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Research report

Abnormal functional connectivity density in Parkinson's disease

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HIGHLIGHTS

- Voxel-wise contrasts of FCD were performed between PD patients and controls.
- PD showed decreased FCD mainly in the ventral stream and frontal regions.
- PD showed increased FCD in bilateral precuneus and PCC.

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ABSTRACT

The pathology of Parkinson's disease (PD) is not confined to the nigrostriatal pathway, but also involves widespread cerebral cortical areas. Using seed-based resting state functional connectivity, many previous studies have demonstrated that PD patients have abnormal functional integration. However, this technique strongly relies on a priori selection of the seed regions and may miss important unpredictable findings. Using an ultrafast voxel-wise functional connectivity density approach, this study performed a whole brain functional connectivity analysis to investigate the abnormal resting-state functional activities in PD patients. Compared with healthy controls, PD patients exhibited decreased short-range functional connectivity densities in regions that were mainly located in the ventral visual pathway and decreased long-range functional connectivity densities in the right middle and superior frontal gyrus, which have been speculated to be associated with visual hallucinations and cognitive dysfunction, respectively. PD patients also exhibited increased short- and long-range functional connectivity densities in the bilateral precuneus and posterior cingulate cortex, which may represent a compensatory process for maintaining normal brain function. The observed functional connectivity density alterations might be related to the disturbed structural connectivity of PD patients, leading to abnormal functional integration. Our results suggest that functional connectivity density mapping may provide a useful means to assess PD-related neurodegeneration and to study the pathophysiology of PD.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that is characterized by tremor, rigidity, slowness of movements, and postural instability, and is associated with progressive neuronal loss of the substantia nigra and other brain structures [1]. Although it has been extensively investigated, the underlying pathophysiology of this disorder remains unclear. Extensive neuroimaging studies using positron emission tomography (PET), single photon emission computed tomography (SPECT) and perfusion magnetic resonance imaging (MRI) have reported widespread cortical hypometabolism and hypoperfusion in PD

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patients during rest [2–4]. Morphometric studies based on structural MRI have also documented significant reductions in gray matter volume [5,6], cortical thickness [6–9], and cortical gyrification, as well as subcortical volumetric atrophy [8,10,11], in PD patients. These univariate approaches have provided important information on the roles played by each brain region in the pathogenesis of PD. Nevertheless, they do not allow us to evaluate the interactions or functional integration among brain regions. Resting-state functional connectivity (FC), which measures the temporal correlations of spontaneous fluctuations in brain activity between spatially remote regions, has been extensively used to explore the functional interactions between brain regions. Using resting-state FC, many studies have been conducted to investigate abnormal functional integrations in PD patients. For example, abnormal cortico-striatal FC has frequently been reported in PD patients [12–14]. Another study demonstrated impaired FC in motor control networks in PD [15]. A recent study revealed altered FC of the dentate nucleus in PD patients [16]. However, all of these studies adopted seed-based FC analyses, which strongly rely on a priori selection of the seed regions and may miss important unpredictable findings. Whole brain FC analyzes are needed to obtain a complete picture of the abnormalities of the functional networks in PD.

Functional connectivity density (FCD) mapping, an ultrafast graph theory method, measures the number of functional connections between a given voxel and others voxels [17]. In contrast to traditional FC, FCD does not require a priori selection of seed regions and allows for the identification of functional hubs (densely connected regions) with high sensitivity. Higher FCDs for particular voxels indicate that those voxel are functionally connected to a large number of other brain voxels and suggest that those voxels play more important roles in information processing. Based on the neighboring relationships between brain voxels, FCD can be further divided into short- and long-range FCDs [18]. In previous neuroimaging investigations, FCD was successfully used to study the abnormal functional integration in children with attention-deficit/hyperactivity disorder [19], children with anisometropic amblyopia [20] and blind subjects [21].

Therefore, the present study aimed to use FCD to investigate the functional connectivity in PD patients compared with matched healthy controls. Specifically, voxel-wise contrasts of the short- and long-range FCDs were performed between healthy controls and PD patients using a general linear model (GLM) tool.

2. Materials and methods

2.1. Participants

Thirty-one PD patients without dementia and 34 healthy controls were included in the study. The subjects were all right-handed as measured by the Edinburgh Inventory [22]. The clinical diagnosis of PD was confirmed according to the UK Parkinson's Disease Society Brain Bank criteria [23]. All participants underwent extensive neurologic, neuropsychological, and clinical imaging examinations. Participants with a history of neurologic or psychiatric disease or neurologic sequelae induced by brain trauma were excluded. Patients were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS)-III motor scale [24], the Hoehn and Yahr disability scale [25] and mini-mental state examination (MMSE) by a trained physician during off states which is defined by withholding administration of anti-parkinsonian drugs for at least 12 h overnight. The total dose of dopaminomimetics was converted to a levodopa equivalent daily dose using a previously described conversion rate [26]. Detailed demographic and clinical data are shown in Table 1. This study was approved by the institutional review board and written informed consent was obtained from all participants.

Table 1
Demographics and clinical details of the subjects.

	PD patients (n = 31)	Controls (n = 34)	P value
Age (years)	56.71 ± 11.95	57.74 ± 9.11	0.70[a]
Sex (male/female)	16/15	12/22	0.18[b]
Disease duration (years)	4.18 ± 2.74	NA	NA
UPDRS motor score (off medication)	21.26 ± 12.06	NA	NA
H&Y (off medication)	1.55 ± 0.47	NA	NA
LEDD (mg/day)	317.56 ± 162.35	NA	NA
MMSE	28.5 ± 1.2	29.3 ± 1.1	0.36[a]

Abbreviations: PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr staging; MMSE, Mini-mental state examination; LEDD, levodopa equivalent daily dose; NA, not available.
[a] The P value was obtained by a two-tailed two-sample t-test.
[b] The P value was obtained by a chi-square test. Data are presented as mean ± SD.

2.2. MRI data acquisition

Functional images were acquired on a 3.0-T Siemens Tim Trio whole-body MRI system (Siemens Medical Solutions, Erlangen, Germany) located at Southwest Hospital, Chongqing, China. The subjects were instructed to rest with their eyes closed, not think of anything in particular, and not fall asleep. Imaging data were collected transversely with an echo-planar imaging (EPI) sequence using the following settings: TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 192 mm × 192 mm, slices = 36, in-plane matrix = 64 × 64, thickness = 3 mm, no slice gap, and voxel size = 3.0 mm × 3.0 mm × 3.0 mm. For each subject, a total of 240 volumes were acquired, resulting in a total scan time of 480 s. To minimize the impact of dopaminergic medication, the MRI scans were performed during a relatively hypodopaminergic state (12 h after a last dose of dopamimetic treatment), that is, in off state.

2.3. Preprocessing

Images were realigned and normalized to the standard MNI (Montreal Neurological Institute) space using the Statistical Parametric Mapping package (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). A fourth degree B-spline function without weighting and warping was used for image realignment, and a 12 parameter affine transformation with medium regularization, 16 nonlinear iterations, and a voxel size of 3 mm × 3 mm × 3 mm was used for spatial normalization. Motion-related fluctuations were removed from the MRI signals using a multi-linear regression with six time-varying realignment parameters (three translations and three rotations). Band-pass temporal filtering (0.01–0.1 Hz) was used to remove magnetic field drifts of the scanner [27] and to minimize the physiologic noise of the high-frequency components [28]. Voxels with a signal-to-noise ratio (as a function of time) <50 were eliminated to minimize unwanted effects from the susceptibility-related signal-loss artifacts on the FCD mapping [17].

2.4. FCD mapping

After the preprocessing procedures, we calculated the short- and long-range FCDs of each voxel using an in-house script written on Linux platform based on the method proposed by Tomasi and Volkow [17,29]. FCD calculations were restricted to voxels within the gray matter regions with a signal to noise ratio of >50 to minimize the effects of susceptibility-related signal loss artifacts. The