



Alterations of regional homogeneity in freezing of gait in Parkinson's disease

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ABSTRACT

Introduction: Freezing of gait (FOG) is a serious complication in patients with Parkinson's disease (PD), and is more common in the late state of the disease. The high risk of falling in patients with FOG impacts their quality of life.

Objective: To explore altered neuroactivity related to cognitive and executive function of PD patients with FOG. **Methods:** Fourteen PD patients with FOG (FOG +), 20 PD patients without FOG (FOG –), and 18 normal controls (NC) were enrolled. Functional MRI data of all PD patients were collected during OFF medication state. Data were analyzed using software of DPARSF and REST. Resting brain activity was measured by regional homogeneity (ReHo). ANOVA test was performed for ReHo among FOG, PD, and NC groups.

Results: ReHo alterations of left supplementary motor area (SMA) (Brodmann 6), left superior frontal region (Brodmann 9), and the right putamen (Brodmann 48) were significantly different among the three groups. The ReHo values within left SMA (Brodmann 6) and left superior frontal region (Brodmann 9) were significantly decreased in FOG + patients compared with FOG – patients.

Conclusion: Changes in neural hypoactivity within the frontal region and SMA appear to be associated with FOG in PD patients, which suggests that the mechanism underlying FOG may relate to disruption of execution and cognition.

1. Introduction

Freezing of gait (FOG) is defined as a brief, episodic absence (or a marked reduction) of forward progression of the feet despite the intention to walk. Patients with FOG feel as though “their feet seem to be suddenly glued to the floor”. This concept of FOG was accepted at the 2010 FOG workshop held in Washington DC [1]. FOG is a serious complication of patients with Parkinson's disease (PD) and is reported to occur more commonly in the late state of the disease [2], which is associated with worsening disease severity and longer levodopa treatment. The high risk of falling in patients with FOG can lead to serious health issues (such as injuries to the hips or wrists) which can negatively impact health-related quality of life [3,4].

Since the pathophysiology of FOG still remains unclear, current therapeutic options for PD patients with FOG remain severely limited. Unlike other motor symptoms of PD (such as bradykinesia, tremor, or rigidity), FOG is difficult to manage with dopaminergic medication or deep brain stimulation (DBS). In some individuals, FOG may be

resistant to (or even worsened by) the addition of levodopa [5]. In addition, freezing behavior also shows a variable response to DBS therapy that targets either the subthalamic nucleus (STN) [6] or the pedunculopontine nucleus (PPN). FOG has also been reported as a side-effect of DBS in some studies [7].

A growing body of neuroimaging studies has suggested that FOG is not a pure motor phenomenon but rather a complex interplay between motor and cognitive factors [8]. FOG correlates with postural instability and cognitive decline. In particular, executive dysfunction (including declines in set-shifting, attention span, problem solving, and response inhibition) occur in PD patients [9,10]. Research has also shown that FOG is related to dysfunction within the frontoparietal regions of the brain cortex [11–14] known to subserve cognitive and executive functions. Cognitive training is of particular interest as it may improve executive processes, thus reducing the manifestation of FOG and providing a clue as to its underlying pathophysiology [5].

Resting-state functional magnetic resonance imaging (rs-fMRI) can monitor the pathophysiological changes of PD [15,16]. ReHo is a rs-

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fMRI data-driven analysis method, which is used to measure the synchronizations of temporal changes of blood-oxygen level dependent (BOLD) signals of rs-fMRI. ReHo can examine functional coherence in a voxel-wise manner by calculating the Kendall's coefficient of concordance within a given cluster, based on the hypothesis that a region with a high ReHo can represent a topical functional unit [17]. Decreased or increased ReHo values suggest that functional activity in certain regions is poorly or highly synchronized, respectively, when compared with controls [18].

Recently, ReHo has been applied to imaging studies in PD patients, and ReHo has been used to study the change in local brain function in PD patients with fatigue to provide further insights into the biological mechanism of PD [19,20]. However, it is uncertain whether ReHo values in PD patients with FOG differ when compared with ReHo values in either PD patients without FOG or healthy controls.

In the present study, ReHo was used to examine neural activity in PD patients with FOG as compared with PD patients without FOG and healthy age-matched controls in an attempt to uncover FOG-related neural changes in the cerebral regions related to cognitive and executive function.

2. Materials and methods

2.1. Subjects

Twenty-two PD patients with FOG (FOG+) were recruited from our hospital between January 2014 and January 2015. Patients with FOG who met the following criteria were enrolled: (a) had a diagnosis of Parkinson's disease according to the UK Brain Bank criteria [21]; (b) attained an identified score > 0 to item 3 of the Freezing of Gait Questionnaire ["Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?"] [22]; (c) displayed episodes of foot movement cessation observed by two experienced neurologists when patients performed a brief series of timed up-and-go trials where they were required to make tight 180° turns to the left and right [23]. Twenty-three PD patients without FOG (FOG-), who were age and gender matched to the FOG+ group, were selected from our PD research database. The exclusion criteria for the PD patients were atypical parkinsonism (such as multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy), major neurological and psychiatric illness, abnormal structural MRI, and contraindications to MRI, such as claustrophobia, metallic implants, or devices in the body. To make sure that the included PD subjects did not suffer from those mental disorders, this exclusion for the PD patients is made by two experienced neurologists, based on clinical information and brain MRI findings. Additionally, eighteen age and gender matched normal controls (NCs) were recruited from the community and their health status were evaluated by two experienced neurologists. All NCs were free to neurological and psychological disturbances, brain imaging abnormalities and contraindications to MRI, such as claustrophobia, metallic implants, or devices in the body.

Disease severity of PD was measured using the Unified Parkinson's Disease Rating Scale (UPDRS)-III and the stage of PD was determined by using the Hoehn and Yahr (H-Y) scale. Global cognitive functions of all subjects were evaluated using the Mini-Mental State Examination (MMSE). This study was approved by our Institutional Review Board and written informed consent was obtained from all participants.

2.2. Neuroimaging analysis

2.2.1. Magnetic resonance imaging acquisition protocol

Functional MRI data of all PD patients were collected in the morning during OFF medication state. The OFF medication state was defined as withdrawal from anti-parkinsonian medication for > 12 h to mitigate any pharmacological effects on neural activity. Brain functional MRI was performed using a 3.0 T scanner (Signa Excite HD GE Healthcare,

Milwaukee, WI, USA) with an 8-channel head coil. During scanning, the subject was positioned supine in the gantry of the scanner with foam padding to limit head movement, and wore ear plugs to reduce the impact of acoustic noise. All subjects were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep.

The rs-fMRI data parameters were: gradient-echo echo planer imaging (GRE-EPI) sequence with repetition time (TR)/echo time (TE) = 2000/30 ms, matrix = 64 × 64, 30 axial slices covering the entire brain, field of view = 240 × 240 mm, slice thickness = 4 mm, inter-slice space = 1 mm, NEX = 1, and voxel size = 3.75 mm × 3.75 mm × 4 mm, time points = 186, 30 axial slices covering the entire brain for a total of 5580 images. Axial scans were parallel to the anterior-posterior commissure (AC-PC) line.

High-resolution 3D T1-weighted, anatomical images were obtained for co-registration with the functional data. A fast spoiled gradient recalled echo inversion recovery (FSPGRIR) sequence was used to acquire sagittal T1-weighted images which were acquired with a repetition time (TR)/echo time (TE) = 8.4/3.3 ms, matrix = 256 × 256, flip angle = 13°, slice thickness = 1 mm, and voxel size = 0.94 mm × 0.94 mm × 1 mm.

2.2.2. Data preprocessing

Using Matlab R2012a, the acquired resting state data were analyzed using DPARSF software (DPARSF_V2.0 Basic Edition, DPARSFA; <http://www.restfmri.net>) [24] and software REST (resting-state fMRI data analysis Toolkit V1.8, REST V1.8) [25].

Preprocessing steps included: (1) Convert DICOM into NIFTI; (2) Slice timing correction; (3) Realign; (4) Normalize; (5) Smooth; and (6) Detrend. Individual ReHo maps without smoothing were generated for each subject using DPARSF software; Kendall's coefficient of concordance (KCC) was calculated between 0 and 1. ReHo map normalization was performed using the averaged KCC of the entire brain. The calibrated ReHo maps were further smoothed using an isotropic Gaussian kernel with a full-width at half maximum (FWHM) of 4 mm × 4 mm × 4 mm. Subjects with head motion exceeding 2.5 mm of translation, or 2.5° of rotation throughout the course of the scan were excluded from the study.

2.3. Statistical analysis

Using SPSS 13.0 software (Chicago, IL, USA), the clinical data from FOG+, FOG-, and NC were compared based on age, gender, length of education, disease duration, UPDRS-III score, Hoehn and Yahr Scale (H-Y) and MMSE score. A p-value < 0.05 was considered significantly different. Age and gender were considered as covariates. Results were measured corresponding to a corrected p-value < 0.05 as determined by AlphaSim correction.

ANOVA test was performed for ReHo among FOG+, FOG- and NC groups. Voxels with a p-value < 0.05 and a cluster size > 85 voxels were considered significantly different, corresponding to a corrected p-value < 0.05, as determined by AlphaSim correction. Differences of ReHo between each two groups were compared using two sample *t*-test. Significant regions were shown by XjView software according to Montreal Neurological Institute (MNI) coordinates.

3. Results

Among 22 FOG+ patients, scans from two patients were discarded because of movement artifact, scans from two patients were discarded because of severe artifacts and frontal lobe deformation caused by excessive gasification of the frontal sinuses, and scans from four patients were discarded because of significant head motion (> 2.5 mm) in the z direction.

Among the 23 FOG- patients, scans from two patients were discarded because of movement artifacts and the scan from one patient was discarded because of significant head motion (> 2.5 mm) in the z

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