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Cortical abnormalities in Parkinson's disease patients and relationship to depression: A surface-based morphometry study

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ABSTRACT

Depression is a common occurrence in patients with Parkinson's disease (PD). Brain deficits may be the underlying cause of depression in PD. In the present study, we investigated whether morphometric alterations contribute to depression in PD. Seventeen depressed PD patients, 17 non-depressed PD patients and 45 normal controls were enrolled in the study. All subjects went through neurological and psychiatric clinical assessments. T1 weighted magnetic resonance imaging and surface-based morphometric analyses were performed to examine morphometric abnormalities in PD patients and their relationship to depression. We found that compared with normal controls, PD patients exhibited significantly decreased cortical thickness in the left precentral gyrus and the right postcentral gyrus extending to the middle frontal gyrus. Compared with non-depressed PD patients, depressed patients showed significantly increased cortical areas in the orbitofrontal regions and insula, which may imply white matter atrophy in these areas. The results of orbitofrontal and insula white matter atrophy are consistent with our previous finding that white matter integrity and functional connectivity are damaged in these regions in depressed PD patients, confirming their contribution to depression in PD.

1. Introduction

Depression is one of the most common non-motor symptoms in patients with Parkinson's disease (PD) (Shulman et al., 2001). Although It has been suggested that PD patients get depressed more frequently (Aarsland et al., 2012; Moussavi et al., 2007; Reijnders et al., 2008), the cause of this relationship is still unclear. While PD does cause the onset of negative feelings because of the disabling symptoms, much evidence suggests that there are some common underlying brain mechanisms (Lieberman, 2006).

Lewy body accumulation in the brains of PD patients may damage neuronal functions and induce neuron death (Giasson et al., 2000), and there have been consistent reports of reduced brain volumes in PD patients. A meta-analysis of studies on substantia nigra (SN) volume in PD patients suggests that T1 weighted imaging can effectively detect SN atrophy (Sako et al., 2014). Besides the SN, volume reduction in several other brain regions, such as the frontal lobe and the temporal lobe, have also been reported (Melzer et al., 2012; Pan et al., 2012). These volumetric changes reflected the pathology of PD, and were found to be related to various clinical symptoms, such as dementia (Burton et al., 2004) and impulse control disorders (Biundo et al., 2011).

Depression in PD has also been found to be related to brain structural abnormalities. Feldmann et al. (2008) showed reduced gray matter density in the bilateral orbitofrontal gyrus, bilateral rectal gyrus, and the right superior temporal regions of depressed PD patients compared with non-depressed PD patients. Reijnders et al. (2010) suggest that lower gray matter density in the cingulate gyrus and inferior frontal gyrus is related to apathy and depression in PD patients. A recent study revealed that the amygdala and hippocampus volumes are negatively correlated with depression (Mierlo et al., 2015). While decreased brain volumes were consistently reported, some have also shown increased brain volumes. Cardoso et al. (2009) found larger mediodorsal thalamic nuclei volumes in depressed PD patients compared with patients without depression, which is consistent with findings from depressed patients in the general population. Although these studies revealed some abnormalities, inconsistencies still exist.

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While traditional studies mostly use manual depiction measurements or voxel-based morphometry methods, surface-based analysis has recently attracted interest from researchers investigating the neural mechanisms of PD (Pellicano et al., 2012; Pereira et al., 2012, 2014). Analysis of local cortical thickness and surface area can give detailed information about both the volume and geometry of brain gray matter. A separate analysis of these orthogonal characteristics also enhances reliability and sensitivity (Clarkson et al., 2011). To date, cortical thickness analysis has been successfully used to address PD pathologies (Zarei et al., 2013), including the mechanism of non-motor symptoms (Pagonabarraga et al., 2013), although it is still unclear how these brain matrices are related to depression in PD. Here we investigated whether cortical thickness and brain area changes contribute to depression in PD. In our previous studies, we found white matter damage in the frontal lobe and insula (Huang et al., 2014), and functional alterations in the left dorsolateral prefrontal cortex and right superior temporal gyrus (Lou et al., 2015). Therefore, we expected to find cortical abnormalities in similar regions.

2. Methods

2.1. Subjects

Two groups of PD patients (with and without depression, 17 for each group) were recruited from the Department of Neurology, Second Affiliated Hospital of Zhejiang University. Diagnosis of PD was made by a senior neurologist according to the UK PD Brain Bank criteria. Unipolar depression was diagnosed by an experienced psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria. Scores of the Unified Parkinson's Disease Rating Scale (UPDRS), the Hamilton Rating Scale for Depression (HRSD), Hamilton Anxiety Rating Scale (HAMA) and the Mini-Mental State Examination (MMSE) were obtained from all subjects. Table 1 shows detailed characteristics of the two groups. For exclusion criteria, we ruled out any subjects who had other neurological or psychiatric disorders or brain trauma at any time in their lives. Seventeen normal controls (NC) matched for age and sex were also enrolled. All the subjects had signed written informed consent forms before taking part in the study. This research was approved by the Medical Ethics Committee of Zhejiang University.

2.2. Scanning parameters

All the scans were performed on a 3.0T GE Signa MR scanner in the Department of Radiology, Second Affiliated Hospital of Zhejiang University. Ear plugs and foam pads were used to reduce noise and head motion. Structural brain images were acquired using a fast spoiled gradient recalled echo sequence (TR/TE = 5100 ms/1.2 ms; FOV = 24 × 24 cm; matrix = 256 × 256; slices = 124; thickness = 1.2 mm; and space = 0 mm). Several other sequences were also scanned and the entire acquisition time was about 40 min.

2.3. Data processing

Cortical based analysis was performed using FreeSurfer (v5.3.0). The reformatted MR images were subjected to preprocessing steps for the correction of magnetic inhomogeneity, skull strip, and segmentation into gray and white matter. Minor segmentation errors were corrected with minimal manual adjustment. Cortical thickness was measured as the distance between the gray/white matter boundary and the nearest corresponding gray matter surface. Each thickness value was overlaid on the white matter surface. By inflating the cortical sulci, three-dimensional inflated and spherical white matter models were created for spatial normalization and further statistical analysis. Details of FreeSurfer segmentation have been previously described (Fischl, 2012).

2.4. Statistical analysis

Age was compared among the three groups using one-way analysis of variance. Sex and Hoehn and Yahr stage were compared using chi-square test among the three groups. Scale scores were compared between the two PD groups using two-sample *t*-test. Statistical analysis of image data was performed using the two-sample *t*-test in the Qdec tool of FreeSurfer, during which the age and sex were controlled as covariables. We first analyzed the abnormal changes from NC to all PD patients. Then we compared the differences between depressed and non-depressed PD patients. Surface characteristics (cortical thickness, pial area, volume) were included for the comparison. We first set the statistical significance to a voxel level of $p < 0.01$. Then, multiple comparisons were corrected with cluster-based Monte-Carlo simulation with 10,000 permutations, and we searched for significant clusters with a cluster-level of $p < 0.05$.

3. Results

As shown in Table 1, there were no age and sex differences among the three groups. Disease characteristics such as duration, Hoehn and Yahr Scale, UPDRS and MMSE scores also showed no difference between the two PD groups. The depressed PD patients had higher HRSD and HAMA scores compared to the non-depressed

Table 1
Demographic characteristics.

Index	dPD	ndPD	NC	Degrees of freedom	Test value	*p* value
Gender (m/f)	8/9	9/8	24/21	2	0.204###	0.903
Age, y, mean ± SD	59.4 ± 8.9	59.1 ± 9.9	57.0 ± 10.0	78	0.507##	0.604
Duration, mean ± SD	3.6 ± 3.3	4.3 ± 3.7	–	32	−0.565#	0.576
Hoehn and Yahr stage, median	2.5	2.5	–	2	3.159###	0.206
UPDRS-III, mean ± SD	44.1 ± 12.3	40.5 ± 9.2	–	32	0.962#	0.343
MMSE, mean ± SD	26.2 ± 2.5	26.1 ± 2.7	–	32	0.131#	0.897
HRSD, mean ± SD	30.0 ± 6.1	8.2 ± 5.6	–	32	6.125#	0.000
HAMA, mean ± SD	16.1 ± 8.1	7.1 ± 6.8		32	3.501#	0.001

dPD: depressed PD; ndPD: non-depressed PD.

Pearson Chi-Square.

F value.

t value.