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Cognitive and cortical thinning patterns of subjective cognitive decline in patients with and without Parkinson's disease

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ABSTRACT

Background: Subjective cognitive decline (SCD) has gained attention as a predictor of future cognitive decline in neurodegenerative diseases. Based on the hypothesis that different pathologies may distinctly contribute to SCD, we investigated the cognitive profiles and cortical thickness of patients with SCD, with and without Parkinson's disease (PD).

Methods: In total, 96 patients experiencing SCD were classified as having PD (SCD-PD$^+$, $n = 49$) or no neurological disease (SCD-PD$^-$, $n = 47$); cognitively normal subjects without SCD ($n = 23$) were included as controls. Neurocognitive profiles and cortical thickness were examined using standardized neuropsychological tests and magnetic resonance imaging-based analysis.

Results: No significant differences in demographic characteristics were found among the three groups. Neuropsychological tests demonstrated that the SCD-PD$^+$ patients had lower semantic fluency than SCD-PD$^-$ patients and controls, and showed poorer performance in visual memory and confrontational naming than controls, whereas no significant difference in cognitive performance was observed between the SCD-PD$^-$ patients and controls. Cortical thickness analysis revealed that the SCD-PD$^+$ patients had focal cortical thinning in the dorsolateral prefrontal, orbitofrontal, parietal, and parahippocampal areas compared with controls. Compared with SCD-PD$^-$ patients, SCD-PD$^+$ patients had cortical thinning in the frontal, parahippocampal, and posterior cortical areas.

Conclusion: Our data show that cortical thinning and cognitive performance in patients with SCD may differ based on the presence of PD, suggesting that SCD in patients with PD reflects disease-related cortical thinning and cognitive dysfunctions more closely than SCD without PD.

1. Introduction

Mild cognitive impairment (MCI) is a transitional state between normal aging and dementia that has been used for the early detection and treatment of dementia. Amnestic MCI, a subtype of MCI, has 10–15% annual conversion rate to Alzheimer's disease (AD) [1]. Several studies have reported that amyloid burden and cortical atrophy at the diagnosis of MCI are already extensive, which is comparable to AD stage [2]. More recently, subjective cognitive decline (SCD) has gained attention as a predictor of future dementia. Although the predictive value is controversial, increasing evidence suggests SCD to be a possible predictor of AD [3–7].

In patients with Parkinson's disease (PD), the cumulative incidence of dementia is up to 80% [8], and thus, cognitive decline is a major issue in PD. As in AD, patients with PD and MCI (PD-MCI) have a higher risk of developing dementia. Janvin et al. [9] reported that patients with PD-MCI had an increased risk of developing dementia than did cognitively intact PD patients (62% vs. 20%). Although few studies have examined the significance of SCD in patients with PD (PD-SCD), evidence suggests that SCD in PD patients is related with cognitive status. Previously, we reported that

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patients with PD-SCD had more cortical atrophy and performed more poorly on neuropsychological tests than those without SCD, suggesting that SCD in PD is possibly related to PD-related pathological changes [10]. Another cross-sectional study also showed that self-rating and proxy-rating subjective memory functions were correlated with objective cognitive performance in patients with PD [11]. Importantly, our recent longitudinal study demonstrated that cognitively normal patients with PD and SCD exhibited more severe annual cognitive decline and converted to MCI status more frequently than those without SCD [12].

However, the similarity or difference of SCD between patients with and without PD has not been investigated. In this study, based on the hypothesis that different pathologies contribute distinctly to SCD, we investigated the patterns of cognitive profiles and cortical thickness in patients having SCD with (SCD-PD$^+$) and without PD (SCD-PD$^-$) to explore whether the neuroanatomical basis of SCD differs.

2. Materials and methods

2.1. Participants

Participants included 96 patients with SCD recruited consecutively from the movement disorders and dementia outpatient clinic at Yonsei University Severance Hospital. The presence of SCD was assessed by the question: "Do you feel that you have a declining memory?" PD was diagnosed following the clinical diagnostic criteria of the UK PD Society Brain Bank. Depending on the presence of PD, patients with SCD were classified into the SCD-PD$^+$ ($n = 49$) and SCD-PD$^-$ ($n = 47$) groups. In addition, 23 healthy age- and sex-matched volunteers were recruited as controls. The controls had neither an active neurologic disorder nor SCD.

The exclusion criteria included evidence of focal brain lesions or multiple lacunar infarctions in the basal ganglia based on magnetic resonance imaging (MRI). Possible medical comorbidities affecting cognition were excluded by laboratory testing, including thyroid function tests, vitamin B_{12} and folic acid levels, and the VDRL test. Patients with a history of drug use causing parkinsonian symptoms were also excluded.

We received approval from the Yonsei University Severance Hospital ethical standards committee on human experimentation for use of human subjects. Written informed consent was obtained from all subjects participating in this study.

2.2. Neuropsychological assessment

The neuropsychological performance was evaluated using a standardized neuropsychological test, the Seoul Neuropsychological Screening Battery (SNSB) [13]. The SNSB consists of the following cognitive subsets, as described previously: attention (forward digit span and color stroop test); language function (the Korean version of the Boston Naming Test [K-BNT]), visuospatial function (the Rey Complex Figure Test [RCFT]), verbal memory (20-min delayed recall using the Seoul Verbal Learning Test), visual memory (20-min delayed recall using the RCFT), and executive function (semantic and phonemic Controlled Oral Word Association Test [COWAT]). Abnormal cognitive function was defined as a score below the 16th percentile of the normal population. All patients showed normal performance in the neuropsychological test, and did not meet the MDS criteria for mild cognitive impairment in PD (PD-MCI) [14]. Additionally, all study subjects scored above the 16th percentile (1 standard deviation below mean) for their age- and education-appropriate norm on the Korean version of the Mini-Mental State Examination (K-MMSE). The participants showed no evidence of abnormal activities of daily living (ADL), judged both clinically and on an ADL scale.

2.3. Clinical assessment

Parkinsonian motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale motor score (UPDRS III). A score for general white matter hyperintensities (WMH) was determined by grading the extent of the increased white matter signal intensity on fluid-attenuated inversion recovery images in the periventricular and subcortical white matter. It was graded was on a 10-point scale from 0 to 9, with a higher score indicating a more severe white matter grade [15]. An [^{18}F] FP-CIT PET scan was performed on all SCD-PD$^+$ subjects who had decreased dopamine transporter uptake in the posterior putamen. The self-rated Beck Depression Inventory (BDI) was used to assess depressive symptoms in patients with PD.

2.4. MRI acquisition

A Philips 3.0T scanner (Philips Achieva; Philips Medical System, Best, Netherlands) with a SENSE head-8 coil was used to obtain MR images. A high-resolution T1-weighted MRI volume dataset was obtained using a three-dimensional T1-TFE sequence configured with the following acquisition parameters: axial acquisition with a 224 × 224 matrix; 256 × 256 reconstructed matrix; 220 × 220-mm field of view; 0.86 × 0.86 × 1.0-mm voxels; echo time, 4.6 ms; repetition time, 9.6 ms; flip angle, 8°; and slice gap, 0 mm.

2.5. Image processing for cortical thickness

Images were processed using the standard Montreal Neurological Institute (MNI) anatomical pipeline. The native MR images were normalized into a standardized stereotaxic space using affine transformation and intensity nonuniformity artifacts in normalized images was corrected using the N3 algorithm [16]. Skull removal was performed to the images after correction using brain extraction tool (BET) and then classified into white matter (WM), gray matter (GM), cerebrospinal fluid (CSF) and background using an advanced neural net classifier. The cortical surfaces of the inner and outer cortex which consisted of 40,962 vertices were extracted automatically using the Constrained Laplacian-based Automated Segmentation with Proximities (CLASP) algorithm [17]. The cortical surfaces were inversely transformed to native space. Cortical thickness was defined using the t-link method, which measures the Euclidean distance between the linked vertices of the inner and outer surfaces [17,18]. The vertex-wise sphere-to-sphere warping nonlinear surface registration was performed to unbiased iterative surface template [19]. Using the surface registration, thickness information on native surfaces was transformed to a template after diffusion smoothing with 20-mm full-width half-maximum to increase the signal-to-noise ratio and improve the detection ability of population changes [18].

The statistical analysis of cortical thickness was performed in vertex-wise level using an analysis of covariance (ANCOVA) with intracranial volume, age, sex, and the side of parkinsonian motor dominance as covariates for comparisons among the groups. *Post hoc* analyses were performed to investigate the following contrasts: (1) controls vs. SCD-PD$^+$, (2) controls vs. SCD-PD$^-$, (3) SCD-PD$^+$ vs. SCD-PD$^-$. We performed false-discovery-rate (FDR) correction for comparison between SCD subjects and controls at a corrected probability value of $p < 0.05$. When comparing SCD-PD$^+$ and SCD-PD$^-$, a discriminative threshold was lowered at uncorrected $p < 0.001$.

2.6. Statistical analysis

The chi-square test was used for categorical variables, while independent *t*-test, one-way analysis of variance (ANOVA), and ANCOVA were adopted for continuous variables. For comparison of specific cognitive performance in the SNSB, age, sex, and years of education were used as covariates of multivariates analysis of covariance (MANCOVA), and *post-hoc* analyses were conducted following the Bonferroni method. Statistical analyses were performed using SPSS Statistics 20 (IBM SPSS, Armonk, NY, USA), and a $p < 0.05$ was considered to indicate statistical significance.

3. Results

3.1. Demographic characteristics

The demographic characteristics of the subjects are shown in Table 1. No significant differences were observed among the three

Table 1
Demographic characteristics of controls, patients having subjective cognitive decline with (SCD-PD$^+$) and without (SCD-PD$^-$) Parkinson's disease.

	SCD-PD$^+$	SCD-PD$^-$	Control	*p*-Value
Participants	49	47	23	
Age, y	63.2 ± 7.5	62.3 ± 8.5	66.4 ± 6.9	0.126[c]
Number of male	22	11	5	0.120[a]
Education duration, y	11.3 ± 4.2	11.8 ± 4.4	12.4 ± 4.3	0.576[c]
Memory complaints duration, y	2.6 ± 2.4	2.3 ± 2.1	N/A	0.630[b]
K-MMSE	28.7 ± 1.0	28.8 ± 1.0	28.6 ± 1.0	0.546[c]
CDR	0.26 ± 0.25	0.22 ± 0.25	0.26 ± 0.26	0.776[c]
WMH score	1.5 ± 1.5	1.2 ± 1.2	1.0 ± 1.0	0.355[c]
BDI	13.5 ± 9.4	15.2 ± 8.4	11.3 ± 8.7	0.213[c]
PD duration, y	2.5 ± 1.9	N/A	N/A	N/A
UPDRS III	20.7 ± 12.1	N/A	N/A	N/A
Levodopa dose, mg	357.0 ± 191.5	N/A	N/A	N/A

SCD-PD$^+$: subjective cognitive decline with Parkinson's disease; SCD-PD$^-$: subjective cognitive decline without Parkinson's disease; K-MMSE: the Korean version of the Mini-Mental State Examination; CDR: Clinical Dementia Rating scale; WMH: white matter hyperintensity; BDI: Beck depression inventory; UPDRS III: Unified Parkinson's Disease Rating Scale motor score; N/A: not applicable. Values are expressed as mean ± SD.

[a] Chi-square test.
[b] Independent *t* test.
[c] One-way ANOVA.