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ORIGINAL ARTICLE

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Impaired long contact white matter fibers integrity is related to depression in Parkinson's disease

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Summary

Aims: Depression is one of the most common nonmotor symptoms in Parkinson's disease (PD). But the pathogenesis is still unclear. Studies have shown that depression in PD is closely related to the white matter abnormalities, but the number of studies is still very small and lack of whole brain white matter lesions study.

Methods: In this study, we investigated whole brain white matter integrity in 31 depressed PD patients and 37 nondepressed PD patients by diffusion tensor imaging.

Results: There was no difference in age, gender, age of onset, disease duration, Hoehn-Yahr scale, Unified Parkinson's Disease Rating Scale scores-III, and Mini-Mental State Examination scores between the two groups. The only difference was the Hamilton Depression Rating Scale. Depressed PD patients showed reduced fractional anisotropy values in the left anterior corona radiata, left posterior thalamic radiation, left cingulum, left superior longitudinal fasciculus, left sagittal stratum (including inferior longitudinal fasciculus and inferior fronto-occipital fasciculus), and left uncinate fasciculus. In patients with depression, the Hamilton Depression Rating Scale (HDRS) was negatively correlated with the FA value in the left cingulum (r = −0.712, P = .032) and left superior longitudinal fasciculus (r = −0.699, P = .025).

Conclusions: This study suggested depression in PD was related to impaired white matter integrity especially the long contact fibers in the left hemisphere. These findings may be helpful for further understanding the potential mechanisms underlying depression in PD.

KEYWORDS
depression, diffusion tensor imaging, Parkinson's disease, white matter fibers

1 | INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, which have typical motor symptoms including resting tremor, rigidity, bradykinesia, and postural reflex abnormalities.[1,2] Increasing studies have shown that most PD patients will experience a series of nonmotor symptoms such as paresthesia, sleep disorders, autonomic dysfunction, neuropsychiatric symptoms, and behavioral disorders.[3,4] Depression is the most common neuropsychiatric symptom, and up to 50% PD patients have suffered from this psychiatric disorder.[5] Depressive symptoms can exist in the various stages of the course of PD, but the clinician recognition is still at a low level. Early

The first two authors contributed equally to this work.

recognition, diagnosis, and treatment of depression in PD patients will help to improve the quality of life and delay the progress of PD. But till now, the pathophysiological mechanism of depression in PD is still unclear.[4]

Pathological studies show that PD patients exhibit limbic system degeneration before the onset of dyskinesia, which suggest depressive symptoms can not only be secondary to motor disorders, but also be the initial symptom of PD[4,6] With the development of neuroimaging, studies have shown that there are abnormalities of neurotransmitters, cortical and subcortical structures, network connections, and white matter fibers in PD with depression.[7,8] Positron emission tomography (PET) has shown a selective decrease in dopamine and noradrenaline innervation in the limbic system in PD with depression (PDD) patients. Magnetic resonance imaging (MRI) shows that there are changes in cortex and subcortical structures in PDD patients, mainly in the prefrontal lobe, temporal lobe, and limbic system. Resting-state functional MRI (RS-fMRI) shows that PDD patients have increased spontaneous neural activity in orbitofrontal cortex, while reduced network functional connectivity of the prefrontal-limbic system. These results suggest the abnormalities of prefrontal-limbic network may be involved in the complex pathophysiological mechanisms in PDD patients.[7,8]

White matter degeneration is very common in PD, and the abnormal fiber connectivity can affect the network connections of the prefrontal-limbic system and other brain regions.[9-12] Therefore, abnormal white matter fiber may be one of the important pathogenesis of depression in PD. The presence of disturbed emotional network in depression individuals in the general population further supports above assumption.[13]

Studies have attempted to identify abnormal white matter fibers connections in PDD patients. Using diffusion tensor imaging (DTI), PDD patients show decreased fractional anisotropy (FA) in the anterior cingulate bundle compared with PD without depression.[12] The only one study which focuses on the whole brain white matter fibers connections using DTI has shown reduced FA in left uncinate fasciculus, superior longitudinal fasciculus, anterior thalamic radiation, forceps minor, and the inferior longitudinal fasciculus in PDD patients.[10] But another study has shown no specific abnormalities in the uncinate fasciculus and corpus callosum in PDD patients,[14] which are frequently damaged in major depressive disorder (MDD) patients.[15] These inconsistencies are due to the less number of current related researches especially the whole brain white matter fibers study.

Therefore, the aim of this study was to investigate the whole brain white matter fibers integrity in PD patients with or without depression using DTI. The FA value of every region of interest (ROI) was analyzed by an automated approach based on an International Consortium of Brain Mapping (ICBM) template. We hoped to further identify and confirm the white matter fibers defects in PDD patients by a simple and automated method, which may help us to further understand the pathogenesis and diagnosis the depression in PD patients.

2 | METHODS

2.1 | Participants

A total of 68 PD patients were recruited from the Department of Neurology, Affiliated Drum Tower Hospital of Nanjing University Medical School, from January 2013 to December 2015. Diagnosis of PD was performed according to UK PD Brain Bank criteria by two neurologists experienced in movement disorders. Patients over 75 years old, course of disease greater than 10 years, and Hoehn-Yahr (H-Y) scale greater than 4 were excluded. Unipolar depression was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria by an experienced psychiatrist. Patients who had used antidepressants or had significant cognitive impairment or mental disorders were excluded too.

68 PD patients were divided into two groups: PD with depression (PDD, n = 31) and PD with no depression (PDnD, n = 37). All the subjects had signed an informed consent, and this study was approved by ethics committee of the Affiliated Drum Tower Hospital, Nanjing University Medical School. Motor disability was evaluated using the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-III) and H-Y scale, depression was measured by the Hamilton Depression Rating Scale (HDRS), and cognitive impairment was assessed with Mini-Mental State Examination (MMSE). The clinical assessments and MRI scans were proceeded in the same period, and anti-parkinsonian medicine was suspended at least 12 hours prior to the measurements. Detailed features of the two groups were showed in Table 1.

2.2 | Diffusion tensor imaging acquisition and data processing

All DTI scans were performed on a 3.0 Tesla MR scanner (Achieva 3.0T TX, Philips Medical Systems, Netherlands), using an 8-channel head coil. DTI was performed with an echo planar imaging (EPI)

TABLE 1 Demographical and clinical data

Index	PDD	PDnD	*P* value
N	31	37	-
Age (years±SD)	58.8 ± 8.67	59.1 ± 11.4	0.902
Age of onset (years±SD)	55.3 ± 8.26	56.7 ± 10.7	0.547
Duration (years±SD)	3.23 ± 3.04	2.40 ± 2.53	0.229
Male/Female	18/13	23/14	0.731
UPDRS-III	20.6 ± 11.8	17.8 ± 12.8	0.355
H-Y scale	2.16 ± 1.02	1.84 ± 1.00	0.216
MMSE	27.6 ± 1.87	27.7 ± 1.80	0.937
HDRS	25.2 ± 3.96	5.43 ± 3.99	<0.001[a]

[a]Indicates statistical significant difference ($P < 0.01$).
PDD, PD with depression; PDnD, PD with no depression; UPDRS-III, Unified Parkinson's Disease Rating Scale scores-III; H-Y scale, Hoehn-Yahr scale; MMSE, Mini-Mental State Examination scores; HDRS, Hamilton Depression Rating Scale.

sequence with echo time (TE)/repetition time (TR)=55/8400 msec, 32 diffusion-sensitive gradient directions (b = 1000 msec/mm$^{2)}$, in-plane resolution of 2.0 mm, and a slice thickness of 2.5 mm. All participants were scanned on the same MR scanner.

Diffusion tensor imaging data analysis was performed by a pipeline toolbox for analyzing brain diffusion images (PANDA).[16] The main procedure includes: (i) correcting for the eddy current effect and calculating diffusion tensor (DT) metrics using the *flirt* and *dtifit* command of FSL, respectively; (ii) normalizing: registrations of all the individual FA images to the FMRIB58_FA template by calling the *fnirt* command of FSL; (iii) output for atlas-based analysis: calculating the regional diffusion metrics by averaging the FA values within each region of the International Consortium of Brain Mapping template (ICBM-DTI-81).[17] Visualization of the results was performed by the BrainNet Viewer.[18]

2.3 | Statistical analysis

Statistical analysis was performed using SPSS version 17. Descriptive data were presented as mean ± standard deviations. Categorical data were analyzed using chi-square test. Comparison of continuous data between two groups was performed using Student's *t* test. Analysis of variance was used to compare the FA difference between depression and nondepression groups of PD patients with UPDRS-III and MMSE as covariate. Correlations between the FA values and HRDS in PD with depression patients were examined using Pearson correlation. $P < 0.05$ was considered as statistically significant.

3 | RESULTS

3.1 | Demographical and clinical data

As shown in Table 1, 68 PD patients were divided into PD with depression (PDD, n = 31) and PD with no depression (PDnD, n = 37). There were no significant differences in age, age of onset, disease duration, or gender between the two groups. Clinical assessments including UPDRS-III, H-Y scale, and MMSE had also shown no difference between the two groups. The only difference between the two groups was the HDRS ($P < 0.001$). All patients were right-handed and with right onset.

3.2 | FA changes in different brain regions

In this study, we defined the ROIs based on the Johns Hopkins University (JHU) White Matter (WM) tractography atlas.[17] The FA values of every ROI were measured by PANDA.[16] Compared to the PDnD group, PDD patients showed lower FA values in several brain regions including left anterior corona radiata, left posterior thalamic radiation, left cingulum, left superior longitudinal fasciculus, left sagittal stratum (including inferior longitudinal fasciculus and inferior fronto-occipital fasciculus), and left uncinate fasciculus (Table 2 and Figures 1 and 2). In these six regions of the right hemisphere, there was no significant difference between the two groups (Table 2).

3.3 | Correlation between FA values and disease characteristics

Correlation analysis showed that the FA values in the left cingulum ($r = -0.712$, $P = .032$) and left superior longitudinal fasciculus ($r = -0.699$, $P = .025$) of the PDD group were negatively correlated with HDRS scores (Table 3), but no correlation was found with other disease characteristics including age, duration, UPDRS-III, H-Y scale, and MMSE. After controlling for age, duration, UPDRS-III, H-Y scale, and MMSE, the negative correlation mentioned above was still significant.

TABLE 2 FA values between groups of different regions

Regions	Hemisphere	PDD (n = 31)	PDnD (n = 37)	F	*P* value
Anterior corona radiata	L	0.670 ± 0.203	0.780 ± 0.121	4.68	0.033[a]
	R	0.725 ± 0.210	0.777 ± 0.119	4.35	0.264
Posterior thalamic radiation	L	0.720 ± 0.135	0.806 ± 0.096	5.15	0.01[a]
	R	0.773 ± 0.151	0.799 ± 0.106	5.11	0.473
Cingulum	L	0.686 ± 0.157	0.785 ± 0.115	4.74	0.025[a]
	R	0.716 ± 0.168	0.742 ± 0.120	3.71	0.25
Superior longitudinal fasciculus	L	0.694 ± 0.151	0.776 ± 0.107	5.01	0.027[a]
	R	0.728 ± 0.161	0.757 ± 0.115	4.67	0.462
Sagittal stratum	L	0.717 ± 0.147	0.797 ± 0.105	4. 68	0.027[a]
	R	0.771 ± 0.155	0.802 ± 0.109	4.50	0.407
Uncinate fasciculus	L	0.598 ± 0.150	0.695 ± 0.115	4.34	0.045[a]
	R	0.634 ± 0.168	0.647 ± 0.115	5.54	0.728

[a]Indicates statistical significant difference ($P < .05$).
PDD, PD with depression; PDnD, PD with no depression; L, left; R, Right.

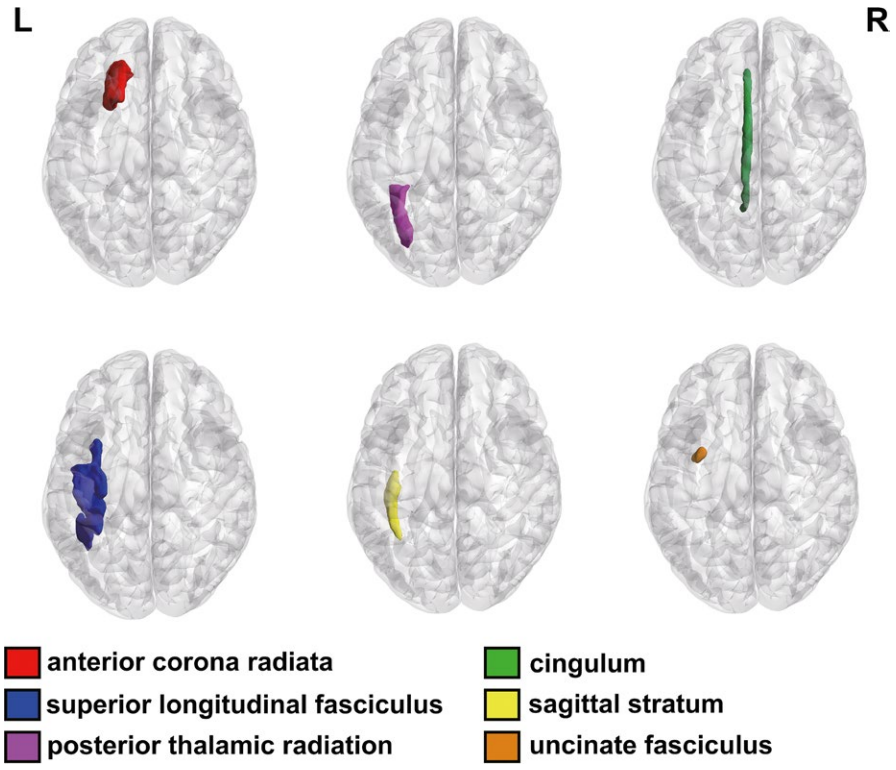

FIGURE 1 Regional patterns of FA changes in PD with depression. (Left anterior corona radiata, left posterior thalamic radiation, left cingulum, left superior longitudinal fasciculus, left sagittal stratum, and left uncinate fasciculus. L, Left; R, Right)

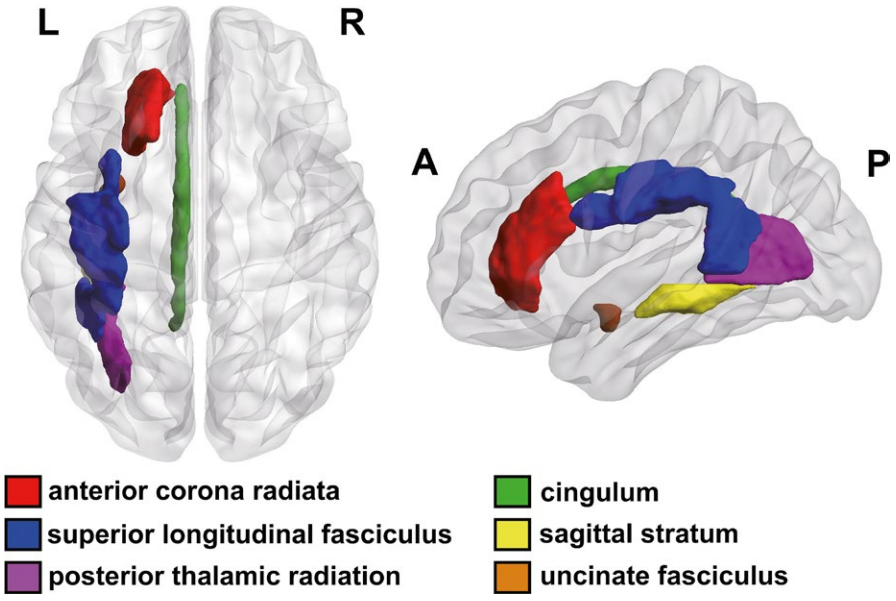

FIGURE 2 Localization of FA change regions in depressed PD patients. (Left anterior corona radiata, left posterior thalamic radiation, left cingulum, left superior longitudinal fasciculus, left sagittal stratum, and left uncinate fasciculus. L, Left; R, Right; A, Anterior; P, Posterior)

4 | DISCUSSION

In this study, we explored the association between depressive symptoms and whole brain white matter lesions in PD patients using DTI technology. Results showed depressed PD patients exhibited degeneration of several fibers including left anterior corona radiata, left posterior thalamic radiation, left cingulum, left superior longitudinal fasciculus, left sagittal stratum (including inferior longitudinal fasciculus and inferior fronto-occipital fasciculus), and left uncinate fasciculus. And the degree of degeneration in left cingulum and left superior longitudinal fasciculus was positively associated with the severity of depression.

Depression is one of the most common mood disturbances in PD, but its pathogenesis is unclear.[4] Studies using advanced neuroimaging generally suggest increased neural activity in the prefrontal regions and decreased functional connectivity between the prefrontal-limbic networks in depressed PD patients.[7] Most of these studies have adopted position emission tomography, single-photon emission computed tomography, structural MR, or RS-fMRI. Given the dysfunction of the prefrontal-limbic network

TABLE 3 Correlation analysis between FA values and HDRS scores

Regions	*r*	*P* value
Left anterior corona radiata	−0.309	0.203
Left posterior thalamic radiation	−0.234	0.563
Left cingulum	−0.712	0.032[a]
Left superior longitudinal fasciculus	−0.699	0.025[a]
Left sagittal stratum	−0.464	0.309
Left uncinate fasciculus	−0.541	0.207

[a]Indicates statistical significant difference ($P < .05$).
FA, fractional anisotropy; HDRS, Hamilton Depression Rating Scale.

connectivity may be one of the most important pathogenesis involved in PD with depression, DTI, the only noninvasive method to detect, track, and display the white matter tracts in vivo, might help us better to explore the pathogenesis. But to the best of our knowledge, there are only four relevant research using DTI and only one report on the study of whole brain white matter integrity was reported.

So, our study investigated the whole brain white matter fibers lesions in depressed PD patients using DTI and the DTI data were postprocessed by PANDA based on the JHU WM tractography atlas. PANDA is a pipeline toolbox for fully automated analyzing brain diffusion images which can help us analyze DTI data faster and better.[16] The JHU WM tractography atlas is well established for parcellation of the entire WM into multiple ROIs automatically. This WM atlas in the standard space may provide better statistical sensitivity and accuracy.[17] Therefore, this was a new study which focused on whole brain WM fibers in depressed PD patients by a more convenient and reliable DTI analyzation method.

Previous DTI studies have shown WM fibers lesions in depressed PD patients, such as the bilateral anterior cingulate cortex, bilateral mediodorsal thalamic areas, and multiple tracts connecting to the left frontal and deep temporal lobes including left uncinate fasciculus, left superior and inferior longitudinal fasciculus, left anterior thalamic radiation, and left forceps minor.[10-12] In this study, we also found WM fibers degeneration in left cingulum, left superior and inferior longitudinal fasciculus, and left uncinate fasciculus in PD with depression patients. All of the above regions belong to the long contact WM fibers in the brain. These findings further confirmed that the dysfunction of the prefrontal-limbic networks may be the vital pathological basis in PD with depression patients.

Studies using T1-weighted imaging have shown the depressed PD patients had decreased gray matter (GM) volumes in the prefrontal, parietal, and insular regions as well as the limbic system (anterior cingulate cortices and amygdala).[19-23] These structural abnormalities were found to further support our DTI findings. As we know, the prefrontal cortex and limbic systems are the main brain regions for emotion regulation. The prefrontal cortex connects with various sensory areas, such as the visual and the somatic sensory cortex. Neurons in the prefrontal network are responsible for responding to multimodal sensory stimuli and assessing these stimuli.[24] Malfunction of this area may cause disturbance in decision making and evaluation of emotional stimuli, which may give rise to various psychotic disorders such as depression.[25,26] Similarly, abnormalities of the WM fibers that connect the prefrontal cortex to each region of the brain especially the limbic systems can also cause abnormal assessment of mood. In primary depression, DTI studies also have found significant correlations between depression and altered integrity of white matter tracts that contribute to emotional regulation,[27,28] such as the superior longitudinal fasciculus, corpus callosum, uncinate fasciculus, internal and external capsule, cingulum and anterior corona radiata, thalamic projection fibers, and other association fibers in the limbic system.[29,30] Compared to our findings in depressed PD patients, white matter damage is more extensive in patients with primary depression, but all these impaired WM regions or fibers mainly located in the prefrontal cortex, limbic system, and the contact fibers between them. Studies using RS-fMRI have also shown decreased functional connectivity between the prefrontal-limbic networks[31-33] and impaired interhemispheric synchrony[34] in PD with depression patients. Therefore, the abnormal sensory integration and evaluation caused by white matter deficits which we found might be an important reason for depression in PD.

In addition to the above findings of long contact WM fibers abnormalities, we also found degeneration of left anterior corona radiata and left posterior thalamic radiation in depressed PD patients. These two degenerated fibers have been found in primary depression[29,30] but were not reported in previous DTI studies in PD. Corona refers to the radial white matter between the internal capsule and the cerebral cortex. The posterior thalamic radiation is a bundle of fibers projecting from the thalamus to the occipital lobe. They connect with multiple sensory areas, including somatosensory cortex and visual cortex. Degeneration of these two fibers can also cause disturbance of sensory integration and evaluation, which might give rise to depression.[25,26]

However, one study reported no difference of the FA in the corpus callosum and uncinate fasciculus in PD with depression patients.[14] This inconsistency may be due to the small sample size (6 PDD and 6 PDnD patients) and mild depressive symptoms. More importantly, this study adopted ROI strategy rather than the whole brain WM evaluation and this may add to selection bias of the brain regions. In our study, a larger sample size and better whole brain WM evaluation method enabled us to reveal the WM degenerations and the results were basically consistent with other DTI studies.

Furthermore, we found the degree of degeneration in left cingulum and left superior longitudinal fasciculus was positively associated with the severity of depression. This result was different to the previous DTI studies which have shown the inverse correlation between depression and FA values mainly in left deep temporal cortex[10] or mediodorsal thalamic areas.[11] Studies also found inverse correlation between depression and WM or GM volume mainly in orbitofrontal, temporal, and limbic regions.[19,20,23] But cingulum and superior longitudinal fasciculus are important long contact fibers connecting prefrontal cortex and limbic system. Based on the critical

role of communication in prefrontal-limbic networks for assessing stimuli and regulating emotions, the more severe degeneration in these fibers might cause more serious depression. The similar results have been reported in major depressive disorder.[35] In PD, RS-fMRI studies have shown depression was inversely correlated with functional connectivity between the amygdala and prefrontal and posterior cingulate cortices.[32,33] These findings further support our results.

In this study, we also found degenerated fibers mainly in the left hemisphere. These results were consistent with previous reports.[10] Previous studies have shown that depression and anxiety are associated with prefrontal dysfunction, especially in the left prefrontal lobe.[36] Epidemiological studies have also shown that PD patients with right onset are more likely to suffer from depression.[37] In this study, all PD patients were right-handed and with right onset. The above left hemisphere WM fiber abnormalities may be related to the right onset and may also be the inherent characteristics of PD with depression. These uncertainties need our further studies to confirm.

5 | CONCLUSION

In summary, our study showed impaired long contact fiber integrity in white matter was related to depression in PD by a more convenient and reliable whole brain WM DTI analyzation method. But the pathogenesis of depression in PD is very complicated and the mechanisms are still need to be explored. Imaging study is noninvasive, and it provides us an objective idea of the possible connectivity between symptoms and the brain structures. However, the imaging features are not unique and studies using DTI on depression in PD are still scarce. We are in urgent need of more larger samples and more comprehensive researches to reveal the unique features or imaging markers in depressed PD patients. These findings may underlie the neural mechanisms of depression in PD and contribute to the diagnosis and treatment of depression in PD.

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CONFLICT OF INTEREST

The authors declared no potential conflict of interests with respect to the authorship and/or publication of this article.

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