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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

Table 1
Demographic and clinical details of patients with Parkinson's disease and the healthy controls.

	FOG (+) (n = 15)	FOG (−) (n = 13)	HC (n = 30)	Significance
Women: Men	5:10	4:9	10:20	NS
Age (years ± SD)	54.5 ± 11.4	50.3 ± 8.9	52.5 ± 10.3	NS
AAO (years ± SD)	46.1 ± 11.6	46.5 ± 9.7	–	NS
Duration of symptom	4.1 ± 2.1	3.9 ± 1.7	–	NS
MMSE	26.5 ± 3.4	27.9 ± 1.8	30.0	NS
UPDRS-III (OFF state)	36.8 ± 9.8	32.0 ± 8.2	–	NS
UPDRS-III (ON state)	23.8 ± 7.5	21.6 ± 10.5	–	NS
HY stage	1.8 ± 0.5	1.6 ± 0.6	–	NS
FOGQ score	12.7 ± 2.9	2.6 ± 1.5	–	$p < 0.001$
Total LEDD	636.7 ± 238.3	577.7 ± 108.9	–	NS
Fazekas score	1.8 ± 1.2	1.6 ± 1.1	1.3 ± 1.1	NS

FOG (+): Patients with freezing of gait, FOG (−): Patients without freezing of gait, HC: Healthy controls, AAO: Age at onset of symptoms, MMSE: Mini mental status examination score, UPDRS-III: Unified Parkinson's disease rating scale, part III (motor part), HY: Hoehn and Yahr staging for Parkinson's disease, FOGQ: Total score from FOG questionnaire, LED: Levodopa equivalent dose/day, NS: Not significant.

time-series for each subject was extracted for each ROIs and band pass filtered (0.009–0.09 Hz). This WM and CSF-related physiologic noise source reduction was carried out by using the CompCor algorithm [19]. The 132 seed ROIs consisted of 3-mm-radius spheres centered on MNI coordinates used to identify the corresponding networks. Bivariate analysis was performed between each pair of ROIs. A general linear model was designed with the canonical hemodynamic response functions for entire BOLD signal of rs-fMRI data to determine significant connections at the individual level. The connectivity maps were estimated for correlating seed region signals with voxel signals throughout the whole brain, thereby creating seed region-to-voxel Fisher-transformed connectivity maps. Second-level random-effects analysis was used to create within-group SPMs for each network and to examine connectivity differences between groups [20].

The group mean effects were estimated for the 3 groups with false-discovery rate (FDR) correction $P < 0.02$. Between group effect were estimated using voxel-wise ANOVA test analyses, between FOG (+), FOG (−) and healthy control by defining the contrast [1–10] respectively. The statistical threshold was set at a whole-brain cluster level-corrected $p < 0.02$, FDR correction. The ROIs showed significant brain connectivity difference were visualized in brain surface rendered image using the BrainNet viewer (https://www.nitrc.org/projects/bnv/).

Furthermore the linear correlation was computed with FOGQ score with the connectivity strength of individual seed to ROI connections, which were significantly different between FOG (+) and FOG (−) patients.

3. Results

3.1. Demography and clinical evaluation

Among the 28 patients recruited for this study, 15 were identified as FOG (+) (5 women, 10men) and 13 were identified as FOG (−) (4 women, 9 men). The groups did not differ significantly from in terms of age, age at onset of symptoms, duration of symptoms, MMSE, UPDRS-OFF and ON scores and HY scores. The mean FOGQ score of the FOG (+) group was 12.7 ± 2.9 whereas the FOGQ score of FOG (−) group was 2.6 ± 1.5. Details of demography and clinical characteristics are provided in Table 1.

3.2. Functional connectivity

3.2.1. FOG (−) versus healthy controls

Compared to the healthy controls, patients with FOG (−) had reduced connectivity of left perirhinal cortex with lateral occipital cortex and inferior, middle and superior temporal gyrus in left hemisphere. Left primary auditory cortex also had reduced connectivity with ipsilateral putamen and insula in FOG (−) patients. Significant reduction in the connectivity was observed between left somatosensory association cortex with bilateral frontal pole and ipsilateral superior frontal gyrus in FOG (−) patients.

3.2.2. FOG (+) versus healthy controls

Patients with FOG (+) had a widespread areas having abnormal functional connectivity compared to the healthy controls. The structure having maximum abnormality in the connectivity in FOG (+) was left parietal opercular cortex which had reduced connectivity with (i) contralateral frontal and central opercular cortex, (ii) contralateral superior temporal and inferior frontal gyrus, (iii) right insular cortex, (iv) left supplementary cortex, (v) left Heschl's gyrus, (vi) bilateral planum polare.

The primary somatosensory cortex in both hemispheres had reduced connectivity with contralateral pre and post-central gyrus. Primary somatosensory cortex also had reduced connectivity with insular and supplementary cortex in left side and the right parietal opercular cortex. Left central opercular cortex had reduced connectivity with left Heschl's gyrus and right central opercular cortex. Left somatosensory association cortex had reduced connectivity with bilateral paracingulate cortex. We also observed reduced connectivity of left anterior cingulate and left perirhinal cortex with multiple seeds in FOG (+). Left anterior cingulate had reduced connectivity with right frontal pole, right superior frontal gyrus and left lateral occipital cortex whereas the left perirhinal cortex had reduced connectivity with left inferior temporal gyrus and both anterior and posterior cingulate cortex.

3.2.3. FOG (+) versus FOG (−)

The seed to voxel analysis of the resting state images of the patients with FOG (+) and FOG (−) revealed reduced connectivity in FOG (+) in multiple seeds when compared to the FOG (−) group. Primarily we observed reduced connectivity of the left cerebral hemisphere seeds involving the parietal opercular cortex, central opercular cortex, supramarginal gyrus and pallidum in FOG (+) patients. It was the interhemispheric connectivity of these seeds, which were significantly reduced in FOG (+) patients compared to the FOG (−) patients. In addition we also found opercular seed connectivity correlating negatively with the FOGQ scores.

3.2.4. Connectivity of left parietal opercular cortex

We observed maximum decrease in the connectivity involving the left parietal opercular seed in FOG (+). Compared to the FOG (−), we observed reduced interhemispheric connectivity of parietal

operculum with multiple regions in the right hemisphere such as right superior temporal gyrus, right primary somatosensory cortex (BA3), right central opercular cortex, right parietal opercular cortex, right primary auditory cortex and right insula. In addition left Heschl'sgyrus and left primary somatosensory cortex also showed decreased connections.

3.2.5. Connectivity of left central opercular cortex

In addition to the left parietal opercular cortex, we also observed reduced connectivity of the left central opercular cortex seed with several regions of the brain in FOG (+) patients. Decreased connectivity was observed with the right superior temporal gyrus, right primary auditory cortex and left somatosensory cortex. The pattern of alteration in connectivity had an overlap with that of left parietal operculum as all the three seeds having reduced connectivity with left central opercular cortex had also reduced strength of connectivity with left parietal opercular cortex.

3.2.6. Connectivity of other seeds

We observed reduced strength of connectivity of left pallidum with crus of right cerebellum in FOG (+) patients compared to FOG (−) patients. Left supramarginal gyrus had reduced connectivity with accumbens in the FOG (+) group.

Details of the seeds with reduced connectivity are provided in Table 2 and the differences in the pattern of connectivity among the seeds are provided in Fig. 1.

3.2.7. Correlation with FOGQ score

We also did correlation analysis between the FOGQ score and the connectivity of seeds having significantly reduced connectivity in FOG (+) group. We observed the connectivity between bilateral parietal operculum, left parietal operculum to right central operculum and right insular cortex, left central operculum to left primary somatosensory cortex to be negatively correlated with the FOG score. Graphical representation of the negative correlations is provided in Fig. 2.

4. Discussion

As the literature on rs-fMRI based comparative studies on FOG is sparse, we undertook this study to explore the alterations, if any, in the resting state functional connectivity in FOG (+) patients. Unlike the previous studies based on rs-fMRI, which have analyzed connectivity in selected networks [12,13], we have done seed-to-voxel wise analysis at the whole brain level. The major finding of our study is reduced inter-hemispheric connectivity of left parietal opercular cortex with multiple seeds primarily involving the primary somatosensory and auditory areas. We also observed significant negative correlation of the several seed pair's connectivity with FOGQ scores further supporting the role of these areas in the pathogenesis.

Parietal operculum is important as this region corresponds to the secondary somatosensory area (S2). In studies based on cats, Adrian first suggested existence of this somatosensory area as he reported additional representation of forefoot and hind foot located lateral to the representation of face in primary somatosensory area (S1). However Penfield in 1950 first suggested the existence of S2 in humans in his studies based on electrical stimulation. Eickhoff et al. described four distinct architectonic areas in parietal operculum (OP1, OP2, OP3 and OP4) [21], which are associated with basic sensorimotor processing, action control and higher order somatosensory processing. We observed significant reduction in the connectivity of left parietal operculum with the contralateral parietal operculum as well as bilateral primary somatosensory cortex (S1) and primary auditory cortex, which underscores the possibility of derangement in the integration of S1 and S2 in FOG (+) patients. Studies have reported either alleviation or aggravation of FOG in response to several sensory stimulation [22,23]. Extrinsic sensory inputs such as rhythmic auditory stimulation and instructions to walk on a striped floor have been reported to improve FOG [24,25]. This finding partially explains the improvement of FOG in response to the auditory cues. Shine et al. in a review suggested a possible decrease in compensatory capacity in patents with FOG and the extrinsic sensory cues are utilized to liberate the higher cortical regions for completion of simultaneous tasks [26]. The finding of decreasing connectivity between bilateral parietal operculum, left parietal operculum to right central operculum and right insular cortex, left central operculum to left primary somatosensory cortex to be negatively correlating with the FOG score additionally supports the finding that decreased connections in these areas are indeed the cause of poorer FOG scores.

Apart from the bilateral parietal, somatosensory and superior temporal connections, reduced connections were also noted with right insula, left pallidum, right cerebellum and Accumbens and supramarginal gyurs. In FOG (+) patients, Shine et al. have reported reduced activations in the ventral attention network, of which the insular cortex is an important component [27]. As insular cortex may have a role in motor learning especially in the initial learning phase of the action-perception associations [28], reduced connectivity with left parietal operculum may be one of the substrates of

Table 2
Result of Seed-to-voxel–based connectivity comparison between patients with and without freezing.

Seed regions	Connectivity regions	β	T	p
	Right superior temporal gyrus	−0.24	−4.09	0.019
Left central opercular cortex (−50, −6, 6)	Right primary auditory cortex	−0.27	−3.91	0.019
	Left primary somatosensory cortex	−0.29	−3.82	0.019
Left parietal opercular cortex (−52, −32, 18)	Right superior temporal gyrus	−0.24	−3.99	0.017
	Right primary auditory cortex	−0.26	−3.66	0.017
	Left primary somatosensory cortex	−0.34	−4.34	0.017
	Right primary somatosensory cortex	−0.27	−3.97	0.017
	Right parietal opercular cortex	−0.42	−3.7	0.017
	Right central opercular cortex	−0.33	−3.81	0.017
	Right insular cortex	−0.34	−3.66	0.017
	Left Heschl's gyrus	−0.39	−3.64	0.017
Left pallidum (−20, −6, 0)	Right cerebellum	−0.29	−4.33	0.012
Left supramarginal gyrus (−60, −32, 36)	Accumbens	−0.18	−4.42	0.015

β values represent Fisher-transformed correlation coefficient values.
T values represent the strength of connectivity between the source seed region and correlated-voxels regions.

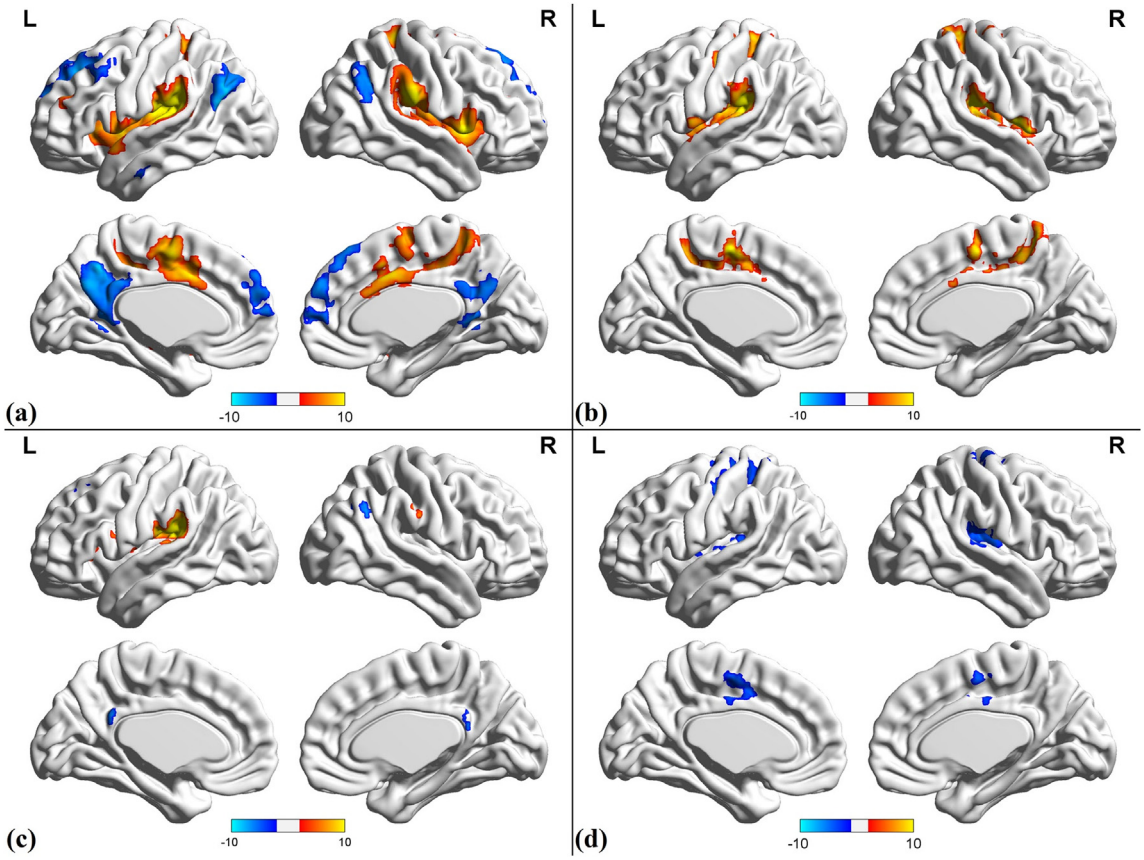

Fig. 1. Surface rendered image of seed to voxel based connectivity of the left parietal operculum in (a) healthy controls (b) in patients without FOG (c) in patients with FOG. The warm metal colors indicate the strength of connections. Fig. 1 (d) reveals represents the contrast of the differences between FOG (+) and FOG (−) which shows decreased connections of the left parietal operculum to bilateral somato sensory, bilateral superior temporal and right parietal operculum in patients with FOG (+).

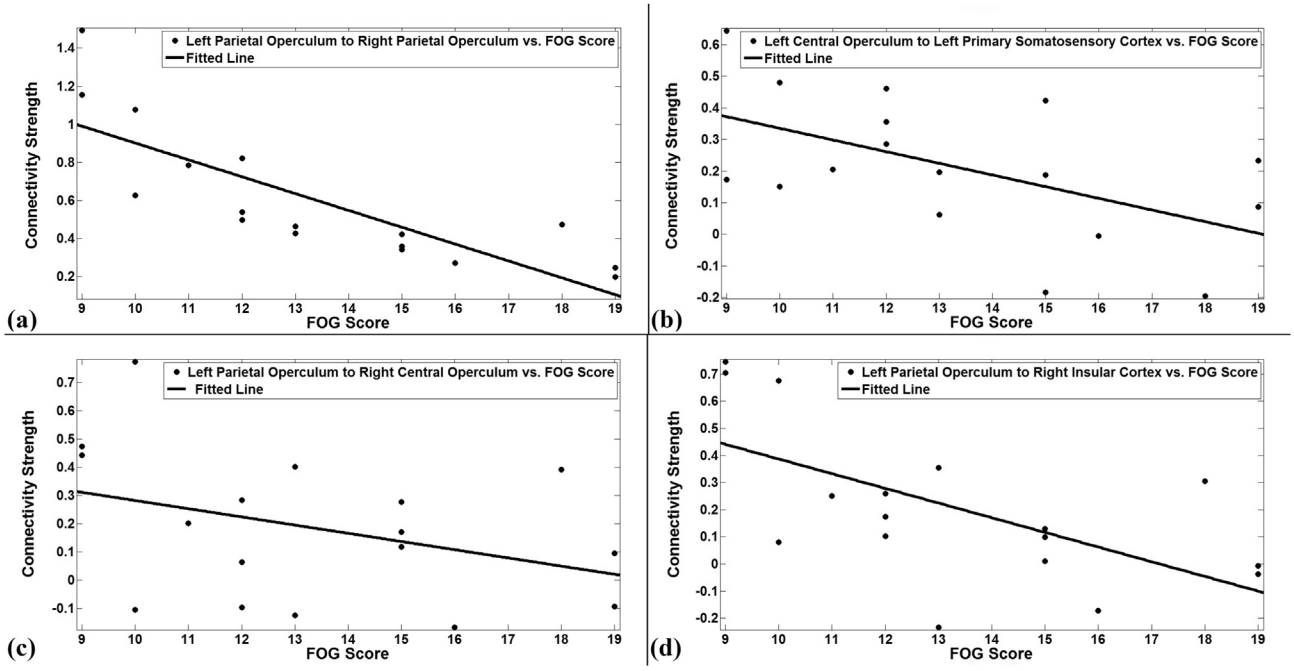

Fig. 2. Graphical representation of the seed pairs, which revealed significant negative correlation with FOGQ scores. (a) Bilateral parietal operculum ($r = -0.81$, $p = 0.0001$), (b) Left central operculum to left primary somato sensory cortex ($r = -0.54$, $p = 0.002$ (c), Left parietal operculum to right central operculum ($r = -0.37$, $p = 0.05$) (d) and Left parietal operculum to right insula ($r = -0.62$, $p = 0.008$).

FOG in PD. Previous studies have suggested possible alterations in the frontal lobe-basal ganglia-cerebellar-brainstem network that controls initiation and maintenance of gait [29]. Cerebellum has been regarded as one of the major components of origin of locomotion and several studies have reported alterations in the cerebellar locomotor region (CLR) in PD patients with FOG [13]. Fling et al. using a similar design as ours have reported altered functional connectivity of supplementary motor area with the mesencephalic locomotor region and cerebellar locomotor region [13]. Stoodley et al. have reported involvement of lobule VI and VII of cerebellum in both complex motor and cognitive tasks [30] which reinforces our finding regarding reduced connectivity of pallidum with cerebellum. We also observed reduced strength in the connectivity of left supramarginal gyrus with accumbens in FOG (+) compared to FOG (−); however we do not have any substantial support for this finding in the existing literature.

One of the major findings of our study, which has not been reported earlier, was reduction in the inter-hemispheric connectivity in FOG (+) group. This underscores a possible impairment of bilateral coordination in FOG (+) patients. Most of the patients have FOG predominantly during initiation of gait and while taking turns. During these two movements, the actions of the lower extremities are different from each other as one extremity takes a step and the pivot extremity provides support. Hence high degree of coordination between the extremities is essential during gait initiation and while taking turns, which perhaps is impaired in FOG (+) patients. Previous studies have also reported impairment in the bilateral coordination of the leg movement in FOG (+) patients [31,32].

Tessitore et al. in a rs-fMRI based study comparing FOG (+) with FOG (−) have reported decreased connectivity in the components of RFPN (in the right middle frontal gyrus and angular gyrus) and visual network (in the right occipito-temporal gyrus) in FOG (+) patients [12]. The brain regions observed by Tessitore et al. was different from our observation, which may be attributed to differences in the methodology of the two studies as Tessitore et al. used group independent component analysis of two networks to drive the differences whereas we have used seed-to-voxel analysis of the whole brain.

One of the limitations of this study is the absence of detailed neuropsychological evaluations as poor cognition has been described in PD patients with FOG. Though MMSE score was matched between FOG (+) and FOG (−), the mean score of FOG (+) group (26.9) was close to the cut-off for dementia. However the regions of the brain which were observed to have abnormal connectivity in this study could still play a role in freezing of gait as these areas are different from those implicated in patients with PD having cognitive deficits [33]. Small sample size of our study is also a limitation because of which findings of this study may not be generalized for all patients with PD and FOG. As this was a cross-sectional study, patients who did not have freezing of gait could develop freezing later during the course of the illness. Improvement in these connections with neurocognitive training or with sensory stimulation will further support our findings and may be a point for future studies.

5. Conclusion

This is the first comparative study between FOG (+) and FOG (+) using seed to voxel analysis of mean connectivity by RS-fMRI at whole brain level and we observed few novel findings. The principal finding of our study was significantly reduced inter-hemispheric connectivity between bilateral parietal operculum, somatosensory cortex and primary auditory areas in patients with freezing of gait and these area thus might be crucial in the pathogenesis of freezing. Future studies on the effect of sensory stimulation or neurocognitive therapy on these networks in larger group will further support our findings.

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None of the authors have any financial disclosure to make or have any conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2015.12.016.

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