RESEARCH ARTICLE

Altered Brain Network Centrality in Depressed Parkinson's Disease Patients

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ABSTRACT: Background: Depression is a relatively common and serious nonmotor symptom of Parkinson's disease (PD), which reduces the quality of patients' life. Although disturbances in some related brain networks have been reported, the pathophysiology of depression in PD is still unclear. Here, we aim to investigate whole-brain functional connectivity patterns in depressed PD patients.
Methods: We recruited 17 PD patients diagnosed with major depressive disorder, 17 PD patients without depression, and 17 healthy control subjects. Resting-state functional MRI and eigenvector centrality mapping were used to identify functional connectivity alterations among these groups.
Results: Results showed that depressed PD patients had decreased functional connectivity in the left dorsolateral prefrontal cortex and right superior temporal gyrus and increased functional connectivity in the right posterior cingulate cortex, compared to nondepressed patients. In addition, there was a significant negative correlation between functional connectivity and depression scores in the posterior cingulate cortex.
Conclusions: This study suggests that functional connectivity changes in certain nodes of brain networks might contribute to depression in patients with PD.
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Key Words: Parkinson's disease; depression; functional connectivity

Depression is a relatively common and serious nonmotor symptom of Parkinson's disease (PD) that occurs in approximately 40% of patients.[1] The typical symptoms of depression in Parkinson's disease (dPD) patients are persistent depressed mood and markedly diminished interest or pleasure; excessive guilt and suicidal behavior are observed less frequently.[2,3] Several studies have shown that dPD may have a negative effect on quality of life, motor function, and disability.[2,4] Our previous cross-sectional study of 151 PD patients found that nearly 29.1% of them suffered from major depression and that depression was one of the most important factors affecting their quality of life.[5] However, given that the underlying pathophysiology of dPD patients is complex and still unclear,[3] a better understanding of it should be helpful for diagnosing and treating dPD patients.

Modern advances in imaging methods have provided useful tools for investigating the neural basis of depression in PD. Within the last few years, a number of functional imaging studies using PET, single-photon emission CT, and functional MRI (fMRI) have found that abnormalities in the prefrontal cortex, basal

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ganglia, and the limbic system (including the cingulate cortex, thalamus, amygdala, and ventral striatum) were associated with dPD.[3,6-8] These studies suggest that pathophysiology of dPD may be associated with the regional brain abnormalities just mentioned. However, the studies did not determine the specific changes in the brain network that distinguished between dPD and nondepressed PD (ndPD) patients.

Some recent researches on brain network analyses had investigated the functional changes that are associated with the symptoms of depression in patients with PD.[9,10] An analysis of the amplitude of low-frequency fluctuations (ALFF) and functional connectivity in the whole brain found that dPD patients had increased regional spontaneous neural activity in the orbitofrontal area and decreased functional integration within the prefrontal-limbic network, compared to ndPD patients and healthy controls.[9] Consistent with these results, an fMRI study that analyzed regional homogeneity (ReHo) and functional connectivity revealed decreased functional connectivity within the prefrontal-limbic system and increased functional connectivity in the prefrontal cortex and lingual gyrus in a dPD group, compared to an ndPD group.[10] However, these two studies had to select regions of interest to conduct the functional connectivity analysis, which may have resulted in selection bias, depending on the researchers' selections.

To further determine the nodes of the functional brain network that may play an important role in the psychopathology and pathophysiology of dPD, we conducted resting-state fMRI to compare dPD and ndPD patients. We used a model-free, data-driven approach with eigenvector centrality mapping (ECM).[11] This analysis method can accurately and objectively detect all the brain areas serving as communication hubs, which have greater connectivity with other parts of the brain. Because the method does not require manual selection of the seed regions, it is independent of researchers' selections and therefore free of selection bias.[12]

Patients and Methods

Participants

We recruited 34 patients with idiopathic PD according to the UK Parkinson's Disease Brain Bank. All of the PD patients received a Mini–International Neuropsychiatric Interview (MINI) interview,[13] which was used as a preliminary screening tool to select patients who probably had depression and exclude other psychiatric comorbidities. Seventeen of these patients suffered from major depressive disorder (MDD), which was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria,[4] by an experienced, board-certified psychiatrist. The 17 ndPD patients were matched to the dPD patients by age, gender, and PD motor severity (according to UPDRS Part III and H & Y Scale). Patients were excluded from the study if they had: (1) cerebrovascular disorders, including a previous stroke, a history of seizure, hydrocephalus, intracranial mass, a history of head injury, previous neurological surgery, or other neurological diseases; (2) any current DSM-IV Axis I diagnosis other than MDD, as determined by an experienced psychiatrist; (3) treatment with antidepressants or other psychiatric therapy; or (4) dementia. For technical reasons, participants who were unable to keep still during the MRI because of head motion were not eligible to be in the study. Seventeen healthy, age- and sex-matched, control participants who did not have depression or any neurological or psychiatric disorders were recruited as normal controls (NCs). Informed written consent was obtained from all participants, and the study was approved by the medical ethics committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China).

Psychiatric and Neurological Evaluation

Disease stage and severity were assessed with the UPDRS Part III and the H & Y Scale while patients were in the *off* state (free of medicine for more than 12 hours). All neurological scales were evaluated by four neurologists who underwent special training before the study. Then, the four neurologists separately evaluated the UPDRS Part III and the H & Y Scale for 4 PD patients; Kendall's coefficient of concordance was used to assess agreement among the doctors. Results indicated a high degree of agreement among the various responses (UPDRS Part III: Kendall's $W = 0.925$; $\chi^2 = 11.1$; $P < 0.05$; H & Y Scale: Kendall's $W = 0.850$; $\chi^2 = 10.2$; $P < 0.05$). The psychiatric evaluation included the Mini–Mental State Examination (MMSE) and the Hamilton Depression Scale (HAMD-24), which was used to assess severity of depression. All clinical evaluations were performed on the day the MRI scans were acquired.

fMRI Data Acquisition

Allscans were performed in the *off* state, on a 3.0T GE SIGNA MR scanner (GE Healthcare Wauwatosa, WI) in the Department of Radiology of the Second Affiliated Hospital of Zhejiang University. Ear plugs and foam pads were used to reduce noise and head motion. Traditional T1 and T2 images were taken first and viewed by a radiologist to exclude participants with apparent brain abnormalities. Blood-oxygenation-level–dependent (BOLD) images were acquired using a gradient recalled echo (GRE)/echo planar imaging sequence (repetition time [TR] = 2,000 ms; echo time [TE] = 30 ms; flip angle = 90 degrees; field of view

TABLE 1. Demographic and neuropsychological characteristics of all subjects

Index	dPD	ndPD	NCs	Statistic	*P* Value
Sex, male/female	8/9	9/8	9/8	$F = 0.157$	0.925
Age, years	59.35 ± 8.89	59.06 ± 9.90	59.18 ± 9.95	$F = 0.004$	0.996
MMSE	26.18 ± 2.53	26.06 ± 2.70	26.76 ± 2.54	$F = 0.362$	0.698
H & Y	2.71 ± 0.25	2.62 ± 0.28	NA	$F = 1.091$	0.580
UPDRS-III	44.06 ± 12.34	40.47 ± 9.19	NA	$t = 0.962$	0.343
HAMD-24	30.01 ± 6.11	8.24 ± 5.58	NA	$t = 10.872$	<0.005

Values are represented as the mean ± standard deviation.
NA, not applicable.

[FOV] = 240 × 240 mm^2; matrix = 64 × 64; slice thickness = 5 mm; slice gap = 1 mm; 23 interleaved slices). A total of 185 resting-state BOLD images were acquired from each subject. Anatomical images, acquired after functional imaging, consisted of a three-dimensional GRE T1-weighted sequence (TR = 5.14 ms; TE = 1.17 ms; flip angle = 13 degrees; FOV = 256 × 256 mm^2; voxel size = 1 × 1 × 1 mm^3). Subjects were instructed to relax with their eyes closed, without falling asleep, and without directed systematic thought. This was confirmed after completion of the scanning.

Preprocessing

Data processing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF; http://www.restfmri.net)[14] and the Resting-State fMRI Data Analysis Toolkit (Rest, V1.8; http://www.restfmri.net).[15] The first 10 images were excluded from the analysis. The remaining images were corrected for slice timing with the middle slice used as a reference, realigned to remove head motion, normalized into the standard space using DARTEL,[16] and resampled to a 3 × 3 × 3 mm^3 voxel size. The resulting images were then smoothed using a 4-mm Gaussian kernel before proceeding to the next step.

ECM

The human brain is organized as a complex network with small-world properties. Therefore, graph-based analysis could provide valuable information for elucidating the brain's network structures. Eigenvector centrality is a particular type of graph-based method that identifies important nodes in the network. It does so by counting both the number and quality of connections so that a node with few connections to some other high-ranking nodes may outrank one with a larger number of low-ranking connections. Google's "PageRank" algorithm is a variant of eigenvector centrality. As with its success in the Web search engine, eigenvector centrality has also been proven valuable in analyzing human brain networks.

Here, the ECM of the pre-processed image data was performed using the fast ECM (fECM) tool (https://code.google.com/p/bias/source/browse/matlab/fastECM), which yielded a voxel-wise measure of relevance to the functional brain network. Compared to the traditional ECM calculation method, the fECM tool is faster and computationally more efficient because it computes matrix-vector products without having to compute or store the connectivity matrix.[17]

Statistical Analysis

One-way analysis of variance (ANOVA) was first used to identify differential brain regions among the three groups. The threshold was set at single voxel $P < 0.05$ and cluster size >85 voxels, corresponding to a corrected $P < 0.05$, using AlphaSim for multiple comparison corrections. Post-hoc analyses were performed using two-sample *t* tests in a pair-wise manner within the areas identified by the ANOVA. It should be noted that the use of post-hoc multiple comparisons after ANOVA remains an open issue. The term "multiple" here includes two levels, that is, multiple voxels and multiple *t* tests (three in the current study). To reduce false-positive results, we used the same mask and criteria as those used in the ANOVA. In this way, the whole-brain mask has much more voxels than the brain areas identified by the ANOVA. Signals from the significant clusters were also extracted to test the correlation between FC and disease severity (HRSD scores). The correlation analysis was performed using partial Pearson's correlation, with age, sex, UPDRS, and MMSE controlled as covariates.

Analyses of the descriptive variables was done using one-way ANOVAs, two-tailed *t* tests, and χ^2 tests, as appropriate. Statistical significance was set at $P < 0.05$. All analyses were performed using SPSS statistical software (version 19; SPSS, Inc., Chicago, IL).

Results

Population Characteristics

Demographic and clinical features of the participants are shown in Table 1. We found no significant

TABLE 2. Difference of functional connectivity for patients between dPD and ndPD patients

Brain Regions	L/R	Cluster Size	BA	MNI Coordinate			T Value
				x	y	z	
dPD < ndPD							
Middle frontal gyrus	L	101	9	−36	30	48	3.42
Superior frontal gyrus							
Superior temporal gyrus	R	178	22	66	−3	12	3.17
Precentral gyrus							
Infeior frontal gyrus							
dPD > ndPD							
Posterior cingulate gyrus	R	97	30	9	−48	21	3.35

L, left; R, right; BA, Brodman area; MNI, Montreal Neuroscience Institute template.

differences in age, sex, or MMSE scores among the three groups. No significant differences between dPD and ndPD patients were observed on the H & Y Scale or UPDRS III scores. However, HAMD-24 scores were significantly higher for the dPD group.

dPD Patients Versus ndPD Patients

Compared to ndPD patients, dPD patients showed decreased functional connectivity in the left superior and middle frontal gyrus, right superior temporal gyrus, right precentral gyrus, and right inferior frontal gyrus. In contrast, increased functional connectivity in the right posterior cingulate cortex was observed in the dPD group (Fig. 1A; Table 2).

dPD Patients Versus NC Group

Compared to the NC group, the ndPD group showed significantly decreased functional connectivity

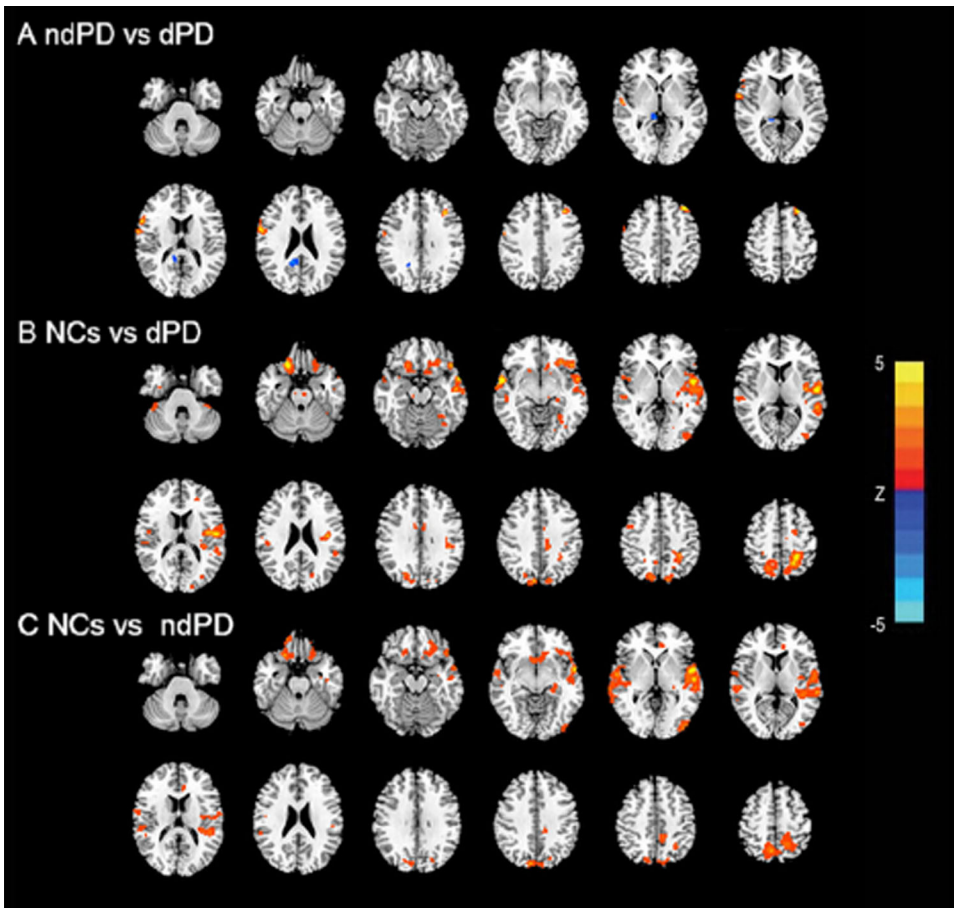

FIG. 1. Statistical parametric map showing the significant differences in functional connectivity between three groups: dPD, ndPD, and NCs: differences between dPD and ndPD (A); differences between dPD and NCs (B); and differences between ndPD and NCs (C). The threshold for display was set to $P < 0.05$. Areas in red indicate regions in which the former group who had increased functional connectivity, compared to the latter group, and areas in blue represent the opposite. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 3. Difference of functional connectivity for patients between dPD patients and NCs

Brain Regions	L/R	Cluster Size	BA	MNI Coordinate			T Value
				x	y	z	
dPD < NCs							
Superior temporal gyrus Middle temporal gyrus Insula Precentral gyrus Postcentral gyrus Inferior parietal lobule	L	977	22	−57	−15	9	4.54
Middle temporal gyrus Superior temporal gyrus	R	114	22	63	−3	−6	4.35
Inferior frontal gyrus Orbital gyrus	R	170	11	21	24	−21	4.56
Inferior frontal gyrus Middle frontal gyrus	L	247	47	−48	24	−12	3.87
Superior parietal lobule Inferior parietal lobule Postcentral gyrus	R	619	7	−24	−45	54	4.35

L, left; R, right; BA, Brodman area; MNI, Montreal Neuroscience Institute template.

in the bilateral superior and middle temporal gyrus, bilateral inferior frontal gyrus, left middle frontal gyrus, bilateral postcentral gyrus, right orbital gyrus, left insula, right superior parietal lobule, and bilateral inferior parietal lobule (Fig. 1B; Table 3).

ndPD Patients Versus NC Group

Compared to NC group, ndPD patients showed significantly decreased functional connectivity in the bilateral superior and middle temporal gyrus, bilateral inferior frontal gyrus, left middle frontal gyrus, bilateral postcentral gyrus, right orbital gyrus, right superior parietal lobule, left middle and inferior occipital gyrus, and right precuneus and left insula (Fig. 1C; Table 4).

Correlation Between Depression Scores and Functional Connectivity in dPD Patients

We studied the relationships between HAMD-24 scores and functional connectivity in the dorsolateral prefrontal cortex (dlPFC, BA9), superior temporal gyrus (STG, BA22), and the right posterior cingulate

TABLE 4. Difference of functional connectivity for patients between ndPD patients and NCs

Brain Regions	L/R	Cluster Size	BA	MNI Coordinate			T Value
				x	y	z	
ndPD < NCs							
Superior temporal gyrus Middle temporal gyrus Inferior frontal gyrus Middle frontal gyrus Anterior cingulate Insula Postcentral gyrus Precentral gyrus	L	1,138	22	−57	−3	3	5.28
Superior temporal gyrus Middle temporal gyrus Postcentral gyrus	R	425	22	60	−6	−3	4.19
Inferior frontal gyrus Orbital gyrus	R	144	11	21	21	−24	3.64
Middle occipital gyrus Inferior occipital gyrus	L	109	19	−45	−87	0	3.38
Precuneus Postcentral gyrus Superior parietal lobule	R	717	7	9	−54	69	4.5

L, left; R, right; BA, Brodman area; MNI, Montreal Neuroscience Institute template.

(PCC, BA30), given that these regions differed significantly between dPD patients and ndPD patients. A significant correlation was found between functional connectivity and depression scores in the PCC ($r = -0.737$; $P < 0.01$). No significant correlation was found between functional connectivity and depression scores in the dlPFC ($r = 0.458$; $P > 0.05$) and STG ($r = -0.193$; $P > 0.05$).

Discussion

The present study looked for specific abnormalities of functional connectivity in brain regions between the dPD and ndPD patients. Reduced functional connectivity of the brain cortex was revealed in both PD subgroups, compared to the NC group. Compared to ndPD patients, dPD patients had lower functional connectivity in the left dlPFC and right STG and increased functional connectivity in the right PCC. In addition, a significant negative correlation was found between HAMD-24 scores and functional connectivity within the right PCC.

To the best of our knowledge, this is the first study to demonstrate differences in the whole-brain functional connectivity of dPD and ndPD patients. The dlPFC, which includes portions of the middle and superior frontal gyri on the lateral surface of the frontal lobes, receives strong input from specific sensory cortices, and it is a communication hub of the prefrontal-limbic network.[18] It is reported to be involved in cognitive or executive functions,[19,20] as well as playing a role in the episodic buffer, which is a feedback loop in depressive schemata, and is defined as a component of working memory integration. Thus, the dlPFC can lead to depressive symptoms by failing to receive and integrate polymodal sensory information from posterior cortical areas.[21] The present study's findings of significantly decreased function in the dlPFC, which is regarded as a hallmark of depression, has been found in many previous studies.[6,8,22-24] Early PET studies of dPD patients revealed that decreased regional cerebral blood flow in the dlPFC was associated with depression.[6] A recent ALFF study of healthy controls and dPD and ndPD patients found decreased ALFF in the dlPFC of dPD patients, compared to ndPD patients, and a positive correlation between HDRS scores and ALFF values in the dlPFC.[8] Furthermore, increased perfusion was found in the dlPFC after taking repetitive transcranial magnetic stimulation or fluoxetine, both of which are treatments for depression in PD.[22-24] Consistent with these studies, the lower functional connectivity of the dlPFC may have an important role in the pathogenesis of major depression in PD by reducing polymodal sensory information integration within the episodic buffer.

The STG has been found to be involved in the perception of emotions in facial stimuli. It also plays a role in attention bias, which is important because it was one of the cognitive models of depression. The attention bias means that increased attention to negative stimuli by depressed patients results in increased processing of stimuli with negative valences and decreased processing of stimuli with positive valences.[21] Previous studies have shown that hypoactivity, decreased metabolism, and reduced density of the STG in dPD patients and patients with MDD.[25-29] Compared to ndPD patients, a voxel-based morphometry study showed a significantly decreased gray mater density (GMD) of the left inferior orbital frontal gyrus, bilateral rectal gyrus, and the right superior temporal pole of dPD patients. In addition, the GMD of the right superior temporal gyrus had a negative correlation with depression scores.[25] Benedicte et al., an [^{18}F]MPPF-PET study that used a selective serotonin 1A receptor antagonist, found that dPD patients had reduced tracer uptake in the left hippocampus, the right insula, the left superior temporal cortex, and the orbital frontal cortex.[26] Decreased ReHo was found recently in the STG of patients with major depression, compared to healthy controls.[27,28] A previous study also found decreased functional connectivity in the left superior temporal cortex of patients with major depression,[29] which is similar to our results. Combining our findings and those of previous studies, we propose that disturbed functional connectivity of the STG may be related to the depressive symptoms in patients with PD owing to increased attention to negative stimuli.

The PCC has a role in information processing, given that its structural and functional connectivity is related to other brain regions.[30,31] The PCC shows a highly complex pattern of connectivity, with prominent connections to the prefrontal cortex and the medial temporal lobes, and it appears to be highly integrated with the default mode network (DMN), which has been reported to be associated with major depression in recent years; the PCC also is involved in internally directed cognition, such as memory retrieval and planning.[31,32] The DMN is active during the resting state and becomes deactivated during externally oriented processes, such as goal-directed tasks in normal individuals,[33,34] whereas there is a failure to deactivate this network in depressed patients.[21] The PCC is not only involved in DMN, which is active in self-referential processes, but it also is associated with rumination. Depressive rumination—defined as a tendency to repetitively analyze one's problems, concerns, feelings of distress, and depressed mood states—has been reported to be a critical cognitive factor contributing to mood depletion, repletion, relapse, and maintenance of depression.[21,35,36] Thus, patients with major depression fall into rumination and fail to deactivate the DMN through cognitively demanding tasks, which results in increased functional connectivity in

the PCC, in accord with our result. Similar imaging results have been observed in recent studies in patients with major depression, but few in studies on dPD patients.[37-39] For example, a study of resting-state functional connectivity in patients with major depression found increased functional connectivity that was primarily located in the PCC and the medial orbital frontal cortex, which are involved in episodic memory, self-reflection, and emotional regulation.[37] Bluhm et al. found that patients with major depression had abnormal functional connectivity between the precuneus/PCC and the bilateral caudate during the early stage of depression, compared to NCs.[38] Given these findings, we speculate that increased functional connectivity of the PCC is a contributing factor for depressive symptoms in PD patients, the process of which may be linked to engaging in self-referential processes and rumination. The significant negative correlation between the depression and functional connectivity of the PCC may provide new insight into the relative importance of the PCC in the development of depressive symptoms in PD patients.

The current study has several limitations. First, we did not control for the doses and kinds of Parkinson's drugs taken by the participants, which may be confounders. However, we conducted all clinical evaluations and MRI scans during the *off* state in order to reduce the effects of medication. Second, we used the MMSE instead of the Montreal Cognitive Assessment scale (MoCA) to exclude demented patients in this study. Although the MMSE scores were not significantly different between dPD and ndPD patients, the MoCA is preferred over the MMSE for screening in future studies to exclude mild cognitive impairment and ensure proper matching.[40]

Mean HAMD-24 scores of the ndPD patients in our study were a bit higher than 8, which means that the patients may or may not have depression. Previous clinical studies showed that some nonmotor symptoms in PD overlap with depressive symptoms (e.g., fatigue and sleep changes), so depression scales such as the HAMD-24 tend to be more useful for assessing severity of depression than standardized diagnostic criteria for depression. Thus, a higher HAMD-24 score may not mean that a PD patient has a depressive disorder. However, given that all the ndPD and dPD patients were diagnosed by an experienced psychiatrist according to DSM-IV criteria for depression, we think that the HAMD-24 scores of the ndPD patients had little influence on our results. Nevertheless, stricter inclusion and exclusion criteria for ndPD and NC participants should be used in the future.

In summary, resting-state fMRI revealed an association between MDD and abnormal functional connectivity in the dlPFC, STG, and PCC in dPD patients. We presume that functional connectivity changes in certain nodes of the brain networks mentioned above might contribute to depression in patients with PD. Our study also provides new insight into the role of the PCC in the underlying development of depressive symptoms in PD patients. Further studies are needed to replicate these findings and clarify the specific roles of these three brain regions on the psychological processes of depression in PD. ■

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