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Research article

Alterations of the amplitude of low-frequency fluctuations in anxiety in Parkinson's disease

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ABSTRACT

Object: Anxiety disorders are very common in Parkinson's disease (PD), but neural mechanisms underlying these symptoms still remain elusive. In the present study, we aim to investigate the neural substrates in anxiety disorders in PD.

Methods: The present study comprised 48 PD patients and 19 healthy subjects. According to a Hamilton Anxiety Rating Scale cutoff score of 12, we divided PD patients into PD with anxiety groups (n = 15) and PD without anxiety groups (n = 33). Patients with apparent depressive symptoms and cognitive decline were excluded. All subjects were evaluated for demographic and clinical characteristics and performed 3.0 T MRI scans. The alterations of neural activity were examined utilizing resting-state fMRI (rs-fMRI) combined with the amplitude of low-frequency fluctuations (ALFF) approach.

Results: Results of the analysis of covariance indicated that PD patients with anxiety displayed increased ALFF mainly in right cerebellar posterior lobe (CPL), bilateral brainstem and right orbitofrontal gyrus (OFG). Subsequently, the Spearman correlation demonstrated negative correlation between ALFF values in right cerebellum_9 and the Hamilton Anxiety Rating Scale scores.

Conclusion: Our findings demonstrated that anxiety disorders in PD were associated with increased activities in anxiety-related brain regions, including OFG, brainstem and CPL, using the ALFF approach.

1. Introduction

Anxiety disorders are common in PD and the presenting is up to 55% in PD patients [1]. They contribute to increased severity of motor symptoms and negatively impact life quality of PD patients [2]. Although depression and anxiety are often concurrent in PD patients [3,4], they were correlated with different clinical/therapeutic features [4], suggesting different underlying pathophysiological mechanisms. However, the PD research has been mainly concentrated on depression in recent decades and less attention has been given to anxiety. Thus the pathogenesis of anxiety in PD is still not clear. At present, treatment of anxiety in PD is also a tough problem, as antiparkinsonism drugs can't improve anxiety symptoms [5]. A better understanding of the neural substrates of anxiety in PD is urgently required to direct effective and targeted treatment strategies.

Advanced neuroimaging techniques have been extensively employed to explore the neural substrates of neurologic and psychiatric diseases, such as various mood disturbances in PD [6]. Resting-state functional magnetic resonance imaging (rs-fMRI) examined spontaneous fluctuations in the blood oxygen level dependent (BOLD) signal of brain without any explicit stimulation, namely revealing the phenomenon of spontaneous neuronal activity at rest [7]. Alternatively, the amplitude of low-frequency fluctuations (ALFF) [8], a resting-state data analysis measuring the spontaneous amplitude of low-frequency (0.01–0.08 Hz) BOLD signal, has been widely applied to access spontaneous neural activity relating to cerebral physiological and pathological states.

To date, studies on spontaneous BOLD activity alterations have shed light on the neural substrates for depression in PD [9], but less rs-fMRI studies have explored whether anxious PD patients present an abnormal cerebral activities. In this study, we aim to compare the resting-state cerebral activity changes among PD patients with anxiety (PD-A), PD patients without anxiety (PD-NA) and healthy controls (HC) using ALFF approach.

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2. Materials and methods

2.1. Participants

Patients were consecutive cases diagnosed by a movement disorder specialist according to the UK PD Brain Bank criteria [10] for idiopathic PD between July 2014 and February 2016 at the outpatient clinic of our hospital. Exclusion criteria: patients with (1) corticobasal degeneration, progressive supranuclear palsy, multiple system atrophy, vascular parkinsonism, and other forms of parkinsonism; (2) contraindications to MRI, such as claustrophobia, metallic implants, or devices in the body; (3) intake of psychoactive medications at present; (4) suffering from severe neurological and psychiatric diseases; (5) diagnosis of other sever acute and chronic diseases. To exclude potential confounding factors, patients with severe cognitive decline, defined as a Mini Mental State Examination (MMSE) score ≤ 24 and clinically prominent depressive symptoms (17-item Hamilton Depression Rating Scale, HAMD score ≥ 14) were eliminated. MRI scans and clinical examinations were performed at least 12 h after withdrawal from anti-parkinsonian medications to mitigate the pharmacological effects on neural activity. Meanwhile, nineteen HC without psychological and neurological disturbances or neuroimaging abnormalities were recruited into our scientific research voluntarily. All subjects were right-handed. Written informed consent was obtained from all participants before beginning the experiment, and the study was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University.

2.2. Clinical assessments

Patients were classified into PD-A (n = 15) and PD-NA (n = 33) by the cut off score of 12 on the Hamilton Anxiety Rating Scale (HAMA) score [3,11,12]. The HAMA scale was suggested to be potentially useful in the evaluation of anxiety severity in clinical practice and research [12]. It was a fourteen-item scale (total scores ranging 0–56) with a satisfactory inter-item correlation, convergent validity, and factorial structure [11], measuring both psychic and somatic anxiety symptoms. Anxiety disorders of PD patients were assessed by the trained movement disorder specialist (Kezhong Zhang) sensitized to psychiatric disorders in PD. In all patients, we used the Unified Parkinson's Disease Rating Scale (UPDRS-III) and Hoehn and Yahr (H&Y) staging to assess disease severity and disease stage, respectively. Total mental status, behavior, emotion and daily life activities in PD patients were evaluated via UPDRS-I and UPDRS-II. Total levodopa-equivalent daily dose (LEDD), LEDD of levodopa preparations and LEDD of dopamine receptor agonists in each PD patient of the two subgroups were calculated [13]. Disease duration of each PD patient, education duration and work activity (manual or intellectual work with any musical skill, any scientific or artistic skill) of each subject was recorded. Global cognitive function, executive function and symptoms of depression were also quantified separately for each subject using MMSE, Frontal Assessment Battery (FAB) and HAMD.

2.3. Image acquisition

MRI scanning were performed with a 3.0 T Siemens MAGNETOM Verio whole-body MRI system (Siemens Medical Solutions, Germany) equipped with eight-channel, phase-array head coils. Tight foam padding was used to minimize head movement, and ear-plugs were used to reduce noise. Subjects were instructed to remain motion less, close their eyes, remain awake, and not to think about anything in particular. Three-dimensional T1-weighted anatomical images were acquired using the following volumetric 3D magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (repetition time (TR) = 1900 ms, echo time (TE) = 2.95 ms, flip angle (FA) = 9°, slice thickness = 1 mm, slices = 160, field of view (FOV) = 230 × 230 mm^2, matrix size = 256 × 256 and voxel size = 1 × 1 × 1 mm^3). Resting-state functional images were collected using an echo-planar imaging (EPI) sequence (TR = 2000 ms, TE = 21 ms, FA = 90°, FOV = 256 × 256 mm^2, in-plane matrix = 64 × 64, slices = 35, slice thickness = 3 mm, no slice gap, voxel size = 3 × 3 × 3 mm^3, total 4 vol = 240).

2.4. Processing of fMRI

The data were analyzed using the data processing assistant for resting-state fMRI (DPARSF, http://www.restfmri.net/forum/dparsf) [14] with Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk). These steps included: 1) removal of the first 10 time points; 2) slice timing correction; 3) head motion correction via six-parameter rigid body spatial transformation during data acquisition; 4) nonlinear registration of the high-resolution T1 structural images to the Montreal Neurological Institute (MNI) template, in which T1 structural images were segmented as white matter, gray matter, and cerebrospinal fluid using a new segment algorithm with DARTEL (diffeomorphic anatomical registration through exponentiated lie algebra), followed by further structural analyses of the resulting segments; 5) nuisance signal removal (white matter, cerebrospinal fluid, global signal, 6-head motion parameters as covariates) via multiple regression; 6) spatial normalization to the Montreal Neurological Institute template; 7) resampling of images into a spatial resolution of 3 × 3 × 3 mm^3; 8) spatial smoothening with a Gaussian kernel (full width at half-maximum = 4 × 4 × 4 mm^3). In this study, we excluded subjects from further analysis if the translation or rotation of head movement was > 2 mm or 2° in any direction. Additionally, the mean head translation, mean head rotation, and frame-wise displacement were calculated for each group [15]. Analysis of those head motion parameters did not reveal differences among the three groups ($p > 0.05$).

2.5. ALFF calculation and statistical analysis

ALFF analysis was performed using the Resting-State fMRI Data Analysis Toolkit (http://restfmri.net/forum/REST). The ALFF calculation procedure: 1) Fast Fourier Transform (FFT) was used to convert all voxels from the time domain to the frequency domain; 2) the ALFF of every voxel was calculated by averaging the square root of the power spectrum across 0.01 Hz to 0.08 Hz; 3) the resulting ALFF was converted into z-scores by subtracting the mean and dividing by the global standard deviation for standardization purposes. After that, band-pass filtering ($0.01 < f < 0.08$ Hz) was performed and linear trend was removed.

An analysis of covariance (ANCOVA) was performed to identify brain areas with significant differences among three groups with age, gender, education, HAMD scores, FAB scores and gray matter volume as covariates (voxel-level $p < 0.01$, cluster size > 22 voxels, corresponding to a corrected $p < 0.01$ as determined by AlphaSim correction) (http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf). These areas were then extracted as a mask. Then, two-sample post hoc *t*-tests were performed within this mask, with age, gender, education, HAMD scores, FAB scores and gray matter volume as covariates, to further detect significant differences between groups (voxel-level $p < 0.01$, cluster size > 6 voxels, corresponding to a corrected $p < 0.01$ as determined by AlphaSim correction). Subsequently, the clusters that showed significant differences in ALFF between PD-A and PD-NA groups were extracted separately. Then the average ALFF value of each cluster was calculated to explore the correlations with anxiety severity, age and other neuropsychological scores, which were examined using the Spearman correlation by IBM SPSS statistics v20.0.0 software (SPSS, Chicago, IL, USA) and the significance was set at $p < 0.05$.

2.6. Statistical analysis of demographic and clinical data

Clinical data of the three groups were analyzed using IBM SPSS