard ratio (95% CI)	*p*-value
(A) PDD conversion		
Group (PD-MCI reverter vs. stable PD-CogN)	1.439 (0.204, 10.151)	0.715
Age	0.993 (0.852, 1.158)	0.932
Sex	1.720 (0.225, 13.135)	0.601
Education	0.857 (0.685, 1.072)	0.176
(B) Cognitive worsening[a]		
Group (PD-MCI reverter vs. Stable PD-CogN)	1.104 (0.387, 3.147)	0.853
Age	1.101 (1.010, 1.200)	0.030
Sex	0.456 (0.157, 1.322)	0.148
Education	1.014 (0.915, 1.123)	0.797

Key: CI, confidence interval; PD-CogN, Parkinson's disease with cognitively normal status; PD-MCI, Parkinson's disease with mild cognitive impairment; PDD, Parkinson's disease with dementia.
[a] The subjects were classified into the cognitively worsened status when they were subsequently diagnosed as having an advanced cognitive status, that is, conversion to dementia from MCI or conversion to MCI or dementia from the cognitively normal status.

3.5. Group comparison of resting-state functional connectivity

3.5.1. Default mode network

Compared with the controls, the reverter group exhibited decreased functional connectivity in the lingual and superior frontal gyri in the DMN, whereas the nonreverter group did in the anterior cingulate cortex, parahippocampal gyrus, superior temporal, superior frontal, and medial frontal cortices, and postcentral gyrus. The reverter group exhibited less severely decreased functional connectivity in the right postcentral gyrus and bilateral medial frontal and right middle temporal cortices than did the nonreverter group (Fig. 4I).

3.5.2. Executive control network

Compared with the controls, the reverter group exhibited decreased functional connectivity in the middle frontal gyrus in the ECN, whereas the nonreverter group did in the middle frontal gyrus and insula. The reverter group exhibited less severely decreased functional connectivity in the right inferior frontal gyrus than did the nonreverter group (Fig. 4II).

3.5.3. Dorsal attention network

Compared with the controls, the PD groups exhibited decreased functional connectivity in the left frontal cortex in the DAN (Fig. 4III). There were no significant differences between the PD groups in cortical functional connectivity with the DAN.

3.5.4. Substantia innominata

Compared with the controls, the reverters exhibited decreased functional connectivity in the bilateral frontal cortices, whereas the nonreverter group did in the bilateral frontal and left temporal cortices and left precuneus in the substantia innominata (Fig. 4IV). No areas were found where cortical functional connectivity was significantly different between the reverter and nonreverter groups. The anatomical locations of the significant peaks are listed in Supplementary Table 4.

4. Discussion

The present study investigated the clinical relevance of the MCI-to-CogN reversion in patients with PD by performing comprehensive neuroimaging analyses and assessing longitudinal cognitive changes. The major findings were as follows: (1) Compared with nonreverters, PD-MCI reverters were younger and showed better cognitive performance on all cognitive domains, with increased prevalence of the single-domain MCI type and amnestic type with retrieval failure. (2) The PD-MCI reverter group had a lower risk of PDD conversion relative to that in the PD-MCI nonreverter group. In addition, the risk of reconversion to MCI or progression to dementia in the reverter group was similar to that of cognitive worsening in either the PD-CogN group or stable PD-CogN group. (3) The PD-MCI reverter group exhibited greater cortical thickness in the right parahippocampal gyrus compared with that in the nonreverter group, whereas WM integrity was similar between the groups. (4) The PD-MCI reverter group exhibited less severely decreased resting-state functional connectivity in the DMN and ECN compared with that in the nonreverter group. These findings suggest that the cognitive defect and neurodegenerative burden in the reverter group are less severe relative to those in the nonreverter group, which may be accompanied by better cognitive prognosis.

Although it has been consistently reported that PD-MCI increases the risk of progression to dementia (Janvin et al., 2006; Litvan et al., 2012), a considerable proportion of patients with PD-MCI remain stable over extended periods of time or even revert to PD-CogN (Jones et al., 2018; Pedersen et al., 2013, 2017). In non-

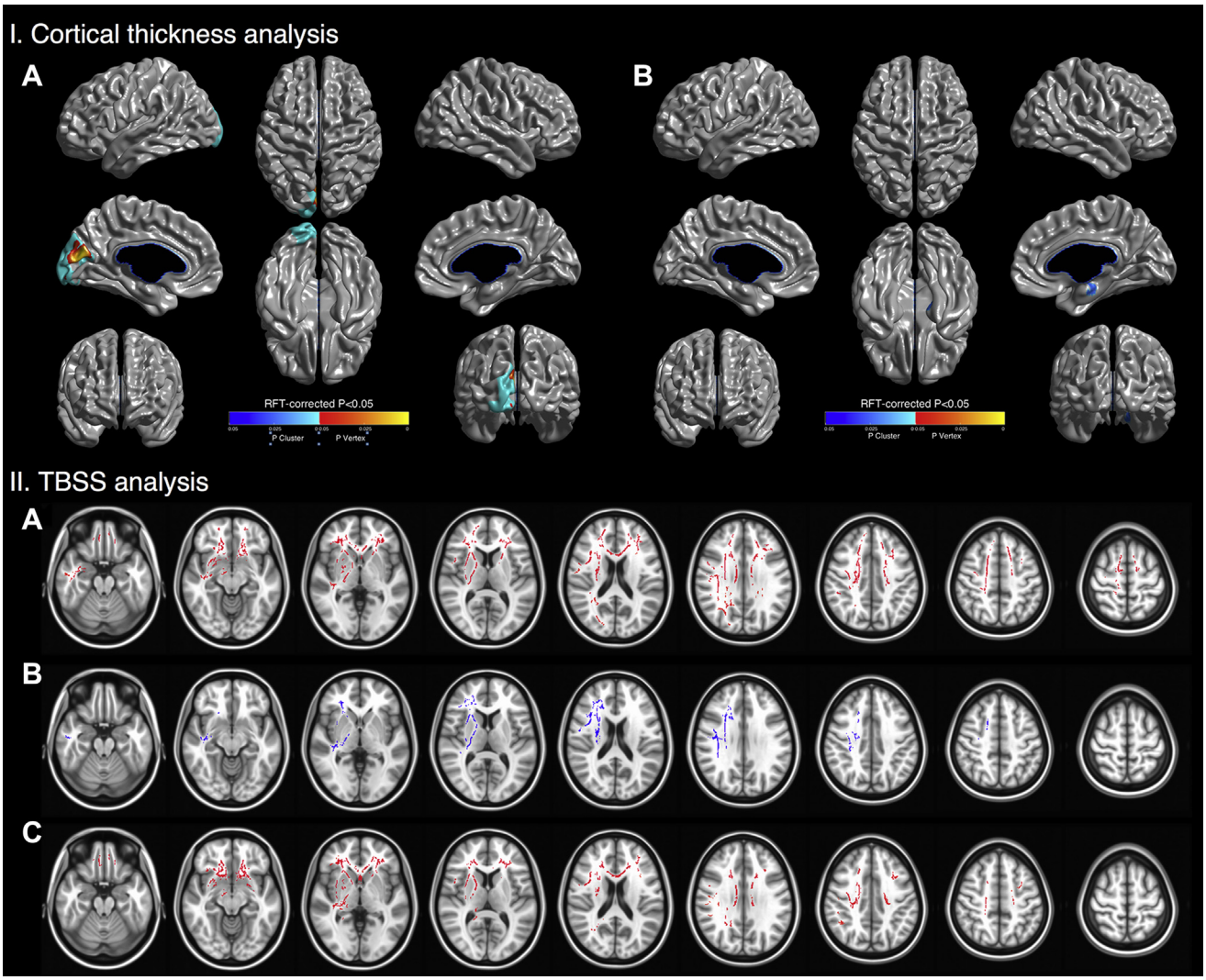

Fig. 3. Cortical thickness and TBSS analyses. (I) Cortical thickness analysis. (A) Control > PD-MCI nonreverter. (B) PD-MCI reverter > PD-MCI nonreverter (RFT-corrected $p < 0.05$). There were no regions of different cortical thickness between the PD-MCI reverters and controls. (II) TBSS analysis. (A) FA: Control > PD-MCI nonreverter. (B) MD: PD-MCI nonreverter > Control. (C) FA: Control > PD-MCI reverter (FWE-corrected $p < 0.05$). There was no significant difference in FA and MD values between the PD-MCI groups. Abbreviations: FA, fractional anisotropy; FWE, familywise error; PD-MCI, Parkinson's disease with mild cognitive impairment; RFT, random-field theory; TBSS, tract-based spatial statistics.

PD populations, the predictive factors for reversion to normal cognition and its natural course have been extensively investigated (Aerts et al., 2017; Diniz et al., 2009; Ganguli et al., 2011; Gao et al., 2014; Koepsell and Monsell, 2012; Roberts et al., 2014; Sachdev et al., 2013). These studies have found that individuals who were younger had single-domain nonamnestic MCI, less-severe cognitive defects, and increased volumes of the hippocampus and amygdala, and did not have an APOE ε4 allele were more likely to revert to normal cognition. In terms of cognitive prognosis, reverters remained at increased risk of retransitioning to MCI or developing dementia in the longer term, although their relative risk of progression to dementia was smaller than that of MCI nonreverters. However, few studies have reported on the clinical implications of reversion from MCI to CogN in PD populations (Jones et al., 2018; Pedersen et al., 2017), and to the best of our knowledge, no studies have explored the differences in the patterns of structural and functional alterations between PD-MCI reverters and nonreverters. The strength of our study is that we performed comprehensive neuroimaging analyses and interpreted the results in conjunction with the clinical outcomes to differentiate the PD-MCI reverters from nonreverters.

In the present study, the PD-MCI reverters had greater cortical thickness in the right parahippocampal gyrus compared with that in the nonreverters. The parahippocampal gyrus is associated with visuospatial processing and episodic memory (Aminoff et al., 2013), and its atrophy appears to be a predictor of MCI converting to dementia or reverting to normal cognition in non-PD populations (Tokuchi et al., 2014). Several studies have implicated the parahippocampal gyrus in cognitive functions in patients with PD (Christopher et al., 2015; Pagonabarraga et al., 2013), and our previous work has also demonstrated that the risk of cognitive decline correlates with cortical thinning in the parahippocampal gyrus in PD (Ye et al., 2017). In addition, the PD-MCI reverter group exhibited less severely decreased functional connectivity within the DMN and ECN relative to that in the PD-MCI nonreverter group. An increasing body of evidence suggests that functional disruption within the DMN is part of the neural substrate underlying PD-MCI (Baggio et al., 2015), and that the ECN, which is coupled with the DMN during cognitively demanding tasks (Sridharan et al., 2008), also appears to be important for cognitive processes in PD (Amboni et al., 2015). Furthermore, the progressive loss of functional integrity is closely associated with the risk of cognitive decline in

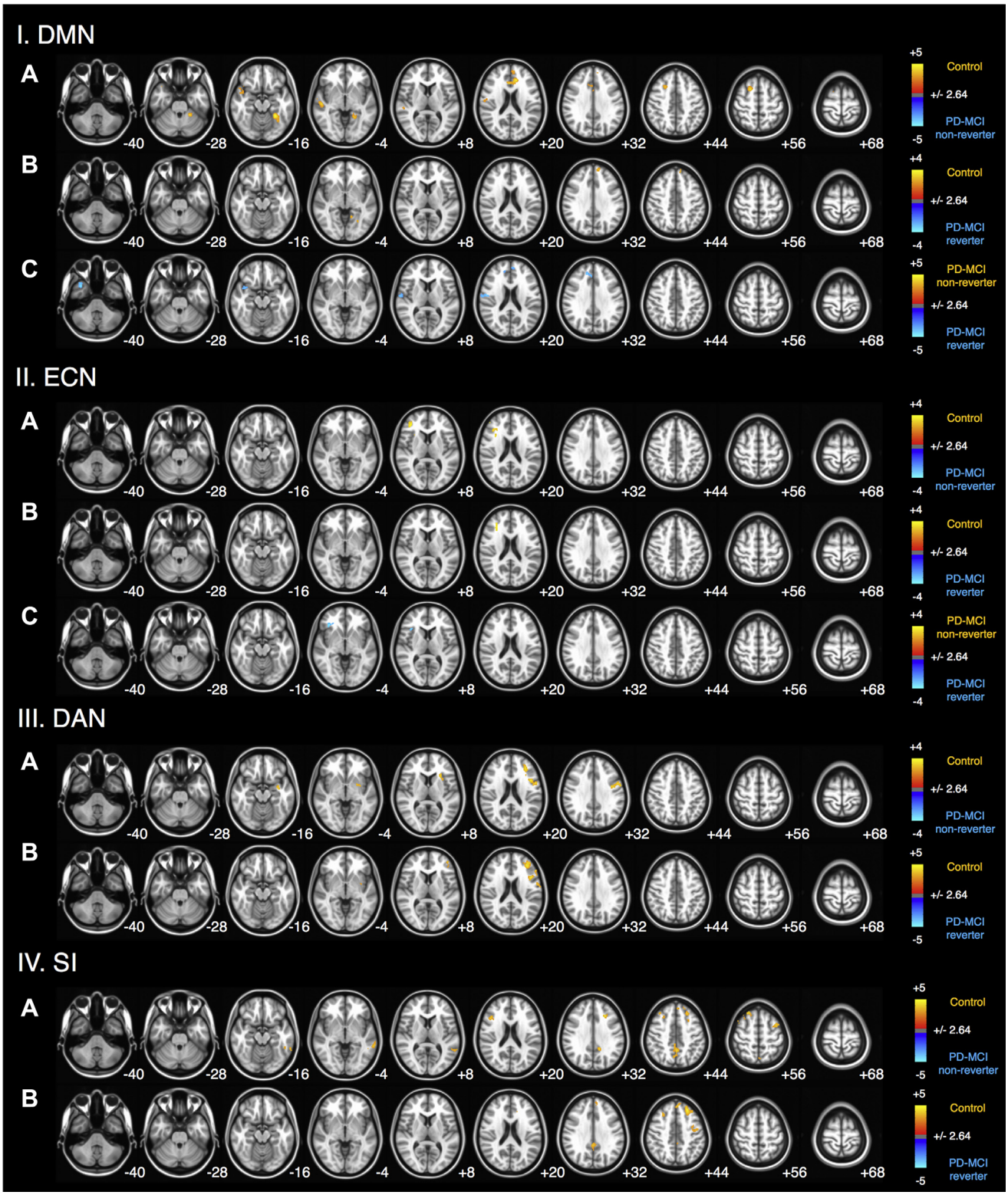

Fig. 4. Comparison of resting-state functional connectivity with regions of interest (ROIs). ROIs in the (I) default mode network (DMN), (II) executive control network (ECN), (III) dorsal attention network (DAN), and (IV) substantia innominata (SI). Groupwise comparisons between (A) PD-MCI nonreverters and controls; (B) PD-MCI reverters and controls; and (C) PD-MCI nonreverters and PD-MCI reverters (the DMN and ECN showed significant differences in a direct comparison). Abbreviation: PD-MCI, Parkinson's disease with mild cognitive impairment.

patients with PD (Olde Dubbelink et al., 2014). However, in the present study, WM disintegration was found to play a less crucial role in determining the reversion from PD-MCI to PD-CogN, although it has been associated with cognitive impairment in PD (Shin et al., 2012; Sunwoo et al., 2014). Therefore, our results suggest that the extents of structural and functional changes, which were less severe in the PD-MCI reverters, are important in determining the cognitive prognosis of PD-MCI.

This study demonstrated that, compared with PD-MCI non-reverters, PD-MCI reverters were younger and had less severe cognitive defects with a higher frequency of single-domain MCI. These findings are in line with the results of previous studies identifying predictive factors for reversion in MCI individuals (Roberts et al., 2014; Sachdev et al., 2013). Interestingly, the frequency of amnestic MCI with retrieval failure was higher in the PD-MCI reverter group, whereas the overall proportion of amnestic MCI was similar between the reverter and nonreverter groups. Episodic memory dysfunction could manifest as impairments in both recall and recognition memory, and an isolated retrieval deficit or impaired recall with intact recognition is a reflection of frontostriatal failure (Knowlton and Squire, 1995). Thus, retrieval failure in PD-MCI reverters may not always reflect true memory dysfunction which is related to rapid cognitive decline and incident dementia (Kehagia et al., 2013; Levy et al., 2002).

Our results showing that PD-MCI reverters had a favorable cognitive prognosis are not consistent with previous studies: Pedersen et al. recently demonstrated that PD-MCI reverters continued to be at increased risk of dementia (Pedersen et al., 2017), which was reproduced by Jones et al., 2018, highlighting the critical clinical implication of PD-MCI once diagnosed in early PD, regardless of MCI reversion. This inconsistency may be mainly attributable to the different PD-CogN groups compared with the PD-MCI reverters in these studies. Previous studies defined "stable" PD-CogN as a reference group who remained cognitively normal at the first 2 assessments (Jones et al., 2018) or during 3-year follow-up (Pedersen et al., 2017), whereas our study used a reference group composed of subjects who were PD-CogN at the baseline assessment only (i.e., they were not necessarily stable PD-CogN). Indeed, the previous studies showed that patients who were PD-CogN at baseline but converted to PD-MCI at the second assessment also had an increased risk of dementia compared with those with stable PD-CogN (Jones et al., 2018; Pedersen et al., 2017). In addition, the previous studies had the limitations of a small number of reverters (Pedersen et al., 2017) or the lack of comprehensive neuropsychological tests (Jones et al., 2018). Indeed, when we compared cognitive prognoses between the patients with PD-MCI reversion and those with stable PD-CogN who retained normal cognition for at least 3 years, the risk of PDD conversion or cognitive worsening was still comparable between the groups. Therefore, the present study suggests that reversion in individuals with PD-MCI may be a predictor of favorable cognitive prognosis, although PD-MCI reverters showed an intermediate level of cognitive performance between the PD-CogN subjects and PD-MCI nonreverters at baseline. In addition, this study underlines the importance of repeated neuropsychological assessment. The initial diagnosis of PD-MCI did not provide accurate information on long-term cognitive prognosis, although a high risk of PDD conversion in the PD-MCI nonreverters supports the validity of the MCI concept in patients with PD (Pedersen et al., 2013).

Taken together, the clinical and neuroimaging findings of the present study indicate that pathological changes may be less severe in PD-MCI reverters than in nonreverters. The reduced pathological burden may play a protective role against further cognitive decline in PD-MCI reverters (Valenzuela and Sachdev, 2006). Alternatively, reversion may represent nonpathological cognitive fluctuations (i.e., measurement errors) (Jones et al., 2018), particularly in individuals with cognitive scores just below the cutoff. In addition, other factors potentially affecting reversion from PD-MCI to PD-CogN should be considered: comorbid conditions including depression, stress, and apathy (Pedersen et al., 2017); effects of dopaminergic medications (Kulisevsky et al., 2000); and the learning effects of repeated neuropsychological assessments (de Jager and Budge, 2005). Therefore, cognitive heterogeneity may exist within the PD-MCI reverter group, and the results of this study need to be carefully interpreted with consideration for possible confounding effects.

Our study has some limitations. First, the sample size for the neuroimaging analyses was relatively small; however, significant differences in cortical thickness and resting-state functional connectivity between the PD-MCI groups were observed even with the limited number of participants (contrary to the high likelihood of nonsignificant results because of the small statistical power). Second, the criteria for identifying PD-MCI (cognitive domain scores were classified as abnormal when they were 1 standard deviation [SD] below the norm) might not be sufficiently stringent, although 1 SD is one of the recommended cutoffs in the Movement Disorder Society Task Force guidelines (Litvan et al., 2012). If we defined cognitive deficits as at least 1.5 SD below the norm, 22 of 46 PD-MCI reverters and 81 of 247 PD-MCI nonreverters would be reclassified into PD-CogN. However, 31 (30.1%) of these reclassified 103 patients eventually progressed to dementia, and thus, the 1 SD cutoff may be sufficiently sensitive to identify patients with PD at high risk for future cognitive decline. In addition, only a single test was designated to represent the language function domain in this study. Third, the retrospective nature of the study supposes the individual variability in the follow-up time and intervals between neuropsychological assessments, although we tried to perform a neuropsychological test with an interval of 1.5–2 years regularly. In addition, a considerable number of patients with PD-MCI from our database did not undergo repeated neuropsychological assessments (see Supplementary Methods), which may potentially serve as a sampling bias; however, there were no significant differences in the demographic characteristics between the patients who underwent serial neuropsychological assessments and those who did not (data not shown). Finally, although PD pathology was identified with a clinical diagnosis and with ^{18}F-fluorinated N-3-fluoropropyl-2-beta-carboxymethoxy-3-beta-(4-iodophenyl) nortropane positron emission tomography scans, the effects of other neurodegenerative or vascular pathologies should be considered.

In conclusion, the present study demonstrated that PD-MCI reverters had relatively preserved brain structural and/or functional integrity and a favorable cognitive prognosis compared with PD-MCI nonreverters. These findings suggest that the cognitive defect and neurodegenerative burden are less severe in PD-MCI reverters and further studies are needed to identify the predictors for reversion to avoid unnecessary intervention.

Disclosure

The authors have no actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.02.023.

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