Am J Transl Res 2024;16(6):2423-2434
www.ajtr.org /ISSN:1943-8141/AJTR0157215

Original Article

Altered connectivity between frontal cortex and supplementary motor area in various types of Parkinson's disease

Fengbo Xing[1,3,4], Jingjing Feng[1,3,4], Lingling Lv[1,3,4], Jiaqiu Liu[1,3,4], Xin Chen[1,3,4], Jinmei Sun[1,3,4], Panpan Hu[1,2,3,4,5,6], Kai Wang[1,2,3,4,5,6]

[1]*Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei 230000, Anhui, China;* [2]*School of Mental Health and Psychological Sciences, Anhui Medical University, Hefei 230000, Anhui, China;* [3]*Anhui Province Key Laboratory of Cognition and Neuropsychiatric Disorders, Hefei 230032, Anhui, China;* [4]*Collaborative Innovation Centre of Neuropsychiatric Disorder and Mental Health, Hefei 230000, Anhui, China;* [5]*Institute of Artificial Intelligence, Hefei Comprehensive National Science Center, Hefei 230088, Anhui, China;* [6]*Anhui Institute of Translational Medicine, Hefei 230000, Anhui, China*

Received April 16, 2024; Accepted May 14, 2024; Epub June 15, 2024; Published June 30, 2024

Abstract: Background: Tremor-dominant (TD) and postural instability/gait difficulty (PIGD) are common subtypes of Parkinson's disease, each with distinct clinical manifestations and prognoses. The neural mechanisms underlying these subtypes remain unclear. This study aimed to investigate the altered connectivity of the frontal cortex and supplementary motor area (SMA) in different types of Parkinson's disease. Methods: Data of 173 participants, including 41 TD patients, 65 PIGD patients, and 67 healthy controls, were retrospectively analyzed. All subjects underwent resting-state functional magnetic resonance imaging (rs-fMRI) and clinical assessments. Differences in amplitude of low frequency fluctuation (ALFF), voxel-wise functional connectivity (FC), and functional network connectivity (FNC) among the three groups were compared, followed by partial correlation analysis. Results: Compared to healthy controls, the left dorsolateral superior frontal gyrus (DLSFG) ALFF was significantly increased in both PIGD and TD patients. The FC between the left DLSFG and the left SMA, as well as between the left paracentral lobule and the right DLSFG, was significantly decreased. Similarly, the FNC between the visual network and the auditory network was reduced. Compared to TD patients, PIGD patients showed a significantly higher ALFF in the left DLSFG and a notably reduced FC between the left DLSFG and left SMA. Additionally, the FC of the left DLSFG-SMA was inversely correlated with the PIGD score exclusively in PIGD patients. The FNC of the visual-auditory network was inversely associated with the tremor score only in TD patients. Conclusion: Decreases in the left DLSFG-SMA connectivity may be a key feature of the PIGD subtype, while reduced VN-AUD connectivity may characterize the TD subtype.

Keywords: Postural instability/gait difficulty, tremor-dominant, amplitudes of low frequency fluctuation, functional connectivity

Introduction

Tremor-dominant (TD) and postural instability/gait difficulty (PIGD) are two common subtypes of Parkinson's disease (PD). The TD subtype typically progresses more slowly, resulting in fewer cognitive impairments and better outcomes following deep brain stimulation [1, 2]. In contrast, the PIGD subtype is associated with faster disease progression, an increased risk of dementia, and poorer motor outcomes [3]. The neural mechanisms underlying these differences remain unclear.

The application of resting-state functional magnetic resonance imaging (rs-fMRI) provides researchers with a better way to explore structural and functional brain characteristics in PIGD and TD patients. Prior investigations have revealed that PIGD patients exhibit more cortical and subcortical gray matter atrophy in various brain regions associated with motor and cognitive impairment compared to TD patients [4-6], potentially explaining the poorer prognoses of PIGD patients. However, Al-Bachari et al. did not find significant differences in gray matter volume between PIGD and TD patients, even

https://doi.org/10.62347/GTVB7800

when accounting for factors such as disease severity, duration, and medication [7]. One study reported that PIGD patients had reduced cortical thickness in the dorsolateral frontal, anterior temporal, and precuneus lobes compared to TD patients [5]. In contrast, another study involving PD patients with mild cognitive impairment (MCI) found no significant differences in cortical thickness between MCI-TD and MCI-PIGD patients [8]. Additionally, a longitudinal cohort study observed fewer age-related white matter changes in TD compared to PIGD patients [9], while another study found no differences in white matter hyperintensities at the voxel level between TD and PIGD patients, regardless of the severity of white matter hyperintensity scores [10]. Due to the inconsistent findings in brain structure in PD subtype, some researchers suggest that exploring brain function may better reflect the most susceptible regions and the characteristics of different PD subtypes [11], especially in the early stages of the disease before any structural damage occurs.

Amplitude of low-frequency fluctuation (ALFF) is employed to detect the local spontaneous fluctuation intensity of the blood-oxygen-level-dependent (BOLD) signal, reflecting the degree of local brain activity [12]. Few studies have examined ALFF in PIGD and TD patients. Among them, Chen et al. reported increased ALFF in the putamen, posterior cerebellum, temporal gyrus, and left parietal lobe in PIGD patients compared to TD patients [13]. However, Zheng did not find significant differences between the subtypes [14]. A recent study found significantly increased ALFF in the occipital lobe of PIGD patients compared to TD patients [15]. Voxel-based functional connectivity (FC) is used to identify interconnections between neurons. Shuting Bu et al. found a significant decrease in connectivity between the thalamus and parietal occipital lobes in PIGD patients compared to TD patients, but no difference in gray matter volume was found [16]. In addition, two studies reported that TD was associated with increased connectivity between the basal ganglia (putamen or subthalamic nucleus) and the cerebellum, while PIGD was associated with decreased connectivity between the putamen and the subthalamic nucleus or sensorimotor cortex [17, 18]. These studies suggest that PIGD patients are more likely to experience dysfunction in the corticobasal ganglio-thalamocortex circuit, whereas TD may involve more extensive brain regions, such as the cerebellum. However, findings based on regions of interest are challenging to replicate, and interpretations of neural mechanisms remain controversial.

In recent years, independent component analysis (ICA)-based brain network analysis has become a prominent research metho. ICA uses blind source separation to isolate spatially independent and temporally related functional networks, allowing for the observation of functional brain integration on a macro scale [19]. A few studies have reported changes in the basal ganglia, frontoparietal, and default mode axes between and within networks in TD patients compared to non-TD patients and healthy controls [20]. However, no studies have specifically investigated the PIGD and TD subtypes.

This study, based on rs-fMRI, further complements the understanding of the pathophysiology of different PD subtypes by examining local brain function, functional connectivity between voxels, and connectivity between brain networks. The findings have the potential to contribute to the development of more precise and reliable clinical biomarkers, as well as personalized treatments in the near future.

Materials and methods

Sample population

In total, 126 idiopathic PD patients were retrospectively included for analysis. The inclusion criteria were as follows: (1) meeting the Movement Disorder Society diagnostic standards for PD [21], (2) a modified Hoehn-Yahr (H&Y) grade of 1-3, and (3) aged between 42 and 80 years. Patients were excluded if they had a history of (1) serious neuropsychiatric illness, (2) trauma or tumors, (3) long-term smoking or alcohol abuse, (4) multiple systemic diseases, (5) blood donation or blood loss ≥ 400 mL within the past 3 months, (6) inherited diseases caused by known gene mutations, or (7) impaired communication abilities.

Sixty-seven matched healthy controls were also enrolled. It was ensured that all participants, both patients and controls, were right-handed based on the results of the Edinburgh Hand-

edness Inventory. Signed informed consent was obtained from all participants. The study was reviewed and ethically approved by the First Affiliated Hospital of Anhui Medical University (NO. PJ2022-13-55).

Clinical assessments

Clinical evaluations and MRI scans were conducted on patients who had abstained from medication for at least 12 hours (the "off" state). Clinical evaluations included assessments of disease severity using the H&Y stage and the Unified Parkinson's Disease Rating Scale (UPDRS), as well as evaluations of cognitive function using the Montreal Cognitive Assessment (MoCA) and emotional status using the Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD). The medication dosages taken by patients during the study were measured as the levodopa equivalent daily dose (LEDD). In addition, tremor (8 items) and PIGD scores (5 items) were calculated based on the UPDRS. The tremor to PIGD score ratio was used to classify patients as TD (ratio ≥ 1.5), PIGD (ratio ≤ 1), or indeterminate (ratios > 1.0 and < 1.5). Patients with a positive numerator and a zero denominator value were designated as TD, and those with the reverse were classified as PIGD. Patients with zero numerators and denominators were classified as indeterminate [22].

Imaging data acquisition

MRI data were generated using a 3-T scanner (Discovery 750, GE Healthcare, Milwaukee, Wisconsin). Foam padding and headphones were used to reduce scanner noise and limit head movement. High-resolution T1-weighted anatomical images were acquired with the following parameters: repetition time, 8.16 ms; echo time, 3.18 ms; flip angle, 12°; field of view, 256 × 256 mm^2; matrix: 256 × 256; slice thickness, 1 mm; voxel size, 1 × 1 × 1 mm^3; and 188 slices with no gap between them. Participants were instructed to remain still with their eyes closed and to avoid falling asleep during the rs-fMRI scan. A total of 217 volumes of functional images were captured using an echo-planar imaging sequence with a repetition time of 2,400 ms and an echo time of 30 ms. The flip angle was set to 90°. Forty-six transverse slices were captured with a field of view measuring 192 × 192 mm^2, matrix size of 64 × 64, and slice thickness of 3 mm with no gaps. Images were obtained parallel to the anteroposterior commissure line with a voxel size of 3 × 3 × 3 mm^3.

Image processing

Preprocessing: Functional images were preprocessed using the DPARSF (http://rfmri.org) and SPM12 toolkits [23]. The preprocessing procedure involved discarding the first 10 images to ensure steady-state magnetization. Slice timing and realignment were performed, and individuals exhibiting head movement greater than 3 mm or rotation exceeding 3° were excluded from the study. Anatomical and functional images were aligned. Functional images were normalized using structural segmentation based on DARTEL. Additionally, regression correction for confounding variables was conducted, which included six motion parameters, the whole brain signal, white matter signal, and cerebrospinal fluid signal.

ALFF: Based on the preprocessed data, ALFF values were obtained as follows. Data smoothing was performed using a Gaussian kernel with a 6 mm full-width half-maximum. The frequency domain was obtained for each voxel in the filtered time series using a Fast Fourier Transform, and the power spectrum was determined. The square root of the signal was measured across the 0.01-0.08 Hz frequency range for each voxel and then divided by the standard deviation of all brain voxels after subtracting the mean value. ALFF values were standardized using a Z transformation.

Voxel-wise FC: Utilizing the preprocessed data, we conducted linear detrending analysis. A 0.01-0.08 Hz band-pass filter was applied for signal processing. Different regions of the brain were defined using a Gaussian kernel with a 6 mm full-width at half maximum, followed by spatial smoothing. After excluding the regions of interest (ROIs), the study extracted the average time series and assessed the functional connectivity between the ROIs and other brain regions using Pearson's correlation analysis. The correlation coefficients were then transformed to Z-scores using Fisher's r-to-z transformation. Functional connectivity maps were generated to show the connectivity between specific ROIs and the remaining brain regions.

Inter-network functional connectivity: The preprocessed data were analyzed to determine the functional networks using the fMRI Toolbox's group independent component analysis (ICA) found in GIFT v4.0a (http://icatb.sourceforge.net). ICA data with a relatively high model order were selected, and the infomax algorithm was used to evaluate the reliability of the information, maximizing ICA algorithm estimation by comparing ICASSO implemented in GIFT with 20 iterations of estimation. Independent components with an average intra-cluster similarity higher than 0.8 were chosen for examination to understand their characteristics. Independent components were estimated by maximizing spatial independence, and 30 components were identified as part of the resting-state network based on their anatomical and putative functional properties. This was done using templates from the Functional Imaging Laboratory of Neuropsychiatric Disorders at Stanford University (http://findlab.stanford.edu/index.html), by assessing high to low frequency power in the component spectrum, and determining whether peak activation occurred in the gray matter. By analyzing the spatial correlation values between the independent components and the template, the researchers categorized the chosen 30 independent components into seven distinct functional networks. These networks included the default mode network (DMN), the left and right frontoparietal networks, the visual network (VN), the auditory network (AUD), the sensorimotor network (SMN), and the dorsal attention network. Design matrices were created using the Mancovan toolbox in GIFT to analyze connectivity among components obtained through ICA. To minimize interference from components outside the aforementioned seven networks, the correlation features of functional network connectivity (FNC) were selected. The initial step involved time series detrending, followed by applying a fifth-order Butterworth low-pass filter with a 0.15 Hz threshold frequency to eliminate high-frequency components. The Fisher-z transformation was then applied to transform Z-values, enabling the generation of connection patterns and FNC matrix plots.

Statistical analysis

Statistical analyses of clinical data were performed using SPSS 23.0 (SPSS, Chicago, IL, USA). Chi-square tests were used to compare sex ratios among the different groups (TD, PIGD, and control). One-way analysis of variance (ANOVA) was employed to assess MoCA, HAMA, and HAMD scores among the 3 groups, followed by post hoc Bonferroni tests. The independent samples t-test was used to evaluate disease duration, tremor, PIGD, UPDRS scores, H&Y stages, and LEDD between the TD and PIGD patients.

One-way ANOVA was used to assess ALFF and FC among the TD, PIGD, and control groups, accounting for nuisance covariates such as sex, age, education, and total intracranial volume. This statistical analysis utilized the SPM12 toolbox for statistical parametric mapping, employing an image-based ANOVA technique. A voxel-defined cut-off of $P < 0.001$ was established, and voxel-adjusted results were reported using a permutation test to control for family-wise error (FWE, $P < 0.05$). The GIFT toolbox was utilized to conduct a MANCOVA on selected brain networks, comparing FNC differences among the three groups, with nuisance covariates such as sex, age, and education included to control for confounding factors (false discovery rate (FDR) adjusted, $P < 0.05$).

ALFF, FC, and FNC values of clusters showing significant differences among groups were extracted for post hoc two-sample t-tests, following a Bonferroni correction. Partial correlation analysis was used to examine the associations between ALFF, FC, and FNC values and clinical variables, considering sex, age, and education as covariates. Significance level was set at $P < 0.05$.

Results

Patient demographics and clinicopathological profiles

The demographics and clinicopathological profiles of patients and controls are summarized in **Table 1**. Twenty patients classified as indeterminate were not included in the analysis. No significant differences were observed in age, sex ratio, or education level among the three groups ($P > 0.05$). However, the MoCA score was significantly lower in PIGD patients compared to the controls ($P = 0.01$). The HAMA score was significantly higher in PIGD patients compared to the controls ($P = 0.001$), and both

Table 1. Subject demographics and clinicopathological profiles

Profiles	TD	PIGD	HC	χ^2/F/T	P
Sample size (M/F)	27/14	44/21	36/31	3.090	0.213
Age (year)	59.51±9.43	60.65±9.99	59.88±8.02	0.220	0.803
Education (year)	9.23±3.50	8.78±4.62	10.03±4.06	1.505	0.225
MoCA	23.12±4.46	22.10±4.78	24.48±2.97	4.679[b]	0.011
HAMA	5.05±3.39	6.29±3.20	3.84±3.96	6.603[b]	0.002
HAMD	5.51±4.09	6.98±4.07	2.91±2.77	15.853[a,b]	< 0.001
Duration (year)	3.30±2.73	3.85±3.41		-0.878	0.382
UPDRS-I	2.26±2.04	2.38±1.87		-0.533	0.785
UPDRS-II	8.06±3.12	8.27±3.19		-0.475	0.716
UPDRS-III	23.44±10.22	25.72±11.63		-1.031	0.305
Tremor scores	6.49±3.52	1.55±2.34		8.683	< 0.001
PIGD scores	2.54±1.69	4.51±2.74		-4.134	< 0.001
H&Y	1.73±0.60	1.80±0.71		-0.559	0.577
LEDD (mg)	320.60±256.10	354.94±331.11		-0.599	0.550

TD, Parkinson's Disease-Tremor Dominant; PIGD, Parkinson's Disease-Postural Instability and Gait Difficulty; HC, healthy control; M/F, male/female; MoCA, Montreal Cognitive Assessment; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn-Yahr grade; LEDD, Levodopa Equivalent Daily Dose. [a]*P* < 0.05 (post hoc), TD vs. HC; [b]*P* < 0.05 (post hoc), PIGD vs. HC.

TD and PIGD patients had significantly higher HAMD scores compared to the controls (P = 0.001 and P < 0.001, respectively). Tremor and PIGD scores differed significantly between the PD subtypes (both P < 0.001), while no significant differences were found in disease duration, UPDRS-I, UPDRS-II, UPDRS-III scores, H&Y stage, or LEDD (P > 0.05).

Differences in ALFF among the three groups

ALFF in the left dorsolateral superior frontal gyrus (DLSFG, peak MNI coordinate: -18, 60, 12; peak intensity: 11.571; cluster size: 54 voxels) differed among the three cohorts (**Figure 1A**). Our post hoc assessment revealed that the left DLSFG ALFF was significantly increased in both TD (t = -3.048, P = 0.003) and PIGD (t = -5.539, P < 0.001) patients compared to the controls. Furthermore, the left DLSFG ALFF was markedly higher in PIGD patients compared to TD patients (t = -2.094, P = 0.039) (**Figure 1B**).

Differences in FCs among the three groups

The left DLSFG with significant differences in ALFF among the three groups was selected as the ROI. Voxel-wise FC analysis revealed significant differences in the FC between the left DLSFG and the left supplementary motor area (SMA, peak MNI coordinate: -9, 21, 57; peak intensity: 12.419; cluster size: 113 voxels), the right DLSFG (peak MNI coordinate: 21, -12, 60; peak intensity: 12.609; cluster size: 134 voxels), and the left paracentral lobule (PCL, peak MNI coordinate: -9, -30, 78; peak intensity: 11.781; cluster size: 69 voxels) among the three groups (**Figure 2A**). Post hoc assessment revealed that the FC between the left DLSFG and the left SMA was considerably decreased in both the TD (t = -2.199, P = 0.03) and PIGD (t = -5.380, P < 0.001) groups compared to the control group, and it was significantly decreased in PIGD patients compared to TD patients (t = -2.652, P = 0.009) (**Figure 2B**). Similarly, the FCs between the left DLSFG and the right DLSFG, as well as the left PCL, were substantially diminished in both the TD (t = -2.950, P = 0.004; t = -3.066, P = 0.003) and PIGD (t = -5.138, P < 0.001; t = -4.918, P < 0.001) groups compared to the control group. However, no significant differences were evident between the TD and PIGD cohorts (t = -1.664, P = 0.099; t = -1.053, P = 0.295) (**Figure 2C** and **2D**).

Differences in FNCs among the three groups

Thirty independent components were extracted from the three groups using ICA and divided into seven functional networks. Compared with the control group, PIGD patients showed decreased FNC between the anterior DMN (IC2) and the VN (IC8, IC12), between the posterior

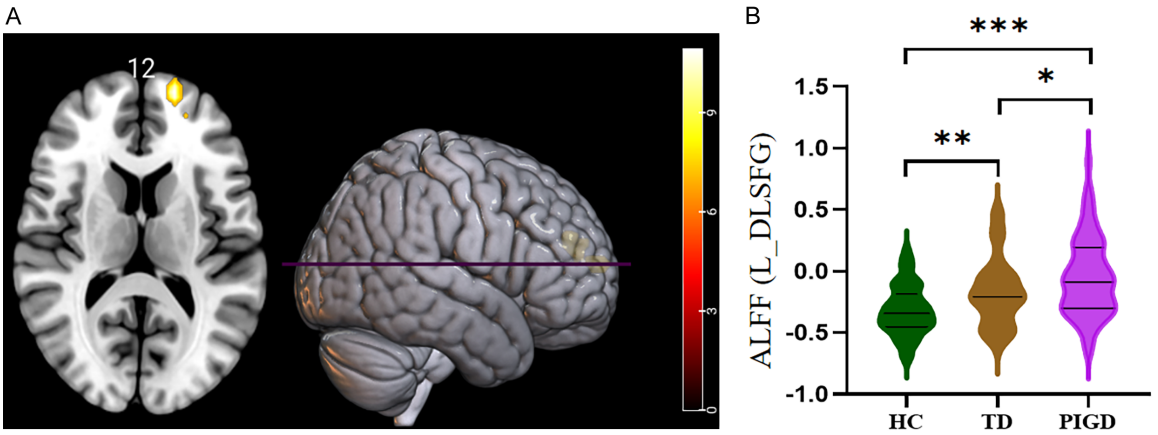

Figure 1. Differences in ALFF among the three cohorts. A. The brain region with marked difference in ALFF among the three groups was the left DLSFG. B. The ALFF in the left DLSFG. *P < 0.05, **P < 0.01, ***P < 0.001. ALFF, amplitude of low-frequency fluctuation; DLSFG, dorsal-lateral superior frontal gyrus; TD, Parkinson's Disease-Tremor Dominant; PIGD, Parkinson's Disease-Postural Instability and Gait Difficulty; HC, healthy control.

DMN (IC13) and the VN (IC12), between the anterior VN (IC11), the SMN (IC10), and the AUD (IC27), and between the VN (IC12) and the SMN (IC10) (P < 0.05, FDR corrected; **Figure 3A-C**). Relative to the controls, TD patients showed decreased FNC between the VN and AUD (P < 0.05, FDR corrected; **Figure 3D**). No significant alterations were evident in inter-network FC between PIGD and TD groups.

Correlation between ALFF, FC, FNC and clinical assessments

The values of ALFF, FC, and FNC from brain regions exhibiting significant alterations among the different cohorts were extracted. Patient age, sex, and educational status were used as covariates to conduct partial correlation assessments with PIGD and tremor scores. The results revealed that the FC between the left DLSFG and left SMA was strongly and inversely associated with PIGD scores only in the PIGD group (r = -0.314, P = 0.011) (**Figure 4A**). Additionally, an inverse relationship was found between VN-AUD connectivity and tremor scores only in TD patients (r = -0.397, P = 0.010) (**Figure 4B**).

Discussion

Compared with healthy controls, both TD and PIGD patients exhibited significantly enhanced ALFF in the left DLSFG and considerably diminished FC between the left DLSFG and left SMA, left PCL, and right DLSFG. Additionally, they showed significantly decreased FNC between the VN and AUD. Furthermore, compared with healthy controls, the PIGD patients displayed significantly diminished FNC between the VN and the DMN, the SMN. Compared to TD patients, PIGD patients had substantially elevated ALFF in the left DLSFG and significantly reduced FC between the left DLSFG and left SMA. Moreover, the severity of PIGD was associated with a reduction in FC between the left DLSFG and left SMA, while the severity of TD may be associated with a reduction in FNC between the VN and AUD. Investigation of local brain activities, functional networks, and brain networks have unveiled the neural processes underlying different subtypes of PD, paving the way for the development of tailored noninvasive interventions.

A previous study using mobile functional near-infrared spectroscopy-electroencephalography (EEG) systems showed that prefrontal cortex activity during walking was higher in PIGD patients compared to TD patients, regardless of obstacles [24]. Similarly, based on rs-fMRI, the DLSFG activity was substantially elevated in PIGD patients compared to TD patients. Overactivation of the DLSFG may represent cognitive compensation for PIGD symptoms in PD. PD patients often experience declines in various cognitive domains. A 5-year follow-up study found that cognitive function in PIGD patients declined faster than that in TD patients [25], and the PIGD patients in this study also exhibited significant cognitive impairment.

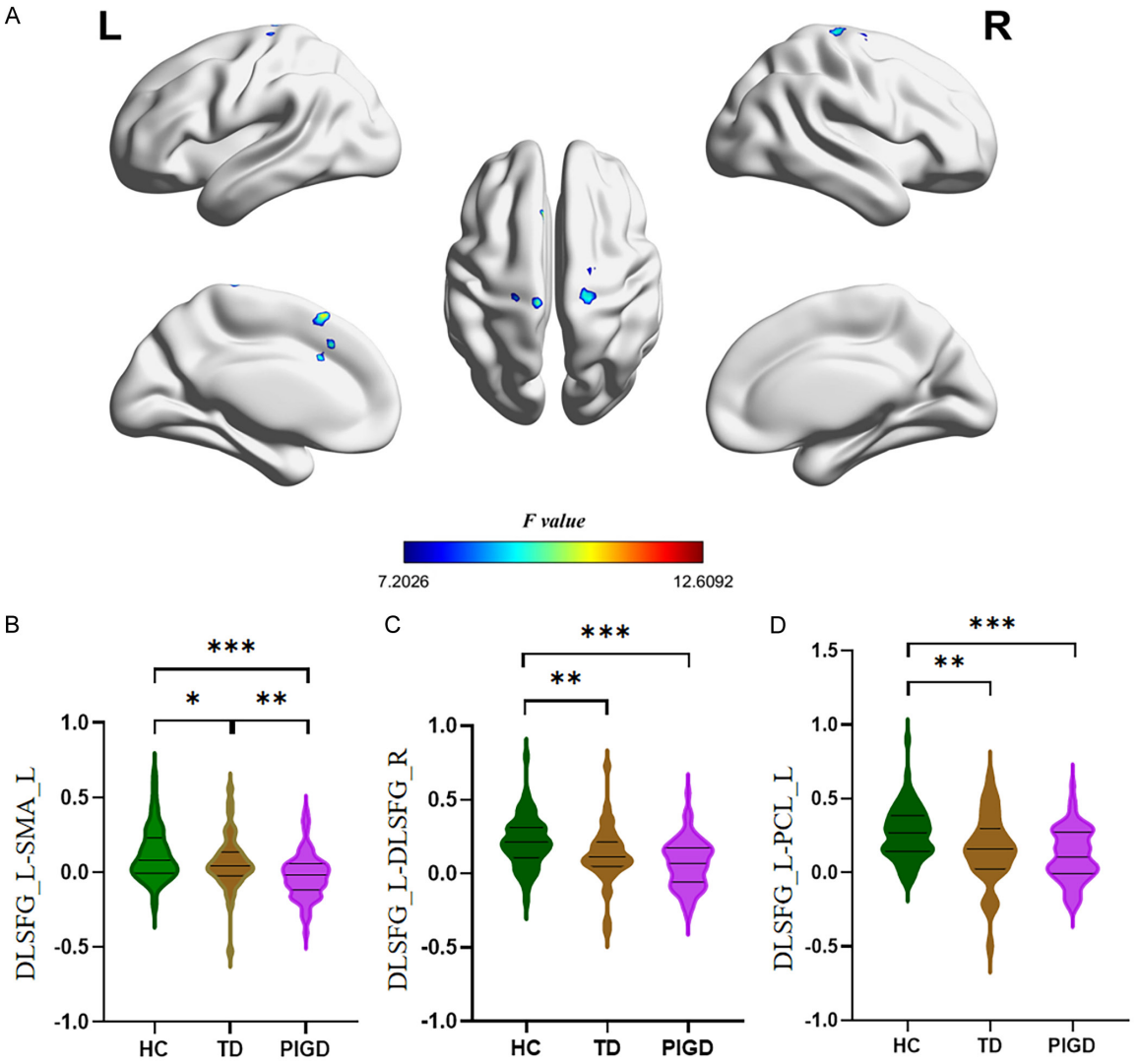

Figure 2. Differences in FC (left DLSFG was selected as ROI) among the three cohorts. A. The brain regions with marked difference in FC among the three groups were the left SMA, right DLSFG, left PCL. B. FC between the left DLSFG and left SMA. C, D. FCs between the left DLSFG and the right DLSFG. *P < 0.05, **P < 0.01, ***P < 0.001.

Increasing cognitive load can aggravate gait disorders in PD patients, while reducing cognitive load through visual cues can alleviate these disorders, as has been well-verified in cases of freezing of gait [26]. These findings reveal a close association between cognition and gait in PD patients, with our study suggesting that the DLSFG may be a key node. In addition, we found that the connectivity between the DLSFG and the SMA was substantially diminished in PIGD patients compared to TD patients and was proportional to gait disorder severity. The SMA plays a critical role in generating and transmitting nerve impulses that control movement and interacts with the basal ganglia to ensure the operation of complex movements [27]. An fMRI meta-analysis of gait disorders in PD showed significantly decreased activation of the SMA during gait [28], and an RCT study found that targeted stimulation of the SMA improved PIGD symptoms in PD patients [29]. Furthermore, coupling between the prefrontal cortex and the SMA has been shown to be decreased in PD patients, suggesting impaired movement monitoring [30]. Combined with our study on PD subtypes, the connectivity between the DLSFG and SMA may directly mediate the development and progression of PIGD in PD patients.

We also found significantly decreased connectivity between the DLSFG and the PCL, as well

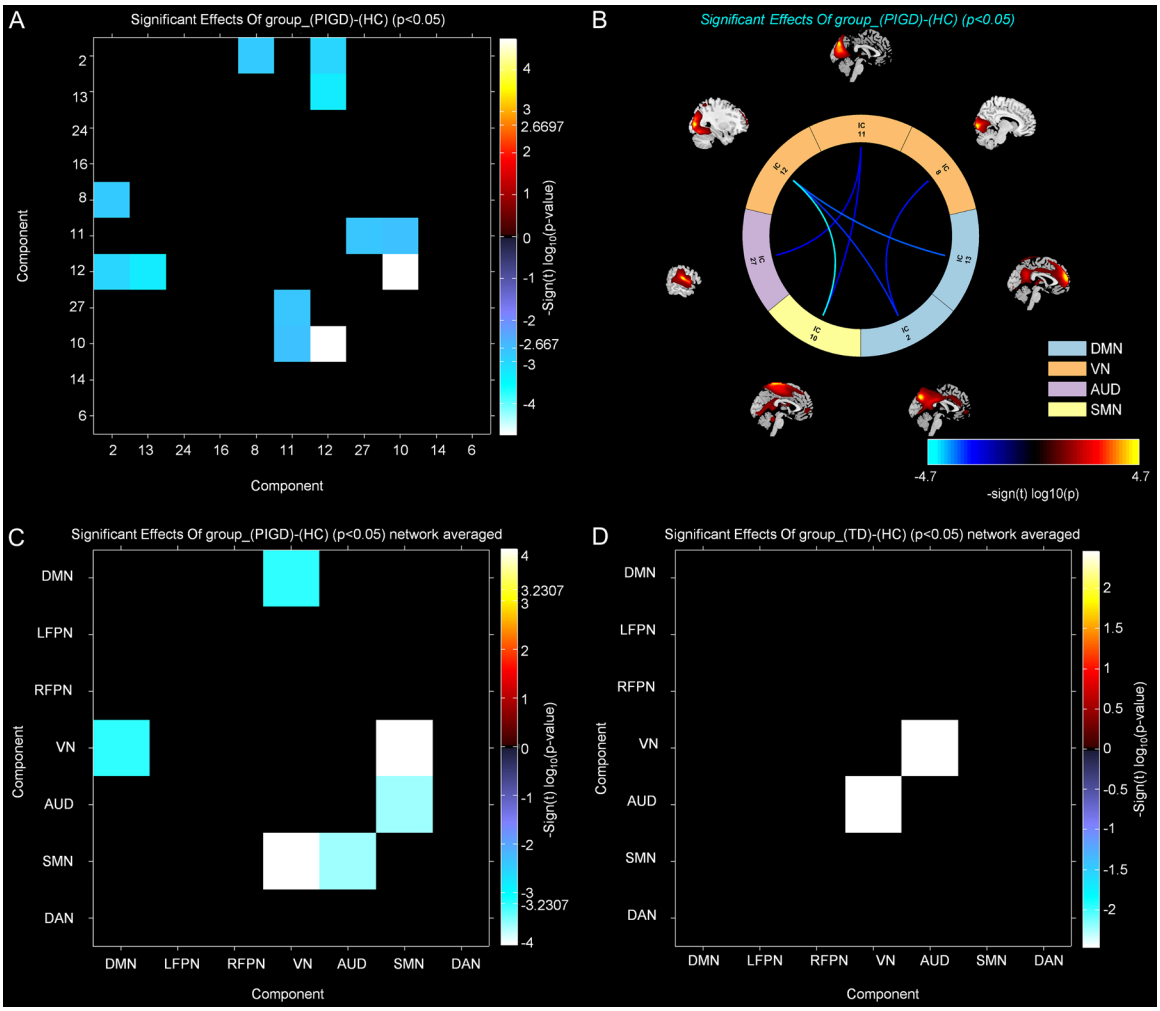

Figure 3. FNCs alterations among the three cohorts. A-C. Compared to HC, FNC between the anterior DMN (IC2) and the VN (IC8, IC12) was decreased, and the FNC between the posterior DMN (IC13) and the VN (IC12) was decreased, and the FNC between the anterior VN (IC11) and the SMN (IC10), the AUD (IC27) were decreased, and the FNC between the VN (IC12) and the sensorimotor network (IC10) was decreased among PIGD sufferers ($P < 0.05$, FDR corrected). D. Relative to HC, the FNC between the VN and the AUN was decreased among TD patients ($P < 0.05$, FDR corrected).

as between the bilateral DLSFG in both PIGD and TD patients compared to healthy controls. This may be related to the non-characteristic symptoms of PD patients. The PCL, which innervates the sensory and motor nerves of the lower limbs, is an important hub of the sensorimotor cortex. Hou et al. demonstrated that PCL connectivity was intricately linked to TD symptoms in PD patients [31], while Liu et al. reported its association with bradykinesia [32]. These findings highlight the important role of the PCL in PD and reflect its involvement in various PD symptomologies. Decreased bilateral DLSFG connectivity has also been reported to correlate with motor, non-motor, and cognitive performance in PD patients [33, 34]. These connections, while significant, may not represent core differences between PIGD and TD patients.

The study meticulously examined changes in FC among large-scale networks linked to motor subtypes of PD. Gratton et al. discovered that diminished integration of brain networks significantly contributed to the dysfunction observed in individuals with PD [35]. In the present study, compared to healthy controls, PIGD patients exhibited reduced connectivity between the VN and the SMN, DMN, and AUD. In contrast, TD patients only showed decreased connectivity between the VN and AUD.

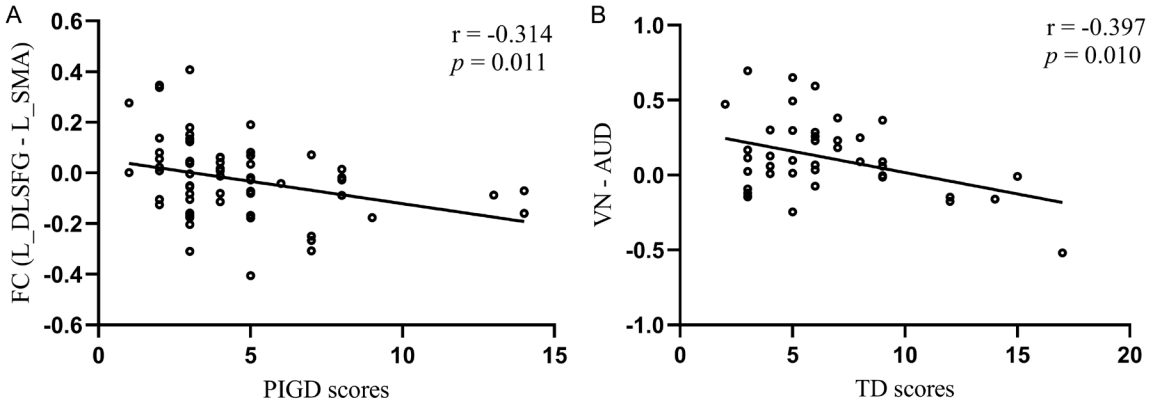

Figure 4. Correlation between FC/FNC and clinical assessments. A. FC between the left DLSFG and left SMA was negatively associated with PIGD scores only among the PIGD group. B. FNC between the VN and the AUD was inversely proportional to the tremor scores only among the TD group.

Traditionally, PD has been perceived primarily as a condition affecting motor functions, with the SMN playing a crucial role in perceiving and interpreting sensory input alongside orchestrating motor actions. Previous research has provided substantial evidence of disrupted sensorimotor integration in PD patients, as demonstrated by abnormal FC of the SMN [36, 37]. The VN is also another major area of complex sensations affected by PD, which can lead to issues such as visual hallucinations, perceptual, executive, and sleep dysfunctions. VN interaction is important for motor control and motor learning [38] and reduced VN-SMN interactions in PD may contribute to postural instability and compromised gait. The robust involvement of the DMN in cognitive functioning has been validated by findings in the context of typical aging and neurodegenerative conditions [39]. The lack of dopamine in PD patients can damage the auditory processing system, altering brain responses to sound and affecting the emotional state of higher brain regions [40]. Our results suggest that PIGD patients exhibited more extensive brain network abnormalities than TD patients, potentially correlating with more severe clinical presentations and poorer prognoses. However, we observed no direct and substantial alterations within brain networks between PIGD and TD patients, consistent with the findings by Wolters [41]. Notably, we report for the first time that VN-AUD connectivity is associated with tremor severity in TD patients. Evidence suggests that the VN and AUD participate in the emotional processing of PD patients, with the cerebellum playing a key role [42]. Increasing studies have reported a close association between the cerebellum and the TD subtype. Our data provide directions for further exploration of the mechanisms associated with the TD subcategory from the perspective of brain networks, emotion, and the cerebellum.

Many resting-state fMRI studies have been conducted to analyze variations in brain functions among different types of PD. The outcomes of these investigations exhibited significant variations across different domains. These differences may be due to the high heterogeneity of PD patients, as subtype analysis based on motor symptoms can be complicated by non-motor symptoms and cognitive function. To enhance the reliability of our results, we matched demographics and disease severity as closely as possible and conducted fMRI scanning and clinical evaluations in the "off" state to exclude the interference of dopaminergic drugs. In future research, we plan to combine advanced data visualization techniques with artificial intelligence methods with greater sensitivity to identify the inherent foundations distinguishing different subtypes of PD.

Moreover, this study offers a comprehensive analysis of the neural mechanisms underlying the varied subtypes of PD. However, some limitations should be considered when interpreting the results. Firstly, this study focused on two common subtypes of PD, namely the TD and PIGD subtypes. Future investigations may consider exploring other subtypes to gain a more comprehensive understanding of the disease.

Secondly, the sample population in this study was relatively small. Although it provided significant results, future studies with larger sample sizes will be essential to validate and enhance the generalizability of our findings. Additionally, the cross-sectional design of this study limits the ability to establish causality. Therefore, longitudinal studies should be pursued to investigate the progression of the disease and its impact on connectivity in these subtypes over time.

Despite these limitations, this study sets the stage for future research in several ways. Firstly, the findings contribute to the growing body of knowledge characterizing the neural underpinnings of distinct subtypes of PD using FC measures. The identification of key connectivity alterations in the left DLSFG among different subtypes may serve as a potential biomarker for diagnosing and monitoring the progression of the disease. Additionally, the exploration of alterations in functional connectivity among large-scale brain networks has the potential to guide the development of targeted interventions and personalized treatment strategies, paving the way for more effective management of PD subtypes. Future studies integrating multimodal neuroimaging techniques and longitudinal designs can offer a more comprehensive understanding of the dynamic changes in functional connectivity across various stages of the disease. This approach can provide valuable insights into potential therapeutic targets and prognostic indicators.

Conclusion

Decreases in the left DLSFG-SMA connectivity may be a key feature of the PIGD subtype, while decreased VN-AUD connectivity may be characteristic of the TD subtype.

Acknowledgements

We thank the members of the First Affiliated Hospital of Anhui Medical University for the helpful discussions. Our sincerest apologies to the scientists whose research could not be cited owing to space limitations.

Informed consent form was obtained from all participants.

Disclosure of conflict of interest

None.

Address correspondence to: Kai Wang, Fengbo Xing and Panpan Hu, Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei 230000, Anhui, China. E-mail: wangkai1964@126.com (KW); xingfengbo1995-0205@126.com (FBX); ORCID: 0000-0002-1683-2739; E-mail: Hpppanda9@126.com (PPH)

References

[1] Oh JY, Kim YS, Choi BH, Sohn EH and Lee AY. Relationship between clinical phenotypes and cognitive impairment in Parkinson's disease (PD). Arch Gerontol Geriatr 2009; 49: 351-354.

[2] Eggers C, Pedrosa DJ, Kahraman D, Maier F, Lewis CJ, Fink GR, Schmidt M and Timmermann L. Parkinson subtypes progress differently in clinical course and imaging pattern. PLoS One 2012; 7: e46813.

[3] van der Heeden JF, Marinus J, Martinez-Martin P, Rodriguez-Blazquez C, Geraedts VJ and van Hilten JJ. Postural instability and gait are associated with severity and prognosis of Parkinson disease. Neurology 2016; 86: 2243-2250.

[4] Rosenberg-Katz K, Herman T, Jacob Y, Giladi N, Hendler T and Hausdorff JM. Gray matter atrophy distinguishes between Parkinson disease motor subtypes. Neurology 2013; 80: 1476-1484.

[5] Herb JN, Rane S, Isaacs DA, Van Wouwe N, Roman OC, Landman BA, Dawant BM, Hedera P, Zald DH, Neimat JS, Wylie SA, Donahue MJ and Claassen DO. Cortical implications of advancing age and disease duration in Parkinson's disease patients with postural instability and gait dysfunction. J Parkinsons Dis 2016; 6: 441-451.

[6] Benninger DH, Thees S, Kollias SS, Bassetti CL and Waldvogel D. Morphological differences in Parkinson's disease with and without rest tremor. J Neurol 2009; 256: 256-263.

[7] Al-Bachari S, Vidyasagar R, Emsley HC and Parkes LM. Structural and physiological neurovascular changes in idiopathic Parkinson's disease and its clinical phenotypes. J Cereb Blood Flow Metab 2017; 37: 3409-3421.

[8] Danti S, Toschi N, Diciotti S, Tessa C, Poletti M, Del Dotto P and Lucetti C. Cortical thickness in de novo patients with Parkinson disease and mild cognitive impairment with consideration of clinical phenotype and motor laterality. Eur J Neurol 2015; 22: 1564-1572.

[9] Moccia M, Tedeschi E, Ugga L, Erro R, Picillo M, Caranci F, Barone P and Brunetti A. White matter changes and the development of motor phenotypes in de novo Parkinson's disease. J Neurol Sci 2016; 367: 215-219.

[10] Herman T, Rosenberg-Katz K, Jacob Y, Auriel E, Gurevich T, Giladi N and Hausdorff JM. White matter hyperintensities in Parkinson's disease: do they explain the disparity between the postural instability gait difficulty and tremor dominant subtypes. PLoS One 2013; 8: e55193.
[11] Droby A, Nosatzki S, Edry Y, Thaler A, Giladi N, Mirelman A and Maidan I. The interplay between structural and functional connectivity in early stage Parkinson's disease patients. J Neurol Sci 2022; 442: 120452.
[12] Zang YF, He Y, Zhu CZ, Cao QJ, Sui MQ, Liang M, Tian LX, Jiang TZ and Wang YF. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev 2007; 29: 83-91.
[13] Chen HM, Wang ZJ, Fang JP, Gao LY, Ma LY, Wu T, Hou YN, Zhang JR and Feng T. Different patterns of spontaneous brain activity between tremor-dominant and postural instability/gait difficulty subtypes of Parkinson's disease: a resting-state fMRI study. CNS Neurosci Ther 2015; 21: 855-866.
[14] Zheng JH, Sun WH, Ma JJ, Wang ZD, Chang QQ, Dong LR, Shi XX, Li MJ, Gu Q, Chen SY and Li DS. Differences in neuroanatomy and functional connectivity between motor subtypes of Parkinson's disease. Front Neurosci 2022; 16: 905709.
[15] Lan Y, Liu X, Yin C, Lyu J, Xiaoxaio M, Cui Z, Li X and Lou X. Resting-state functional magnetic resonance imaging study comparing tremor-dominant and postural instability/gait difficulty subtypes of Parkinson's disease. Radiol Med 2023; 128: 1138-1147.
[16] Bu S, Pang H, Li X, Zhao M, Wang J, Liu Y, Yu H and Fan G. Structural and functional alterations of motor-thalamus in different motor subtype of Parkinson's disease: an individual study. Acad Radiol 2024; 31: 1605-1614.
[17] Wang Z, Chen H, Ma H, Ma L, Wu T and Feng T. Resting-state functional connectivity of subthalamic nucleus in different Parkinson's disease phenotypes. J Neurol Sci 2016; 371: 137-147.
[18] Shen B, Pan Y, Jiang X, Wu Z, Zhu J, Dong J, Zhang W, Xu P, Dai Y, Gao Y, Xiao C and Zhang L. Altered putamen and cerebellum connectivity among different subtypes of Parkinson's disease. CNS Neurosci Ther 2020; 26: 207-214.
[19] van den Heuvel MP and Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 2010; 20: 519-534.
[20] Hou Y, Yang J, Luo C, Ou R, Zou Y, Song W, Gong Q and Shang H. Resting-state network connectivity in cognitively unimpaired drug-naïve patients with rigidity-dominant Parkinson's disease. J Neurol Sci 2018; 395: 147-152.
[21] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH and Deuschl G. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015; 30: 1591-1601.
[22] Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK and Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. Mov Disord 2013; 28: 668-670.
[23] Yan CG, Wang XD, Zuo XN and Zang YF. DPABI: data processing & analysis for (Resting-State) brain imaging. Neuroinformatics 2016; 14: 339-351.
[24] Orcioli-Silva D, Vitório R, Beretta VS, da Conceição NR, Nóbrega-Sousa P, Oliveira AS and Gobbi LTB. Is cortical activation during walking different between Parkinson's disease motor subtypes? J Gerontol A Biol Sci Med Sci 2021; 76: 561-567.
[25] Arie L, Herman T, Shema-Shiratzky S, Giladi N and Hausdorff JM. Do cognition and other non-motor symptoms decline similarly among patients with Parkinson's disease motor subtypes? Findings from a 5-year prospective study. J Neurol 2017; 264: 2149-2157.
[26] Monaghan AS, Gordon E, Graham L, Hughes E, Peterson DS and Morris R. Cognition and freezing of gait in Parkinson's disease: a systematic review and meta-analysis. Neurosci Biobehav Rev 2023; 147: 105068.
[27] Hensel L, Hoffstaedter F, Caspers J, Michely J, Mathys C, Heller J, Eickhoff CR, Reetz K, Südmeyer M, Fink GR, Schnitzler A, Grefkes C and Eickhoff SB. Functional connectivity changes of key regions for motor initiation in Parkinson's disease. Cereb Cortex 2019; 29: 383-396.
[28] Gilat M, Dijkstra BW, D'Cruz N, Nieuwboer A and Lewis SJG. Functional MRI to study gait impairment in Parkinson's disease: a systematic review and exploratory ALE meta-analysis. Curr Neurol Neurosci Rep 2019; 19: 49.
[29] Shirota Y, Ohtsu H, Hamada M, Enomoto H, Ugawa Y; Research Committee on rTMS Treatment of Parkinson's Disease. Supplementary motor area stimulation for Parkinson disease: a randomized controlled study. Neurology 2013; 80: 1400-1405.
[30] Rowe J, Stephan KE, Friston K, Frackowiak R, Lees A and Passingham R. Attention to action in Parkinson's disease: impaired effective con-

nectivity among frontal cortical regions. Brain 2002; 125: 276-289.
[31] Hou Y, Ou R, Yang J, Song W, Gong Q and Shang H. Patterns of striatal and cerebellar functional connectivity in early-stage drug-naïve patients with Parkinson's disease subtypes. Neuroradiology 2018; 60: 1323-1333.
[32] Liu W, Shen Y, Zhong Y, Sun Y, Yang J, Zhang W, Yan L, Liu W and Yu M. Levodopa improved different motor symptoms in patients with Parkinson's disease by reducing the functional connectivity of specific thalamic subregions. CNS Neurosci Ther 2024; 30: e14354.
[33] Mi TM, Zhang W, Li Y, Liu AP, Ren ZL and Chan P. Altered functional segregated sensorimotor, associative, and limbic cortical-striatal connections in Parkinson's disease: an fMRI investigation. Front Neurol 2021; 12: 720293.
[34] Crowley SJ, Banan G, Amin M, Tanner JJ, Hizel L, Nguyen P, Brumback B, Rodriguez K, McFarland N, Bowers D, Ding M, Mareci TA and Price CC. Statistically defined Parkinson's disease executive and memory cognitive phenotypes: demographic, behavioral, and structural neuroimaging comparisons. J Parkinsons Dis 2021; 11: 283-297.
[35] Gratton C, Koller JM, Shannon W, Greene DJ, Maiti B, Snyder AZ, Petersen SE, Perlmutter JS and Campbell MC. Emergent functional network effects in Parkinson disease. Cereb Cortex 2019; 29: 2509-2523.
[36] Lewis GN and Byblow WD. Altered sensorimotor integration in Parkinson's disease. Brain 2002; 125: 2089-2099.
[37] Tessitore A, Giordano A, De Micco R, Russo A and Tedeschi G. Sensorimotor connectivity in Parkinson's disease: the role of functional neuroimaging. Front Neurol 2014; 5: 180.
[38] Glickstein M. How are visual areas of the brain connected to motor areas for the sensory guidance of movement? Trends Neurosci 2000; 23: 613-617.
[39] Sambataro F, Murty VP, Callicott JH, Tan HY, Das S, Weinberger DR and Mattay VS. Age-related alterations in default mode network: impact on working memory performance. Neurobiol Aging 2010; 31: 839-852.
[40] Jafari Z, Kolb BE and Mohajerani MH. Auditory dysfunction in Parkinson's disease. Mov Disord 2020; 35: 537-550.
[41] Wolters AF, Michielse S, Kuijf ML, Defebvre L, Lopes R, Dujardin K and Leentjens AFG. Brain network characteristics and cognitive performance in motor subtypes of Parkinson's disease: a resting state fMRI study. Parkinsonism Relat Disord 2022; 105: 32-38.
[42] Adamaszek M, D'Agata F, Steele CJ, Sehm B, Schoppe C, Strecker K, Woldag H, Hummelsheim H and Kirkby KC. Comparison of visual and auditory emotion recognition in patients with cerebellar and Parkinson's disease. Soc Neurosci 2019; 14: 195-207.