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White Matter Microstructure Changes in the Thalamus in Parkinson Disease with Depression: A Diffusion Tensor MR Imaging Study

BACKGROUND AND PURPOSE: Depression occurs frequently in PD; however the neural basis of depression in PD remains unclear. The aim of this study was to characterize possible depression-related white matter microstructural changes in the thalamus of patients with DPD compared with those with NDPD.

MATERIALS AND METHODS: FA and MD maps from DTI were obtained in 14 patients with DPD and 18 patients with NDPD. Region-of-interest-guided VBA was conducted on the FA maps to detect possible microstructural differences in the thalamus between these 2 patient groups. Moreover, mean FA and MD in regions with a detected difference were compared between DPD and NDPD groups, and correlations between diffusion quantities and the severity of depression were analyzed.

RESULTS: White matter microstructure differences were found between the patients with DPD and NDPD in the bilateral mediodorsal thalamic regions. In these regions, patients with DPD showed significantly decreased FA values ($P < .005$) compared with patients with NDPD, and the mean values of FA were negatively correlated with the scores of depression severity ($P < .05$) for patients with PD. No significant differences of MD were found in the mediodorsal thalamus between these 2 groups.

CONCLUSIONS: Our results provide preliminary evidence that the mediodorsal thalamus may play an important role in depression in PD and suggest a relationship between FA in the mediodorsal thalamus and the presence of depressive symptoms in patients with DPD. These findings may be helpful for further understanding the potential mechanisms of depression in PD.

ABBREVIATIONS: DPD = depressed PD; DSM = Diagnostic and Statistical Manual of Mental Disorders; DTI = diffusion tensor imaging; FA = fractional anisotropy; fMRI = functional MR imaging; FMRIB = Functional MR Imaging of the Brain; FSL = FMRIB Software Library; HAMD = Hamilton Depression Scale; H-Y = Hoehn-Yahr staging; LEDD = L-dopa equivalent daily dosage; MD = mean diffusivity; MDD = major depressive disorder; mFA = mean value of FA; mMD = mean value of MD; MMSE = Mini-Mental State Examination; MNI = Montreal Neurological Institute; NDPD = nondepressed PD; NS = not significant; PD = Parkinson disease; UPDRS = Unified Parkinson Disease Rating Scale; VBA = voxel-based analysis; VBM = voxel-based morphometry

Depression occurs frequently in PD, in approximately 40% of patients,¹⁻³ which is much higher than that in other equivalently disabled patients.³⁻⁶ Researchers have realized that depression may not just be a reaction to PD disabilities but rather results from neurodegenerative changes occurring in PD.^{7,8} However, the pathophysiology and neural basis of depression in PD remain unclear.^{3,5}

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The thalamus has reciprocal connections with the amygdala and dorsolateral prefrontal, orbitofrontal, cingulate, and insular cortices,⁹⁻¹¹ and it plays an important role in the perception and regulation of emotion.^{12,13} Converging evidence suggests that there is a relationship between depression and morphologic and metabolic changes in the mediodorsal or "limbic" thalamus.^{5,11,14,15} For example, in a recent study, Young et al¹¹ found an increased neuron count in individuals with MDD relative to the nonpsychiatric comparison subjects. Furthermore, it has been shown that depression and anxiety induced by the tyrosine hydroxylase inhibitor are associated with a marked reduction of glucose metabolism in the thalamus.¹⁴ The research by Cardoso et al⁵ showed a decreased activation in the left mediodorsal thalamus in patients with DPD compared with patients with NDPD in an fMRI study. In this same sample, a region-of-interest VBM study showed increased volume in the mediodorsal thalamus bilaterally. Research on the biochemical markers also suggests a role of the thalamus in depression in PD. Using [¹¹C]RTI-32, a marker of dopaminergic and noradrenergic metabolism, Remy et al³ showed decreased binding in patients with DPD compared with patients with NDPD in a variety of regions, including the thalamus.

DTI¹⁶⁻¹⁹ has been increasingly used in the analysis of psychiatric disease.²⁰⁻²⁴ With DTI techniques, diffusion anisotropy characteristics can be fully extracted, characterized, and exploited, providing even more exquisite details on white matter microstructural integrity.^{18,25} Diffusion quantities, such as FA and MD, can be derived from DTI and are usually used for white matter integrity analysis.^{25,26} Previous DTI studies have also demonstrated a close relationship between depression and the thalamus.^{27,28} However, there are few studies characterizing white matter diffusion changes in patients with DPD. Matsui et al²⁰ examined the FA value changes between patients with DPD and those with NDPD. In this study, 14 regions of interest were compared, and they found significant reductions in FA values in bilateral frontal regions of interest.²⁰ However, the thalamic regions were not selected, and only FA values were analyzed in the selected regions.²⁰

All the above findings led us study the possible white matter microstructural changes related to depression in the thalami of patients with DPD. Here we conducted a DTI study to analyze possible white matter microstructural differences in the whole thalamus between patients with DPD and those with NDPD and to investigate the relationship between the severity of depression and diffusion quantities in the thalamus of patients with PD.

Materials and Methods

Subjects and Clinical Assessment

Thirty-six individuals with idiopathic PD with or without depression were enrolled in the present study. Patients had already been excluded if they had any other organic or central nervous system diseases. All patients fulfilled the UK Parkinson's Disease Society Brain Bank criteria for idiopathic PD.²⁹ Motor and mental states were evaluated by the UPDRS III,³⁰ the H-Y,³⁰ and the MMSE.³¹ Patients with MMSE scores lower than the corresponding education level were also excluded. The included patients with PD were then divided into DPD and NDPD groups by the DSM-IV criteria.³² The HAMD³³ was implemented to evaluate the severity of depression. Higher HAMD scores reflect greater severity of depressive symptoms. For every patient, all the psychometric and neurologic evaluations were conducted during a practically defined "off" state. The LEDD was also calculated on the basis of every patient's daily dosage as per Matsui et al.²⁰ Between DPD and NDPD groups, unpaired 2-tailed *t* tests were used for parametric comparison of data for age, PD duration, MMSE, UPDRS, H-Y, HAMD, and LEDD; the Mann-Whitney *U* test was used for the nonparametric comparison for sex.

All patients were recruited from Xuanwu Hospital-Capital Medical University (Beijing, China), and written informed consent was obtained. The study was approved by Medical Research Ethical Committee of Xuanwu Hospital.

DTI

All the patients had taken their habitual anti-Parkinson dosage 30 minutes before MR imaging, and they were in the "on" state before and during MR imaging. DTI was performed with a 3T MR imaging scanner (Magnetom Trio; Siemens, Erlangen, Germany). The images were obtained by using echo-planar imaging sequences with 20 different motion-probing gradient directions (TR/TE, 6000/93 ms; matrix, 128 × 128; FOV, 256 × 256 mm; section thickness, 4 mm; b-value, 1000 s/mm²). In addition, 1 reference image without diffusion

weighting (*b* = 0 image with a b-value of 0 s/mm²) was acquired. For each subject, DTI scans were acquired twice for subsequent averaging to improve the signal intensity-to-noise ratio.

Image Preprocessing and Diffusion Quantity Calculation

All of the following image preprocessing, diffusion quantity calculation, and data analysis were implemented by using the FSL 4.1 tools (FMRIB, Oxford, UK); Statistical Package for the Social Sciences, Version 17.0 (SPSS, Chicago, Illinois); and in-house software based on Matlab (MathWorks, Natick, Massachusetts).

Before calculating the diffusion tensors from DTI images, volume data were first re-sampled to a spatial isotropic dataset (voxel size, 1 × 1 × 1 mm) and then were preprocessed to remove skull data and correct the effects of head movement and eddy currents by using FSL.^{34,35} After the above image preprocessing, mean DTI images were calculated from the 2 preprocessed DTI acquisitions for every subject. Diffusion quantities of FA and MD were calculated subsequently on the mean DTI images. These diffusion quantities provide in vivo information about the organization of white matter.^{18,36}

Region-of-Interest-Guided VBA in Bilateral Thalamic Regions

A region-of-interest-guided VBA method was used to detect significant white matter microstructure changes in the bilateral thalami between patients with DPD and those with NDPD. First, all FA images of every subject were aligned to a 1 × 1 × 1 mm MNI 152 standard space by using a nonlinear registration method provided by TBSS script in FSL tools,³⁷ and all MD images were also registered to MNI 152 space by using the same calculated conversion matrixes. Subsequently, a neuroradiologist (J.L.) manually drew a 3D region-of-interest mask to cover the whole thalamic region on the standard MNI 152 T1 brain images. Finally, region-of-interest-guided VBA was performed on FA maps within the defined mask to detect the significantly different regions in the bilateral thalami between patients with DPD and those with NDPD. Statistical analysis was performed by using a voxelwise unpaired 2-tailed *t* test. Significance was indicated with *P* < .05.

Group Comparison

For every subject, the mean value of the diffusion quantities, FA and MD, would be calculated for regions in which there were significant differences detected by the previous region-of-interest-guided VBA method. On the basis of individual data, group comparisons were conducted between patients with DPD and NDPD.

Correlation Analysis

The correlations between the clinical score for the HAMD and diffusion quantities (mean FA or mean MD) in the confirmed significant regions were assessed respectively for all patients with PD by using a Pearson correlation coefficient with statistical significance evaluated by using nonparametric methods (*P* < .05) by SPSS.

Results

Clinical Results

Of the 36 recruited candidates, 4 patients were excluded from this study (2 due to claustrophobia and 2 due to motion artifacts). On the basis of the DSM-IV criteria, the 32 included patients were divided into 2 groups: 14 patients with DPD and 18 patients with NDPD. The clinical and demographic char-

Table 1: Clinical and demographic characteristics of patients

Groups	DPD (n = 14)	NDPD (n = 18)	P Value ^a
Sex (M/F)	4/10	10/8	NS
Age (yr)	65.28 ± 8.89	61.05 ± 10.17	NS
PD duration	6.29 ± 5.51	5.67 ± 2.57	NS
MMSE	29.5 ± 0.7	29.2 ± 1.0	NS
UPDRS	39.04 ± 22.28	33.83 ± 15.09	NS
H-Y	1.96 ± 0.99	1.83 ± 0.75	NS
HAMD	15.64 ± 4.21	4.44 ± 2.14	<.001
LEDD (mg/day)	315 ± 201	363 ± 197	NS

^a Unpaired 2-tailed t tests were used for parametric comparison of data between the 2 groups for age, PD duration, MMSE, UPDRS, H-Y, HAMD, and LEDD; The Mann-Whitney U test was used for nonparametric comparison of sex between the 2 groups. Significance was set at $P < .05$.

acteristics of the patients are given in Table 1. There was no significant difference between the DPD and NDPD patient groups as to age, sex, PD duration time, MMSE, UPDRS, H-Y, or LEDD. The 2 groups showed statistically significant differences in the HAMD score ($P < .001$).

VBA in the Whole Thalamus

By region-of-interest—guided VBA analysis, a decreased FA value was found in the thalamus bilaterally in patients with DPD compared with patients with NDPD ($P < .05$). As shown in red in Fig 1A, the 2 regions differed significantly. These regions were in the right and left mediodorsal thalami, respectively. Compared with those in patients with NDPD, no regions in the thalamus of patients with DPD showed significantly increased FA values.

Group Comparisons

These 2 detected regions were taken as regions of interest for a further comparison of patients with DPD and NDPD. Figure 1B shows the scattergraphs of the mean FA values in the detected bilateral mediodorsal thalami for every subject. Table 2 shows the mean values and SDs of FA and MD in the detected regions of interest of DPD and NDPD groups respectively and the comparison results of mean FA and mean MD between these 2 groups. Patients with DPD show significantly decreased mean FA values in the bilateral mediodorsal thalami compared with patients with NDPD (Fig 1A, right region of interest, $P = .003$; left region of interest, $P = .002$). There were no significant differences in MD between patients with DPD and NDPD in the same regions ($P > .05$).

Correlation Analysis

Mean FA and MD in the detected mediodorsal thalamic regions were used for correlation analysis with HAMD. Higher HAMD scores reflect greater severity of depressive symptoms. Table 3 shows the results of the Pearson correlation between HAMD and the diffusion quantities, mean FA and mean MD, for all patients with PD. Parameter r represents the Pearson correlation coefficient. Figure 2 shows the scatterplots with trend lines indicating the correlation relationship of mean FA and MD with HAMD for all subjects with PD. From Table 3 and Fig 2, one can see that HAMD was significantly negatively correlated with mean FA values in the bilateral mediodorsal thalami for all subjects with PD ($P < .05$). The mean FA did not show a correlation with HAMD for patients with DPD or

NDPD separately. The mean MD did not show a correlation with HAMD for all patients with PD or for those with DPD or NDPD. Results showed that there was a negative correlation between the severity of depression (HAMD scores) and FA values in the detected right and left mediodorsal thalami for all subjects with PD.

Discussion

To the best of our knowledge, this is the first study of FA and MD differences in the thalami of patients with DPD compared with patients with NDPD by using DTI. On the basis of the VBA of FA maps in the whole thalamus, a significant difference was detected between patients with DPD and NDPD in the bilateral mediodorsal thalami (Fig 1A). In the detected regions showing a difference, patients with DPD had decreased mean FA values in the right ($P = .003$) and left ($P = .002$) mediodorsal thalami, compared with patients with NDPD (Fig 1B and Table 2). Our findings are consistent with a recent study of Cardoso et al,⁵ who found a decreased activation in the mediodorsal thalamus between their patients with DPD and those with NDPD by using fMRI. Decreased FA in the thalamus of patients with DPD indicates a change in neuron cell integrity or a possible fiber degeneration in the bilateral mediodorsal thalami relative to patients with NDPD. This finding may be the cause or result of a decrease in either incoming or projecting white matter pathways associated with the mediodorsal thalamus. The mediodorsal thalamus receives strong dopaminergic projections, which are important for modulation of thalamic activity,^{5,13} and loss of dopamine was found in the limbic system in patients with DPD compared with patients with NDPD, including the mediodorsal thalamus.³ An increased neuronal count was reported in the mediodorsal thalamus of patients with MDD in previous studies,¹¹ indicating that there may also be a change in the diffusion style and anisotropy of free water inside the brain. Our results of decreased FA in the mediodorsal thalamus of patients with DPD, together with other reports,^{5,11} highlight the importance of the limbic thalamus in depression in PD.

While we show a decreased FA in the mediodorsal thalamus, no significant differences in MD were found in the same mediodorsal thalamic regions between these 2 groups. MD characterizes the average magnitude of overall molecular displacement by diffusion^{17,18} and represents the integrity of the cellular matrix.²⁴ FA describes how much molecular displacement varies in space^{17,18} and can reflect the degeneration of axons in the major fiber bundles.²⁴ Therefore, our findings suggest that the arrangement and organization of white matter in the mediodorsal thalamus of patients with DPD were different from such organization in patients with NDPD, while the integrity of the cellular matrix did not change obviously in the same regions between these 2 groups in our study.

Our study also showed a significantly negative correlation between the severity of depression (HAMD scores) and the mean FA values in bilateral mediodorsal thalamic regions ($P < .05$) for patients with PD (Fig 2 and Table 3). The lower FA values in this region correlated with the increased depressive symptoms in patients with PD. This finding provides new information for further understanding the potential mechanisms of depression in patients with PD.

DTI provides information about white matter microstruc-

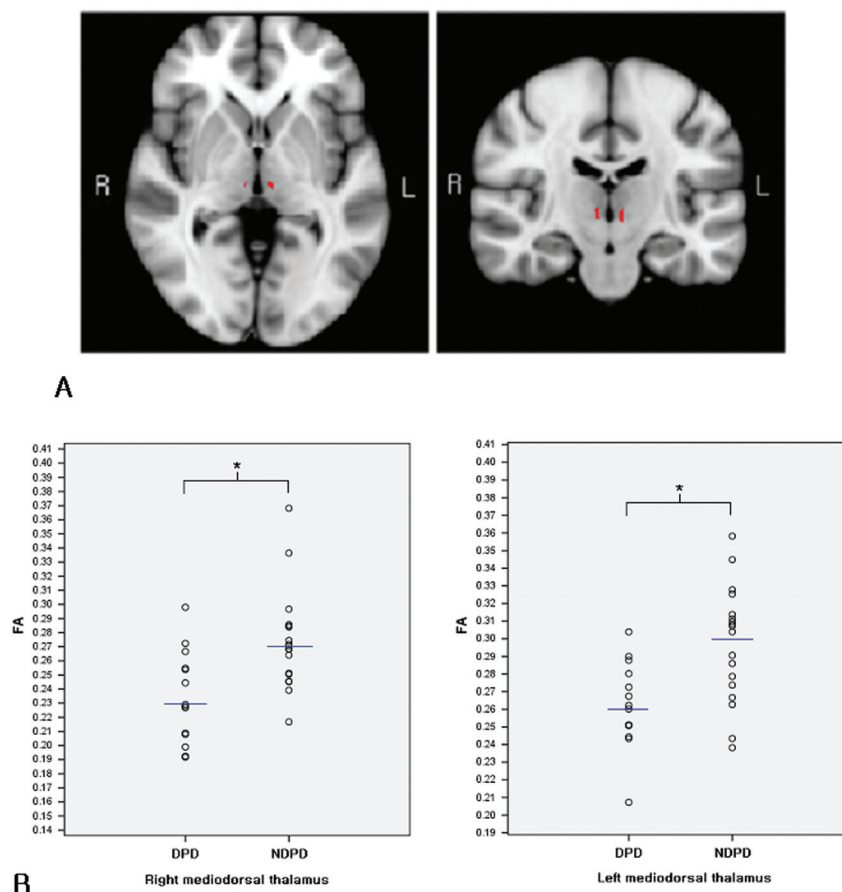


Fig 1. Illustration of regions of difference in patients with DPD and NDPD in the bilateral thalami. *A*, Standard MNI 152 T1 brain images (in axial and coronal directions) are overlaid with the statistically significant differing regions (in red). FA in the mediodorsal thalamus differs in patients with DPD compared with patients with NDPD. *B*, Scatterplots show the mean FA values in the detected significant regions for every subject in the DPD and NDPD groups. Blue lines denote the mean values for each group. Asterisks indicate significant differences between these 2 groups with $P < .005$.

Table 2: Diffusion quantity comparison between patients with DPD and those with NDPD

Mediodorsal Thalamus	mFA		<i>t</i> Value ^a	<i>P</i> Value	mMD ($\times 10^{-4}$ mm ² /s)		<i>t</i> Value ^a	<i>P</i> Value
	DPD	NDPD			DPD	NDPD		
Right	0.23 $\pm$ 0.03	0.27 $\pm$ 0.04	−3.300	.003 ^b	8.92 $\pm$ 2.06	8.26 $\pm$ 1.22	1.061	.301
Left	0.26 $\pm$ 0.02	0.30 $\pm$ 0.03	−3.463	.002 ^b	8.27 $\pm$ 1.03	7.97 $\pm$ 0.71	0.924	.365

^a Indicates unpaired 2-tailed *t* test.

^b Indicates statistical significance with $P < .005$.

Table 3: Pearson correlation between HAMD and diffusion quantities for PD^a

Regions	mFA		mMD	
	<i>r</i>	<i>P</i> Value	<i>r</i>	<i>P</i> Value
Right mediodorsal thalamus	−0.362	.041 ^b	0.134	.466
Left mediodorsal thalamus	−0.404	.022 ^b	0.063	.731

^a SPSS, Version 17.0, was used for correlation analysis. For correlation coefficient calculation, the Pearson test was selected; for the significance test of *r*, a 2-tailed *t* test was selected.

^b Indicates statistical significance with $P < .05$.

ture integrity. This unique imaging technique enables us to quantify the thermal random motion of water molecules.^{18,38,39} As mentioned above, the literature on DPD research using DTI is quite limited. Matsui et al²⁰ examined FA changes between NDPD and DPD groups by using a region-of-interest-analysis method, but the authors did not evaluate thalamic regions. Their method depended on a priori assumptions of the location, size, and shape of the regions.²⁰ Moreover, their

method was labor-intensive, and their results were operator-dependent. In our study, a region-of-interest-guided VBA method was adopted. Compared with the region-of-interest-analysis method, the region-of-interest-guided VBA method can reliably locate the regions with diffusion quantity differences, providing a feasible approach to obtaining more accurate clinical results.

Although the region-of-interest-guided VBA method has the above advantages, it still has some disadvantages. The VBA method is sensitive to various image preprocessing steps, such as image registration. Moreover, the region-of-interest-guided VBA method requires conducting a VBA within the defined region of interest. In our study, the thalamus was studied as a specific region of interest, but the thalamus may be involved in a complex system with other related regions, which together modulate the depressive symptoms of patients with PD.

There are several limitations of the present study, which

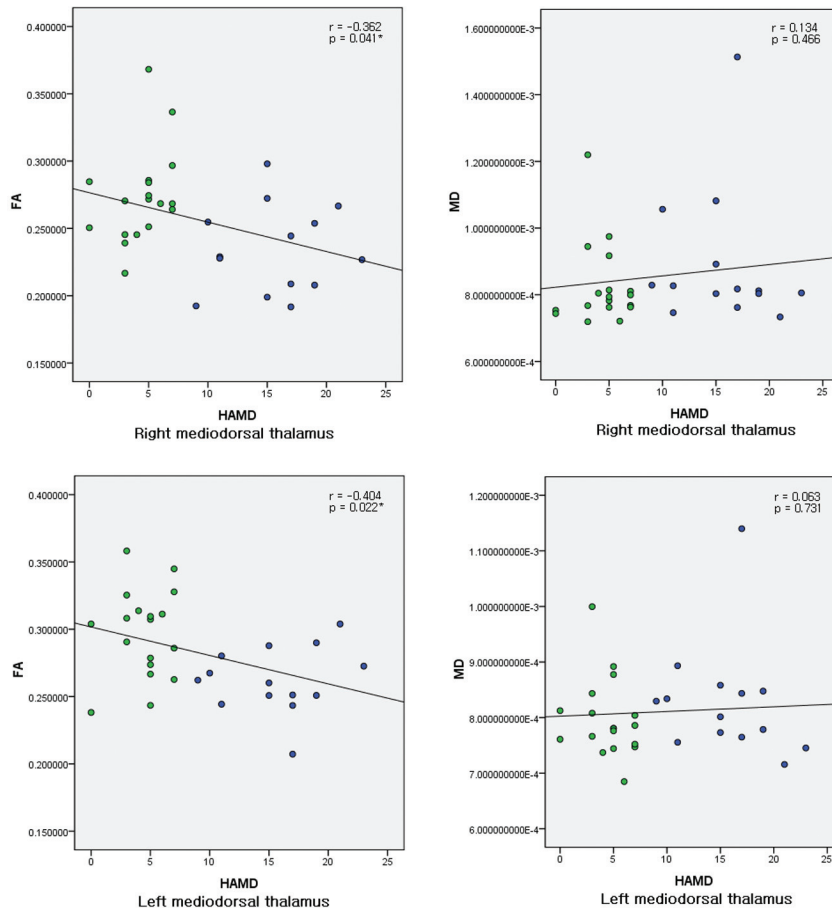


Fig 2. Scatterplots with trend lines showing the correlations of diffusion quantities (FA and MD) with HAMD for 32 PD subjects in the right and left mediodorsal thalami. Green represents patients with NDPD; blue represents patients with DPD. The asterisks indicate that a significant negative correlation was found between FA and HAMD.

future studies can address. First, because we conducted a preliminary analysis, the relatively small sample size decreased the power of our results. Although we obtained significant difference in FA between patients with DPD and NDPD, more subjects are now being recruited for subsequent research to obtain a larger sample size. Second, subjects with more consistent demographic characteristics will be considered. In the current study, though there were no significant differences between DPD and NDPD groups with regard to age, sex, PD duration, MMSE, UPDRS, H-Y, and LEDD, the distribution of sex for these 2 groups was not exactly equal. Subjects in our future studies will be recruited to obtain a sample that is better matched for sex. Third, in further studies, DTI data will be collected with a higher spatial resolution. In this study, the section thickness of DTI was 4 mm. To get more accurate analysis results and for further fiber tractography-based analysis, we will acquire images with higher spatial resolution. Finally, although our current study suggested the mechanistic importance of the thalamus in depression in patients with PD by comparing patients with DPD with patients with NDPD, it is still a preliminary study. Healthy control subjects, together with individuals with de novo depression, will be recruited in the future. Through comparison among DPD, NDPD, de novo depression, and healthy controls, we should have a clearer view of white matter microstructure evolution in the thalamus associated with depression in patients with PD.

Conclusions

It is striking that decreased FA was found in the bilateral mediodorsal thalamic regions of patients with DPD compared with patients with NDPD, and the mean value of FA was negatively correlated with depression severity for patients with PD. Our preliminary results provided evidence that the mediodorsal thalamus may play an important role in depression in PD, and there is a relationship between FA in the mediodorsal thalamus and the presence of depressive symptoms in patients with DPD. These findings may be helpful for further understanding potential neural mechanisms of depression in PD.

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