ORIGINAL COMMUNICATION

Cerebellar functional abnormalities in early stage drug-naïve and medicated Parkinson's disease

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Abstract

Parkinson's disease (PD) is a progressive neurological degenerative disorder characterized by impaired motor function and non-motor dysfunctions. While recent studies have highlighted the role of the cerebellum in PD, our understanding of its role in PD remains limited. In the present study, we used resting-state fMRI to evaluate dysfunctions within the cerebellum in PD patients treated with medication and drug-naïve PD patients. We applied amplitude of low-frequency fluctuation (ALFF) and degree centrality (DC) analysis methods. Thirty-one patients with early stage PD (22 drug-naïve and 9 medicated patients) and 31 gender- and age-matched healthy controls were recruited in this study. ALFFs increased in the left cerebellar areas (lobules VI/VIIb/CruI/CruII and the dentate gyrus) and right cerebellar areas (lobules VI/VIIb/VIIIa/CruI/CruII and the dentate gyrus) of all PD patients and in the left and right cerebellar areas (lobules VI/VIIb/CruI and the dentate gyrus) of drug-naive PD patients but were not significantly changed in medicated PD patients. DC increased in the right cerebellar areas of all PD patients and medicated PD patients. All PD patients and all drug-naive PD patients showed significantly weaker functional connectivity (FC) between the left cerebellum and the left medial frontal gyrus. However, FC was significantly stronger between the right cerebellum and the left precentral and right middle occipital gyri in the medicated PD patients than in controls. Furthermore, a correlation analyses revealed that ALFF z scores in the left cerebellum (lobule VI) and right cerebellum (lobule VI/CruI and dentate gyrus) were negatively correlated with Mini-Mental State Examination (MMSE) scores in all PD patients and drug-naive patients. These results indicate that the cerebellum plays an important role in PD, mainly by exerting a compensatory effect in early stage PD. Additionally, antiparkinsonian medication would modified PD-induced changes in local neural activity and FC in PD patients. The results of this study offer novel insights into the roles of the cerebellum in early stage drug-naïve PD.

Keywords Cerebellum · Parkinson's disease · Functional connectivity · Amplitudes of low-frequency fluctuation · Degree centrality

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Introduction

Parkinson's disease (PD) is a progressive neurological degenerative disorder characterized by impaired motor function with resting tremors, bradykinesia, akinesia/rigidity, postural instability and gait disturbance as well as a variety of non-motor dysfunctions [29]. Traditionally, the mechanisms underlying the pathophysiology of and treatments for PD have focused on basal ganglia dysfunction, Lewy bodies and the loss of dopaminergic neurons in the substantia nigra [14]. More recent studies have highlighted the role of the cerebellum in PD [15, 18, 20, 24, 34]. The cerebellum is involved in processing sensorimotor, cognitive and affective information [27, 28, 32], and the cerebellum and basal ganglia are thought to communicate with each other through multi-synaptic cortical loops, including motor and cognitive circuits [4, 8, 17, 22]. The subthalamic nucleus in the basal ganglia is the source of a dense disynaptic projection to the cerebellum. Similarly, the dentate nucleus in the cerebellum is the source of a dense disynaptic projection to the striatum [4, 5]. Thus, the cerebellum may be affected secondary to abnormal basal ganglia outflow, and it may also experience a compensatory effect as a result of basal ganglia dysfunction. Wu et al. proposed that the cerebellum is involved in both the pathological and compensatory effects of PD [17].

Magnetic resonance imaging (MRI) has been applied as a non-invasive tool in many studies to assess the structural and functional abnormalities observed in PD. Previous studies performed using voxel-based morphometry MRI demonstrated that structural changes occur in the cerebellum in PD. For example, Borghammer et al. [3] used deformation-based morphometry MRI and observed that the left cerebellum showed significantly more contraction in patients with early stage PD than in control subjects [3]. In another study, the authors investigated gray matter volume and found that it was lower in the declive of the cerebellum in PD patients with tremor than in those without tremor [2]. Additionally, the regional gray matter volume was reduced in the cerebellum in PD patients with impaired cognition but not in PD patients without impaired cognition [19]. Zhang et al. found that disruption in the cerebellar white matter was associated with olfactory dysfunction in patients with PD [43]. Camicioli et al. investigated cerebellar atrophy in older PD patients [7]. Zeighami et al. used deformation-based morphometry and tensor probabilistic independent component analysis to identify the brain regions affected in de novo PD, and propagator analysis revealed that the substantia nigra was one of the likeliest propagators, but numerous cerebellar regions also appeared as potential propagators of the disease to the supratentorial central nervous system [42].

More recently, O'Callaghan et al. revealed gray matter loss across the motor and cognitive cerebellar territories in the medicated PD patients, and the extent of cerebellar atrophy correlated with increased resting-state connectivity between the cerebellum and frontoparietal networks, and with decreased connectivity between the cerebellum and several cortical networks, including the sensorimotor, dorsal attention and default networks [20].

Functional abnormalities were also observed in PD patients. Previous studies performed using functional MRI (fMRI) to analyze cerebellar areas have often shown that they are more activated during motor execution motor learning processes in patients with PD than in normal subjects [1, 23, 34, 35, 38, 40]. Resting-state fMRI has also been used to assess functional abnormalities in PD patients not performing tasks. It has been reported that the extent of cerebellar atrophy is correlated with decreased resting-state connectivity between the cerebellum and sensorimotor, dorsal attention and default networks but increased connectivity between the cerebellum and frontoparietal networks [17]. A previous study found that cortical–striatal connectivity was reduced in unmedicated PD patients [30]. A meta-analysis also observed that compared to healthy controls, PD patients exhibited functional disturbances in the parietal lobule and the pre- and postcentral gyri [13, 31]. Liu et al. found that in PD, some regions of the cerebellum showed enhanced connectivity with the bilateral dentate nucleus [16]. Other studies have observed medication-variant cerebellar connectivity in patients with PD [10, 25], suggesting that PD is associated with cerebellar changes that moderate the effects of medication. More recent studies have also highlighted the role of the cerebellum in PD.

Until now, our understanding of the role of the cerebellum in PD has remained limited. Some previous studies have found that the alterations that occur in the cerebellum in PD are modified by medication [10, 25, 34], while other studies have focused primarily on PD treated with off/on medication; however, few studies have focused on drug-naïve PD. Further investigations are needed to clarify the functional alterations that occur in the cerebellum in patients without medication effects. Previous studies have focused on large-scale network changes in PD, but few studies have focused on spontaneous neuronal activity in the cerebellum in PD. We hypothesized that local neuronal activity in the cerebellum would exhibit different characteristics in drug-naïve PD and mediated PD. In the present study, we analyzed resting-state fMRI to evaluate dysfunctions within the cerebellum in medicated PD and drug-naive PD. For these experiments, we applied amplitude of low-frequency fluctuation (ALFF) and degree centrality (DC) analysis methods. ALFF is widely used to investigate global and regional fluctuations in spontaneous low-frequency oscillations, and changes in ALFF values are thought to be associated with local neuronal

activity [41]. DC analysis selects each voxel (or brain area) as a node and then calculates the number of connections between each node and all other nodes; the results indirectly reflect the centrality or functional importance of the node within a whole-brain network [6, 44]. Furthermore, whether local dysfunction in spontaneous neuronal activity in the cerebellum is associated with clinical data, such as cognitive scores, was investigated. Finally, we used seed-based functional connectivity (FC) to investigate whether the dysfunctional areas within the cerebellar exhibit abnormal FC with other brain areas.

Materials and methods

This study was carried out in accordance with the recommendations of the East China of Normal University Ethics Committee and the Independent Ethics Committee of Shanghai Ninth People's Hospital. The study was approved by the East China of Normal University Ethics Committee (HR062-2018) and the Independent Ethics Committee of Shanghai Ninth People's Hospital (2016-44-T1). All subjects provided signed written informed consent documents approved by the East China of Normal University Ethics Committee and the Independent Ethics Committee of Shanghai Ninth People's Hospital.

Subjects

Thirty-one PD patients [Hoeln & Yahr (H&Y) stages 1 through 2 including 22 drug-naïve patients and 9 medicated patients] and 31 gender- and age-matched healthy controls were recruited in this study. All patients were diagnosed by a neurologist in the Department of Neurology at Shanghai Ninth People's Hospital according to the Movement Disorder Society clinical diagnostic criteria for PD [12]. The neurologist also collected patient data, including handedness, age, gender, disease duration, treatment and some rating scales. Three patients' clinical data were incomplete. H&Y stage and Unified PD Rating Scale (UPDRS) scores were

used to assess the severity of PD. The Mini-Mental State Examination (MMSE) was used to rate global cognitive function. All enrolled controls had no history of neurological or common chronic diseases and had normal cognitive function. In the medicated patients group, seven patients were treated with madopar tablets, whose main ingredient is levodopa. And two patients were treated with levodopa and dopaminergic agonist. See Table 1 for details.

MRI acquisition

We used a 3.0 Tesla Siemens Trio Tim system equipped with a 12-channel head coil to obtain structural and resting-state MRI data at the Shanghai Key Laboratory of Magnetic Resonance (East China Normal University, Shanghai, China). All subjects were instructed to remain still, and the patient's head was fixed with custom-fit foam pads. Magnetization-prepared rapid acquisition gradient-echo (MPRAGE) pulse sequences were applied to obtain high-resolution T1-weighted 3-dimensional whole-brain anatomical images. The following parameters were used for the MPRAGE pulse sequences: repetition time = 2530 ms, echo time = 2.34 ms, inversion time = 1100 ms, flip angle = 7°, number of slices = 192, sagittal orientation, field of view = 256 × 256 mm^2, matrix size = 256 × 256, slice thickness = 1 mm, and a 50% gap. The fMRI images were acquired using a T2*-weighted echo-planar imaging pulse sequence with the following parameters = 2000 ms, echo time = 30 ms, flip angle = 90°, number of slices = 33, transverse orientation, field of view = 220 × 220 mm^2, matrix size = 64 × 64, slice thickness = 3.5 mm, 25% dist factor, and total volume = 210. Additionally, the subjects were instructed to relax, remain still and close their eyes.

rs-fMRI preprocessing

All MRI data were analyzed using statistical parametric mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12) based on MATLAB (The Math Works, Natick, MA, USA) software. For resting-state

Table 1 Demographic and clinical characteristics of Parkinson's disease (PD) patients and controls

	Control ($n = 31$)	All PD ($n = 31$)	Drug-naïve PD ($n = 22$)	Medicated PD ($n = 9$)
Age (mean ± SD, years)	64.7 ± 9.7	64.7 ± 10.0	63.4 ± 10.3	68 ± 9.0
Disease duration (mean ± SD, years)	–	2.3 ± 2.8	1.3 ± 1.1	4.6 ± 4.0
Hoehn and Yahr scores	–	1.4 ± 0.4	1.3 ± 0.3	1.6 ± 0.5
UPDRS-III scores	–	14 ± 7.5	13 ± 7.4	16 ± 7.8
MMSE scores	29.0 ± 1.0	26.0 ± 2.1 (29)	26.4 ± 2.3 (20)	25.2 ± 1.2
MoCA scores	28.1 ± 1.3	–	–	–

MMSE Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment, *UPDRS-III* Unified Parkinson's Disease Rating Scale part III

data, the first ten volumes of each subject were discarded because of scanner instability and to allow the participants to adapt to the scanner noise. Next, slice-timing was performed to correct for intra-volume differences in acquisition time and head motion using six-parameter rigid-body linear transformation to the remaining volumes. Then, we set the anterior commissure as the origin on T1-weighted images and fMRI data to coregister the structural images to the mean functional images. Then, the time series of six head motion parameters, the signal from the white matter and the cerebrospinal fluid, considered noisy signals, were regressed out by a general linear mode. Then, we segmented the cerebellum from coregistered high-resolution T1-weighted images using a spatially unbiased infratentorial template (SUIT) [9].

All subjects' head-motion data (translation and rotation) were calculated as exclusion criteria. The participants were excluded if their maximum translation was > 2.5 mm or if their maximum rotation was > 2.5° in any direction.

Data analysis

ALFF and DC analysis

We performed ALFF analysis and DC analysis using DPABI (Data Processing and Analysis of Brain Imaging) based on preprocessed functional data in individual space [39]. For all voxels in each subject, the time series was converted to the frequency domain by fast Fourier transforms, and the averaged square root of the power spectrum was obtained across 0.01–0.1 Hz as ALFF values. Finally, to reduce individual differences, the ALFF value for each voxel was submitted to z standardization by subtracting the mean ALFF value and then dividing by the standard deviation of the whole-brain ALFF map.

An individual DC map was obtained by calculating the temporal correlation between each voxel and all other voxels of the brain within a gray matter mask. Thus, we obtained a matrix of Pearson's correlation coefficients. To eliminate low temporal correlations caused by signal noise, we set a correlation $r > 0.25$ as the threshold. Then, we counted the sum of the weights of all positive connections for each voxel as a DC value [6, 44]. The DC value of each voxel was converted into a standardized z score by subtracting the mean DC value and then dividing by the standard deviation of the whole-brain DC map so that the maps could be compared across subjects.

The ALFF and DC of each participant's cerebellum were then calculated in individual space. Finally, the resulting data were normalized to the MNI space with SUIT, and normalized functional images were smoothed with a 6-mm full-width half-maximum (FWHM) Gaussian filter.

FC analysis

The preprocessed fMRI data in MNI space were filtered (0.01–0.1 Hz) to reduce the influence of both low-frequency drift and high-frequency physiological noise. All surviving ALFF and DC clusters were defined as regions of interest (ROIs). The mean time series were extracted for all ROIs, and their correlations with the time series of each voxel within the whole brain were calculated to obtain FC maps. Finally, Fisher's z transformation was performed to transform the FC maps into z score maps to improve the normality of the data distribution.

Correlation analysis

All PD patients' mean ALFF z scores, DC z scores and FC z scores for all survival clusters were obtained and correlated with MMSE scores and UPDRS-III. Significant correlations are reported in Tables 2, 3 and 4.

Statistical analysis

Intergroup differences in ALFF, DC and FC were performed using voxel-wise two-sample t tests with age and gender as covariates. All results were corrected for multiple comparisons. We applied a threshold for all results at voxel-level uncorrected p values < 0.001 and cluster-level familywise error (FWE) corrected p values < 0.05. The survival clusters are reported.

Results

Neuropsychological and behavioral performance

The demographic and clinical data of the PD patient and control groups are presented in Table 1. Age and gender did not significantly differ between the PD patients and controls.

Functional MRI data

Comparison of ALFF, DC and FC between all PD patients and controls

Compared with the controls, PD patients exhibited significantly higher ALFF values in the left cerebellum (including lobules VI/VIIb/CruI/CruII and the dentate gyrus) and the right cerebellum (including lobules VI/VIIb/VIIIa/CruI/CruII and the dentate gyrus) (Fig.1 and Table 2). The PD patients also had significantly higher DC values in the

Table 2 Significant differences observed between PD patients and controls in ALFF, DC and FC in the cerebellum

Predominant regions in each cluster	Cluster size	Peak T value	MNI coordinates			Cluster-level $P_{\text{FWE-corrected}}$	Correlation with MMSE
			x	y	z		
ALFF was higher in all PD patients than in controls							
Cluster 1	171					0.036	
Left VI	32	4.49	− 8	− 70	− 31		− 0.401*
Left CrusI	34	4.41	− 8	− 72	− 33		−
Left VIIb	25	4.36	− 6	− 70	− 33		−
Left CrusII	32	4.31	− 6	− 72	− 39		−
Left dentate	29	4.25	− 10	− 68	− 33		−
Cluster 2	398					0.003	
Right Dentate	105	4.56	12	− 68	− 35		− 0.392*
Right VIIb	45	4.18	10	− 68	− 35		−
Right CrusII	158	3.98	10	− 72	− 37		−
Right VIIIa	11	3.93	12	− 66	− 39		−
Right CrusI	67	3.91	16	− 70	− 33		− 0.372*
Right VI	12	3.84	14	− 68	− 31		− 0.577**
DC was higher in all PD patients than in controls							
Cluster	157					0.020	
Right CrusI	77	4.21	30	− 68	− 37		−
Right CrusII	80	4.12	32	− 70	− 43		−
FC was lower in all PD patients than in controls (cluster 1 as ROI)							
Left medial frontal gyrus	66	− 4.79	− 9	39	18	0.005	−
	74	− 4.36	− 3	39	− 18	0.003	−
Right cingulate gyrus	116	− 4.24	3	− 24	30	0.000	−

The threshold assigned to surviving clusters of ALFF, DC and FC was $p < 0.001$, while that of FWE corrected was $p < 0.05$ at the cluster level

ALFF amplitude of low-frequency fluctuation, *DC* degree centrality, *FC* functional connectivity, *MMSE* Mini-mental State Examination

*$p < 0.05$ (two-tailed) indicates the correlation was significant; **$p < 0.01$ (two-tailed) indicates the correlation was significant

Table 3 Significant differences between drug-naive PD patients and controls in ALFF and FC in the cerebellum

Predominant regions in the cluster	Cluster size	Peak T value	MNI coordinates			Cluster-level $P_{\text{FWE-corrected}}$	Correlation with MMSE
			x	y	z		
ALFF was higher in drug-naive PD patients than in controls							
Cluster 1	376					0.007	
Left VI	19	4.06	− 8	− 70	− 31		− 0.613**
Left VIIb	23	3.99	− 8	− 70	− 37		−
Left dentate	78	3.98	− 10	− 58	− 33		− 0.641**
Left CrusI	32	3.92	− 8	− 72	− 31		− 0.511*
FC was lower in drug-naive PD patients than in controls (cluster 1 as ROI)							
Left medial frontal gyrus	53	− 4.89	6	24	− 12	0.016	−

The threshold assigned to surviving clusters of ALFF was $p < 0.001$ while that assigned for FWE-corrected was $p < 0.1$ at the cluster level. The threshold assigned to surviving clusters of FC was $p < 0.001$ while that of FWE corrected was $p < 0.05$ at the cluster level

ALFF amplitude of low-frequency fluctuation, *FC* functional connectivity, *MMSE* Mini-mental State Examination

*$p < 0.05$ (two-tailed), the correlation was significant; **$p < 0.01$ (two-tailed), the correlation was significant

right cerebellum (including lobules CruI/CruII) than were observed in the controls (Fig. 1 and Table 2).

The FCs of the three clusters within other brain areas were compared between PD patients and controls. The PD patients exhibited significantly weaker FC between the left cerebellum (cluster 1 in Table 2) and the left medial frontal and right cingulate gyri.

Table 4 Significant differences between medicated PD patients and controls in DC and FC in the cerebellum

Predominant regions in the cluster	Cluster size	Peak T value	MNI coordinates			Cluster-level	Correlation with MMSE
			x	y	z	$P_{\text{FWE-corrected}}$	
DC was higher in medicated PD patients than in controls							
Cluster 1	702					0.000	
Right CrusII	332	5.57	32	− 76	− 49		–
Right_VIIb	20	4.37	32	− 76	− 53		–
Right CrusI	342	4.36	24	− 80	− 27		–
FC was higher in all PD patients than in controls (cluster 1 as ROI)							
Left precentral gyrus	84	5.03	− 24	− 15	75	0.001	–
Right middle occipital gyrus	40	4.17	51	− 72	0	0.036	–

The threshold assigned to surviving clusters of DC and FC was $p < 0.001$, while that of FWE corrected was $p < 0.05$ at the cluster level

DC degree centrality, *FC* functional connectivity, *MMSE* Mini-mental State Examination

Fig. 1 Compared with controls, PD patients showed significantly increased ALFF in the left cerebellar and right cerebellar regions and increased DC in the right cerebellum
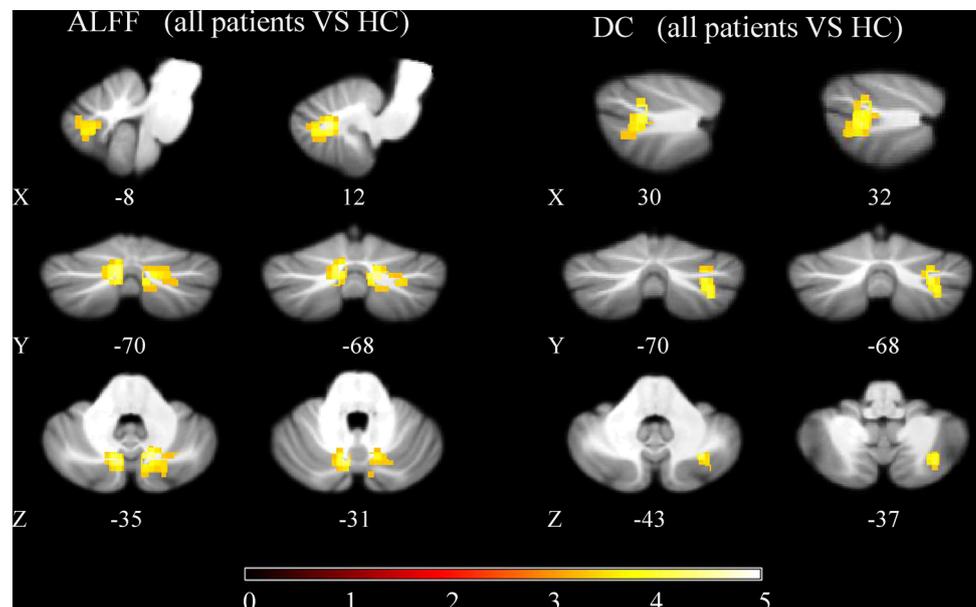
Comparison of ALFF and FC in drug-naive PD patients versus controls

Compared with the controls, the drug-naive PD patients exhibited significantly higher ALFF values in the left cerebellum (lobules VI/VIIb/CruI and the dentate gyrus) (Fig. 2a and Table 3). The drug-naive PD patients also showed significantly weaker FC between the left cerebellum (cluster 1, as shown in Table 3) and the left medial frontal gyrus.

Comparison of DC and FC in medicated PD patients versus controls

Compared with the controls, the medicated PD patients exhibited significantly higher DC values in the right cerebellum (including lobules VIIb, CruI, and CruII) than were observed in the controls (Fig. 2b and Table 4). The

medicated PD patients also showed significantly stronger FC between the right cerebellum (cluster 1 in Table 4) and the left precentral and right middle occipital gyri.

Correlation with clinical scores

We found that ALFF z scores in the left cerebellum (lobule VI) were negatively correlated with MMSE scores in all PD patients. Additionally, ALFF z scores in the right cerebellum (lobules VI/CruI and the dentate gyrus) were negatively correlated with MMSE scores in all PD patients.

The ALFF z scores in the left cerebellum (lobules VI/CruI and the dentate gyrus) were negatively correlated with MMSE scores in drug-naive patients. There were no significant correlations among DC, ALFF z scores or FC within significantly altered brain regions and other behavioral

Fig. 2 Significant differences in ALFF and DC between PD patients with and without medication and healthy controls. **a** Drug-naive PD patients exhibited significantly lower ALFF values in the right cerebellum than were observed in the controls. **b** Compared with controls, the medicated PD patients showed significantly higher DC values in the right cerebellum
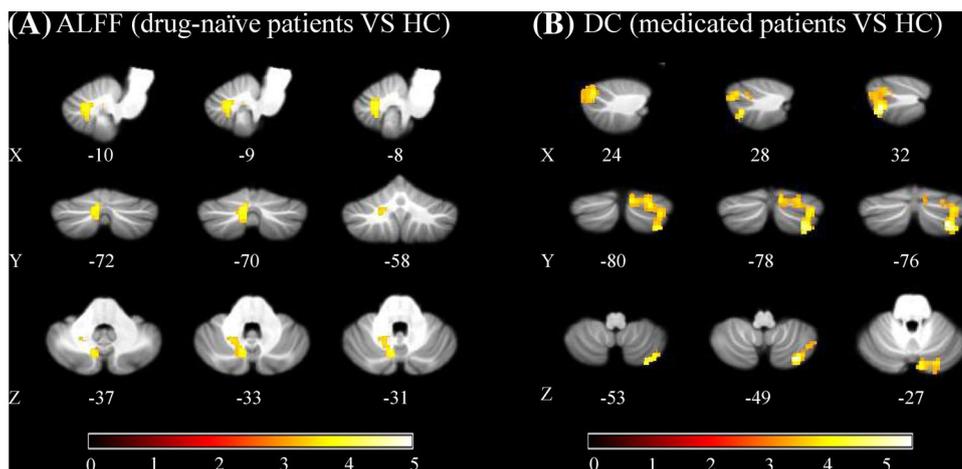
Discussion

In this study, we focused on cerebellar activity in the resting state based on a cerebellar atlas. The fMRI data obtained here provide evidence showing that local cerebellar spontaneous neural activity is altered in PD patients. In patients with PD, ALFF was increased in some cerebellar areas, while DC was increased in right cerebellar areas in all PD patients and medicated PD patients but not in drug-naïve PD patients. This study is the first to report that cerebellar activity is abnormal in a resting state in drug-naive PD patients and to observe that compared with the heathy group, drug-naïve and medicated PD patients exhibit different functional alterations.

The increased ALFF and DC observed in the cerebellum in this study are consistent with some previous task fMRI studies that have shown that cerebellar areas are more activated in patients with PD than in control subjects during motor execution and during the motor learning process [1, 23, 34, 35, 38, 40]. Several previous studies reported that neural activity in the cerebellum was increased in PD patients [24, 33, 37]. Wu et al. showed that compared to controls, in medicated PD patients, regional homogeneity (ReHo), which can be used to evaluate the nature of local intrinsic activity in a resting state, was increased in the cerebellum, primary sensorimotor cortex, and premotor area [36]. A meta-analysis found that ReHo was consistently higher in the left cerebellum of PD patients than in healthy controls [21]. Skidmore et al. used ALFF to investigate whether PD patients who were off medication exhibited changes in activity in both the left cerebellum (lobules VII/VIII) and right cerebellum (lobules IV/V) [26].

The mechanism underlying the increases observed in ALFF and DC in the cerebellum in PD patients remains unclear. Wu et al. proposed that the major roles of the cerebellum in PD include both pathological and compensatory effects [34]. Pathological changes in the cerebellum might be induced by dopaminergic degeneration, abnormal drives from the subthalamic nucleus and dopaminergic treatment. The compensatory effect may represent an attempt to maintain relatively normal motor and non-motor functions. Based on the hypothetical model of functional changes that occur in the cerebellum during the progression of PD proposed in a paper by Wu et al., the compensatory effect strengthens during a relatively early stage of PD but may diminish or eventually fail as the pathology progresses [34]. In the present study, the PD patients were in early stage PD, and most of them were first-diagnosis, drug-naive PD patients. Thus, the increased ALFF and DC observed in the cerebellum in these PD patients are likely to represent compensatory effects that may play leading roles in PD patients. Furthermore, correlation analysis showed that most cerebellar regions that showed increased ALFF were negatively correlated with MMSE scores, supporting the notion of compensatory effects in the cerebellum of PD patients. These results indicate that compensatory effects may be related to how early stage PD patients maintain relatively normal cognitive functions. We speculate that as the disease develops, these compensatory effects in the cerebellum may be limited and cognitive functions, therefore, continue to decline.

In our study, there were 21 drug-naïve PD patients and 9 treated PD patients. To further evaluate the effects of drugs, we performed a subtype analysis. Compared to healthy subjects, ALFFs were increased in the cerebellum in drug-naïve PD patients but not in treated PD patients. These results indicate that medication modified the changes that occurred in the cerebellum in PD patients. DC was also increased in the cerebellum in treated PD patients but not in drug-naïve PD patients, suggesting that medication modified the changes

measures, such as disease duration, and UPDRS-III scores, in PD patients.

that occurred in the cerebellum in PD patients by increasing local activity. All PD patients and all drug-naive PD patients showed significantly weaker FC between the left cerebellum and the left medial frontal gyrus. The drug-naive PD patients showed increased local cerebellar activity but decreased FC to the medial frontal gyrus, supporting their compensatory role in the cerebellum. However, the medicated PD patients showed significantly stronger FC between the right cerebellum and the left precentral and right middle occipital gyri than that observed in the controls, indicating that medication increased the FC between the cerebellum and the sensorimotor cortex in PD patients and that it contributed to improved motor symptoms in PD patients. The resting state connectivity of the local cerebellum is disrupted in PD, as has been reported in previous studies. Hu et al. observed that in medicated PD patients, while the cerebellum exhibited enhanced connectivity with the bilateral dentate nucleus, the connectivity between the dentate nucleus and a set of regions consistent with the default mode network was disrupted as was the connectivity between the dentate nucleus and the inferior parietal lobule [16]. O'Callaghan et al. found that resting-state connectivity was decreased between the cerebellum and large-scale cortical networks, including the sensorimotor, dorsal attention and default networks, but increased between the cerebellum and frontoparietal networks in medicated PD patients [23]. In our study, drug-naïve and medicated PD patients exhibit different functional alterations that are more likely due to the effect of antiparkinsonian medications. Although the mean disease duration and UPDRS-III score of the two groups are also different, they are not correlated with fMRI signals. Our results indicate that antiparkinsonian medications may modify or even reverse the changes in local neural activity or FC observed in PD patients; thus, medication could have a potential confounding effect functional activity or connectivity and should, therefore, be carefully considered in future studies.

Limitations

While our research reveals that PD patients exhibit dysfunctions in the local cerebellum, our study has several limitations. First, the sample size was not large, especially for treated PD patients, and most of the patients were drug-naïve; thus, the results obtained for all patients were similar to those obtained in drug-naive patients. Second, the cerebellum may play different roles in different PD subtypes [11]. In future studies, we should investigate the structural and functional changes that occur in the cerebellum in different subtypes of PD. Furthermore, the patients in our study were in the early stages of the disease, and longitudinal studies should investigate the role of the cerebellum in PD as the disorder progresses. In addition, we did not compare the differences between before and after taking the medication.

A longitudinal study would be able to observe changes in brain function before and after taking medication, which may be a better way to observe the effects of drugs on cerebellar function.

In conclusion, we found that the local cerebellum exhibited functional abnormalities in PD patients in a resting state. The drug-naive PD patients showed increased left local cerebellum activity and decreased FC between the left cerebellum and left prefrontal cortex. The treated PD patients showed increased right local cerebellum activity and increased FC between the right cerebellum and the left precentral and right middle occipital gyri. These results suggest that the cerebellum may play an important role in PD by exerting a compensatory effect and that antiparkinsonian medications could modify the changes that occur in local neural activity or FC in PD patients.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards This study was carried out in accordance with the recommendations of the East China of Normal University Ethics Committee and the Independent Ethics Committee of Shanghai Ninth People's Hospital. The study was approved by the East China of Normal University Ethics Committee (HR062-2018) and the Independent Ethics Committee of Shanghai Ninth People's Hospital (2016-44-T1). All subjects provided signed written informed consent documents approved by the East China of Normal University Ethics Committee and the Independent Ethics Committee of Shanghai Ninth People's Hospital.

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