Original Article

Amplitude of Low-frequency Oscillations in Parkinson's Disease: A 2-year Longitudinal Resting-state Functional Magnetic Resonance Imaging Study

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Abstract

Background: Neuroimaging studies have found that functional changes exist in patients with Parkinson's disease (PD). However, the majority of functional magnetic resonance imaging (fMRI) studies in patients with PD are task-related and cross-sectional. This study investigated the functional changes observed in patients with PD, at both baseline and after 2 years, using resting-state fMRI. It further investigated the relationship between whole-brain spontaneous neural activity of patients with PD and their clinical characteristics.
Methods: Seventeen patients with PD underwent an MRI procedure at both baseline and after 2 years using resting-state fMRI that was derived from the same 3T MRI. In addition, 20 age- and sex-matched, healthy controls were examined using resting-state fMRI. The fractional amplitude of low-frequency fluctuation (fALFF) approach was used to analyze the fMRI data. Nonlinear registration was used to model within-subject changes over the scanning interval, as well as changes between the patients with PD and the healthy controls. A correlative analysis between the fALFF values and clinical characteristics was performed in the regions showing fALFF differences.
Results: Compared to the control subjects, the patients with PD showed increased fALFF values in the left inferior temporal gyrus, right inferior parietal lobule (IPL) and right middle frontal gyrus. Compared to the baseline in the 2 years follow-up, the patients with PD presented with increased fALFF values in the right middle temporal gyrus and right middle occipital gyrus while also having decreased fALFF values in the right cerebellum, right thalamus, right striatum, left superior parietal lobule, left IPL, left precentral gyrus, and left postcentral gyrus ($P < 0.01$, after correction with AlphaSim). In addition, the fALFF values in the right cerebellum were positively correlated with the Unified PD Rating Scale (UPDRS) motor scores ($r = 0.51$, $P < 0.05$, uncorrected) and the change in the UPDRS motor score ($r = 0.61$, $P < 0.05$, uncorrected).
Conclusions: The baseline and longitudinal changes of the fALFF values in our study suggest that dysfunction in the brain may affect the regions related to cortico-striato-pallido-thalamic loops and cerebello-thalamo-cortical loops as the disease progresses and that alterations to the spontaneous neural activity of the cerebellum may also play an important role in the disease's progression in patients with PD.

Key words: Functional Magnetic Resonance Imaging; Longitudinal; Parkinson's Disease; Resting State

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is characterized by a slow and progressive degeneration of dopaminergic neurons in the substantia nigra, which leads to a loss of dopamine terminals in the striatum.[1] At the clinical level, the disease is characterized by deficits in motor control, which are clinically apparent as bradykinesia, hypokinesia, and akinesia.[2] Several neuroimaging studies have been performed to investigate the functional changes of the brain in PD.[3-6] However, the results obtained in the above functional studies are mostly task-related, and so we could not determine that these areas are also abnormal during the resting state. Thus, studying abnormal brain areas in patients with PD during the resting state will yield meaningful insights into the illness.

Resting state functional magnetic resonance imaging (fMRI) has been suggested as a promising approach to studying neurodegenerative diseases. Resting state fMRI not only avoids performance-related confounders for the patients, but also is easier to implement than is event-related fMRI because of its lower cost, noninvasiveness, and greater availability. In recent years, resting-state fMRI has been more widely applied in the study of neurodegenerative diseases,

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like PD. Wu *et al*. showed that patients with PD, when compared to normal subjects, had increased connectivity between the presupplementary motor area (pre-SMA) and the right primary motor cortex (M1) and decreased connectivity between the pre-SMA and the left putamen, right insula, right premotor cortex, and left inferior parietal lobule (IPL).[7]

However, the majority of fMRI studies in patients with PD are cross-sectional; therefore, the pattern and course of functional changes over time are not well-characterized. Findings from the relatively few functional imaging, longitudinal studies in patients with PD are heterogeneous.[8] Such inconsistencies demonstrate a need for longitudinal studies that investigate regional functional changes in the brain.

As previously mentioned, the brain dysfunction in PD will likely progressively affect all of the areas described as being involved in motor function, including the cerebellum and the lateral premotor and parietal regions.[9,10] To test this hypothesis, longitudinal MRI studies are needed; however, there are presently few longitudinal neuroimaging studies in patients with PD. This current study extends the efforts to understand the neural implications of the fractional amplitude of low-frequency fluctuations (fALFF), which provide a more specific measure of low-frequency oscillatory phenomena that reflect spontaneous neural activity, by studying PD longitudinally in which abnormalities in neural oscillations have been identified. Based on prior neurophysiological investigations of PD, we hypothesized that there will be a significant change in the fALFF power for patients with PD, particularly in the cerebellum and parietal regions. More importantly, we also investigated the effect of clinical indicators on the fALFF measures, enabling us to determine whether the changes in the clinical indicators in PD are reflected in the fALFF.

Methods

Subjects

Seventeen right-handed PD patients and 20 healthy control subjects were recruited. The patients and healthy control subjects were recruited at the Department of Neurology of Southwest Hospital. The local ethics committee approved this study, and all patients and healthy control subjects gave written, informed consent for their participation in this study. The 17 patients had a mean age of 59.11 ± 13.00 years; there were 10 women (mean age 57.80 ± 10.50 years) and 7 men (mean age 60.00 ± 16.68 years). The mean duration of their symptoms was 3.94 ± 2.58 years. The 17 patients were studied again after 2 years, with an inter-scan interval range from 875 to 973 days, with a median interval of 899.47 ± 36.61 days.

All patients met the UK Brain Bank criteria and were examined clinically, wherein their Parkinsonian motor disorder was rated using the motor subsection of the Unified PD Rating Scale-III (UPDRS-III).[11] All patients did not take any medication that might affect the central nervous system, except their anti-Parkinson medication, for at least 2 weeks prior to the MRI scans. All subjects needed a mini-mental state examination score of more than 26 to ensure that no patients met the criteria for dementia.[12] In addition, the Self-rating Depression Scale was administered to measure the severity of depression.[13]

Exclusion criteria included: (1) Prior cerebrovascular disease; (2) preexisting neurological or psychiatric disorders (including a history of seizures, global cognitive impairment, aphasia, neglect, substantial sensory disturbances, severe depression or claustrophobia); (3) use of an electrically sensitive biomedical device (e.g., cardiac pacemaker or cochlear implant); (4) metal clips in the brain; or (5) pneumonia at the time of enrolment.

All control subjects had a normal neurological examination, no history of a stroke and no significant active neurological problems. Brain MRI (T1- and T2-weighted images) was inspected by an experienced neuroradiologist, and no gross abnormalities were found in any of the participants. The same exclusion criteria listed above were applied to the control group.

Magnetic resonance imaging data acquisition

All image data were obtained using a 3T MR imaging system (TIM Trio, Siemens, Erlangen, Germany) equipped with eight-channel, phase-array head coils. After a conventional localizer scan and T2 anatomic scan, the resting-state functional images were acquired using an echo-planar imaging (EPI) sequence with the following parameters: 36 axial slices with slice thickness = 4 mm and no slice gap, repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, field of view = 256 mm^2 × 256 mm^2, data matrix = 64 × 64, resulting in a voxel size of 4 mm^3 × 4 mm^3 × 4 mm^3, and total volumes = 240.

Data processing

The functional MRI data preprocessing and statistical analyses were performed with SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/). The first 10 volumes were discarded to allow the magnetization to reach equilibrium. Then, the EPI were corrected for slice timing and realigned for head movement correction (subject data with movement of more than 1.5 mm of translation or more than 1° of rotation in any direction were excluded). Afterward, all of the realigned images were spatially normalized into the Montreal Neurological Institute EPI template, and each voxel was resampled to isotropic 3 mm^3 × 3 mm^3 × 3 mm^3. As a final step, the resting state images were spatially smoothed with an isotropic Gaussian kernel (full-width at half-maximum = 8 mm).

The fALFF analysis was performed using the REST software (http://resting-fmri.sourceforge.net). After preprocessing, the linear trend of the time series was removed and band pass filtering (0.01–0.08 Hz) was performed to reduce the effect of low-frequency drift and high-frequency physiological noise, such as respiratory and cardiac rhythms. Next, to acquire the power spectrum, the

time series was transformed to a frequency domain using fast Fourier transform. Then, the power spectrum was square-rooted and averaged across 0.01–0.08 Hz at each voxel. This averaged square root was viewed as the ALFF. A ratio of the amplitude averaged across 0.01–0.08 Hz to that of the entire frequency range (0–0.25 Hz) was computed at each voxel to obtain the fALFF, creating an amplitude map for the whole brain.

A prior study has suggested that functional connectivity at rest could be affected by micro-movements from volume to volume;[14] therefore, for each subject, we calculated frame-wise displacement (FD) values, which can reflect the temporal derivatives of the movement parameters. One control subject who had FD > 0.5 mm on more than 35 volumes was excluded from the group-level analyses. The mean FD was added as a covariate in the group statistical analyses of fALFF.

Statistical analysis

To investigate the differences in age, gender, disease duration, and years of education between the PD and control groups, two-sample *t*-tests were performed with SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Here, a $P < 0.05$ was deemed significant. For the between-group comparisons, a two-sample *t*-test model ($P < 0.001$, uncorrected) was used to explore the differences between the patients and healthy control subjects. To examine the fALFF differences between the baseline and the 2 years follow-up, the paired *t*-test was performed in REST, and the results were displayed using the REST software with a threshold of $P < 0.01$ with multiple comparisons corrected by the AlphaSim method.[15] The corrected threshold corresponded to $P_{uncorrected} < 0.001$ with a minimum cluster size of 405 mm^3. Finally, we also performed a correlative analysis between the fALFF values and clinical characteristics, including the change in the UHDRS motor score, for those regions showing fALFF differences. Given the exploratory nature of the study, we adopted a relatively liberal statistical threshold ($P_{uncorrected} < 0.05$).

Results

A total of 17 patients with PD underwent MRI at both baseline and after 2 years, using resting-state fMRI derived from the same 3T MRI. The results are presented for the 17 patients with PD between the baseline and after 2 years. The demographic and clinical characteristics of the subjects are summarized in Tables 1 and 2. No significant differences were found between the two groups with respect to gender, age, education and head motion.

Compared with the healthy control subjects, the patients with PD showed increased fALFF values in the left inferior temporal gyrus (ITG), right IPL and right middle frontal gyrus (MFG) ($P < 0.01$, after correction with AlphaSim) [Table 3, Figures 1 and 2]. A paired *t*-test showed that when compared with the baseline, the patients with PD who were analyzed during the 2 years follow-up presented with increased fALFF values in the right middle temporal gyrus (MTG) and right middle occipital gyrus (MOG) and with decreased fALFF values in the right cerebellum posterior lobe (CPL), right thalamus, left superior parietal lobule, left IPL, left precentral gyrus, and left postcentral gyrus ($P < 0.01$, after correction with AlphaSim) [Table 4, Figures 3 and 4]. In addition, the fALFF values in the right cerebellum were positively correlated with the UPDRS motor scores (correlation analysis in REST: $r = 0.51$, $P < 0.05$, uncorrected) [Figures 5 and 6].

Table 1: Demographic information for study subjects

Variables	PD ($n = 17$)	NC ($n = 20$)	*P*
Gender (male/female)	10/7	11/9	0.54*
Mean age (year)	60.29 ± 12.03	58.48 ± 6.89	0.41†
Education (year)	8.76 ± 3.70	7.45 ± 1.98	0.17†
MMSE	27.94 ± 1.71	27.40 ± 1.42	0.09†
Mean SDS	41.85 ± 7.75	43.45 ± 4.08	0.49†

SDS: Self-rating depression scale; MMSE: Mini mental state examination; PD: Parkinson's disease. *The *P* value for gender distribution in the two groups was calculated using Chi-squared test; †The *P* value was calculate using two-tail two-sample *t*-test.

Table 2: Demographic information for study subjects

Variables	$PD_{baseline}$	$PD_{follow-up}$	*P*
Number of subjects	17	17	
Mean DD (year)	3.94 ± 2.57	5.91 ± 2.81	0.00*
Mean MMSE	28.05 ± 1.85	27.94 ± 1.71	0.17*
Mean SDS	41.85 ± 7.75	43.23 ± 6.46	0.15*
UPDRS-III	17.11 ± 6.12	17.29 ± 6.30	0.98*

PD: Parkinson's disease; MMSE: Mini mental state examination; DD: Disease duration; UPDRS-III: Unified Parkinson's Disease Rating Scale-motor section. *The *P* value was calculate using pared-samples *t*-test.

Table 3: Regions showing fALFF differences between patients with PD baseline and 2 years later

Brain regions	BA	Clusters	Max *t*-statistics	*P*	MNI coordinates (mm)		
					X	Y	Z
Left MTG/ITG	20	79	4.11	<0.01	−48	0	−36
Right IPL	40	83	4.31	<0.01	−48	−69	48
Right MFG/SFG	6 8	175	4.65	<0.01	30	12	57

x, y, z, coordinates of primary peak locations in the MNI space; BA: Brodmann's area; MTG: Middle temporal gyrus; ITG: Inferior temporal gyrus; IPL: Inferior parietal lobule; MFG: Middle frontal gyrus; SFG: Superior frontal gyrus; N/A: Not applicable; ($P < 0.01$, corrected with Alphasim).

Discussion

Parkinson's disease is a common neurodegenerative disorder that primarily results from the loss of nigrostriatal dopaminergic neurons, thereby resulting in classic extrapyramidal motor impairment.[1] In addition to the dopaminergic system, PD also widely affects the nondopaminergic system in the nervous system, causing various non-motor symptoms.[16] Pathophysiological studies[1]

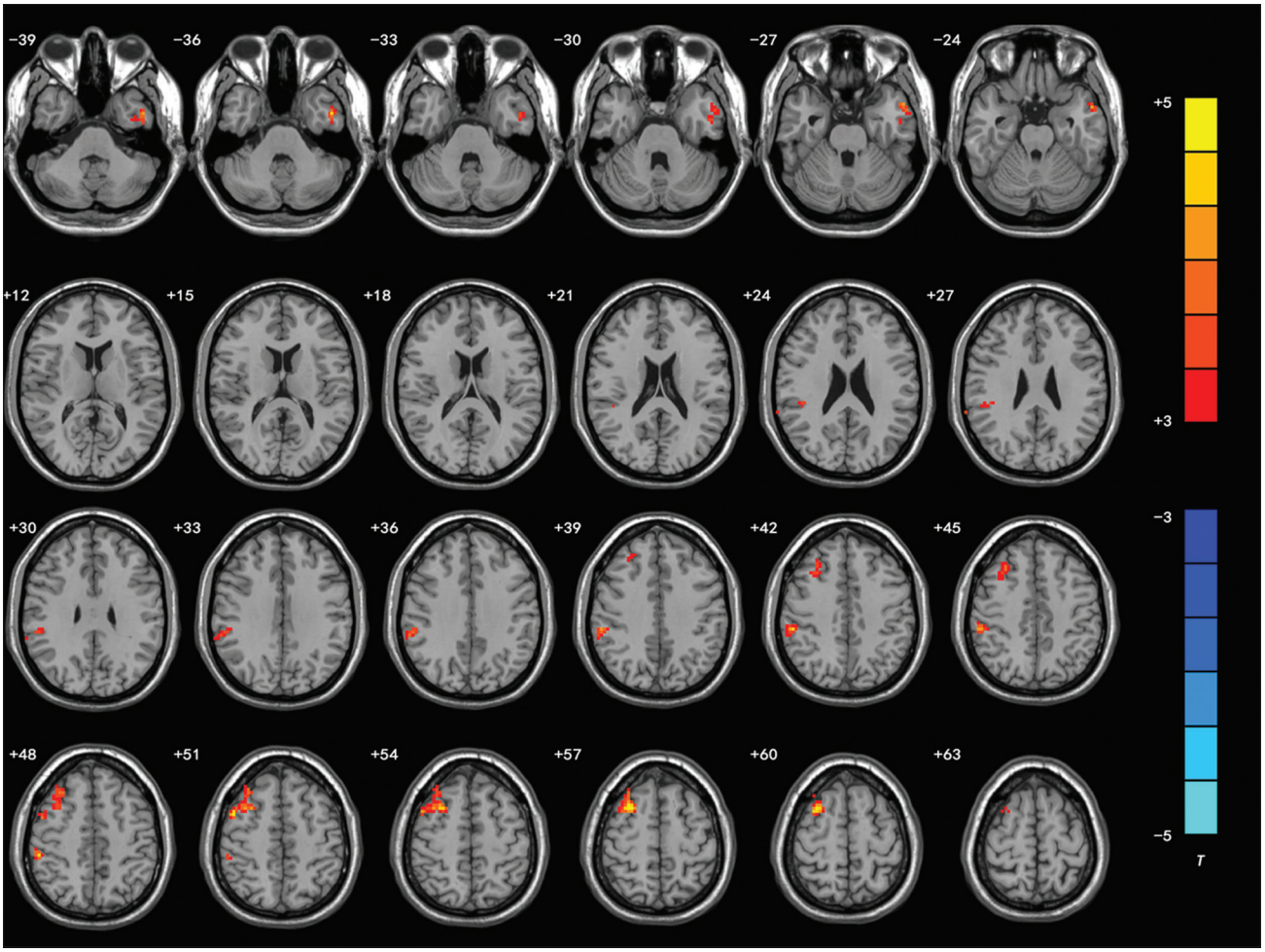

Figure 1: T-statistics maps between patients and normal control. Significantly increased fractional amplitude of low-frequency fluctuation (fALFF) value in multiple areas ($P < 0.01$ alphasim corrected), including left inferior temporal gyrus, right inferior parietal lobule and right middle frontal gyrus was exhibited. T-score bars are shown on the right. Hot and cold colors indicate fALFF increase or decrease, respectively. The left side of the image corresponds to the right side of the brain.

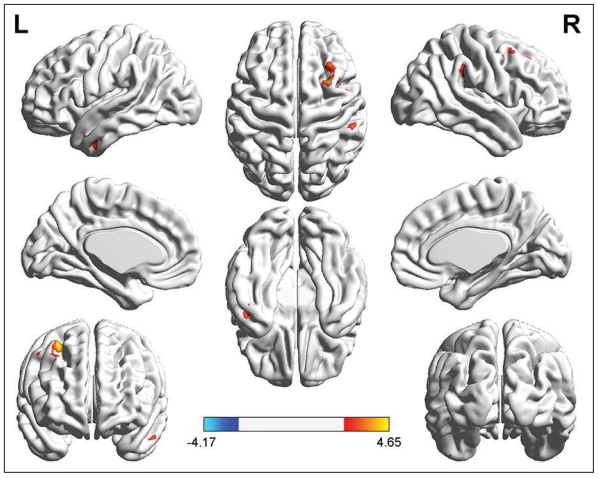

Figure 2: The anatomical distribution of the altered normalized fractional amplitude of low-frequency fluctuation between patients and normal control visualized by BrainNet Viewer v1.41 software (http://www.nitrc.org/projects/bnv/) ($P < 0.01$, 74 voxels, Alphasim corrected $P_{alpha} = 0.01$ intensity threshold >2.9208).

Table 4: Regions showing fALFF differences between patients with PD baseline and 2 years later

Brain regions	BA	Clusters	Max. *t*-statistics	MNI coordinates (mm)		
				X	Y	Z
Increased ALFF						
Right MTG/MOG	19	118	4.90	36	−78	21
Decreased ALFF						
Right CPL	NA	120	−5.09	21	−66	−60
Right LN/CN	NA	166	−6.44	15	−3	15
Left SPL/IPL/PrCG/PoCG	40/39	150	−6.39	−48	−69	48

X, Y, Z, coordinates of the primary peak locations in the MNI space. BA: Brodmann's area; MTG: Middle temporal gyrus; MOG: Middle occipital gyrus; CPL: Cerebellum posterior lobe; LN: Lentiform nucleus; CN: Caudate nucleus; SPL: Putamen superior parietal lobule; IPL: Inferior parietal lobule; PrCG: Precentral gyrus; PoCG: Postcentral gyrus; NA: Not applicable; fALFF: Fractional amplitude of low-frequency fluctuation; PD: Parkinson's disease; MNI: Montreal Neurological Institute. $P<0.01$, corrected with Alphasim.

and functional imaging studies[17] of patients with PD have shown that cortico-striato-pallido-thalamic (CSPTC) loops and cerebello-thalamo-cortical loops are typically involved in the mediation of the disease's symptoms.

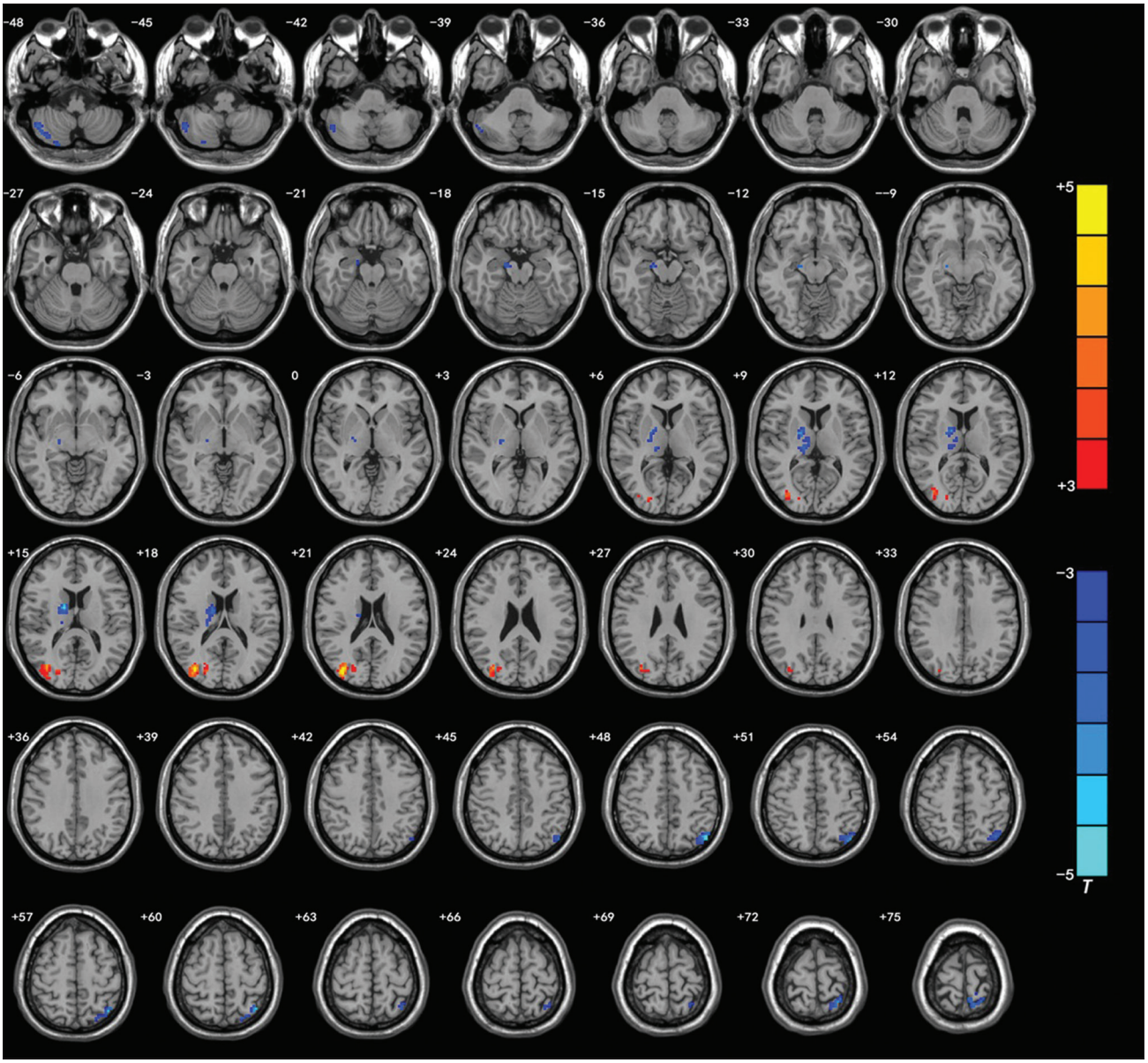

Figure 3: T-statistics maps between patients' baseline and 2 years later. Significantly increased fractional amplitude of low-frequency fluctuation (fALFF) value in multiple areas ($P < 0.01$ alphasim corrected), including right temporal lobe and occipital lobe was exhibited; while apparently decreased fALFF in the right cerebellum, right rhalamus and left parietal cortex. T-score bars are shown on the right. Hot and cold colors indicate fALFF increase or decrease, respectively. The left side of the image corresponds to the right side of the brain.

In this study, we determined the pattern and course of the structural pathology of PD with a longitudinal analysis of resting-state fMRI signals over 2 years. We also analyzed the longitudinal, within-subject, dysfunctional changes in PD and showed the relationship between whole-brain, voxel-based, spontaneous neural activity of patients with PD and their clinical characteristics. However, significant regional changes were identified across time as well. Surprisingly, declines in the fALFF values during disease progression were restricted to the right CPL, right thalamus, left superior parietal lobule, left IPL, left precentral gyrus, and left postcentral gyrus, but did not include primary or secondary motor areas. In contrast, increasing activation was localized only to the right MTG and the right MOG. In addition, the fALFF values in the right cerebellum were positively correlated with the UPDRS motor scores.

Spontaneous, LFFs (0.01–0.08 HZ) in the blood-oxygen-level-dependent (BOLD) fMRI signal is suggested to be physiologically meaningful and to reflect the brain, spontaneous neural activity.[18,19] Several studies have shown changes in low-frequency neural oscillations (0.3–2.5 Hz) in rodent models of PD. Furthermore, these studies have also shown an elevation of synchronous activation between the cortical and basal ganglia neurons or an augmentation of oscillatory activity within the basal ganglia nuclei at low frequencies.[20,21] This current study compared the magnitude of resting state BOLD signal oscillations in patients with PD, who are either taking

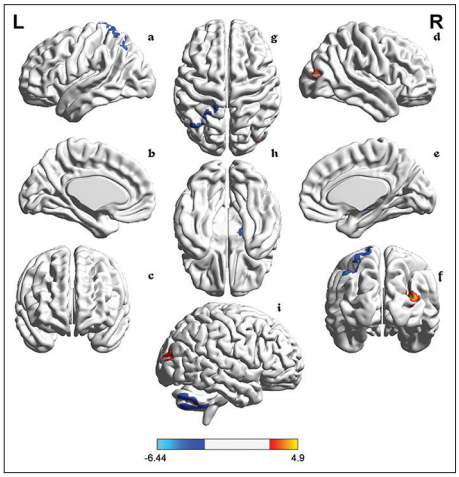

Figure 4: The anatomical distribution of the altered normalized fractional amplitude of low-frequency fluctuation between patients baseline and 2 years later visualized by BrainNet Viewer v1.41 software (http://www.nitrc.org/projects/bnv/) ($P < 0.01$, 74 voxels, Alphasim corrected $P_{alpha} = 0.01$ intensity threshold >2.9208). The cerebellum posterior lobe was especially showed with another surface file.

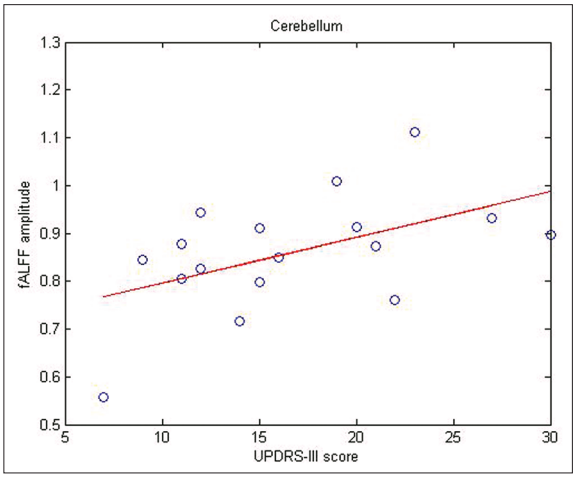

Figure 5: Scatter plots show significant positive correlations between Unified Parkinson's Disease (PD) Rating Scale motor scores and regional fractional amplitude of low-frequency fluctuation value in the right cerebellum in patients with PD ($P < 0.05$, uncorrected).

L-DOPA or are not as well as healthy, age-matched control subjects using the ALFFs.[22] Developed by Zang *et al*.,[23] this approach involves the spectral decomposition of the time-series data with a focus on amplitude in the low-frequency domain that is relevant to the hemodynamic response function (i.e., below 0.08 Hz). The fALFF is used as a normalized index of ALFF by providing the relative amplitude of the low-frequency domain as compared to the entire spectrum of frequencies.[24] In contrast, as a normalized index of ALFF, fALFF can provide a more specific measurement of low-frequency oscillatory phenomena. fALFF can weaken the biases of physiological noise and provide more accurate measures of the impacts of ALFF within a specific frequency band,[24] which will differ from the conventional BOLD analyses. The BOLD method focuses more on neuronal activity. However, fALFF analysis is used to measure neuronal fluctuations, and fALFF has been applied in the research field of neuropsychiatric illnesses, such as schizophrenia and the amnestic type of mild cognitive impairment.[25,26] Because fALFF can be used to study the magnitude of the low-frequency BOLD signal oscillations in a voxel-wise fashion across the whole brain, using this approach allows us to test the regional specificity of PD on spontaneous BOLD signal oscillations.

Fractional amplitude of low-frequency fluctuation changes between the Parkinson's disease patients and normal controls

In our current study, we found significant fALFF differences between the patients with PD and the healthy control subjects using resting-state fMRI. Compared with healthy control subjects, the PD patients showed increased fALFF values in the left ITG, right IPL, and right MFG.

The lateral premotor and inferior parietal cortex have been implicated in controlling cued movements and guiding spatial tracking, respectively.[27] Functional neuroimaging studies have repeatedly shown changes in the activation of frontal areas and the parietal lobule in patients with PD during performance of motor tasks.[9,28] Performing a positron emission tomography[29] scan in the resting state, regional metabolism was found to be abnormal in patients with PD in the IPL and the MFG using. Furthermore, there was a significant change in the regional homogeneity using resting state fMRI,[30] which is consistent with our findings. Dysfunction of the medial frontal areas and IPL, which presumably results from altered basal ganglia interactions due to nigrostriatal dopaminergic loss, can explain the impaired motor performance in patients with PD. Temporal lobe structures, including the IT cortex, are implicated in visual memory processes including storage of visual representations and associations with reward.[31] Hence, the change in ITG, along with the tail of the caudate and the ventral putamen, which receive projections from the IT cortex, appear to be involved in discrimination learning deficits in patients with PD.

Longitudinal changes in fractional amplitude of low-frequency fluctuation

Most brain regions of the patients with PD that experienced a decrease in fALFF are involved in the CSPTC loops. The CSPTC loops include several parallel circuits, such as the sensorimotor, associative, and limbic circuits.[32] The sensorimotor circuit projects somatotopically from the primary sensorimotor area (SM1), parietal motor area, and SMA to the putamen[32] and then throughout the thalamus before the circuit projects back to these cortical motor areas. The dysfunction of the sensorimotor circuit has been recognized as a crucial reason for the motor difficulties in patients with PD, such as akinesia and bradykinesia.[33] Voluntary movements appear to be initiated at the motor cortical level, with simultaneous output to multiple subcortical regions, including the putamen and thalamus.

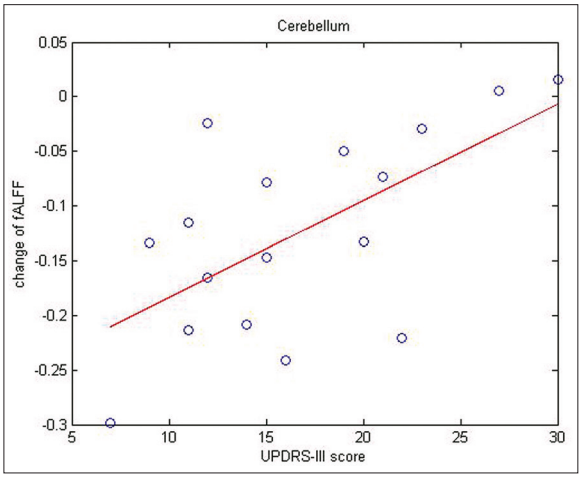

Figure 6: Scatter plots show significant positive correlations between Unified Parkinson's Disease (PD) Rating Scale motor scores and longitudinal changes of fractional amplitude of low-frequency fluctuation value in the right cerebellum in PD patients ($P < 0.05$, uncorrected).

In PD, the striatum has a reduced update of dopamine, with the most severely affected region being the putamen.[34] The putamen is hypoactivated in patients with PD during the performance of various movements compared with normal subjects.[35,36]

We found that the fALFF values were decreased in the right thalamus and striatum, especially in the putamen and globus pallidus. The putamen is located in a key position in CSPTC loops and is heavily implicated in models of PD. In our cohort, the fALFF values of the putamen decreased over time. Our finding of less functional synchronization of the putamen in PD is consistent with a previous cross-sectional study in PD patients by Wu and Hallett.[5] These results are also consistent with the findings of Playford *et al*.,[35] who showed decreased the putamen activation during self-initiated movements in comparison to the healthy control subjects.

Our data also suggest that pallidal function was decreased as the disease progressed, potentially serving as a compensatory or pathological activity. The loss of the functional segregation of CSPTC loops has been suggested to be a specific consequence of the decreasing dopaminergic input into the pallidum.[37] Mink suggested that pallidal disinhibition leads to the downstream disinhibition of competing motor programs and to a failure in facilitating desired motor programs.[38] These observations suggest that as the disorder progresses, neural activity in the basal ganglia in the resting state becomes more abnormal. The basal ganglia are also less activated at the automatic stage and may have a role in shifting a learned performance to the automatic stage.[39] The basal ganglia may support a basic attentional mechanism to bind input to output in the executive forebrain, which provides the automatic link between the voluntary effort and the operation of a sequence of motor programs or thoughts.

We also found a longitudinal decline in the activation of the superior parietal lobule and inferior parietal cortex (BA 40). This area is known to be involved in the visual–spatial integration of reaching movements.[40] The parietal cortex is related to motor selection with external information, such as auditory and visual cues, based on the integration of spatial information.[41,42] Parietal areas also play a role in the temporal aspects of the sequence to ensure that each movement occurs after successfully completing the preceding movement. Patients with parietal cortex damage have difficulty in predicting the time required to perform differentiated finger movements.[43] Posterior parietal areas could be recruited to store information about the motor sequence[44] and may have a role in selecting and monitoring a sequence. The decline of the fALFF values in the parietal cortex may point to increasing difficulties in processing visual-spatial demands with disease progression.

In addition to the changes in the striatal-thalamo-cortical loops, we further observed decreased fALFF values in the right cerebellum in patients with PD. Similar to the basal ganglia, the cerebellum is also critical to motor activity. Considerable evidence supports the cerebellum as being critical in both the acquisition and execution of automatic movements.[45,46] However, the cerebellum and basal ganglia apparently have distinct roles in the learning process[47,48] and movement control.[45] For example, the striatum is involved in building a repertoire of motor actions that can be triggered in response to appropriate environmental stimuli, whereas the cerebellum plays a more important role in combining learned movements together to produce a well-executed motor skill behavior.[48] The CSPTC loops and cerebello-thalamo-cortical loops constitute two separate neural systems.[49] The basal ganglia and cerebellum project through the thalamus to diverse target cortical areas, including the motor, premotor, prefrontal, temporal and parietal cortices, and constitute multiple "parallel" channels.[50,51] Our results suggest that although they have different physiological roles, under some pathological conditions or as a result of the reorganization of the central neural system following brain damage, both the cerebello-thalamo-cortical loops and CSPTC loops experience dysfunction.

We also found increased fALFF values in the right MTG and right MOG. These results are consistent with the findings of Kwak *et al*.[22] and Wu *et al*.,[31] who both showed an increase in values from the Resting state fMRI Data Analysis Toolkit (REST), thereby indicating activation of these two regions. Thus, at follow-up, the patients were likely to have invested neural resources to compensate for increasing motor impairment. Nevertheless, the performance measurements for the whole group declined during the follow-up period, suggesting that compensatory brain activation responses were not fully effective.

Correlates of the changes in the movement characteristics over time

All patients were examined clinically, and their Parkinsonian motor disorder was rated using the UPDRS-III score.

Correlation analyses were performed between the fALFF values and clinical data, such as motor disability as assessed by UPDRS-III. The significance level for the correlation analysis was set at $P < 0.05$ uncorrected. Interestingly, the correlation analysis revealed that increased fALFF values in the cerebellum were positively correlated with the patients' UPDRS-III scores over time.

The cerebellum is known to influence motor and cognitive operations via cerebello-thalamo-cortical circuits.[52] Recently, animal studies revealed that the cerebellum communicates with the basal ganglia via a disynaptic pathway.[53] Hyperactivation of the cerebellum has been observed,[5,54] and so deep brain stimulation of the subthalamic nucleus could suppress the cerebellar hypermetabolism of glucose.[55] Hyperactivation of the cerebellum in patients with PD has been proposed to be a functional compensation for the defective basal ganglia.[5]

We were unable to find evidence of associations between the fALFF values and changes in the UHDRS motor score. The use of more than one motor rater may make these longitudinal changes in the scores less reliable. Further work with more patients and longer follow-up will enable us to determine the existence of an association between the fALFF and clinical values as well as to investigate how the brain function changes relate to the motor decline.

Limitations

The sample was rather small, although the sensitivity was enhanced by the use of a longitudinal design and restrictive inclusion criteria. Future studies would benefit from a larger sample size.

Our current group of patients with PD did not show significant differences when compared to the healthy control subjects. However, without longitudinal follow-up data in the healthy control subjects, we cannot exclude the possibility that motor-related brain activation changed during the follow-up period.

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