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Cortical Thickness Alterations in Parkinson's Disease with Mild Cognitive Impairment

Parkinson Hastalığı Hafif Kognitif Bozuklukta Kortikal Kalınlık Değişiklikleri

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Abstract

Objective: This study investigated cortical thickness differences and their relationships with cognitive functions in Parkinson's disease (PD) with mild cognitive impairment (MCI) and cognitively normal (CN).

Materials and Methods: Twenty-two patients with PD-MCI, 23 with PD-CN, and 23 healthy controls with structural brain magnetic resonance imaging scans and complete neuropsychological tests were enrolled in this study. Cortical thickness analysis was performed using the Statistical Parametric Mapping 12 software package. Correlations with cognitive functions were examined.

Results: Cortical thickness was significantly lower in the PD-CN and PD-MCI patient groups than in healthy controls in the left precuneus and isthmus-cingulate cortex, right pars orbitalis, insula, and lateral orbitofrontal cortex. In addition, the PD-MCI group also exhibited cortical thinning in the left superior temporal gyrus, transverse temporal cortex, supramarginal gyrus, and bilateral posterior cingulate cortex compared with healthy controls. Correlation analyses among cortical thickness and cognitive scores of PD also revealed moderate associations between memory and the posterior cingulate cortex; language and the precuneus; and executive functions and the insula and isthmus-posterior cingulate cortices.

Conclusion: MCI in PD may be related to cortical alterations in the posterior cingulate cortex and the left temporoparietal cortex, which has been associated with subtle cognitive deficits in PD.

Keywords: Mild cognitive impairment, Parkinson's disease, magnetic resonance imaging, cortical thickness, neurocognitive functions

Öz

Amaç: Bu çalışmada, Parkinson hastalığında (PH) hafif kognitif bozukluk (HKB) ve kognitif bozukluğu olmayan PH'de (PH-N) kortikal kalınlık farklılıkları ve kognitif işlevlerle ilişkileri araştırıldı.

Gereç ve Yöntem: Bu çalışmaya yapısal beyin manyetik rezonans görüntüleme taramaları ve tam nöropsikolojik testleri olan 22 PH-HKB, 23 PH-N hasta ile 23 sağlıklı kontrol dahil edildi. SPM12 yazılım paketi kullanılarak kortikal kalınlık analizi yapıldı. Kognitif işlevlerle olan korelasyonlar da incelendi.

Bulgular: PH-N ve PH-HKB hastalarında sol prekuneus ve isthmus-singulat korteks, sağ pars orbitalis, insula ve lateral orbitofrontal kortekste kortikal kalınlık sağlıklı kontrollere göre anlamlı olarak daha düşüktü. Ek olarak, PH-HKB grubu kontrollere kıyasla sol superior temporal girus, transvers temporal korteks ve supramarjinal girusta ve ayrıca bilateral posterior singulat kortekste kortikal incelme gösterdi. PH'nin kortikal kalınlık ve kognitif puanları arasındaki korelasyon

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analizleri bellek ile posterior singulat korteks; dil ile prekuneus; yürütücü işlevler ile insula ve isthmus-posterior singulat korteks arasında orta düzeyde ilişkiler ortaya koydu.

Sonuç: PH'de HKB, PH'de hafif kognitif bozukluklarla ilişkilendirilen sol temporoparietal korteks ile birlikte posterior singulat korteksteki kortikal değişikliklerle ilişkili olabilir.

Anahtar Kelimeler: Hafif kognitif bozukluk, Parkinson hastalığı, manyetik rezonans görüntüleme, kortikal kalınlık, nörokognitif işlevler

Introduction

Parkinson's disease (PD) is clinically considered the most prevalent movement disorder, manifesting specific motor symptoms, including tremors, bradykinesia, and rigidity (1). Cognitive impairment is a common non-motor symptom among patients with PD (2). Cognitive impairment usually occurs in about 25% of newly diagnosed patients at an early stage (3). Patients with PD with mild cognitive impairment (MCI) are in a transitional state between PD cognitively normal (CN) and PD dementia (PDD) (4). Longitudinal studies have revealed that nearly 80% of PD-MCI patients develop dementia within 10 to 20 years, and the incidence of dementia is 2–6 times higher than the general population (4). Hence, it's necessary to find objective biomarkers to detect patients with PD at a higher risk of PDD in the early phases and establish efficient therapeutic strategies for these patients. Structural magnetic resonance imaging (MRI) offers a useful tool to assess structural alterations in PD accurately.

The neuropathological basis of cognitive deficits in PD has recently been thoroughly investigated. Gray matter (GM) abnormalities were primarily investigated using voxel-based morphometry (VBM), which is widely used to examine volume differences at the voxel level in the whole brain (5). VBM studies demonstrated brain atrophy, including in the infratentorial and subcortical structures, and the involvement of the frontotemporal cortex (6). However, the topographic distribution of morphometric changes and their clinical relationships remains unclear (7).

GM volume is a composite of two separate morphometric measurements, namely, surface area and cortical thickness. Surface area measurements reflect the number of columns, while cortical thickness measurements reveal the number of cells in each column. It has been proposed that cortical thickness measurements provide more valuable information than GM volume measurements as a neuroimaging endophenotype in the assessment of neurodegenerative disorders (8).

In this study, the authors investigate early cortical thickness alterations in patients with PD-MCI and PD-CN through structural MRI. The authors also examine the correlations between cortical structures and cognitive domains. This is the first study investigating the association between cortical thickness measurements and neuropsychological tests in demographically and clinically matched PD-MCI and PD-CN with relatively shorter disease duration. The authors assume that PD-MCI and PD-CN would be characterized by specific cortical thinning patterns and that MRI measurements would correspond to potential changes in cognition-related brain regions.

Materials and Methods

Subjects

A total of 23 patients with PD-CN (mean age: 65.83 ± 8.62 years) and 22 patients with PD-MCI (mean age: 68.36 ± 5.94 years) were enrolled. Twenty-three age-, gender-, education- and handedness-matched healthy individuals (mean age: 65.13 ± 5.87 years) were also included for comparison. The diagnosis of PD-CN and PD-MCI was performed according to the UK Parkinson's Disease Society Brain Bank criteria (9). The Hoehn and Yahr scale (10) and the Movement Disorder Society (MDS) Unified Parkinson's Disease Rating scale (UPDRS) part III (11) were also used to assess disease severity and motor disability.

The inclusion criteria for patients with PD were being diagnosed with idiopathic PD, at a Hoehn and Yahr stage III or less, and under stable dopaminergic treatment. The exclusion criteria for all participants included medication usage affecting cognition and the presence of strokes, seizures, head trauma, chronic alcoholism, and drug abuse. Other exclusion criteria for PD were the presence of PDD (12), a history of psychiatric disorders or visual hallucinations, or having depression as a comorbidity (geriatric depression scale >14) (13). All assessments were performed during patients' "on" periods, and the levodopa equivalent daily dose was calculated using a standardized formula (14). The local ethical committee approved this protocol, and informed consent was provided by all participants.

Neuropsychological Assessment and Diagnostic Criteria

The global cognitive status of the participants was evaluated using the montreal cognitive assessment for dementia (15) and the mini-mental state examination for Alzheimer's (16). A PD-MCI classification was performed based on the MDS task force level II criteria (17) evaluating five cognitive domains. Accordingly, visuospatial skills were evaluated using simple copying tests and the Benton Line judgment orientation test (18); executive functions using the Wechsler memory scale-revised (WMS-R) digit span backward test (19), verbal fluency task, stroop test (20), and trail making test (TMT) part B (21); episodic memory using the Öktem (22) verbal memory processes test measuring immediate recall, delayed recall, and total learning scores; attention using TMT part A (21) and the WMS-R digit span forward test (19); and language using a semantic fluency task and Boston naming test (23). For PD-MCI classification, impaired performance was required in at least two neuropsychological tests covering the same domain (17). After converting the raw test scores into z-scores, composite scores were calculated by averaging the z-scores of the neuropsychological tests in the same cognitive domain.

Magnetic Resonance Imaging Acquisition and Preprocessing

MRI scans were obtained using a 1.5T Philips Achieva scanner according to the Alzheimer's disease neuroimaging initiative protocol (www.adni.loni.usc.edu). The axial 3D T1-weighted turbo-spin-echo images (repetition time: 9 ms, echo time: 4 ms, matrix: 256, field of view: 240 mm, number of signal averages: 1, slice thickness: 1 mm) were used for cortical thickness analysis. The axial T2-weighted dual-echo images were acquired for radiological

assessment.

The cortical thickness analysis was conducted using the Computational Anatomy Toolbox 12 (CAT12) software (http://dbm.neuro.uni-jena.de/cat/) implemented in Statistical Parametric Mapping 12 (SPM12) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) while running MATLAB (R2018.b; Mathworks, Sherborn, MA, USA) following the relevant manual (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf). The T1-weighted images were spatially registered using the Montreal Neurological Institute 152 template and classified as GM, white matter (WM), and cerebrospinal fluid. The surface and thickness estimation were added for region of interest (ROI) analysis. Finally, the modulated images were smoothed with a 15 mm full-width at half-maximum Gaussian kernel.

Cortical Thickness Analyses

The CAT12 software allowed for the cortical thickness estimation in one step based on the projection-based thickness method. The WM distance was estimated using tissue segmentation, and the local maxima were projected to the other GM voxels using a neighbor relationship described by the WM distance (24). These values equaled cortical thickness. The cortical thickness among groups was analyzed by applying the SPM-full factorial model with the factor group (PD-CN, PD-MCI, and healthy controls) using t-contrasts. Age, gender, and education were included in the model as covariates of no interest, while motor severity, disease duration, and levodopa equivalent daily dose were additional covariates in the comparisons between the PD-NC and PD-MCI groups. A threshold was set for all results at $P < 0.001$ (uncorrected for multiple comparisons) with a minimum cluster size of 50 contiguous voxels.

Brain regions that showed significant differences in the whole brain analysis were identified as significant ROIs. Each participant's mean cortical thickness value of each ROI was then extracted using the CAT12 "extract ROI-based surface values" function. The results of the t-contrasts (PD-MCI vs. HC, PD-CN vs. HC, PD-CN vs. PD-MCI, and vice versa) were saved as cortical thickness maps using the Desikan-Killiany Atlas (25). The mean cortical thickness values for each ROI were extracted separately.

Statistical Analysis

The Statistical Package for Social Sciences program was used for all statistical analyses. Comparisons of the demographic and clinical variables among groups were conducted using the chi-squared test for categorical variables and the independent samples t-test or analysis of variance test for continuous variables.

To assess the relationship between changes in mean cortical thickness, values extracted from the clusters of significant group differences and cognitive domain scores were examined using partial correlation for all subjects with PD, controlling for age, gender, and education.

Results

Table 1 shows the study participants' demographic information and clinical data. There were no statistical differences in the demographic characteristics between the groups. There were also no differences in the clinical features covering the Hoehn and Yahr score, MDS-UPDRS motor score, and disease duration among the PD groups. Table 2 shows the mean composite scores of all participants.

Cortical Thickness Analysis

PD-CN versus HC: The PD-CN group had cortical thinning in the precuneus and isthmus-cingulate cortex in the left hemisphere and the pars orbitalis, insula, and lateral orbitofrontal cortex in the right hemisphere when compared with the healthy controls ($P < 0.001$, uncorrected for multiple comparisons) (Figure 1, Table 3).

PD-MCI versus HC: The PD-MCI group had cortical thinning when compared with the healthy controls in the following areas: the precuneus, isthmus and posterior cingulate cortex, supramarginal gyrus, transverse temporal gyrus, and superior temporal gyrus in the left hemisphere; pars orbitalis, posterior cingulate cortex, insula, and lateral orbitofrontal cortex in the right hemisphere ($P < 0.001$, uncorrected for multiple comparisons) (Figure 1, Table 4).

PD-CN versus PD-MCI: No significant differences were found between the PD-MCI and PD-CN groups.

Correlations Between Cortical Thickness and Cognitive Performance

Correlations were analyzed on the whole patient sample. Partial correlation analysis showed significant correlations between cortical thickness and memory in the left posterior cingulate cortex (r = 0.313, $P = 0.032$). The language scores correlated with cortical thickness in the left precuneus (r = 0.420, $P = 0.015$).

Table 1. Demographic and clinical characteristics of participants

	HC (n = 23)	PD-CN (n = 23)	PD-MCI (n = 22)	*P*
Age (years)	65.1 ± 5.9	65.8 ± 8.6	68.4 ± 5.9	0.268[a]
Education (years)	11.0 ± 4.2	9.6 ± 4.0	10.6 ± 4.6	0.499[a]
Gender (M/F)	16/7	19/4	18/4	0.491[b]
Hand dominance (R/L)	22/1	23/0	21/1	0.590[b]
Hoehn and Yahr score	-	1.9 ± 0.6	2.0 ± 0.5	0.409[c]
UPDRS motor score	-	19.9 ± 9.7	20.8 ± 10.5	0.782[c]
Disease duration (years)	-	3.4 ± 2.3	3.9 ± 2.9	0.549[c]
Daily LED (mg)	-	494.8 ± 273.8	553.6 ± 348.9	0.532[c]

Values are presented as mean ± standard deviation. [a]Analysis of variance test, [b]chi-squared test, [c]Independent samples t-test. HC: Healthy controls, PD: Parkinson's disease, CN: Cognitively normal, MCI: Mild cognitive impairment, M: Male, F: Female, R: Right, L: Left, UPDRS: Unified Parkinson's Disease Rating scale, LED: Levodopa equivalent dose

The executive function domain scores correlated with cortical thickness in several areas, including the right insula (r = 0.421, *P* = 0.015), right isthmus cingulate cortex (r = 0.387, *P* = 0.026), left posterior cingulate cortex (r = 0.388, *P* = 0.007), and right posterior cingulate cortex (r = 0.382, *P* = 0.008). Finally, scores in the attention and visuospatial domains did not correlate with cortical thickness in any cortical area. Figure 2 presents correlation plots for patients with PD.

Discussion

In this study, the authors examined cortical thickness abnormalities in the PD-MCI and PD-CN groups compared with the healthy control group. Cortical thickness was significantly lower in the PD-CN and PD-MCI groups than the healthy control group in the left precuneus and isthmus-cingulate cortex, right pars orbitalis, insula, and lateral orbitofrontal cortex. In addition, the PD-MCI group also exhibited cortical thinning in the left transverse temporal cortex, superior temporal gyrus, supramarginal gyrus, and bilateral posterior cingulate cortex compared with the healthy control group. Moreover, correlation analysis between the cortical thickness and cognitive domains of patients with PD showed moderate associations between memory and the posterior cingulate cortex; language and the precuneus; and executive functions and the insula and isthmus-posterior cingulate cortices. These results indicate that cortical thickness analysis may be useful

Table 2. Neuropsychological performances of participants

	HC (n = 23)	PD-CN (n = 23)	PD-MCI (n = 22)	*P*	PD-CN vs. HC	PD-MCI vs. HC	PD-CN vs. PD-MCI
Global cognitive status							
MMSE	28.9 ± 1.4	28.9 ± 1.2	26.9 ± 3.2	**0.004**	1.000	**0.012**	**0.010**
MoCA	-	25.9 ± 2.7	22.8 ± 5.4	**0.017**	-	-	**0.017**
Cognitive domains							
Memory	0.0 ± 0.9	-0.7 ± 0.8	-2.4 ± 1.3	**<0.001**	0.066	**<0.001**	**<0.001**
Attention	0.0 ± 0.9	-0.4 ± 0.5	-2.0 ± 1.3	**<0.001**	0.408	**<0.001**	**<0.001**
Executive functions	0.1 ± 0.8	-0.3 ± 0.7	-1.3 ± 0.8	**<0.001**	0.443	**<0.001**	**0.001**
Visuospatial	0.1 ± 0.5	-0.2 ± 0.5	-1.6 ± 1.1	**<0.001**	0.464	**<0.001**	**<0.001**
Language	0.0 ± 0.5	-0.1 ± 0.7	-1.2 ± 1.5	**<0.001**	1.000	**0.001**	**0.001**

Values are presented as mean ± standard deviation. Results of the analysis of variance model (*P* values) and pairwise comparisons with Bonferroni correction (*P* values) are reported. HC: Healthy controls, PD: Parkinson's disease, CN: Cognitively normal, MCI: Mmild cognitive impairment, MMSE: Mini-mental state examination, MoCA: Montreal cognitive assessment

Table 3. Anatomical locations of significantly different areas of voxel-wise cortical thickness analysis between PD-CN and HC (*P* < 0.001, uncorrected for multiple comparisons)

Brain regions	Hemisphere	T	Z	k	Peak MNI coordinate		
					x	y	z
Precuneus cortex and isthmus-cingulate cortex	Left	4.5	4.2	205	-3	-53	11
Pars orbitalis, insula, and lateral orbitofrontal cortex	Right	3.8	3.6	52	31	27	-5

PD: Parkinson's disease, CN: Cognitively normal, HC: Healthy controls, MNI: Montreal neurological institute

Table 4. Anatomical locations of significantly different areas of voxel-wise cortical thickness analysis between PD-MCI and HC (*P* < 0.001, uncorrected for multiple comparisons)

Brain regions	Hemisphere	T	Z	k	Peak MNI coordinate		
					x	y	z
Isthmus-cingulate cortex and precuneus cortex	Left	4.3	4.0	97	-4	-51	13
Insula	Right	4.3	3.9	222	35	11	-13
Insula, pars orbitalis, and lateral orbitofrontal cortex	Right	3.9	3.6	-	34	28	-3
Posterior-cingulate cortex	Left, right	4.0	3.8	102	-3	-20	29
Superior temporal gyrus and supramarginal gyrus	Left	3.7	3.5	162	-59	-38	18
Supramarginal gyrus, transverse temporal cortex, and superior temporal gyrus	Left	3.5	3.3	-	-46	-30	7
Supramarginal gyrus	Left	3.4	3.2	-	-61	-45	22

PD: Parkinson's disease, MCI: Mild cognitive impairment, HC: Healthy controls, MNI: Montreal neurological institute

to distinguish patients with PD at the group level based on their cognitive status.

Cortical thickness analysis has been previously used to evaluate cognitive impairment in patients with PD but without dementia. Although many studies observed that cortical thinning appears before cognitive decline in patients with PD (8,26,27,28,29,30,31), others reported no difference (7,32,33,34). Therefore, the hypothesis that cortical atrophy may exist in patients with PD without cognitive impairment is still debatable.

Early degeneration of the frontal cortex in PD-CN is consistent with previous findings (8,27,28). Recently, a longitudinal study demonstrated that frontostriatal cognitive deficits are clear in PD-CN (32). Thus, this suggests that early frontal structural alterations in cognitively healthy subjects contribute to the future development of cognitive decline. Moreover, it was also reported that cortical thinning, which is localized in the parietal and frontal regions in PD-CN, could be an early indicator of cognitive impairment in PD (35). This regional cortical thinning, which the authors observed in PD-CN, supports the increasing evidence that cortical alterations exist at the time of diagnosis before meeting the MCI criteria.

In the present study, cortical thinning in PD-MCI was apparent in similar regions as seen in the PD-CN group, but cortical thinning was also observed in the bilateral posterior cingulate cortex and left temporoparietal areas compared with the control group ($P < 0.001$, uncorrected). Previous studies revealed that frontal deficits are associated with changes in dopaminergic activity in the frontal areas, whereas posterior cognitive deficits are non-dopaminergic and related to structural alterations in the temporoparietal areas (26,36,37). The etiologies of posterior cortical deficits may be related to cholinergic deficits, cortical α-synucleinopathy, and cortical Alzheimer's-type pathology (38). The medial temporal lobe atrophy is often regarded as the hallmark of Alzheimer's disease-related pathology (39). The cortical thinning pattern over the temporoparietal regions in PD-MCI is consistent with an earlier study reporting a comparable atrophy pattern in patients with PD but no dementia and Alzheimer's disease (40). The underlying pathology can be variable and mixed in most dementia patients. Limbic-predominant age-related TDP-43 encephalopathy has also displayed similar neuropathological changes to Alzheimer's disease that affect the medial temporal lobes preferentially and has comorbid brain pathologies (41).

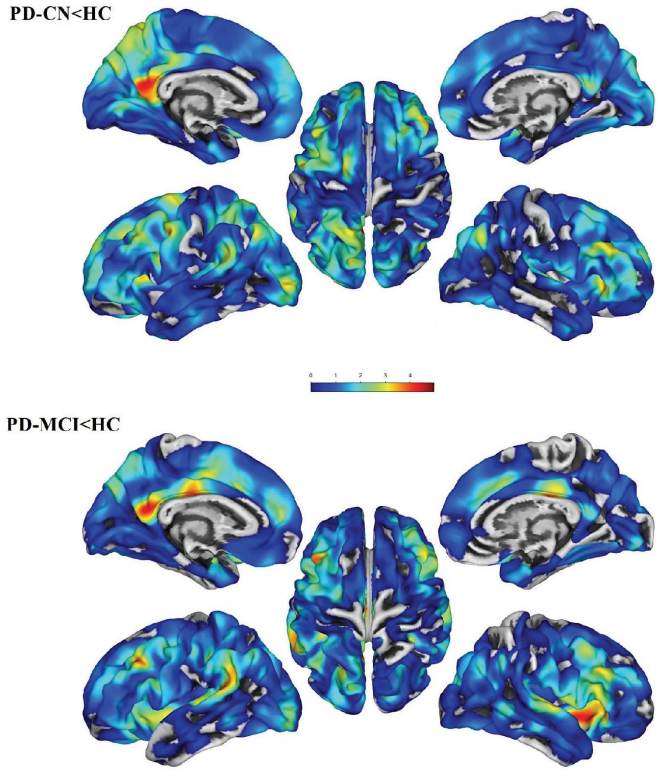

Figure 1. Regions showing significant cortical thinning in PD-CN and PD-MCI relative to HC ($P < 0.001$, uncorrected for multiple comparisons). The color bar represents t values

HC: Healthy controls, PD: Parkinson's disease, CN: Cognitively normal, MCI: Mild cognitive impairment

In the current study, the authors did not find any cortical thickness differences among the PD-CN and PD-MCI groups. This result is compatible with many studies that failed to reveal any differences in cortical thickness between patient groups (2,29,32,34,42). Possible explanations for this may be related to relatively shorter disease duration and well-matched groups in terms of disease severity or medication dose. It has been reported that cortical thinning in the parietal, temporal, frontal, and occipital cortices is associated with motor severity scores and disease duration (1). Furthermore, the variation could result from different statistical procedures undertaken in each study. In this study's cortical thickness analysis, to clarify previous conflicting cross-sectional findings, the authors specifically controlled the group effect with different variables, including age, gender, education level, motor severity, disease duration, and dopaminergic medication dose.

Cognitive impairments in patients with PD are heterogeneous; however, visuospatial, executive function, attention, and memory domains are typically affected during the disease (43). In the authors' study, the PD-MCI group demonstrated cognitive deficits in visuospatial skills, attention, memory, language, and executive functions, compared with the PD-CN group and healthy controls. In accordance with their hypothesis, the authors also detected significant associations between cognitive domains and MRI findings. In the current study, higher cortical thickness values in the posterior cingulate cortex were related to better performance in memory. The posterior cingulate cortex is reported to have connections with the parahippocampal areas, which project spatial information to the entorhinal cortex and thus into the system of the hippocampal episodic memory (44), suggesting that it has a role in memory systems (45). Furthermore, a diffusion MRI study demonstrated that diffusion abnormalities in the posterior cingulate cortex were associated with memory deficits in patients with PD but without dementia, consistent with the authors' findings (46).

Another association was also detected between executive functions, the isthmus, and the cingulate and insular cortices. Executive functions are linked to the connection of large-scale brain networks, including the insular, frontal, and parietal regions, and the frontostriatal circuits (38). The insula is a core region in the salience network that mediates interactions between

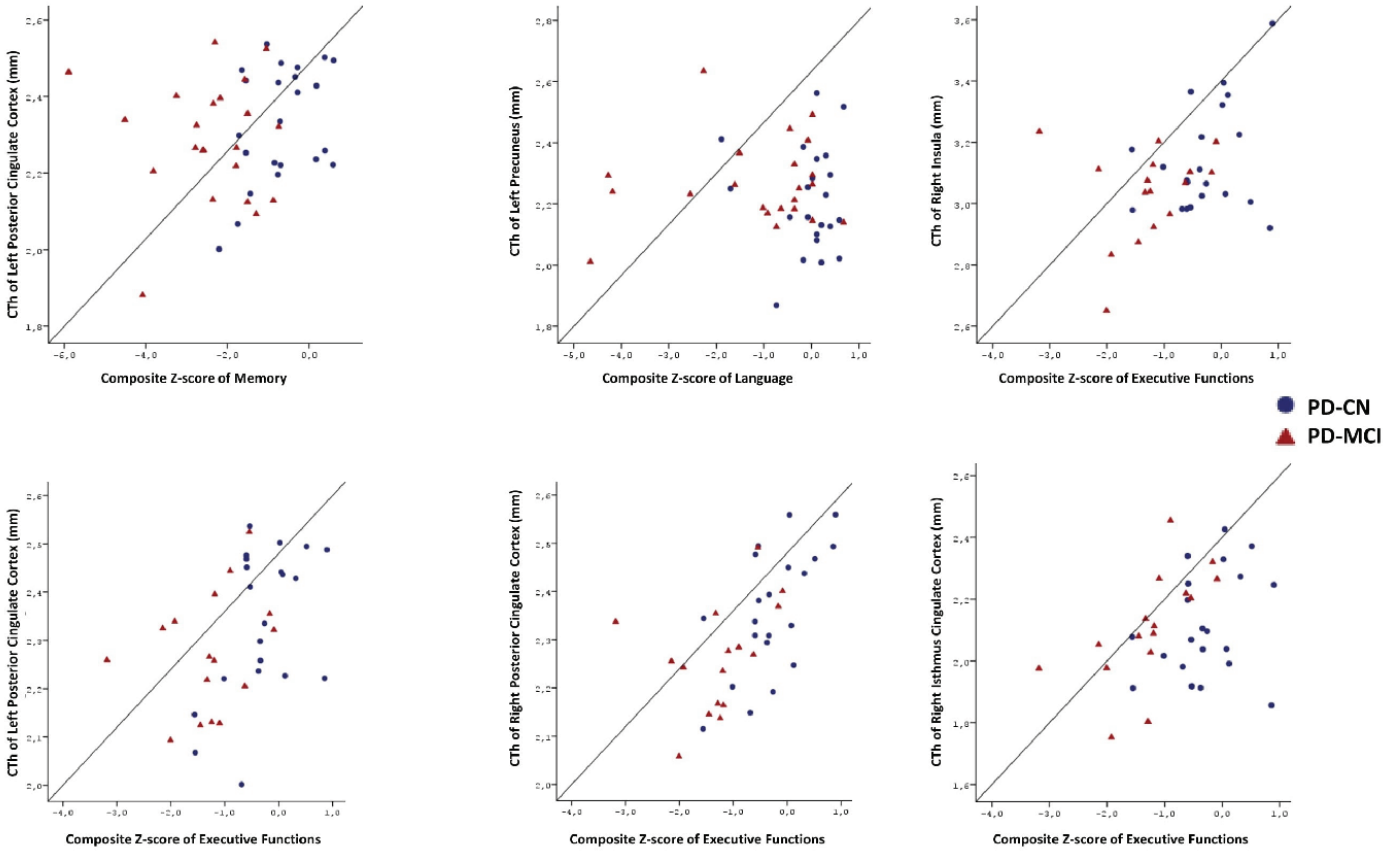

Figure 2. Scatter plots showing the significant associations between cortical thickness and cognitive domains in the Parkinson's disease sample

HC: Healthy controls, PD: Parkinson's disease, CN: Cognitively normal, MCI: Mild cognitive impairment, CTh: Cortical thickness

the central executive network and the default mode network (47,48). Previous studies reported that the atrophy of the insular region is associated with executive-attention dysfunction in mild PD (2,49). Furthermore, Baggio et al. (29) revealed that reduced connectivity between the dorsal attention network and fronto-insular regions might be related to executive dysfunctions, while this association was also supported by a positron emission tomography study, indicating reduced insular dopaminergic D2 receptors also had associations with executive dysfunctions in PD-MCI (34). Previous studies have suggested that insular cortices may affect executive functions, in line with the authors' findings.

Along with the posterior cingulate cortex, the precuneus plays a key role in cognitive functions by having widespread connections with the temporal, frontal, and subcortical regions (50,51), suggesting an involvement in various integrated and associative cognitive functions related to language skills (52). In this study, reduced thickness in the precuneus was related to poor language performance, consistent with its function. The authors' finding is also compatible with a previous study reporting an association between the precuneus and semantic fluency in PD (30).

In line with previous studies (7,29,53), the authors found no associations between cortical thickness and the scores in the attention and visuospatial domains. This might be due to a relatively small sample size or result from the fact that the attention and visuospatial functions were slightly affected in this sample. Thus, these findings must be verified by a further study that consists of a larger-sized sample.

The strengths of the current study include the combined use of voxel-wise and ROI-based MRI measurements and well-matched patient groups in terms of demographic and clinical factors. The limitations of the current study include a relatively small sample size and a lack of robustness in terms of the statistical strength of the study, given that the authors' analysis was obtained only at the uncorrected threshold of $P < 0.001$.

Conclusion

In conclusion, the authors' results of cortical thinning in crucial brain regions, such as the posterior cingulate cortex and the left temporoparietal cortex, may represent an MRI structural marker related to cognitive impairment for the identification of patients with PD at risk of developing MCI. Longitudinal studies are also needed in PD-CN and PD-MCI patient groups to assess the variations in cortical thickness changes between cross-sectional studies.

Ethics

Ethics Committee Approval: Ethics Committee approval for this study was received from the Non-Invasive Research Ethics Board of Dokuz Eylul University (decision no: 2015/07-42).

Informed Consent: Written informed consent was obtained from all patients and healthy elderly participants in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: B.Ç., D.H., G.Y., E.A., Design: B.Ç., D.H., G.Y., E.A., Data Collection or Processing: B.Ç., D.H., İ.K., R.Ç., G.Y., E.A., Analysis or Interpretation: B.Ç., D.H., İ.K., Literature Search: B.Ç., D.H., G.Y., E.A., Writing: B.Ç., D.H., R.Ç., G.Y., E.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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