Parkinsonism and Related Disorders xxx (2018) 1–7

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Decreased interhemispheric homotopic connectivity in Parkinson's disease patients with freezing of gait: A resting state fMRI study

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ARTICLE INFO

Article history:
Received 18 May 2017
Received in revised form
18 February 2018
Accepted 14 March 2018

Keywords:
Parkinson's disease
Resting-state fMRI
Voxel-mirrored homotopic connectivity
Freezing of gait

ABSTRACT

Introduction: Freezing of gait is a common complaint in patients with Parkinson's disease (PD). However, the neural bases of freezing of gait in PD remain uncertain. Existing studies on PD patients with freezing of gait (PD-FOG+) have reported damage of the corpus callosum, the largest commissural bundle of the brain. Thus, in this study we explored homotopic connectivity to investigate FOG-related interehemispheric alterations

Methods: A total of 21 PD-FOG + patients, 33 PD patients without freezing of gait (PD-FOG-), and 24 matched healthy controls were recruited. All PD patients were evaluated via the FOG questionnaire (FOGQ) and all subjects had a resting state functional magnetic resonance imaging (rs-fMRI) scan. The pattern of the homotopic connectivity was measured with the voxel-mirrored homotopic connectivity (VMHC) approach.

Result: The PD-FOG + patients showed decreased VMHC values in the inferior parietal lobe (IPL) compared to both PD-FOG-patients and healthy controls. In PD-FOG + patients, the mean VMHC values in the IPL were negatively correlated with the FOGQ scores. Receiver operating characteristic curves analyses revealed that the VMHC in the IPL had discriminatory function distinguishing PD-FOG + patients from PD-FOG-patients or healthy controls.

Conclusion: Decreased VMHC values of PD-FOG + patients relative to PD-FOG- and healthy controls in IPL maybe a unique feature for PD-FOG+ and it may have the ability to separate PD-FOG + patients from PD-FOG- and healthy controls.

1. Introduction

Freezing of gait (FOG), which affects approximately 50% of people with Parkinson disease (PD), is a disabling phenomenon that seriously affects the quality of life of PD patients [1]. It is defined as "a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" and is often characterized by the episodic feeling of feet "glued" to the floor [2]. Medical and rehabilitation treatment may improve FOG but not to the same extent as other PD symptoms [3].

Although FOG has catastrophic consequences for the PD patients, its pathophysiological mechanisms are still not fully understood. Early studies had shown that impaired control of rhythmicity, bilateral incoordination, and gait asymmetry were important aspects of freezing [4–6]. Similarly, some studies had reported that the poor coordination between the legs or gait cycle disorders were related to FOG [7]. Recently, several studies have found damage of the corpus callosum in PD patients with FOG using structural and functional connectivity [8,9] It is well known that the corpus callosum (CC) is the main collection of white matter bundles connecting both hemispheres so that both sides of the body can be coordinated. Its structural damage may affect the functional coordination between the cerebral hemispheres. Thus, it is reasonable to expect that the deficits of hemispheric interactions play a key role in the pathophysiology of FOG in PD. Therefore, it would be meaningful to examine the inter-hemispheric coordination in PD.

Resting-state fMRI (rs-fMRI), which captures the patterns of coherent spontaneous fluctuations of blood oxygen level

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https://doi.org/10.1016/j.parkreldis.2018.03.015
1353-8020/

dependent (BOLD) signals [10] during rest, can be used to measure the inter-hemispheric coordination. Functional homotopy, defined as the high degree of synchrony in spontaneous activity between geometrically corresponding inter-hemispheric regions, has been suggested to be a key characteristic of the brain's intrinsic functional architecture [11,12]. Thus, homotopic resting-state functional connectivity (RSFC) may be a sensitive index for detecting the PD-related inter-hemispheric coordination alterations. Here, we examined homotopic RSFC in PD FOG + patients using a recently validated approach named "voxel-mirrored homotopic connectivity (VMHC) [13]." Different strengths of VMHC between different symmetric regions could represent different characteristics of hemispheric specialization in the information processing, sensory integration, and motor coordination [12]. Using the VMHC method, abnormal homotopic RSFC has been demonstrated in PD, Luo et al. found that PD patients exhibited significantly lower VMHC in putamen and cortical regions associated with sensory processing and motor control, relative to healthy subject [14]. Hu et al. found that, compared to normal control subjects and subjects with akinetic-rigid PD, tremor-dominant PD exhibited significantly lower VMHC values in the posterior lobe of the cerebellum and akinetic-rigid PD exhibited lower VMHC values in the precentral gyrus compared with normal control subjects [15].

In this study, we hypothesized that the differences of functional coordination between left and right brain may be involved in the pathogenesis of FOG in PD patients, which would be reflected by reduced RSFC in PD FOG + patients. Moreover, given the importance of bilateral hemispheric coordination for motor functions, we also expected that VMHC measures would be clinically relevant.

2. Materials and methods

2.1. Participants

We investigated 54 right-handed patients with a diagnosis of PD according to the UK Parkinson's Disease Society Brain Bank criteria for idiopathic PD [16]. Exclusion criteria comprised: red flags suggestive of atypical parkinsonism, atypical parkinsonism suggestive of multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy, severe tremor, significant comorbidities affecting gait (e.g. acute illness, visual disturbances, orthopedic disease, musculoskeletal disorders, or history of stroke), absence of proper medical treatment, resistance to dopaminergic drugs, significant cognitive dysfunction (mini-mental state exam (MMSE) score <24), contraindications to MRI, such as claustrophobia, metallic implants, or devices in the body. Patients were classified as exhibiting FOG (FOG+) based on the following two conditions that had all to be fulfilled: (1) score ≥1 point on item 3 of the FOG questionnaire (FOGQ) [17], (2) the recognition of typical FOG in the patient's experience when this was identified and described to him or her by a physician. Patients not fulfilling any one of the above conditions were classified as not exhibiting FOG (FOG−). Clinical tests and MRI scans were performed in the morning OFF medication, after at least 12 h withdrawal from anti-parkinsonian medications to mitigate the pharmacological effects on neural activity. Additionally, a group of 24 gender- and age-matched healthy controls (HCs), without neurological and psychological disturbances or imaging abnormalities were also recruited from local individuals who volunteered to participate in scientific studies. This study was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University, and all participants gave their informed written consent before beginning the experiment.

2.2. Clinical assessment

Motor symptoms and PD severity were evaluated via the motor component of the Unified Parkinson's Disease Rating Scale (UPDRS-III). The severity of FOG was evaluated using the FOGQ, a six-item scale (range 0–24) composed of four items assessing FOG severity and two items testing gait difficulties in general. Subjects also perform the Tinetti Mobility Test [18] and timed up and go (TUG) [19] to assess balance and gait. The MMSE [20] was administered to screen the global cognitive function and executive function. In addition, Levodopa equivalent daily dose (LEDD) was calculated according to the established methods [21].

2.3. Image acquisition

MRI scannings 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 motionless, 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 mm2, matrix size = 256 × 256 and voxel size = 1 × 1 × 1 mm3). Resting-state functional images were collected using an echo-planar imaging (EPI) sequence (TR = 2000 ms, TE = 21 ms, FA = 90°, FOV = 256 × 256 mm2, in-plane matrix = 64 × 64, slices = 35, slice thickness = 3 mm, no slice gap, voxel size = 3 × 3 × 3 mm3, total volumes = 240). DTI images were acquired using spin echo planar imaging sequence with the following parameters: TR = 9800 ms, TE = 95 ms, FOV = 256 × 256 mm2, NEX = 1, matrix = 128 × 128, slice thickness = 2 mm, and slice gap = 0 mm. Diffusion gradients were applied in 30 non-collinear directions with a b factor of 1000 s/mm2 after an acquisition without diffusion weighting (b = 0 s/mm2) for reference.

2.4. Preprocessing of fMRI data analysis

Rs-fMRI data preprocessing was then conducted by SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm/), REST (http://restfmri.net/forum/rest) and Data Processing Assistant for Resting-State fMRI (DPARSF). Briefly, the preprocessing steps included the following steps: (1) removal of first 10 time points; (2) correction for differences in the image acquisition time between slices; (3) six parameter rigid body spatial transformation to correct for head motion during data acquisition; (4) coregistration of the T1 image to the mean EPI scans; (5) grey and white matter segmentation using "New Segment" and spatial normalization of the structural image to a standard template (Montreal Neurological Institute) by DARTEL "normalization"; (6) spatial normalization of the EPI images using the normalization parameters estimated in the previous preprocessing step and resampling to $3 \times 3 \times 3\ mm^3$; (7) spatial smoothing with a 6 mm full width half maximum Gaussian kernel; (8) temporally bandpass filtering (0.01–0.08 Hz) and linearly detrended removal; (9) regressing eight nuisance covariates, including the white matter signal, the cerebral spinal fluid signal, and six head motion parameters, to remove the possible variances from time course of each voxel.

According to the record of head motions within each fMRI run, all participants had less than 2.0 mm maximum displacement in the x, y, or z plane and less than 2.0°of angular rotation about each

Please cite this article in press as: J. Li, et al., Decreased interhemispheric homotopic connectivity in Parkinson's disease patients with freezing of gait: A resting state fMRI study, Parkinsonism and Related Disorders (2018), https://doi.org/10.1016/j.parkreldis.2018.03.015