Topography of cortical thinning associated with white matter hyperintensities in Parkinson's disease

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ABSTRACT

Background: Although white matter hyperintensities (WMHs) are associated with cognitive impairments in Parkinson's disease (PD), the relationships between WMHs and cortical atrophy in regard to cognitive impairments are unknown. Here, we investigated the topography of cortical thinning related to deep (DWMHs) and periventricular WMHs (PWMHs) and their differential impacts on cognitive performance in PD.

Methods: We enrolled 87 patients with non-demented PD and evaluated WMH scores using a semi-quantitative visual rating system. The patients were divided into low-, moderate-, and high-grade groups based on WMH severity for total WMHs (TWMHs), DWMHs, and PWMHs, and cortical thickness was measured using a surface-based method according to the WMHs severity. Additionally, the correlations between WMH-associated cortical thinning and neuropsychological performance were analyzed.

Results: The detailed neuropsychological test demonstrated that PD patients with high-grade WMHs showed poorer performance on frontal lobe-based cognitive tasks compared with those with low-grade DWMHs. The areas of cortical thinning were more extensive in patients with DWMHs, involving the entire frontal areas and restricted temporoparietal areas, whereas in patients with PWMHs, cortical thinning was localized in the small frontal areas. A multiple regression analysis of the relationships between WMH-associated cortical thickness and cognition revealed that DWMH-associated frontal thickness had an independent effect on frontal lobe-based cognition, while frontal thickness related to PWMHs did not have a significant correlation with cognitive tasks.

Conclusions: These data suggest that in patients with PD, DWMHs are closely coupled with decreased cortical thickness in the frontal areas and may lead to declines in executive function.

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Cognitive impairments are one of the most disabling non-motor symptoms associated with Parkinson's disease (PD). Patients with PD have a 3- to 6-fold higher risk of developing dementia compared with controls [1], and one-fifth of patients with untreated early PD exhibit mild cognitive impairments (MCI) [2]. A number of possible pathological mechanisms underlying PD-related cognitive dysfunction have been suggested. Of these, α-synuclein is a key pathological contributor to the development of dementia in PD [3]. Moreover, co-existing Alzheimer's disease (AD) pathologies may influence the onset and progression rate of cognitive decline in patients with PD [4]. Some studies have suggested that a silent vascular pathology known as white matter hyperintensities (WMHs) may be associated with cognitive dysfunction in PD. In fact, WMHs are associated with cognitive decline in normal aging [4] and have been identified as a risk factor for the transition to AD in patients with MCI [5].

WMHs, revealed by T2-weighted magnetic resonance imaging (MRI) scans, are typically categorized as deep white matter hyperintensities (DWMHs), patchy areas of WMHs in subcortical

white matter, or periventricular white matter hyperintensities (PWMHs), which are adjacent to the cerebral ventricles [6]. Even though DWMHs and PWMHs are commonly observed on the MRI scans of elderly persons, the differential effects of specific WMHs on neuropsychological function remain controversial. Both DWMHs and PWMHs are significantly associated with executive dysfunction in patients with MCI [7], but only the progression of PWMH volume in non-demented elderly individuals was associated with a decline in cognitive processing speed [8]. Meanwhile, other evidence suggests that DWMHs are primarily related to executive dysfunction in older adults with MCI [9] and in middle-age individuals [10], indicating that DWMHs and PWMHs may have differential effects on cognitive dysfunction. Similarly, several studies have found that WMHs in patients with PD are associated with cognitive impairments [11,12]; however, these results are inconsistent among studies [13]. In terms of association between WMHs and cortical atrophy, unlike AD [14] or vascular cognitive impairments [15], the relationships between different types of WMHs and cortical atrophy in PD, as well as their association with cognitive function, are not yet fully understood. Thus, we evaluated the patterns of cortical thinning related to DWMHs and PWMHs and analyzed the correlations between WMH-associated cortical thinning and neuropsychological performance in patients with non-demented PD.

1. Patients and methods

1.1. Subjects

This cross-sectional study enrolled 87 patients with non-demented PD from a university hospital between January 2008 and January 2013. PD was diagnosed according to the clinical diagnostic criteria of the United Kingdom PD Society Brain Bank [16]. The study subjects were divided into total WMH (TWMH), DWMH, and PWMH groups based on the locations of WMHs and each subgroup was further classified as having high-, moderate- or low-grade WHMs. The Seoul Neuropsychological Screening Battery (SNSB) [17] was employed to determine impairments in specific cognitive subsets. The SNSB measures attention, language, visuoconstructive function, verbal and visual memory, and frontal/executive function. The quantifiable tests consisted of a digit span task, the Korean version of the Boston Naming Test, the Rey Complex Figure Test, the Seoul Verbal Learning Test, the Controlled Oral Word Association Test, a go/no-go test and contrasting programming, and the Stroop Test. Each of these quantifiable cognitive tests has age-, sex-, and education-specific norms available that are based on 447 normal subjects, and the scores on the tests in the current study were classified as abnormal if they were below the 16th percentile for matched normal subjects. Parkinsonian motor symptoms were assessed using the Unified PD Rating Scale Part III. The basic demographic data for gender, age, and histories of hypertension, diabetes mellitus, or cerebrovascular accidents were also analyzed. Patients with a pharmacological history of drugs that induce parkinsonism were excluded. Additionally, exclusion criteria consisted of evidence of focal brain lesions on MRI scans or the presence of other neurodegenerative diseases that might account for cognitive dysfunctions. An [18F] FP-CIT positron emission tomography scan was performed on all subjects, all of whom exhibited decreased dopamine transporter uptake in the posterior putamen. Informed consent was obtained from all patients and control subjects. This study was approved by the Institutional Review Board of Yonsei University Severance Hospital.

1.2. Brain MRI

All scans of patients were acquired using a 3.0-T system (Intera or Achieva, Philips Medical System; Best, The Netherlands). WMHs were determined using fluid attenuated inversion recovery sequence images (TR/TE/TI, 8502/132/2100 ms, 5-mm section thickness) and the WMH scores were rated using a semi-quantitative visual rating system [18]. PWMHs were identified as continuous, confluent areas of high signal intensity adjacent to the anterior or posterior horns of the lateral ventricles ("cap") and along the lateral ventricles ("bands"). Absence of lesions was a score of 0, ≤5 mm lesions was a score of 1, and a score of 2 was given for lesions >5 mm. DWMHs were more than 10 mm from the lateral ventricle, and were located in the deep or subcortical white matter. These rating criteria were also applied to regions of the basal ganglia (caudate, putamen, globus pallidus, thalamus, and internal capsule) and infratentorial regions (cerebellum, midbrain, pons, and medulla). This rating scale provides four sum scores in a semi-quantitative manner: PWMHs (0—6), DWMHs (0—24), basal ganglia WMHs (0—30), and infratentorial WMHs (0—24). That all combined to make TWMHs score (0—84). Based on the distribution of WMH scores, patients with PD were divided into tertiles of the low-, moderate- and high-

grade WMH groups. WMH scores were rated blindly (by H.J.H. and S.M.K.), and the intra- and inter-scorer reliability (expressed as correlation coefficients) were 0.93 and 0.86, respectively. Additionally, a high-resolution T1-weighted MRI 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; $0.86 \times 0.86 \times 1.0$ mm voxels; echo time, 4.6 ms; repetition time, 9.6 ms; flip angle, 8°; and slice gap, 0 mm.

1.3. Image acquisition and processing

T1-weighted images were registered in the ICBM-152 average template using a linear transformation and were corrected for intensity non-uniformity artifacts [19]. The images were then classified as white matter (WM), gray matter (GM), cerebrospinal fluid (CSF), or background using an advanced neural net classifier. Hemispheric cortical surfaces were automatically extracted from each T1-weighted image using the Constrained Laplacian-based Automated Segmentation with Proximities (CLASP) algorithm, which reconstructs the inner cortical surface by deforming a spherical mesh onto the WM/GM boundary and then expanding the deformable model to the GM/CSF boundary [20]. The reconstructed hemispheric cortical surfaces consisted of 40,962 vertices, each forming high-resolution meshes. The inner and outer cortical surfaces had the same number of vertices, and there was a close correspondence between the counterpart vertices of the inner and outer cortical surfaces. Cortical thickness was defined using the t-link method, which captures the Euclidean distance between these linked vertices (Supplementary Fig. 1) [20]. Diffusion smoothing with a full-width half maximum of 20 mm was used to blur each map of cortical thickness, which increased the signal-to-noise ratio and statistical power. Each smoothed individual thickness map was then transformed to a surface group template using a 2-dimensional (2D) surface-based registration that aligns variable sulcal folding patterns through sphere-to-sphere warping [21]. For lobar regional analysis, a lobe-parcellated surface group template was used; the definition of the lobar regions has been described in detail previously [22].

1.4. Statistical analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences, version 20.0 (SPSS, Inc.; Chicago, IL, USA). Differences in the baseline demographic characteristics between low-, moderate-, and high-grade WMH groups were evaluated using an analysis of variance test for continuous variables or the chi-Square test for categorical variables. An analysis of covariance (ANCOVA) was used to compare differences between the low-, moderate- and high-grade WMH groups for the neuropsychological testing, and it was adjusted for age, gender, education level, and Mini-Mental State Examination (MMSE) scores. The global difference and corrected t-statistical maps of cortical thickness were analyzed between the low- and high-grade WMH groups, after adjusting for age, sex, years of education, disease duration, and intracranial volume (ICV) as covariates. Statistical analyses were performed using the SurfStat toolbox (http://www.math.mcgill.ca/keith/surfstat/) for Matlab (R2010b; MathWorks; Natick, MA, USA). The group differences in cortical thickness were considered to be significant at a random-field theory-corrected value of P < 0.05. To investigate the correlation between WMH-associated cortical thickness and cognitive performance, we obtained the mean cortical thickness of cortical thinning regions in all study subjects where cortical thickness in high-grade WMHs was significantly decreased relative to low-grade WMHs. Additionally, the cortical thickness of atrophic region in individual subject where cortical thinning was more severe in the high-grade WMH group than in the low-grade WMH group was parcellated into frontal, parietal, temporal, and occipital lobes, and we used frontal thickness in following correlation and regression analyses. A partial correlation analysis was performed between WMH-associated cortical thickness and WMH severity after controlling age, gender, education, MMSE and ICV. In Model 1 of a multiple regression analysis, we used cognitive subsets, age, gender, education level, MMSE, and ICV as independent variables and the WMH-associated mean cortical thickness (depending on each WMH from the ANCOVA test) as a dependent variable. In Model 2 to explore independent effects of WMH-associated cortical thickness on cognitive performance, the WMH type was added to predictors of Model 1. Next, a multiple regression analysis was performed using cognitive subsets, age, gender, education level, MMSE, and ICV as independent variables and WMH-associated cortical thickness in frontal area as a dependent variable (Model 1). Finally, the WMH type was added to the predictors for each multiple regression model (Model 2). For all tests, a p value <0.05 was considered to be statistically significant.

2. Results

2.1. Demographic characteristics and neuropsychological data

Based on the severity of the WMHs, 29 patients exhibited high-grade TWMHs (>15), while 28 had low-grade TWMHs (0—5); 26 patients had high-grade DWMHs (>10), while 32 had low-grade