



Research report

Specific frequency band of amplitude low-frequency fluctuation predicts Parkinson's disease



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HIGHLIGHTS

- PD has abnormal intrinsic neural oscillations in the corticostriatal network.
- The abnormal intrinsic neural oscillations in PD exhibit different spatial patterns.
- The frequency domain analyses may be useful to study the pathophysiology of PD.

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ABSTRACT

Resting-state functional magnetic resonance imaging (RS-fMRI) has been considered for development as a biomarker and analytical tool for evaluation of Parkinson's disease (PD). Here we utilized analysis of the amplitude low-frequency fluctuations (ALFF) to determine changes in intrinsic neural oscillations in 72 patients with PD. Two different frequency bands (slow-5: 0.01–0.027 Hz; slow-4: 0.027–0.073 Hz) were analyzed. In the slow-5 band, PD patients compared with controls had increased ALFF values mainly in the caudate and several temporal regions, as well as decreased ALFF values in the cerebellum and the parieto-temporo-occipital cortex. Additionally, in the slow-4 band, PD patients relative to controls exhibited reduced ALFF value in the thalamus, cerebellum, and several occipital regions. Together, our data demonstrate that PD patients have widespread abnormal intrinsic neural oscillations in the corticostriatal network in line with the pathophysiology of PD, and further suggest that the abnormalities are dependent on specific frequency bands. Thus, frequency domain analyses of resting state BOLD signals may provide a useful means to study the pathophysiology of PD and the physiology of the brain's dopaminergic pathways.

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1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder diagnosed on the basis of a specific array of motor symptoms (tremor, rigidity, bradykinesia and loss of postural reflexes) [1]. A large body of evidence indicates that the degeneration of dopaminergic nigrostriatal neurons [2] with consequent dysfunction of cortico-striatal-thalamic loops [3–6] is a hallmark of PD. Despite the advances, the underlying disease-related neural mechanism is not completely understood.

Previous functional neuroimaging studies using positron emission tomography (PET) or single photon emission computed

tomography (SPECT) have demonstrated that PD patients exhibit abnormal resting cerebral metabolism in the thalamus, cerebellum, caudate, prefrontal cortex and some cortical motor areas [7–12]. Recently, resting-state functional magnetic resonance imaging (RS-fMRI), with better availability and no radiation exposure, has been used as an effective noninvasive technique for exploring the underlying pathophysiology of this disorder [13–21]. The common findings of those RS-fMRI studies are the altered cortico-striatal connectivity [13,17,19,20] or the connectivity of cortical motor areas [18]. Of particular interest to the present work is the studies by Kwak et al. and Skidmore et al., which suggested the functional brain abnormalities of PD can also be studied with the amplitude of low frequency BOLD signal fluctuations (ALFF) [15,16]. Skidmore et al. found that there are significant ALFF changes in many brain regions (e.g. supplementary motor cortex, right middle frontal gyrus, and cerebellum) which reliably separate PD from healthy controls [15]. In addition, Kwak et al. investigated ALFF abnormalities

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in patients with PD on and off L-DOPA, as well as the effect of L-DOPA on ALFF measures [16]. However, even if abnormal ALFF were observed in PD patients, it remains largely unknown whether the abnormalities are related to specific frequency bands of ALFF. The primary reason we emphasized the specific frequency bands of ALFF is that independent frequency bands are generated by distinct oscillators with specific properties and physiological functions [22,23]. By decomposing RS-fMRI low-frequency fluctuations (LFF) into four distinct frequency bands [slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz), and slow-2 (0.198–0.25 Hz)], Zuo et al. detected that gray matter related oscillatory amplitudes primarily occurred in the slow-5 and slow-4 ranges [24]. Moreover, some new research has suggested that the two frequency bands contribute differentially to the LFF amplitude [24–26]. The slow-4 has greater test–retest reliability for LFF amplitude measure and more reliable BOLD fluctuation amplitude voxels than slow-5 [24]. In addition, the slow-5 showing higher power localizes more within default-mode regions, while slow-4 exhibiting less power is more robust in basal ganglia [24–26]. Those discoveries may reflect the fact that individual frequency bands could be associated with specific properties [22]. Although the origins, relation, and specific physiological functions of different frequency bands have yet to be fully clarified, it has been found that the abnormalities of LFF amplitude detected in the clinical populations are associated with the choice of slow-5 and slow-4 bands, respectively [25,27–29]. Furthermore, the functional brain networks [30] and the relationship of personality and LFF amplitude [31] are separately dependent on the slow-5 and slow-4 bands. The above imply that the pattern of intrinsic brain activity is sensitive to specific frequency bands. Taking into consideration those findings, we divided the full frequency range (0–0.25 Hz) into five distinct bands with a procedure similar to that used in our earlier study [31] and performed the ALFF analysis with the slow-5 and slow-4 bands in PD patients.

In this work, we sought to determine (i) whether the PD patients showed abnormal intrinsic neural oscillations in the corticostriatal network based on prior neurophysiological investigations [13,19–21,32] and (ii) whether the abnormalities are associated with specific frequency bands. To address the above issues, the ALFF approach was applied to calculate the magnitude of intrinsic neural fluctuations, especially slow-5 and slow-4 frequency bands both broadly distributed through gray matter and thought to be mainly linked to neuronal fluctuations were analyzed [24,25,29,33].

2. Materials and methods

2.1. Participants

Resting-state scans were acquired for 72 patients with PD (35 males) and 78 healthy subjects (46 males) in this study. The subjects were all right-handed as measured by the Edinburgh Inventory [34]. The diagnosis of PD was based on medical history, physical and neurological examinations, response to levodopa or dopaminergic drugs, and laboratory tests and MRI scans to exclude other diseases. The clinical diagnosis of PD was confirmed according to the UK Parkinson's Disease Society Brain Bank criteria [35]. Movement symptom severity for each side of the body was assessed using the motor examination of the Unified Parkinson's Disease Rating Scale (UPDRS-III) following overnight withdrawal from medication and within 1 week post-MRI scan examination [36]. All subjects reported no history of heart disease, hypertension, or diabetes. To avoid disturbance of the fMRI signal, patients with PD were chosen to have at most a mild tremor. The Mini-Mental State Exam (MMSE) was ≥ 28 in all subjects, and there was no difference between the patients and controls. The clinical data of PD patients are shown in Table 1. The present study was approved by the local Medical Research Ethics Committee of the Third Military Medical University (Chongqing, China), and informed written consent was obtained from all subjects.

2.2. Data acquisition and analysis

Functional images were acquired on a 3.0T Siemens Tim Trio whole-body MRI system (Siemens Medical Solutions, Erlangen, Germany) located at the Southwest Hospital, Chongqing, China. Subjects were instructed simply to rest

Table 1

Clinical details of patients with Parkinson's disease. UPDRS, Unified Parkinson's disease rating scale; F, female; M, male.

	PD patients	Healthy controls
Age (years)	59.7 $\pm$ 11.9	58.6 $\pm$ 8.5
Sex	35 M, 47 F	31 M, 46 F
Disease duration (years)	7.05 $\pm$ 6.01	
UPDRS motor score (off medication)	20.24 $\pm$ 8.44	

with their eyes closed, not to think of anything in particular, and not to fall asleep. Imaging data were collected transversely by using an echo-planar imaging (EPI) sequence with the following settings: TR=2000 ms, TE=30 ms, flip angle=90°, FOV=192 mm $\times$ 192 mm, slices=36, in-plane matrix=64 $\times$ 64, thickness=3 mm, no slice gap, voxel size=3.0 mm $\times$ 3.0 mm $\times$ 3.0 mm. For each subject, a total of 240 volumes were acquired, resulting in a total scan time of 480 s. Three-dimensional T1-weighted anatomical images were collected sagittally using the following volumetric 3D magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (TR=1900 ms, TE=2.52 ms, flip angle=9°, slice thickness=1 mm, slices, 176, FOV=256 mm $\times$ 256 mm, matrix size=256 $\times$ 256 and voxel size=1 mm $\times$ 1 mm $\times$ 1 mm) on each subject.

All data were analyzed with the SPM8 package (<http://www.fil.ion.ucl.ac.uk/spm/>). The first 5 volumes of each functional data were discarded due to instability of the initial MRI signal and adaptation of participants to the circumstance. The remaining images were first corrected for acquisition delay between slices and head motion. Then, the resulting images were spatially normalized into a standard stereotaxic space at 3 mm $\times$ 3 mm $\times$ 3 mm, using the Montreal Neurological Institute (MNI) echo-planar imaging (EPI) template. The normalized functional data underwent spatial smoothing [8-mm full width at half maximum (FWHM) Gaussian kernel] and removal of linear trends. Finally, six head motion parameters were regressed, since recent studies [16,17,37] demonstrated that head motion had a confounding effect on LFF amplitude analysis in PD.

Anatomical data were processed to separate the gray matter from the 3D T1-weighted structural scans using the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm.html>). Anatomical images were bias-corrected, tissue classified, and registered using linear (12-parameter affine) and nonlinear transformations, within a unified model [38]. Then, the gray matter (GM) partitions were modulated to preserve actual GM values locally. The segmented gray matter volume was treated as an external regressor in the subsequent multiple regression analysis.

2.3. ALFF calculation

ALFF values were calculated using REST software (www.restfmri.net). The time series for each voxel was first transformed to the frequency domain using a Fast Fourier Transform, and then the power spectrum was obtained. The square root of the power spectrum was computed, after that averaged across a predefined frequency interval. This averaged square root was taken as the amplitude of LFF (ALFF) [39]. In current study, we divided the full frequency range (0–0.25 Hz) into five distinct bands with a procedure similar to that used in our earlier study [31]: [slow-6 (0–0.01 Hz), slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz) and slow-2 (0.198–0.25 Hz)] [22–25]. The ALFF and then was computed at the slow-5 and slow-4 bands which mainly related to physiological meanings [24,25,29,33]. In contrast, the signals of slow-6, slow-3, and slow-2 were discarded because they mainly reflect low frequency drift, white matter signals, and high-frequency physiological noises, respectively [25]. Under the studied frequency ranges, ALFF of each voxel was computed for each subject, and it was further divided by the global mean value to reduce the global effects of variability across participants [25,29].

2.4. Statistical analysis

Voxel-by-voxel-based comparisons of ALFF were performed between groups using two sample *t*-tests in SPM8 with gender, age, averaged gray-matter volumes and mean relative displacement [37,40,41] as covariates. The significance of group differences under the slow-5 and slow-4 bands was set at $p < 0.05$ corrected with FWE and FDR, respectively.

In addition, to seek evidence that altered functional activity associated with the disease severity, a correlation analysis of ALFF versus the UPDRS score was performed in the patients with PD.

3. Results

3.1. Head movement parameters

There was no significant difference in head motion measured by mean or maximum relative displacement between the two groups using the two-tailed two-sample *t*-test [mean: $t = 1.324$, $p = 0.19$;

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