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Research paper

Abnormal fronto-striatal functional connectivity in Parkinson's disease

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HIGHLIGHTS

- We mapped and quantified the fronto-striatal network.
- Significantly decreased Γ in the left putamen was found in PD patients.
- Significantly decreased Γ in the right globus pallidum was found in PD patients.
- Negative correlations between η and disease durations were found in PD patients.

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ABSTRACT

Parkinson's disease (PD) is characterized by the relatively selective depletion of dopamine in the striatum, which consequently leads to dysfunctions in cortico–striatal–thalamic–cortical circuitries. It has been shown that the most common cognitive deficits in PD patients are related to the fronto-striatal circuits. In PD, most previous functional connectivity studies have been performed using seed-based methods to identify the brain regions that are abnormally connected to one or more seeds, but these cannot be used to quantify the interactions between one region and all other regions in a particular network. Functional connectivity degree, which is a measurement that can be used to quantify the functional or structural connectivity of a complex brain network, was adopted in this study to assess the interactions of the fronto-striatal network. Compared to healthy controls, PD patients had significantly decreased total functional connectivity degree for the left putamen and the right globus pallidum in fronto-striatal networks. Additionally, negative correlations between the fronto-pallial functional connectivity degree (i.e., the right globus pallidum with the left middle frontal gyrus, and with the right triangular part of inferior frontal gyrus) and disease duration were observed in PD patients. The results of this study demonstrate that fronto-striatal functional connectivity is abnormal in patients with PD and indicate that these deficits might be the result of motor and cognitive dysfunctions in PD patients.

1. Introduction

Parkinson's disease (PD) is characterized by the relatively selective depletion of dopamine in the striatum, which consequently leads to dysfunctions in cortico–striatal–thalamic–cortical circuitries [1]. These dysfunctions are believed to underlie the hallmark motor features of PD, including tremor, muscle stiffness or rigidity, slowness of movement or bradykinesia and postural instability [2]. In addition to these motor symptoms, evidences of non-motor symptoms including cognitive impairment [3,4], executive dysfunctions [5,6] and depression [7], in PD patients are

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accumulating. Moreover, it has been shown that the most common cognitive deficits in PD patients are related to the fronto-striatal circuits [8,9], which are neural pathways that connect the frontal lobe regions with the striatum and that mediate motor, cognitive, and behavioral functions within the brain. Disruptions in these circuits have been demonstrated in PD patients using functional magnetic resonance imaging (fMRI) [10] or positron emission tomography (PET) [11,12]. These findings indicate that fronto-striatal connections might play important roles in the pathophysiology of PD.

With advances in fMRI, studies of functional connectivity have been widely used to explore interregional connectivity and to characterize neural interactions among brain regions during particular tasks [13,14]. Previous studies [15–18] have investigated functional connectivity in cortical–striatal networks using seed-based methods. However, these identify only the functional changes that occur in particular brain areas, and they cannot be used to quantify global changes in functional connectivity in the brain. Recently, the total functional connectivity degree, which is defined as the sum of all of the connectivity degrees between the seed and all other regions, has been used to describe the amount of information that a region receives from other regions in the network and to quantify the importance of a particular brain area within a complex brain network [19–21]. Thus, a larger functional connectivity degree for a particular region indicates that it has more functional connections with more brain regions and suggests that it plays a more important role in the network. Moreover, several previous studies using functional connectivity degree have been successfully performed, and these have presented evidences for significant changes in particular brain networks [20,21].

Studies of interactions in the resting state fronto-striatal network may contribute more to our understanding of the neural substrates underlying the symptoms of PD than simple investigations of regional brain activity because a growing amount of evidence demonstrates that brain functions are implemented by involved networks. Thus, we used resting-state functional connectivity degree to investigate interactions among fronto-striatal networks in PD patients.

2. Methods and materials

2.1. Participants

Thirty-one PD patients without dementia and thirty-three healthy controls were included in the study. All included individuals were right-handed. Detailed demographic and clinical data are shown in Table A1. Clinical diagnosis and measurements of PD were assessed based on the UK Parkinson's Disease Society Brain Bank criteria [22], the Unified Parkinson's Disease Rating Scale (UPDRS)-III motor scale [23], the Hoehn and Yahr disability scale [24] and the Mini-Mental State Examination (MMSE). All assessments were conducted by a trained physician during an off state, which is defined as the withholding of the administration of anti-parkinsonian drugs for at least 12 h overnight. All participants underwent extensive neurological, neuropsychological, and clinical imaging examinations. This study was approved by the institutional review board and written informed consent was obtained from all participants. More detailed information can be found in [25,26].

2.2. MRI data acquisition

Functional images were acquired using a 3.0-T Siemens Tim Trio whole-body MRI system (Siemens Medical Solutions, Erlangen, Germany) at Southwest Hospital, Chongqing, China. During data acquisition, the subjects were instructed to rest with their eyes closed, to avoid thinking of anything in particular, and to not fall asleep. Imaging data were collected transversely using an echo-planar imaging (EPI) sequence. The acquisition parameters were: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, field of view (FOV) = 192 mm × 192 mm, slices = 36, in-plane matrix = 64 × 64, and thickness = 3 mm. These parameters yielded a total of 240 volumes with a voxel size = 3.0 mm × 3.0 mm × 3.0 mm.

2.3. Resting-state fMRI data preprocessing

Pre-processing of the resting-state fMRI data was performed using the MATLAB toolbox named Data Processing Assistant for Resting-State for "pipeline" data analysis of resting-state fMRI (DPARSF, http://rfmri.org/DPARSF). For each participant, the preprocessing steps were: (1) the first 10 volumes of each functional time series were discarded to allow for magnetization equilibrium; (2) the slice times for the remaining 230 images were corrected and realigned to the first volume to account for head motion (subjects with head motion exceeding 1.5 mm in any dimension or 1.5° of angular motion through the resting-state run were removed); (3) all data were spatially normalized to the Montreal Neurological Institute (MNI) template and resampled to $3 \times 3 \times 3\,mm^3$; (4) spatial smoothing was performed using a Gaussian kernel of 6 mm full-width at half maximum (FWHM); (5) temporal band-pass filtering (0.01–0.08 Hz) was performed; (6) linear and quadratic trends were removed; and (7) nuisance signals, such as those from white matter (WM), cerebrospinal fluid (CSF), and six motion parameters, were regressed out. Finally, this pre-processing procedure provided a four-dimensional residual time series in a standard MNI space for each participant.

2.4. Fronto-striatal networks

The striatal regions for network analyses were extracted from the automated anatomical labeling (AAL) template and included the caudate nucleus, the putamen nucleus, and the globus pallidus in each brain hemisphere. The frontal cortex was divided into 14 regions in each brain hemisphere. The detailed information regarding to these regions is shown in Table A2. We then calculated Pearson's correlation coefficients for the average time series between each striatal and frontal region pair and averaged them in the control group. Finally, we set a threshold with a mean correlation value of $R > 0.3$ to eliminate weak correlations that may have resulted from noise to map each striatal region's network (Table A3). We also assessed the effects of the different correlation thresholds on the main results, and no significant changes were found (Table A4). Thus, all further analyses were based on a network threshold of $R > 0.3$.

2.5. Functional connectivity degree analyses

In the current study, we defined the total functional connectivity degree Γ to represent the information that each striatal region receives from the frontal cortex. Similar to previous studies [20,21], the functional connectivity degree η_{ij} is defined as $\eta_{ij} = e^{-\varepsilon d_{ij}}$, where ε is a real positive constant that is fixed to 2, measuring how the strength of the relationship decreases with the distance between the two regions, and d_{ij} is the distance between the two regions. The d_{ij} is defined as $d_{ij} = (1 - c_{ij})/(1 + c_{ij})$, where $< MML : MSUB > cij < /MML : MSUB >$ represents the Pearson's correlation coefficient of the two regions. Thus, we can define the total functional connectivity degree Γ_i of a node i as the sum of all connectivity degrees between i and all other nodes in the network