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Freezing of gait in Parkinson's disease is associated with altered functional brain connectivity

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ABSTRACT

Background: Patients with Parkinson's disease (PD) may develop several gait disturbances during the course of illness and Freezing of gait (FOG) is one of them. Several neuroimaging studies have been conducted to identify the neural correlates of FOG but results have not been uniform. Resting state functional MRI (rs-fMRI) is relatively less explored in PD patients with FOG. This study aims to compare the whole brain resting state connectivity of PD patients with and without FOG using rs-fMRI.
Methods: rs-fMRI was obtained for 28 PD patients (15 with and 13 patients without FOG) who were matched for various demographic and clinical characteristics. Seed to voxel analysis was performed at whole brain level and compared between the two groups.
Results: When compared to patients without FOG, the patients with FOG had reduced functional connectivity across multiple seeds. Major finding was reduced inter-hemispheric connectivity of left parietal opercular cortex with multiple regions of the brain primarily involving the primary somatosensory and auditory areas, which also negatively correlated with the FOGQ scores.
Conclusion: Our findings suggest that alterations in the resting state functional connectivity of the opercular parietal cortex may be one of the substrates of FOG. Reduced interhemispheric connectivity probably is the reason for impairment of control and coordination in bilateral leg movements while walking.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by presence of motor symptoms such as tremor at rest, rigidity, bradykinesia and postural instability [1]. Patients with PD may also develop disturbances of gait and balance. Freezing of gait (FOG) is one of the disabling disturbances related to gait characterized by brief, episodic absence or marked reduction of forward progression of feet despite the intention to walk [2]. Studies have reported longer duration, higher stage and increased severity of PD as risk factors for development of FOG [3–5]. Considering frequent association with impaired cognitive performances in multiple domains such as executive functions and visuospatial functions, FOG is no longer considered as a pure motor phenomenon and a complex interplay between motor and cognitive factors has been speculated to be the cause of FOG [6]. Since the effect of dopaminergic medications on FOG is not as consistent as on other cardinal motor features of PD [7,8], patients with FOG may have a unique neuropathology that exceeds the typical dopaminergic regions. The effect of external cues such as narrow doors and striped floors on the status of FOG further underscores the possibility of existence of a pathophysiology beyond simple gait

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dysfunction. Although advanced neuroimaging techniques have been used to study the imaging correlates FOG in PD, results have been non-uniform; hence neural correlates of FOG in PD still remain elusive. Studies using voxel based morphometry (VBM) have reported reduced grey matter volume in multiple cortical and subcortical regions in patients having FOG [9]. Studies using diffusion tensor imaging (DTI) have reported microstructural white matter alterations in pedunculopontine nucleus [10,11]. Most of the functional magnetic resonance imaging (fMRI) studies in patients with FOG were task based and their results have been non-uniform as widespread regions in brain have been reported to have altered activation patterns [9]. Resting state fMRI (rs-fMRI) is relatively less studied in PD patients with FOG. Unlike the task-base fMRI analyses, which provide insight into the neural activities in isolated regions, rs-fMRI analyses provide integrative analysis of the distributed neural system. Of the two rs-fMRI based studies available in the current literature on PD patients with FOG, Tessitore et al. have reported decreased connectivity in the components of right fronto-parietal network (RFPN) and visual network [12] whereas Fling et al. in a study focusing on the locomotor networks have reported altered functional connectivity of supplementary motor area with the mesencephalic locomotor region and cerebellar locomotor region [13]. However connectivity was not analyzed at the whole brain level in previous rs-fMRI based studies. Hence to explore and to further contribute to the current understanding of the role of different resting state neural networks in patients with FOG, we studied a group of patients with PD with and without FOG using rs-fMRI.

2. Materials and methods

2.1. Patient population

This case control study was conducted in National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India. Fifteen consecutive patients with PD and FOG [FOG (+)], who gave written informed consent for participation in the study, were recruited from the Neurology and Movement disorders services. The FOG (+) patients were matched for age, age at onset of symptoms, duration of illness and mini mental status examination score (MMSE) with 13 patients with PD not having FOG [FOG (−)]. As PD patients with rapid eye movement sleep behavior disorder (RBD), psychosis and cognitive impairment may have specific imaging abnormalities, presence of any of these symptoms was the exclusion criteria along with conditions, which are contraindications for MRI. All patients were screened for presence of cognitive impairment using MMSE and a score of <26 was set as an exclusion criteria. A single movement disorder neurologist (author-PKP) had carefully examined all the patients and had diagnosed PD based on UK Parkinson disease society brain bank criteria [14]. A cohort of thirty age and gender matched healthy controls were recruited to compare the imaging findings with the patient population. Healthy controls were recruited from a population without neuropsychiatric comorbidities or any family history of Parkinsonism. All the subjects recruited for this study were right handed.

2.2. Study approval and patient consent

The Institute Human Ethics Committee of NIMHANS, Bangalore, approved this study and the subjects were recruited for the study after obtaining a written informed consent.

2.3. Clinical assessment

All patients were evaluated both during drug “OFF” state and best “ON” state after taking levodopa. General neurological examination was done in all patients. Unified Parkinson's disease Rating Scale part-III (UPDRS III) was used to assess the severity of motor symptoms and Hoehn and Yahr (HY) scale was used to determine the stage of PD. Patients were classified as having FOG [FOG (+)] if they: (1) had a score ≥1 to the item-3 of the FOG questionnaire [15], and (2) identified the condition after the phenomenon of FOG was demonstrated to them during evaluation. All the fifteen patients in the FOG (+) group reported episodes of freezing during the OFF-state; however three patients also gave history of freezing occasionally during the ON-state. Patients who did not fulfill any of the criteria were classified as non-freezers [FOG (−)].

2.4. Image acquisition

rs-fMRI and structural MRI were acquired using a 3.0 T MR system (Achieva; Philips Medical Systems, Eindhoven, Netherlands) with a 32-channel head coil. 105 volumes of spin echo planar images were obtained with: TR: 3000 ms, TE: 30 ms, sections: 34, section thickness: 6 mm, FOV: 192 × 192 mm, resolution: 64 × 64, and voxel size: 3 × 3 × 6 mm^3. Anatomic images were acquired by using a 3D T1-Weighted MPRAGE sequence in 192 sections with a TR of 1900 ms, a TE of 2.43 ms, 1 mm thickness. Axial FLAIR, T2, and gradient sequences acquired for excluding the subject who have structural lesion. None of the subjects required sedation during the MRI data acquisition.

2.5. Image analysis

2.5.1. Preprocessing

Preprocessing of the images was done after ruling out any space-occupying lesions and after evaluation of the white matter hyperintensity load. Fazekas scale was used to do an objective assessment of white matter hyperintesity load in the two patient groups and healthy controls [16]. There was no significant difference in the mean Fazekas score of the three groups (details in Table 1). The MRI imaging preprocessing was performed using SPM8 [17]. The following preprocessing steps was followed: first 5 images were discarded, realignment, normalization to MNI-152 standard space of 3 × 3 × 3 mm^3, smoothing with Gaussian kernel of FWHM 6 mm, segmentation of the structural data for gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) for WM and CSF noise reduction and for bias correction of magnetization inhomogeneity, motion correction using Friston's 24 motion parameter model regression.

2.5.2. Anatomic parcellation

The fMRI data were segmented into 132 anatomic regions of interest (ROI or seeds) using an atlas which considers cortical and subcortical ROIs from FSL Harvard–Oxford Atlas maximum likelihood cortical and subcortical atlas (HarvardOxford-cort-maxprob-thr25–1 mm.nii, HarvardOxford-sub-maxprob-thr25–1 mm.nii); divided bilateral areas into left/right hemisphere; (106 ROIs), Cerebellar parcellation from AAL Atlas (26 ROIs). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest was used [18].

2.5.3. Functional connectivity analysis

A seed-to-voxel based functional connectivity analysis was performed by computing the temporal correlation between the BOLD signals to create a correlation matrix showing connectivity from the seed region to all other voxels in the brain by using the functional connectivity toolbox (CONN, version 15.e) (http://www.nitrc.org/projects/conn) and was used to create individual subject connectivity maps. To analyze resting state networks the BOLD