Original Paper

European Neurology

Eur Neurol 2017;78:200–209
DOI: 10.1159/000477902

Received: March 28, 2017
Accepted: May 25, 2017
Published online: August 25, 2017

Disrupted Brain Network Hubs in Subtype-Specific Parkinson's Disease

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Keywords
Parkinson's disease · Resting-state fMRI · Hub · Subtypes

Abstract
Background/Aims: The topological organization of brain functional networks is impaired in Parkinson's disease (PD). However, the altered patterns of functional network hubs in different subtypes of PD are not completely understood. ***Methods:*** 3T resting-state functional MRI and voxel-based graph-theory analysis were employed to systematically investigate the intrinsic functional connectivity patterns of whole-brain networks. We enrolled 31 patients with PD (12 tremor dominant [TD] and 19 with postural instability/gait difficulty [PIGD]) and 22 matched healthy controls. Whole-brain voxel-wise functional networks were constructed by measuring the temporal correlations of each pair of brain voxels. Functional connectivity strength was calculated to explore the brain network hubs. ***Results:*** We found that both the TD and PIGD subtypes had comprehensive disrupted regions. These mainly involved the basal ganglia, cerebellum, superior temporal gyrus, pre- and postcentral gyri, inferior frontal gyrus, middle temporal gyrus, lingual gyrus, insula, and parahippocampal gyrus. Furthermore, the PIGD subgroup had more disrupted hubs in the cerebellum than the TD subgroup. These disruptions of hub connectivity were not correlated with the HY stage or disease duration. ***Conclusion:*** Our results emphasize the subtype-specific PD-related degeneration of brain hubs, providing novel insights into the pathophysiological mechanisms of connectivity dysfunction in different PD subgroups.

Introduction

Parkinson's disease (PD) is a neurodegenerative disease with a broad spectrum of motor symptoms including bradykinesia, rigidity, rest tremor, and postural and gait impairments. Increasing evidence suggests that PD is a

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heterogeneous disorder [1]. According to the clinical features, PD can usually be categorized into tremor dominant (TD), postural instability and gait difficulty (PIGD), and mixed subtypes [2, 3]. Each type has its own clinicopathologic phenotypes and natural history. Compared with the TD group, PIGD trends to present with more obvious axial motor involvement, more rapid disease progression, and greater cognitive impairment [2, 4]. The early prominent death of dopaminergic neurons in the substantia nigra (SN) pars compacta leading to dopamine depletion has been identified in PD. However, this cannot explain all the manifestations and pathophysiological mechanisms of the different subgroups. Unlike bradykinesia and rigidity, the dysfunction of the basal ganglia (BG) circuit (Striato-thalamo-cortex pathway) cannot provide a satisfactory explanation for tremor in PD.

Resting-state functional MRI (Rs-fMRI) is a new tool for noninvasively measuring spontaneous or intrinsic brain activity [5]. Using Rs-fMRI and graph theory, researchers have explored PD-related abnormal functional brain network in PD, including topological architecture [6, 7] and spontaneous brain activity [8]. For example, PD patients exhibit marked decrease in nodal and global efficiency [9], local efficiency, and local clustering coefficient [10]. Furthermore, major reductions in long-range connection in PD patients with mild, or no, cognitive impairment were detected [11]. However, different PD subtypes have different pathophysiological mechanisms and altered functional network patterns [12]. While a pathological interaction between the BG and the cerebellothalamic circuit (cerebello-thalamo-cortex [CTC] pathway) may play an important role in the genesis of resting tremor [13], gait disturbance in PD may in part be associated with the dysfunction of the prefrontal-subthalamic-pedunculopontine loop [14]. Furthermore, compared with TD, gray matter (GM) is reduced in areas that involve pre- (supplementary motor area), post central gyri, the cerebellar declive, culmen, and the caudate nucleus in PIGD predominate PD patients [15]. Thus, it is reasonable to explore the brain network based on different PD phenotypes.

The human brain is a complex, interconnected network with a series of nodes and connections that support efficient processing and integration of information [16]. Hubs are defined as nodes occupying a central position in the overall organization of a network [17]. They play influential roles in integrating diverse information and transferring messages rapidly with minimal energy consumption. The high level of centrality of brain hubs also renders them vulnerable to brain disorders. Many diseases, such as Alzheimer disease, and some psychiatric disorders have been found to have disturbed hubs [18, 19]. Although previous studies have demonstrated altered topological organization, the connectivity patterns of brain hubs in Rs-fMRI networks in specific PD subtypes remain to be elucidated.

Here, we used Rs-fMRI and graph-theory approaches to investigate the topological organization of whole-brain functional networks in PD, focusing on the TD and PIGD subtypes. We further tested whether functional connectivity strength (FCS) correlates with motor measures, disease duration, and stage. Investigating the characteristics of hubs in PD will significantly advance our understanding of the pathophysiology of different PD phenotypes.

Material and Methods

Participants

In this study, 45 PD patients and 22 age- and gender-matched healthy participants were enrolled from the Beijing Tiantan Hospital, Capital Medical University. All patients were diagnosed on the basis of the United Kingdom PD Society Brain Bank criteria [20]. Patients who underwent stereotactic surgery were excluded. Healthy controls (HCs) with normal neurological statue and movement function and absence of neurological or psychiatric disease were selected. All subjects were right-handed. Written informed consent was obtained from all individuals. The study was approved by the Ethics Committees of Beijing Tiantan Hospital.

Demographic information (age of disease onset and disease progression), Hoehn and Yahr stage (H-Y stage), motor evaluation scores (Unified Parkinson's Disease Rating Scale (UPDRS) I–IV scores, cognition evaluation scores (MMSE) and L-dopa equivalent daily dosages were collected for each patient. All the parameters and the MRI scans were assessed after at least a 12-h overnight withdrawal from medication ("OFF").

We classified PD cases into 3 groups: TD, PIGD, and mixed. Two parameters were used for classification: The "tremor score" was derived from the mean of the sub-scores of UPDRS II items 16 (tremor) and UPDRS III items 20 and 21 (rest and action/postural tremor); the "PIGD score" was defined by the mean of the sub-scores of UPDRS II items 13–15 (falling, freezing and walking) and UPDRS III items 27–30 (arise, posture and gait stability) [21]. The ratio was calculated as the tremor score/PIGD score. Patients with ratios >1.5 were classified as the TD group and ratios <1 as the PIGD group. The mixed subtype was defined by a ratio of 1–1.5 [2].

Finally, 12 PD patients with TD, 19 with PIGD and 14 with the mixed phenotype were identified. We included the 12 TD, 19 PIGD patients, and 22 healthy subjects in our study.

Image Acquisition

All MRI scans were performed using a 3.0 Tesla MR system (Siemens, Erlangen, Germany) using a standard head coil. During the scanning procedure, we applied foam padding and headphones to minimize head motion and to reduce scanner noise. The par-

ticipants were instructed to stay still, keep their eyes closed, and relax their minds but to not fall asleep. Functional images were collected axially using an echo-planar imaging sequence with the following settings: TR/TE = 2,000 ms/40 ms, FA = 90°, FOV = 256 mm × 256 mm, resolution = 64 × 64, axial slices = 28, thickness/gap = 4 mm/1 mm, voxel size = 4 × 4 × 5 mm^3, bandwidth = 2,230 Hz/pixel. Two lengths of the resting-state fMRI scans were acquired. One was acquired with 239 volumes for all HCs, 6 TD, and 18 PIGD patients, and the other was acquired with 300 volumes for the other 6 TD and 4 PIGD patients. For consistency of the time points, we cut off the posterior 61 volumes for the long time series. Finally, we included 239 volumes for all subjects (HC: 22; TD: 12; PIGD: 19).

Data Preprocessing

Functional imaging data were preprocessed using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI software package (http://www.restfmri.net/forum/DPARSF) [22]. The first 10 volumes of the functional images were discarded due to signal equilibrium issues and subjects' adaptation to the scanning environment. The fMRI time series were first corrected for within-scan acquisition time differences between slices and realigned to the first functional scan to correct for head motion. The participants with head movement exceeding 3.0 mm of translation or 3.0° of rotation in any direction were excluded. All realigned images were then spatially normalized to the Montreal Neurological Institute space and resampled to a 3-mm isotropic resolution. To avoid introducing artificial local spatial correlations, the images were not smoothed. The time series were further linearly detrended and temporally band-pass filtered (0.01–0.08 Hz) to reduce the effects of low-frequency drift and high-frequency physiological noises. Several nuisance variables, including 24 head motion parameters, white matter, cerebrospinal fluid, and global signals, were regressed out from the time course of each voxel. Finally, the images were spatially smoothed using a 4-mm full width at half maximum Gaussian filter to decrease spatial noise. The residual time courses were used for subsequent resting-state FCS analysis.

Whole-Brain Voxel-Wise Functional Connectivity Analysis

Hub regions of the whole-brain network were identified by computing FCS. First, for each subject, we extracted the blood-oxygen-level-dependent time series of each voxel within a GM mask. We then calculated Pearson's correlations between the time series of any pairs of voxel, producing a functional connectivity matrix. The GM mask (N_{voxels} = 57652) was generated by thresholding (cut off = 0.2) the mean GM probability map of all 53 subjects. These individual correlation matrices were then transformed to a z-score matrix using Fisher's r-to-z transformation, to improve normality. We then calculated the sum of the connections between each voxel and all other voxels in the GM mask and then divided by $N_{voxels} - 1$ to get its FCS. We conservatively restricted our analysis to connections with a correlation coefficient above 0.2, which could eliminate the weak correlations possibly arising from noise.

Statistical Analysis

To determine the main effect of groups on FCS, a one-way analysis of covariance (ANCOVA) was performed with age and gender as covariates. The ANCOVA result was thresholded at $p < 0.05$ with a cluster size of 41,310 mm^3 (1,530 voxels), corresponding to a corrected p value of < 0.05 for multiple comparisons. To further examine differences between pairs of groups, a voxel-by-voxel general linear model analysis was conducted with age and gender as covariates. The threshold was set at $p < 0.05$ with a cluster size of 9,504 mm^3 (352 voxels), corresponding to a corrected p value of < 0.05. All cluster sizes were determined by Monte Carlo simulations using the AFNI AlphaSim program (http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf).

To determine the relationship between nodal FCS and clinical measures (tremor score, pigd score, H-Y stage and disease duration), a voxel-wise general linear model analysis was carried out in the PIGD group and the TD group within the GM mask with age and gender as covariates. Multiple comparisons were corrected using Monte Carlo simulations.

Results

Demographics and Clinical Characteristics of the Participants

The clinical and demographic data of the 53 participants are shown in Table 1. There were no significant differences between the 3 groups in terms of age, gender, or MMSE score. A negative association between the TD and PIGD subgroups was noted for disease duration, H-Y stage, and levodopa equivalent daily dosage.

Within-Group and Between-Group FCS Analyses

The whole-brain functional hubs of 3 groups are shown in Figure 1. For the HC group, functional hubs were mainly distributed in the posterior cingulate gyrus/precuneus,superior temporal gyrus, insula, lingual gyrus, as well as several occipital, frontal and cerebellum regions (Fig. 1). This pattern was consistent with that explained in previous studies [23–25]. Visual inspection indicated that despite the different strengths, the spatial distributions of FCS in the PIGD and TD subgroups were quite similar to those of the HC group. Further comparisons revealed that the PD participants had comprehensive decreases in FCS values compared with the HC (Fig. 1). Results derived from the ANCOVA analysis for the TD, PIGD, and HC groups revealed comprehensive significant FCS alterations ($p < 0.05$, corrected, Fig. 2a).

Compared with the HC group, the PIGD and TD patients had lower FCS values in the bilateral BG, cerebellum (bilateral hemisphere, cerebellum anterior lobe, culmen and tonsil), temporal lobe (superior temporal, middle temporal and parahippocampal gyri), insula, frontal lobe (inferior frontal gyrus, precentral gyrus, Brodmann area), occipital lobe (lingual gyrus, middle occipital gy-

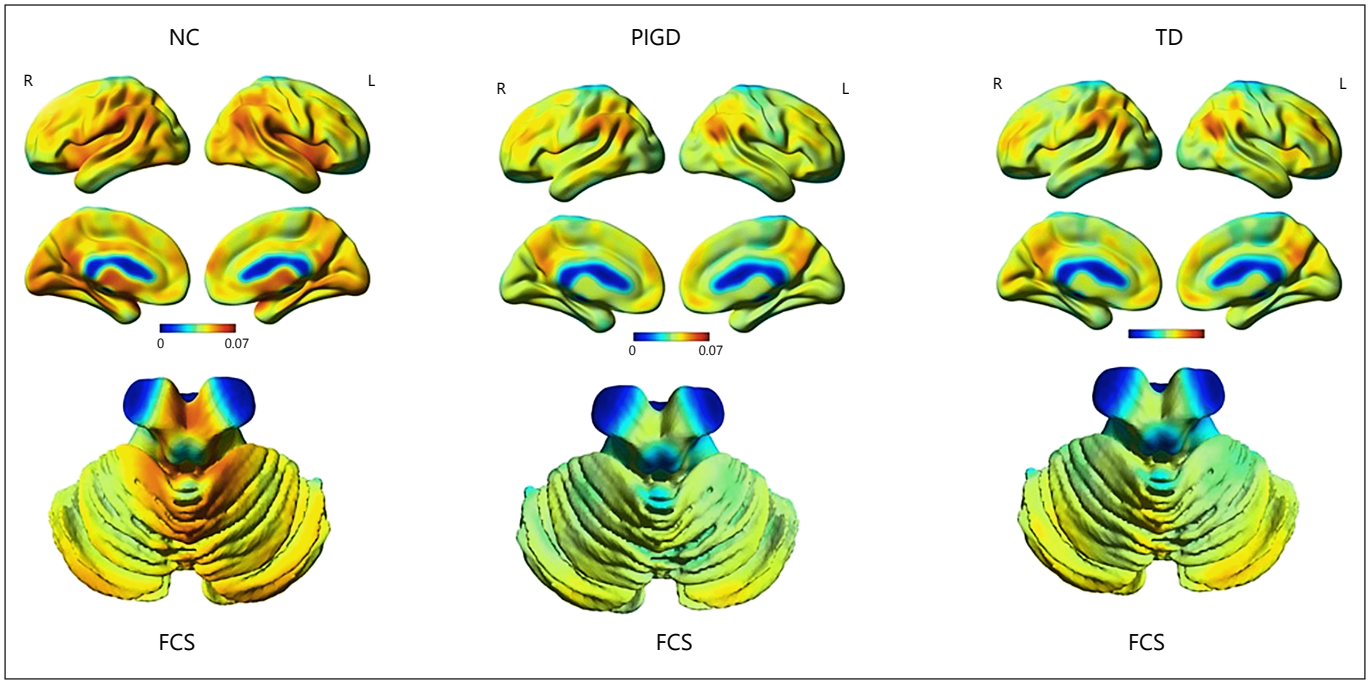

Fig. 1. Mean FCS maps of HC, PIGD, and TD groups.

Table 1. Demographics and clinical characteristics of PD patients and HCs

	PIGD (n = 19)	TD (n = 12)	HC (n = 22)	F or χ^2 or t value	p value
Age, years	64.8±8.34 (42–76)	62.6±8.71 (48–74)	65.1±5.00 (58–75)	$F_{(2, 50)} = 0.489$	0.616[a]
Gender, female:male	7:12	8:4	10:12	$\chi^2_{(2)} = 2.67$	0.263[b]
Disease duration, years	6.68±4.85 (1–22)	6.37±4.01 (2.5–15)	–	$t_{(2, 29)} = 0.184$	0.855[c]
H-Y stage	2.13±0.984 (0–4)	1.88±0.61 (1–3)	–	$t_{(2, 29)} = 0.808$	0.425[c]
UPDRS III	21.6±11.6 (7–57)	19.08±11.52 (6–48)	–	$t_{(2, 29)} = 0.596$	0.556[c]
MMSE	27.5±2.01 (25–30)	28.25±2.67 (20–30)	28.6±1.57 (25–30)	$F_{(2, 50)} = 2.4$	0.101[a]
Levodopa dosage, mg/day	464±284 (125–1,000)	301.52±204.86 (0–750)	–	$t_{(2, 29)} = 1.713$	0.097[c]
Tremor score	3.37±2.99 (0–10)	6.33±3.37 (3–15)	–	$t_{(2, 29)} = -2.565$	0.016[c]
PIGD score	5.00±1.97 (2–10)	2.17±1.53 (0–6)	–	$t_{(2, 29)} = 4.231$	<0.0001[c]

Data are presented as the range of minimum-maximum (mean ± SD).

TD, tremor dominant; PIGD, postural instability and gait difficulty); HC, healthy control; H-Y stage, Hoehn and Yahr stage; UPDRS III, Unified Parkinson's Disease Rating Scale III; MMSE, Mini-Mental State Examination.

[a] The p value was obtained by the one-way ANOVA.

[b] The p value was obtained by the 2-tailed Pearson χ^2 test.

[c] The p value was obtained by the 2-sample t test.

rus, cuneus), parietal lobe (postcentral gyrus), and cingulate gyrus. ($p < 0.05$, corrected; Fig. 2b, c).

Compared to the TD patients, the PIGD patients had lower FCS values in the cerebellum, mainly in the left hemisphere and tonsils ($p < 0.05$, corrected; Fig. 2d).

Correlation Analyses

For all PD patients, we generated voxel-wise correlation maps between FCS values and PIGD subscale scores, tremor subscale scores, H-Y stage, and disease duration. There were positive correlations, mainly in the bilateral cerebellum (Fig. 3), for tremor scores. No regions had

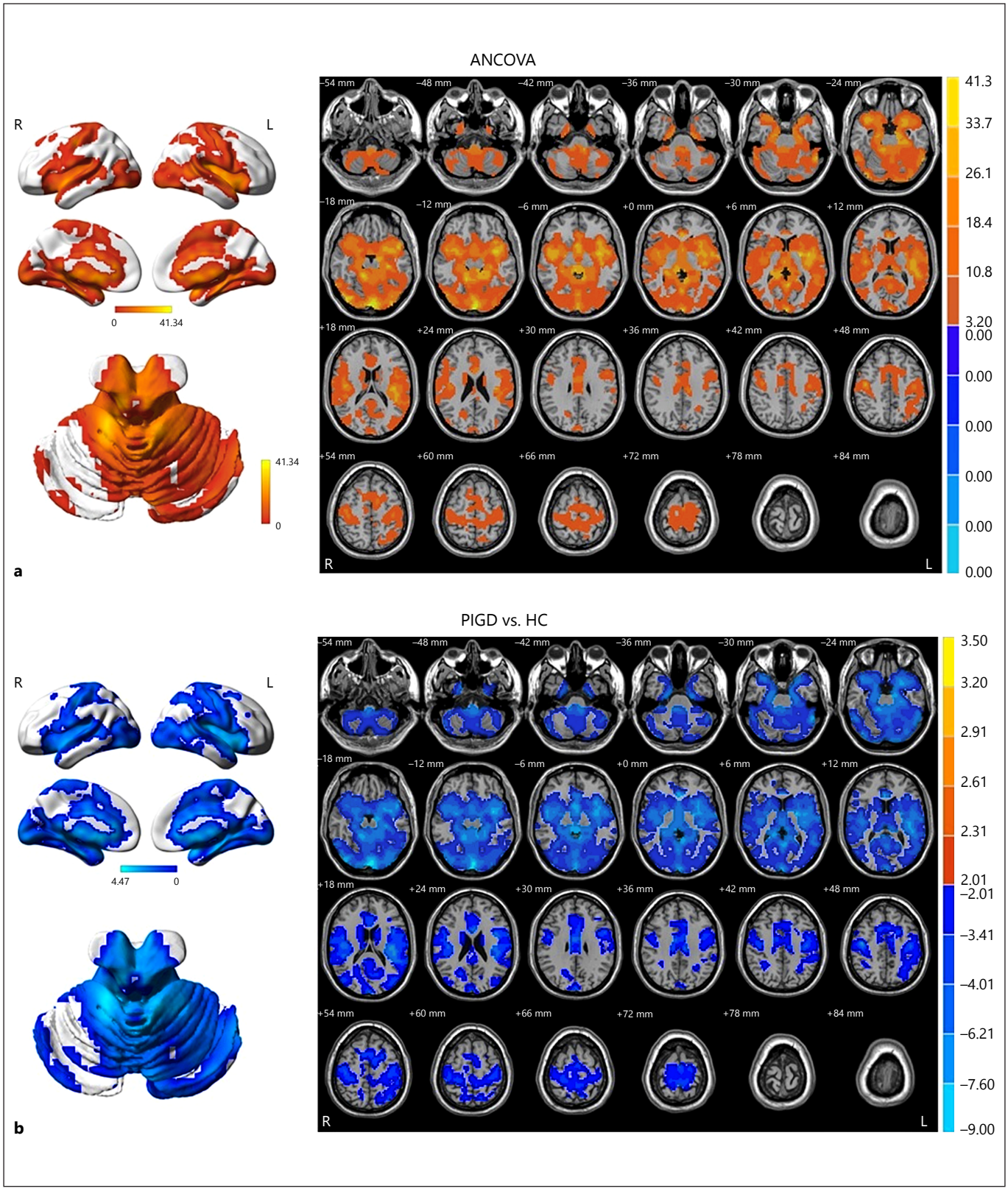

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Fig. 2. Within- and between-group FCS maps. **a** Brain maps for FCS differences between the TD, PIGD, and HC groups. **b** FCS differences between the PIGD and HC groups.

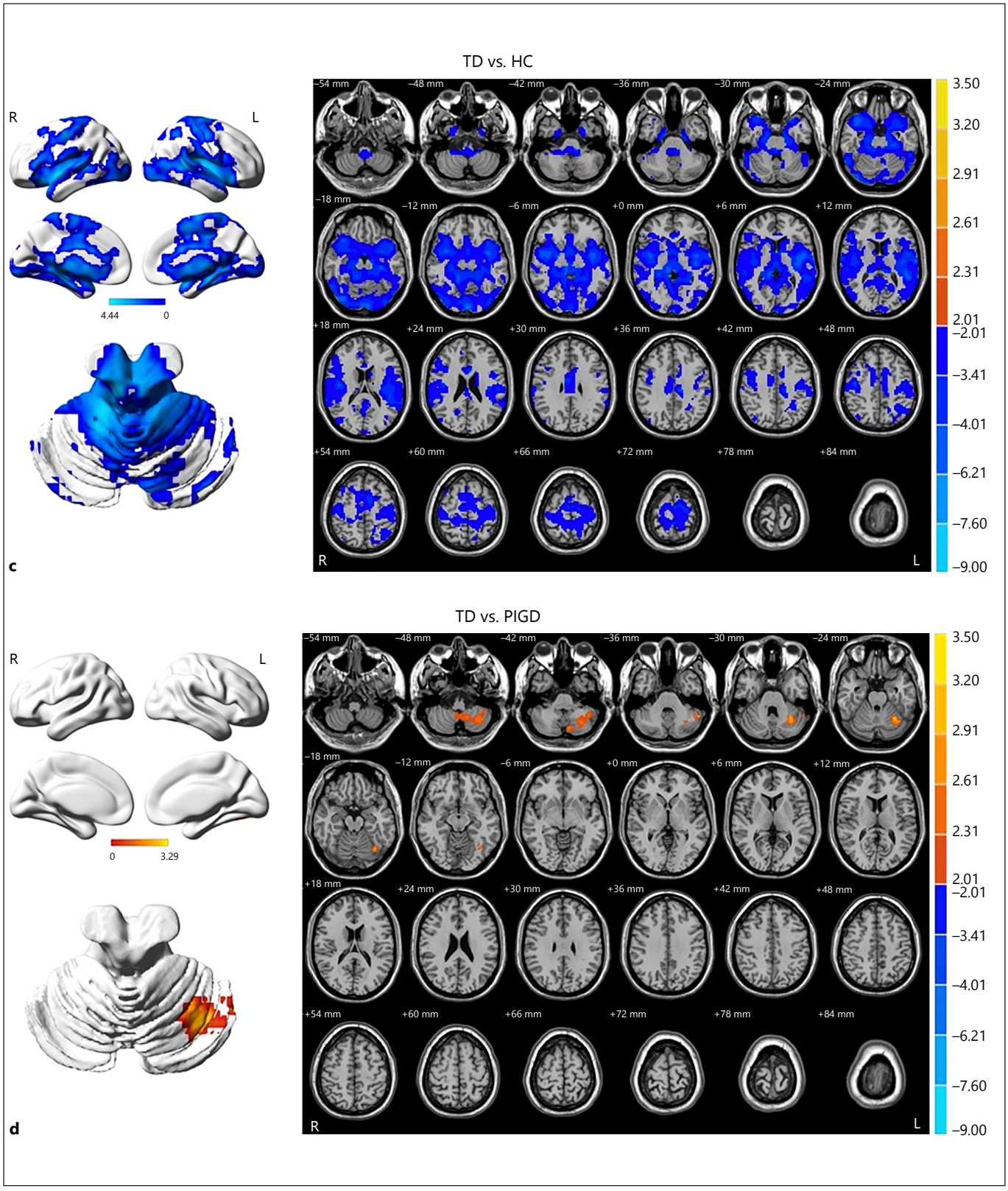

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Fig. 2. Within- and between-group FCS maps. **c** FCS differences between the TD and HC groups. **d** FCS differences between the PIGD and TD groups.

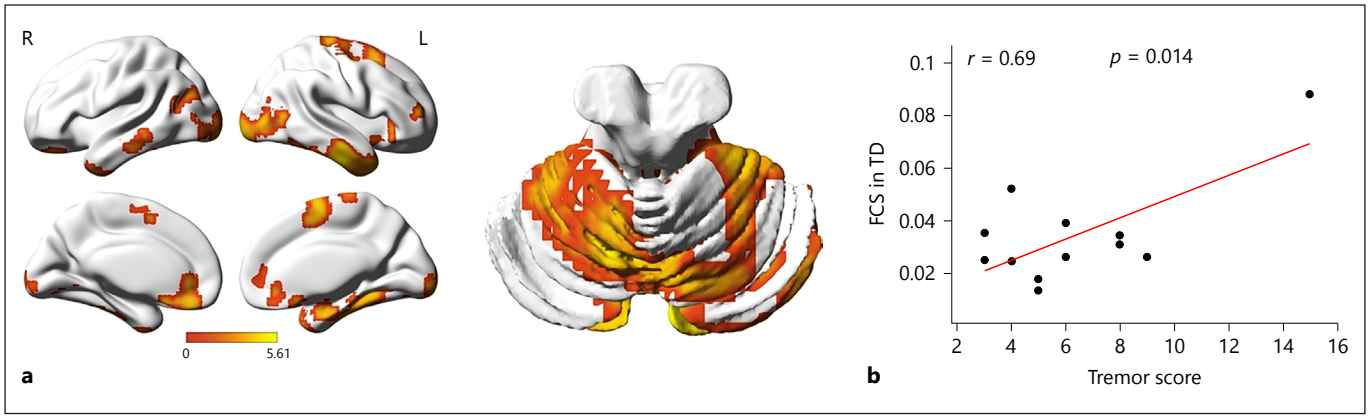

Fig. 3. Correlation map of tremor subscores and FCS values in the TD group. **a** FCS values in the bilateral cerebellar lobule significantly correlated with tremor scores. **b** Scatter plots of FCS values of peak voxels and tremor scores in the bilateral cerebellum.

significant correlations between FCS values and PIGD subscale scores, H-Y stage, or disease duration in our study.

Discussion

Using Rs-fMRI and graph-based network analysis, we found disrupted functional connectivity patterns in different subtypes of PD. Both TD and PIGD patients presented with comprehensive disrupted network hub regions with decreased FCS, with the PIGD subgroup displaying more disrupted hubs in the cerebellum.

Hubs in the human brain are nodes that act as way stations for facilitating traffic over a network [23]. In this study, the functional hubs in HC were primarily located in the posterior cingulate gyrus/precuneus, superior temporal gyrus, insula, lingual gyrus, and several regions in the occipital lobe, frontal lobe, and cerebellum. Similar hub distribution was noted in PD subjects, suggesting a relative functional preservation of these hubs. However, significant FCS decreases were seen in many hub regions, indicating that specific hubs might be preferentially targeted by PD pathology.

Basal Ganglia

Both the PIGD and TD groups had decreased FCS in the bilateral BG. It is widely accepted that the BG-thalamo-cortical indirect and direct pathways model provides an explanation for the origin of akinesia in PD [26, 27]. In PD subjects, dopamine depletion in the SN pars compacta leads to a striatal dopamine deficiency, which causes a cascade of functional changes in BG circuitry. This kind of dopamine deficiency disrupts the corticostriatal balance, leading to increased activity in the indirect circuit and reduced activity in the direct circuit [28]. From a pathological perspective, decreased levels of dopamine, which could cause alterations in receptor function and synaptic activity, have been found in the BG (mainly in the internal and external globus pallidus) of postmortem brain tissue from PD patients [29]. A PET study has reported a significantly reduced mean uptake of ^{18}F-dopa in the BG in PD, with the caudate and putamen severely affected [30]. Similarly, fMRI studies have also found that compared with HCs, a PD cohort had decreased regional homogeneity in the BG, including the putamen and thalamus [31, 32]. However, our results did not reveal any differences in BG FCS between PIGD and TD groups. This indicates that BG involvement in PD is common to both PIGD and TD subgroups.

Occipital Lobe

The visual system, mainly located in the occipital cortex, plays a vital role in PD. It works as an early compensatory mechanism in the generation of motor plans. An fMRI study demonstrated increased reliance on visual processing during motor planning in PD [33]. However, this compensatory mechanism may decay as the disease progresses [34]. Increasing evidence shows that visual system dysfunction occurs in the early stages of PD, and decreased activity in the temporo-occipital regions has be found even in the absence of clinically relevant visual presentation [35]. Moreover, visual deficits have further been correlated with PIGD [36]. In our study, extensive

disturbed hubs were found in the bilateral occipital lobes in patients with PD, with no statistical difference between different subtypes. It appears that information integration in the visual system is seriously attenuated in PD, regardless of the subtype.

Cerebellum

In our observation, compared with controls, PIGD and TD patients had decreased FCS values in the cerebellum. The former group had overall lower functional connectivity in the bilateral cerebellar hemispheres, culmen, and tonsils.

The cerebellum plays an important part in PD, including the development of pathological and compensatory effects [37]. Dopaminergic degeneration [38], α-synuclein deposition [39], and aberrant projections from BG have been found in the cerebellum, which can explain the disruption of hubs in that area. However, the involvement of the cerebellum varies between subtypes. Compared with TD, the PIGD subtype exhibits lower GM volumes in the cerebellar culmen and declive [15] and more cholinergic cell loss. Also, the severity of gait and balance disturbance correlates with cholinergic deficits in the cortex and subcortex, including the cerebellum [40]. Our results reveal that the PIGD group experienced greater loss of functional connectivity than that of the TD group, implying more severe damage to hubs.

Furthermore, previous studies demonstrated that PD tremor may be generated by the dysfunctional CTC loop [13, 41]. To some extent, this circuit is a compensatory mechanism for dopamine deficiency in BG [12, 42] and several task-related fMRI studies have further verified hyperactivity in the cerebellum in TD patients. A fludeoxyglucose-PET study identified a PD-tremor related pattern characterized by covarying increases in metabolic features in the dentate nucleus and primary motor cortex [43]. This supports the CTC hypothesis from a physiological perspective. However, like the visual system in PD, this compensatory effect may diminish as pathological damage becomes more severe [37]. In our study, such hyperactivity and hypermetabolism may in part explain why cerebellar hubs were mildly disturbed in the TD group.

Other Regions

In our study, disrupted hubs were also found in the temporal lobe, frontal lobe, insula, and cingulate gyrus. A pathological study revealed that α-synuclein and amyloid-β burdens were found in multiple regions in PD with dementia, including the anterior cingulate gyrus, superior frontal gyrus, temporal cortex, entorhinal cortex (ERC), amygdaloid complex, and hippocampus [44]. Compared with cognitively normal PD subjects, ERC volumes are smaller in demented PD subjects [45]. Even in nondemented PD, both α-synuclein and amyloid-β have been found in the ERC and could gradually increase the pathological burden in these areas [44]. These findings suggest that the brain hubs that tend to have α-synuclein and amyloid plaque deposition lead to functional disconnections between regions. Apart from pathology and cell loss in medial temporal lobe structures [45], white matter networks connecting temporal lobe and frontal-subcortical dissociation have also been found in nondemented PD patients with verbal memory impairment. One study has also suggested that iron homeostasis is disrupted in the SN and temporal cortex. Unlike the iron accumulation in the SN, decreased iron content has been observed in the temporal cortex of postmortem PD brains [46].

The frontal lobe plays a major role in voluntary movement, and the prefrontal cortex is involved in strategic processes in high-order cognitive and executive functions [47]. In PD, frontal dysfunction is associated with postural deformities and freezing of gait [48]. Both the cortex and white matter of the frontal lobe are involved in PD. An Rs-fMRI study has revealed disturbed functional connectivity between the prefrontal cortex and the putamen [49]. Reduced functional connectivity in the middle frontal, angular, and occipito-temporal gyri have been observed in patients with freezing of gait [50]. Degeneration has also been seen in frontal white matter, especially in subjects with gait difficulties [51]. In addition, from a pathophysiological aspect, lipid peroxidation is increased in the frontal cortex [52] and the activity of complex I (NADH: ubiquinone oxidoreductase), a component of mitochondrial electron transport chain, has been identified as loss of activity in the frontal cortex, as well as in SN in PD brain [53].

The insula is known to be an integrating hub highly involved in interacting somatosensory, autonomic, and cognitive-affective processes [54]. It has wide functional interaction with multiple regions, including the BG, frontal, temporal, parietal, and cingulate cortices and is related to the nonmotor symptoms of PD [55]. In our study, all of the patients complained of various kinds of nonmotor symptoms, such as constipation, hyposmia, or sleep disorder. Thus, a disturbance of the insula hub is not surprising.

Several limitations of our study need to be addressed. First, as this is a hospital-based and small-sample size study, selection bias is unavoidable. Second, the classification used cannot absolutely separate the 2 groups and

there was overlap in both tremor and PIGD scores across groups. Third, some of the hub disruptions may also be correlated with increased severity of motor symptoms and reduced cognitive performance. Finally, as this is a cross-sectional investigation and not a prospective study, we can only speculate about the temporal relationships between disrupted hubs and clinical symptoms. A longitudinal observation is needed to examine FCS-related dynamic changes and PD progression.

Conclusions

Our results emphasize subtype-specific, PD-related degeneration of brain hubs, thus providing novel insights into the pathophysiological mechanisms of the connectivity dysfunction in PD. Further investigations of hub changes in larger samples and longitudinal studies of disease progression are needed in the future.

Funding Sources

This research was supported by Beijing Natural Science Foundation (No.7164254), Natural Science Foundation of China (No. 81571226) and Beijing Municipal Science and Technology Commission (No. Z151100003915117 and No. Z151100003915150).

Disclosure Statement

The authors have no conflicts of interest to disclose.

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