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Neuroanatomical correlates of depressive symptoms in newly diagnosed Parkinson's disease patients

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Abstract

Objective: Depression is the most frequent neuropsychiatric manifestation in Parkinson's disease (PD). Although evidence suggests that depression in PD is related to the degenerative process that underlies the disease, a complete understanding of neural substrates has yet to be achieved. To investigate the neuroanatomical changes underlying depression in PD, we conducted a surface-based morphometry (SBM) study in de novo, drug-naïve Parkinson's disease patients with and without depression. *Methods*: We studied thirty-one patients with idiopathic, de novo, drug-naïve PD. Patient clinical characteristics, including age, sex, disease duration, Hoehn and Yahr stage, UPDRS part III, and brief neuropsychological testing, were assessed. Sixteen Parkinson's disease patients with depression (PD-D) were defined as patients with abnormal geriatric depressions scales (> 17 points), and fifteen patients had Parkinson's disease without depression (PD-ND). The SBM analysis of cortical thickness was performed to determine the difference between the PD-D and PD-ND groups. *Results*: There were no differences in terms of clinical characteristics between the PD-D and PD-ND groups, but the level of education in the PD-ND was higher than that in the PD-D. The cortical thickness was significantly decreased in the left anterior cingulate and left precentral gyrus in the PD-D group compared to the PD-ND group. *Conclusion*: Depression in Parkinson's disease is associated with the left anterior cingulate and left precentral gyrus region reduced cortical thickness.

Keywords: Parkinson's disease; depression; cortical thickness; morphometry

INTRODUCTION

Depression is the most common psychiatric disturbance in Parkinson's disease (PD) patients, with a prevalence of present in approximately 40% of the PD population. It may antecede motor dysfunction.[1,2]

Depression in PD affects patient function and is an important determinant of quality of life. It has also been linked to a more rapid disease progression, cognitive decline, motor worsening, reduced activities of daily living (ADL) and lower quality of life.[1,3,4] Depression is intrinsic rather than reactive to PD because it is more prevalent than in the general elderly population with chronic neurodegenerative diseases.[5,6] In addition, 10% to 15% of PD patients already experience disturbed mood at the time of diagnosis.[5,6] In addition, because of an increasing caregiver burden, it is important to evaluate and understand the potential mechanisms underlying the neural basis of depressive symptoms in PD.

Structural imaging techniques have been used to evaluate the neural basis of depressive symptoms and morphometric abnormalities in PD.[2,7-9] Numerous previous voxel-based morphometry (VBM) studies have showed decreased gray matter (GM) volume in PD patients with depression in multiple brain regions including bilateral orbitofrontal gyrus, bilateral hippocampus, medial-dorsal thalamic nuclei, right temporal gyrus, right anterior and medial cingular gyrus, right amygdala and parahippocampal gyrus.[9,10] The functional magnetic resonance imaging (fMRI) study revealed a decreased activation in the left mediodorsal thalamus and in medial prefrontal cortex in PD with depression.[2]

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The VBM study of the same study showed that volume of bilateral medial-dorsal thalamic nuclei was reduced in PD with depression.[2] Recently, the surface-based morphometry (SBM) analysis has been investigated in PD.[7,8,11,12] The SBM study suggested that a cortical thinning of prefrontal region was a critical area in the depression associated with drug-naïve PD.[8] Another research about cortical thickness of depressed PD revealed increased cortical areas in the orbitofrontal and insula regions.[7]

Herein, we analyzed morphometric changes associated with depression in newly diagnosed PD patients.

METHODS

Patients

This study is a case-control (retrospective) study. We used the database from 340 patients with parkinsonism at the Movement Disorders Clinic of Busan Paik Hospital Inje University between May 2011 and February 2013. Sixty-seven patients were newly diagnosed PD. Of those, 37 subjects were excluded due to 3T-MRI exclusion criteria and irrelevant clinical data. Finally, 31 patients were included in the study. The range of age was 58 to 87 years old. Six subjects were under 65 years old. We showed a flowchart for the inclusion or exclusion of subjects (Figure 1). In addition, 16 age-matched healthy control (HC) were enrolled for analysis of SBM analysis. All data, including the MRI images, were originally obtained as a part of routine clinical practice. The protocol was approved by the Institutional Review Board of Busan Paik Hospital. We obtained written informed consent from all participants in this study.

Assessment

Demographic data, including age, age of onset, sex, level of education and disease duration, were obtained through interviews with the patients and their caregivers. All patients and their caregivers were assessed with the following battery of measures: the Hoehn and Yahr stage (H&Y) to evaluate disease severity, the Unified Parkinson's Disease Rating Scale (UPDRS) Part III to assess motor dysfunction.[13] Global cognitive function was estimated using the Korean Mini-Mental State Examination (K-MMSE)[14], clinical dementia rating (CDR)[15], and the global

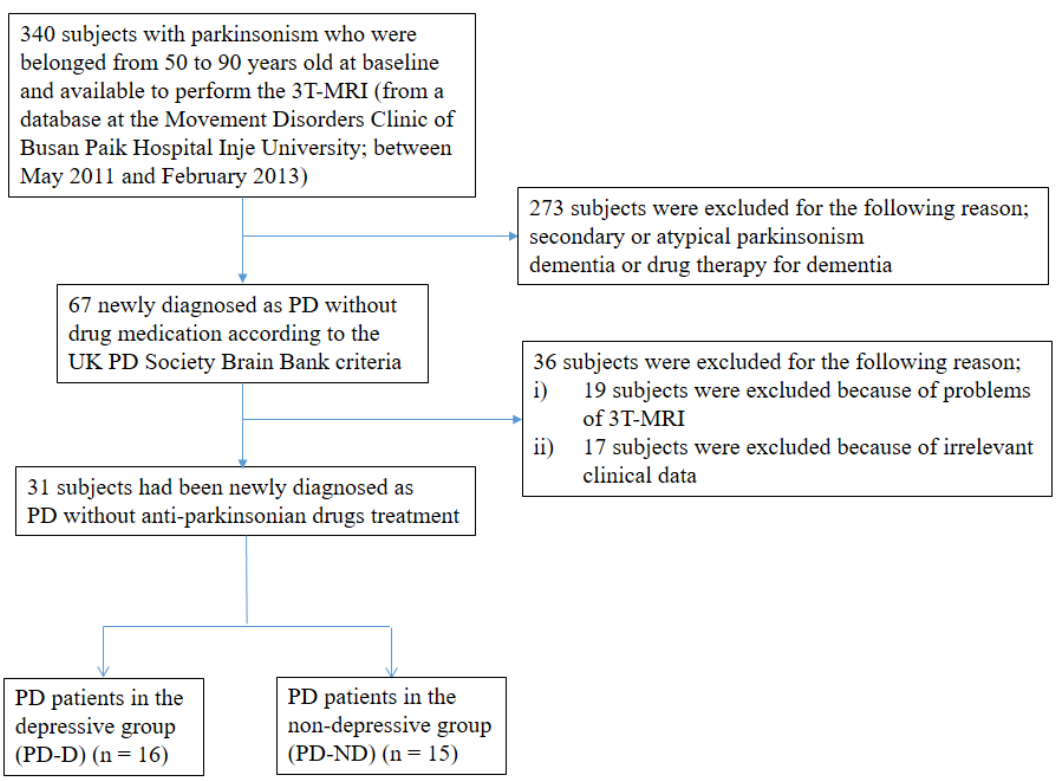

Figure 1. Subjects Flowchart Showing Selection Criteria and Classification
Abbreviations: PD, Parkinson's disease, 3T-MRI, high-resolution magnetic resonance image

deterioration scale (GDS).[16,17] For diagnosis of depression, a neuropsychologist interviewed each patient and checked the the Geriatric Depression Scale (GDeS).[18] Although geriatric depression scale reflects depression in elderly people over 65 years old, for consistency of this study, we applied the GDeS to 6 patients under 65 years old. Depressed mood was defined as a GDeS score >17.[19] We split the patient group into Parkinson's disease with depression (PD-D) and Parkinson's disease without depression (PD-ND) according to depressed mood based on the GDeS score.

MRI acquisition

Scans from both groups were acquired using a Philips 3.0-T scanner (Philips Achieva; Philips Medical System, Best, the Netherlands) with a head coil. Head motion was minimized with restraining foam pads provided by the manufacturer. A high resolution T1-weighted MRI volume dataset was obtained from all subjects using a 3-dimensional T1-TFE sequence configured with the following acquisition parameters: axial acquisition with a 224 × 256 matrix; a 256 × 256 reconstructed matrix with 182 slices; a 220 mm field of view; 0.98 × 0.98 × 1.2 mm3 voxels; echo time 4.6 msec; repetition time 9.6 msec; flip angle 8° and slice gap 0 mm. To accelerate the data acquisition, SENSE (Sensitivity Encoding) parallel imaging with an acceleration factor of 2 was applied.

MR morphometry analysis

Cortical based analysis in image files in DICOM format was performed using the FreeSurfer software (v5.0, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA). FreeSurfer is a semi-automated brain morphometry tool. A single filled white matter (WM) volume was generated for each hemisphere after removal of non-brain tissue, image segmentation using a connected components algorithm,[20] correction of topological defects and intensity normalization.[8] Then, a surface tessellation was generated for each white matter volume by fitting a deformable template.[8] Measures of cortical thickness are the closest distance from the GM and WM boundary to the GM and cerebrospinal fluid (CSF) boundary at each vertex on the tessellated surface.[21] Each thickness value was overlaid on the WM surface.[22] Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a full width at half maximum (FWHM) of 15 mm. One-way ANOVA was performed using a general linear model (GLM) to identify the entire brain volume with significant differences between PD-D and PD-ND. Because multiple-comparison correction methods for comparison between groups would inevitably adjust for statistical error but not for a biological effect, we did not utilize multiple-comparison correction methods,[23] which could have reduced the statistical power. However, each age, disease duration, level of education, and H&Y stage was entered as covariates, and the statistical significance was set at a threshold of $p < 0.001$ with uncorrected multiple comparisons.

Statistical analysis

The statistical comparison of the parametric clinical items between PD-D and PD-ND patients was performed using the t-test and $\chi 2$ test for the categorical and continuous variables, respectively. The nonparametric data were analyzed by the Wilcoxon rank sum and Fisher's exact test for categorical and continuous variables, respectively. The statistical analyses were performed using commercially available software (SPSS, version 19.0). The scores of various neuropsychological tests were adjusted for age and education; $p < 0.05$ was considered statistically significant.

RESULTS

Demographic and clinical characteristics

There was no difference in age between HC (68.0±4.56) and all PD (69.8 ± 6.3) patients. MMSE were significantly higher in healthy controls than in PD patients. There were no significant differences in the age, sex, age at onset, disease duration, H&Y stages, UPDRS Part III, K-MMSE, CDR, and GDS between the PD-D and PD-ND groups, but the level of education in the PD-ND group was higher than that of the PD-D group (Table 1). GDeS was lower scores in the PD-ND (8.5 ± 5.7, range; 1 to 17) than in the PD-D (22.9 ± 3.6, range; 18 to 29) ($P < 0.001$).

SBM analysis

After adjusting age, decreased cortical thickness in left fusiform and precentral gyrus, posterior cingulate and entorhinal cortex, and right middle temporal and lateral occipital lobes have been reported in PD-ND compared to HC. PD-D revealed a cortical thinning in left precentral gyrus, superior frontal, middle temporal lobes and temporal pole, and right insula and precentral gyrus compared to HC.

To investigate the areas of specific loss in PD-D

Table 1: Demographics, clinical characteristics, subtype and motor symptoms of 31 newly diagnosed PD patients in the non-depressive (PD-ND) and depressive group (PD-D).

	PD-ND (n=15)	PD-D (n=16)	*p-value*[b]
Age (yrs)	69.9 ± 7.0	69.7 ± 5.8	0.782
Male (%)	10 (66.7)	6 (37.5)	0.104[a]
Education (yrs)	10.4 ± 4.3	6.7 ± 3.4	0.02
Age at onset (yrs)	68.3 ± 7.2	68.3 ± 5.1	0.487
Disease duration (mo)	20.6 ± 21.0	15.6 ± 17.3	0.258
GDeS	8.5 ± 5.7	22.9 ± 3.6	< 0.0001
H&Y stage	2.2 ± 0.4	2.5 ± 0.6	0.096
UPDRS Part III	16.4 ± 5.8	20.8 ± 10.6	0.163
K-MMSE	28.1 ± 1.5	26.4 ± 3.1	0.107
CDR	0.4 ± 0.2	0.4 ± 0.2	0.687
GDS	2.7 ± 0.7	2.4 ± 0.8	0.107

PD-D, Parkinson's disease patients in the depressive group; PD-ND, Parkinson's disease patients in the non-depressive group; GDeS, Geriatric Depression Scale; H&Y stage, Hoehn and Yahr stage; UPDRS Part III, Unified Parkinson's Disease Rating Scale Part III; K-MMSE, Korean mini-mental status examination; CDR, Clinical Dementia Rating; GDS, Global Deterioration Scale

Data are presented as the means/percent ± standard deviation.

[a] chi-squared test

[b] Mann-Whitney U test

compared to PD-ND, we analyzed the results after adjusting for age, disease duration, level of education, and H&Y stage. The SBM analysis showed that PD-D had a significantly decreased cortical area in the left anterior cingulate and left precentral gyrus compared with the PD-ND group (Table 2, Figure 2).

DISCUSSION

Major depressive disorder patients showed decreased volumes in the various brain regions, such as amygdala, hippocampus, corpus callosum, medial/superior frontal gyrus, insula cortex, cingulate cortex, thalamus, hypothalamus, and nucleus accumbens.[14] Several neuroanatomical studies for evaluating the neural substrates of depression in PD have also suggested that it is associated with more widespread neurodegenerative changes. Structural changes or decreased brain volume were reported in the hippocampus and amygdala,[5] White matter loss in the right anterior cingulate bundle and inferior orbitofrontal region,[15] the left inferior orbitofrontal gyrus, bilateral rectal gyrus, and right superior temporal pole,[16] or the bilateral mediodorsal thalamic nuclei.[1]

According to above results, the brain regions associated with PD with depression are similar to those of major depressive disorder patients. On the SBM analysis of this study, the cortical thinning in PD-D is predominantly concentrated in the left anterior cingulate and left precentral gyrus compared to the PD-ND group after adjusting for age, disease duration, education, and H&Y

Table 2: Differences of cortical thickness or areas between PD-D and PD-ND.

Contrast	L/R	Peak region	Cluster size (mm^2)	Talairach coordinate (x, y, z)
PD–D vs. PD-ND	L	Left anterior cingulate gyrus	66.82	-6.1, 34.7, 6.8
	L	Left precentral gyrus	14.01	-24.1, -6.3, 44.9

PD-D, Parkinson's disease patients in the depressive group; PD-ND, Parkinson's disease patients in the non-depressive group; L/R, left/right

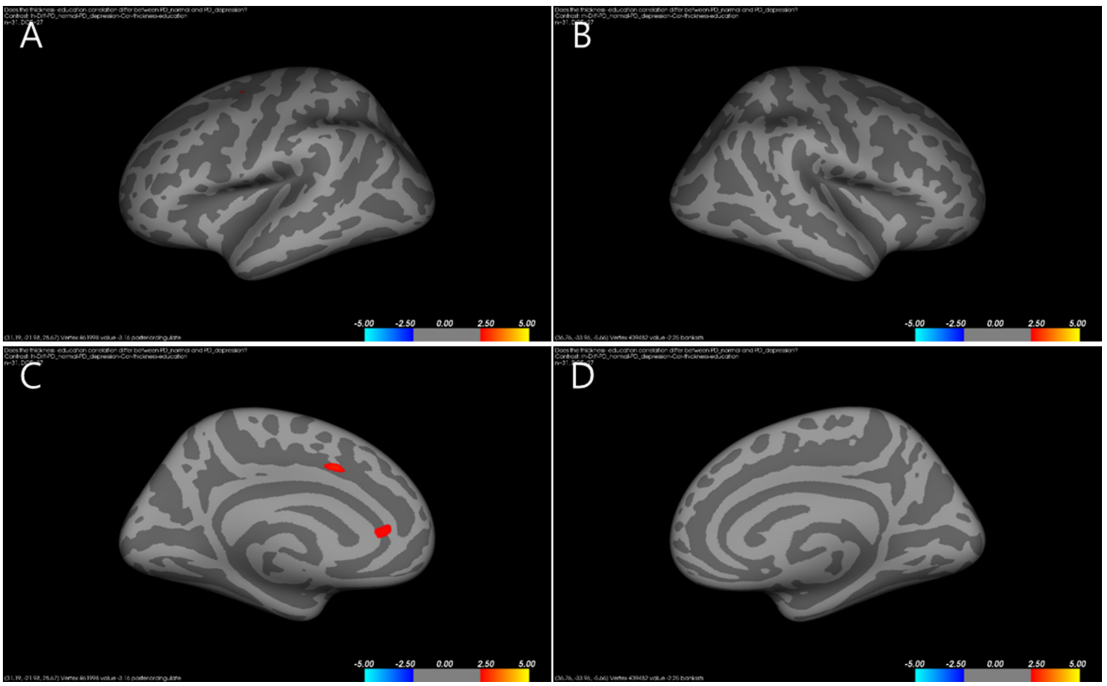

Figure 2. The difference of cortical thickness, surface area and volumes by surface-based analysis technique between the non-depressive (PD-ND) and depressive groups (PD-D) adjusted for age, disease duration, level of education, and H&Y stages. The PD-D had significantly decreased gray matter density in the left rostral anterior cingulate and left precentral gyrus compared with the PD-ND (A, left lateral view; B, right lateral view; C, left medial view; D, right lateral view).

stage. Also, our results showed that depressive symptoms in newly diagnosed PD have been already presented. Depression in newly diagnosed PD is related to a reduced cortical thickness of the anterior cingulate and precentral gyrus. In this study, although the level of education was higher in PD-ND than PD-D, cognitive function tests (K-MMSE, CDR, and GDS) did not show any differences between the two groups. In addition, disease duration and motor severity (H&Y stage and UPDRS Part III) between the two groups were similar.

Recent data also showed altered functional connectivity in the posterior cingulate cortex.[24] Cortical damage in the precentral gyrus may be associated with pathophysiology in the cortico-basal ganglia circuit and could be considered a plausible mechanism underlying motor symptoms of PD.[18] However, we have been unable to find any reports about the volume loss of precentral gyrus in PD-D. Although this study found similar results as other studies for neuroanatomical substrates in PD[15], the relationship between tissue loss in the precentral gyrus and anterior cingulate gyrus and depression in newly diagnosed PD without treatment is a new suggestion in this study.

The limitations of our study include its retrospective nature, the lack of longitudinal follow-up, and the sample size in the case-control study. Although our results cannot be generalized to apply to PD patients because of the inclusion of newly diagnosed de novo PD patients, we suggest that early depression and the dopaminergic drug-free state of PD occurred and is associated with the anterior cingulate and precentral gyrus. Another limitation that should also be considered is the relationship between brain lesions and neurotransmitter changes. We cannot determine whether dopaminergic changes in PD are responsible for these changes or whether the global degenerative process of PD also affects these two areas. In this study, irrespective of global cognitive status, we observed depressive symptoms in de novo PD patients.

In conclusion, our results show that depression is associated with the cortical atrophy of the anterior cingulate and precentral gyrus in newly diagnosed, de novo PD patients. These results should be confirmed in a large population study. To investigate the neural basis of the neuropsychiatric features of PD, future studies should focus on the changes in neurotransmitters and neuroanatomy at the de novo stage and following dopaminergic treatment in PD.

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DISCLOSURE

Conflicts of interest: None

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