RESEARCH ARTICLE

New Insights into Freezing of Gait in Parkinson's Disease from Spectral Dynamic Causal Modeling

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ABSTRACT: Background: Freezing of gait is one of the most disturbing motor symptoms of Parkinson's disease (PD). However, the effective connectivity between key brain hubs that are associated with the pathophysiological mechanism of freezing of gait remains elusive.
Objective: The aim of this study was to identify effective connectivity underlying freezing of gait.
Methods: This study applied spectral dynamic causal modeling (DCM) of resting-state functional magnetic resonance imaging in dedicated regions of interest determined using a data-driven approach.
Results: Abnormally increased functional connectivity between the bilateral dorsolateral prefrontal cortex (DLPFC) and the bilateral mesencephalic locomotor region (MLR) was identified in freezers compared with nonfreezers. Subsequently, spectral DCM analysis revealed that increased top-down excitatory effective connectivity from the left DLPFC to bilateral MLR and an independent self-inhibitory connectivity within the left DLPFC in freezers versus nonfreezers (>99% posterior probability) were inversely associated with the severity of freezing of gait. The lateralization of these effective connectivity patterns was not attributable to the initial dopaminergic deficit nor to structural changes in these regions.
Conclusions: We have identified novel effective connectivity and an independent self-inhibitory connectivity underlying freezing of gait. Our findings imply that modulating the effective connectivity between the left DLPFC and MLR through neurostimulation or other interventions could be a target for reducing freezing of gait in PD. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; freezing of gait; neuroimaging; dynamic causal modeling

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Freezing of gait (FOG) is a common symptom of Parkinson's disease (PD) that can be defined as sudden episodes whereby patients experience an inability to step despite the intention to walk.[1] FOG increases the risk of falling[2] and greatly impacts on the patient's quality of life.[3,4] The exact pathophysiological mechanisms underlying FOG still remain elusive, although multiple conceptual models have been proposed.[5]

A recent review of the structural changes in PD patients with FOG revealed cortical and subcortical gray matter atrophy.[6] Additionally, animal studies[7,8] and many human imaging studies demonstrated a relationship between the mesencephalic locomotor region (MLR) alterations and FOG.[9-13] Indeed, the MLR forms a central node in the initiation of locomotion[14]

and plays a role in the maintenance and modulation of posture and gait[15] as well as in saccadic eye movements.[16] Apart from aberrant local activity and altered structure, dysfunctional interactions between the MLR and cortical regions may also lead to FOG.[12,13] In addition, the MLR seems more directly related to gait dysfunction[17,18] than other gait- and balance-related regions such as the thalamus, the supplementary motor area (SMA), and the cerebellum. This is not surprising, as it is under direct basal ganglia inhibitory control and projects down to reticulospinal neurons, which in turn activates the spinal central pattern generator for locomotion.[19,20] Although it is crucial to study the functional deficits of the MLR, prior neuroimaging studies delineated only FOG-related regions and patterns of brain activation. Yet information regarding how these regions influence each other (ie, via "effective connectivity")[21] was not considered.

One of the challenges in studying task-based brain interactions is that freezers have more movement control deficits compared to nonfreezers.[22] An alternative, task-free approach is to investigate effective connectivity of resting-state functional magnetic resonance imaging (fMRI).[18,23] Given its central role in modulating gait and FOG, the MLR makes for a logical seed region for such an analysis. Here, we applied spectral dynamic causal modeling (DCM)[21] of resting-state fMRI data to investigate altered effective connectivity in freezers compared to nonfreezers with the MLR as the seed region. To enhance interpretation, we also examined whether structural changes contributed to the observed differences and investigated the relationship between the structural changes and effective connectivity. Although a recent review suggested a trend toward right-hemispheric lateralization of the structural abnormalities associated with FOG,[18] evidence on which hemisphere is more affected in freezers is lacking. Therefore, we investigated the relationship between the laterality of hemispheric deficits, altered effective connectivity, and brain structural changes. Based on previous findings,[9,11,12] we hypothesized that PD freezers would have increased effective connectivity between the MLR and cortical regions compared to nonfreezers. Moreover, we predicted that the changes in effective connectivity would be associated with FOG severity and structural decline in the brain.

Patients and Methods

Study Design and Participants

In this retrospective study, participants were enrolled at Osaka University Hospital in Osaka, Japan. Inclusion criteria were as follows: (1) diagnosis of clinically established PD according to the MDS clinical diagnostic criteria as determined by a movement disorder specialist,[24] (2) patients who had no MR contraindications and no deep brain stimulation and underwent resting-state fMRI, and (3) being able to walk ≥10 meters without assistance. Exclusion criteria were as follows: (1) diagnosis of a neurological disorder other than PD, (2) cognitive deficit as assessed using the Mini-Mental State Examination (MMSE) score <24,[25] and (3) any missing data for behavioral tests (Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale [MDS-UPDRS], Part 3,[26] freezing of gait questionnaire [FOG-Q][27]), or cognitive tests (MMSE and Frontal Assessment Battery [FAB]). Based on the definition from previous studies,[28,29] patients were categorized as "freezers" if they had a score of 1 (slight) or higher (2 = mild, 3 = moderate, and 4 = severe) on the MDS-UPDRS, Part 3.11 (freezing of gait),[26] documented by a neurologist ("definite freezers"). None of "nonfreezers" exhibited freezing during behavioral tests or self-reported freezing ("probable nonfreezers"). In our dataset, all clinical and fMRI data were obtained *on* medication during 1 week of hospitalization. Specifically, the total MDS-UPDRS, Part 3, was assessed by a movement disorder specialist within 72 hours before the fMRI scan. Administration of part 3.11 was reconfirmed by another movement disorder specialist during fMRI scanning. Self-reported measures (FOG-Q, number of falls) were collected, and cognitive tests (MMSE and FAB) were administered by a certified clinical psychologist during hospitalization. The following clinical data were collected from the database: age; sex; disease duration; Hoehn and Yahr (H&Y) stage; MDS-UPDRS, Part 3; levodopa equivalent daily dose (LEDD), number of falls in the previous month; and cognitive measures such as the MMSE and FAB.

Considering the laterality of the hemispheric deficits, visual analysis of ^{123}I-fluoropropyl-carbomethoxy-3β-4-iodophenyltropane (FP-CIT) imaging was performed to determine the side with the greater striatal dopaminergic deficit by an experienced radiologist and a neurologist independently using DaT view software (AZE Ltd., Tokyo, Japan). A researcher (S.T.) ensured that no inconsistences were found between the two results through consensus seeking. FP-CIT imaging was performed at the diagnostic stage. Written informed consent was obtained for all participants. The study was approved by the Research Ethics Boards at Osaka University Hospital (number 13471) and registered at the UMIN-CTR (UMIN000036570), which our registry previously reported neuroimaging evidence in patients with PD.[30-34]

Data Analysis

Preprocessing of Imaging Data

The analyses were performed using SPM12 (r7771) implemented in MATLAB (version R2022b, MathWorks Inc., Natick, MA, USA). Details of the

MRI procedures are provided in Supplementary Material 1.

Effective Connectivity: Spectral DCM with Parametric Empirical Bayes

The pipeline used in our imaging analysis is shown in Figure 1. The key steps include preprocessing, regions-of-interest (ROI) selection, and time-series extraction of voxels. Further details are provided in Supplementary Material 2.

Spectral DCM with Parametric Empirical Bayes

We performed an automatic search over the optimal effective connectivity[35] from a four-node fully connected model with 4×4 parameters to represent the effective connectivity among the volumes of interest (VOI) and the self-inhibitory connectivity of each VOI after extracting components. The self-inhibitory connectivity within a region is always inhibitory and thus considered to reflect its sensitivity of a region to the influence of another modeled input[36]; whereas positive values of self-inhibitory connectivity indicate a reduction in sensitivity to inputs from the other network (rather than an excitatory influence), negative values indicate increasing sensitivity to inputs from the network.[36] The parameters of the fully connected model were estimated using the Bayesian model reduction (BMR) option,[37] which is the default estimation type for DCM12 in the first-level DCM with parametric empirical Bayes (PEB). The estimated DCM for each participant was then entered into the second-level DCM with PEB framework,[37] which is an approach that allows group comparisons across model parameters to inform the second-level group results (ie, between-group effect).[36,37] In the second-level analysis, a general liner model (GLM) was

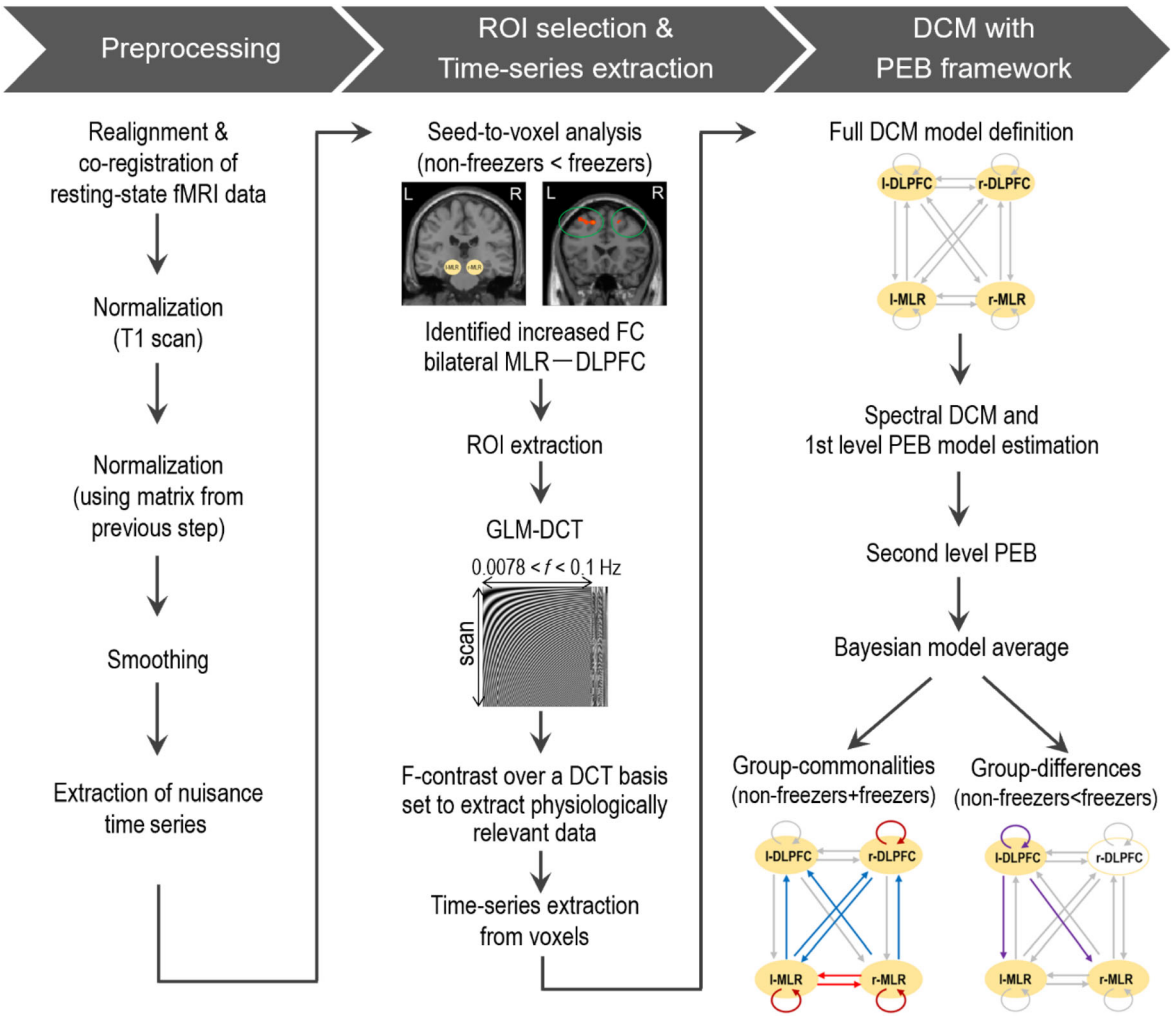

FIG. 1. The pipeline of image analysis in this study. Data processing included three main steps, preprocessing (left panels), region of interest selection identification and time-series extraction of voxels (middle panels), and dynamic causal modeling (DCM) with parametric empirical Bayes framework (right panels). DCM, dynamic causal modeling; DLPFC, dorsolateral prefrontal cortex; FC, functional connectivity; GLM-DCT, general liner model with discrete cosine transform; MLR, mesencephalic locomotor region; PEB, parametric empirical Bayes; ROI, region of interest; rsfMRI, resting-state functional magnetic resonance imaging; T1, T1-weighted images as anatomical reference. [Color figure can be viewed at wileyonlinelibrary.com]

constructed to identify the commonalities in effective connectivity across all groups (nonfreezers + freezers) and the differences in effective connectivity between the nonfreezer and freezer groups (nonfreezers vs. freezers). Four covariates—disease duration, H&Y stage, LEDD, and MDS-UPDRS, Part 3, total score—were added to the GLM as effects of no interest after multicollinearity was checked (variance inflation factors were all <2). After PEB estimation, BMR was performed to automatically search over all nested models within the full model, removing redundant parameters that did not contribute to the model evidence. Then, we calculated the average of the parameters of all possible models, weighted by the posterior probability (Pp) of each model, using the Bayesian model averaging. As the Bayesian analyses directly provide the probability of each effect, further thresholding is not necessary. For better identification, a Pp value >0.99 (defined as "very strong evidence" for a nonspurious effect) was applied. Finally, we performed a correlation analysis between the identified effective connectivity (coupling parameters estimated by DCM) and freezing-severity measures (total FOG-Q, FOG-Q item 3 that specifically questions the frequency of FOG, and the MDS-UPDRS 3.11 score that clinically rated FOG severity). Head movements during MRI scanning were not different between groups in frame-wise displacement (mean $0.172 \pm$ SD [standard deviation] 0.078 in nonfreezers vs. mean $0.178 \pm$ SD 0.081 in freezers, $P = 0.89$). However, there was a difference in the y-translations of the head movement parameters. To control for this, the values of the y-translations were added as covariates to the group-level analyses.

To examine the relationship between hemispheric laterality and the observed effective connectivity in freezers versus nonfreezers, we examined the laterality of the dopaminergic deficit between or within groups. Additionally, subgroup spectral DCM with PEB analyses was performed to determine whether the identified effective connectivity and self-inhibitory connectivity depended on the more affected hemisphere.

Global and Local Volumes: Voxel-Based Morphometry Analysis

To determine whether structural gray matter changes contributed to the observed differences in effective connectivity between groups, voxel-based morphometry (VBM) was utilized using SPM12. For further details on VBM analysis, refer to Supplementary Material 3.

Statistical Analysis

Demographic data and behavioral outcomes were compared between nonfreezers and freezers using the independent sample t test or the Mann-Whitney U test, depending on the distributions. Subsequently, we performed a partial correlation analysis between the identified effective connectivity and the FOG severity measures. Covariates added in the partial correlation analyses were the same as those for the DCM with PEB analysis. A two-sample t test was applied to compare the volumes between the nonfreezers and freezers, adding the same covariates as the DCM with PEB analysis. A partial correlation analysis was also performed between FOG severity and global or local volumes, and Box–Cox transformation[38] was applied to deal with abnormally distributed data and plotted using Python (version 3.9.7). We also conducted a matched group analysis, using the MatchIt method.[39] Statistical analysis was performed using R software (version 4.0.2) for group comparisons and SPSS (version 29) for partial correlations, with a significance level of $P < 0.05$.

Results

Participant Selection

A total of 145 patients were eligible for this study from a cohort of 480 patients. After 24 patients were excluded due to excessive head movements, the remaining 121 patients were categorized into 61 nonfreezers and 60 freezers based on clinical observation of FOG. After the groups were matched for age and sex, 39 of 121 patients were lost, leaving 82 patients in the matched groups (41 nonfreezers and 41 freezers) for the main DCM analysis (Fig. S1). Table 1 shows that significant group differences were found between the matched nonfreezer and freezer groups in disease duration; LEDD; MDS-UPDRS, Part 3; postural instability and gait difficulty score[40]; and FOG-Q score.

Effective Connectivity: Spectral DCM with PEB

ROI Selection

Seed-to-voxel analysis of resting-state fMRI data identified significantly increased functional connectivity between the bilateral 6-mm MLR ROIs (peak voxel MNI [Montreal Neurological Institute] coordinates (x/y/z) for right MLR: 7/−27/−18, and left MLR: −7/−27/−18)[41] and the bilateral 8-mm dorsolateral prefrontal cortex (DLPFC) ROIs (right: 26/36/52, left: −36/20/54) in freezers compared to nonfreezers at voxel threshold at uncorrected $P < 0.001$ (Fig. 2). Thus, these four ROIs were selected as nodes for the DCM analysis (Fig. S2) to investigate effective connectivity in freezers compared to nonfreezers.

Spectral DCM with PEB

Using an unbiased and data-driven PEB algorithm, the excitatory directional connections from the left DLPFC to the bilateral MLR and self-inhibitory connectivity within

TABLE 1 *Demographic and clinical characteristics of the matched group*

Variables	Nonfreezers (n = 41)	Freezers (n = 41)	*P*-value
Age (y)	67.15 ± 10.20	69.10 ± 9.88	0.38
Sex (F/M)[a]	19/22	21/20	0.83
Disease duration (y)	6.71 ± 5.28	10.34 ± 6.07	$P < 0.01$
LEDD (mg/d)	282.32 ± 217.96	491.46 ± 278.59	$P < 0.01$
Hemispheric laterality (Lt deficits/Rt deficits)[a,b]	n = 26/15	n = 27/14	1
MDS-UPDRS, Part 3	26.22 ± 11.43	37.93 ± 15.16	$P < 0.01$
PIGD score (0–20)	3.29 ± 2.58	10.51 ± 5.04	$P < 0.01$
FOG-Q (0–24)	7.78 ± 4.91	15.54 ± 5.49	$P < 0.01$
Number of falls (m)	2.10 ± 9.45	1.32 ± 2.81	0.36
MMSE (0–30)	27.68 ± 2.18	27.76 ± 2.24	0.83
FAB (0–18)	14.59 ± 2.80	14.61 ± 2.76	0.91
QUIP-S (0–13)	0.71 ± 1.29	1.20 ± 1.74	0.13
SCOPA-AUT (0–69)	16.37 ± 8.07	18.46 ± 7.50	0.23

Mean ± standard deviation.
[a]χ^2 test.
[b]More striatal dopaminergic-deficit side in ^{123}I-fluoropropyl-carbomethoxy-3β-4-iodophenyltropane imaging.
Abbreviations: LEDD, a total levodopa equivalent daily dose; Rt, right; Lt, left; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PIGD, postural instability and gait difficulty score (the sum of MDS-UPDRS items 2.12, 2.13, 3.10, 3.11, and 3.12)[38]; FOG-Q, freezing of gait questionnaire; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; QUIP-S, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Short; SCOPA-AUT, Scale for Outcomes in Parkinson's Disease for Autonomic Symptoms.

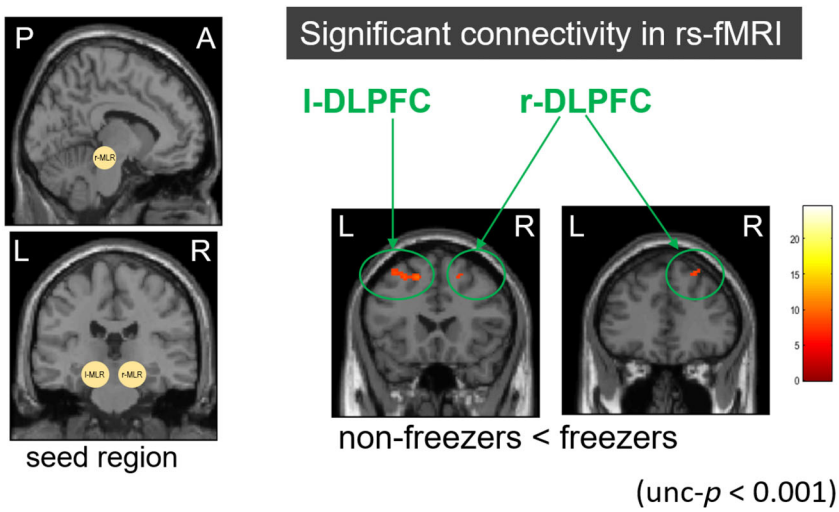

FIG. 2. Results of the seed-to-voxel analysis. Seed-to-voxel analysis of resting-state fMRI (functional magnetic resonance imaging) identified regional increases in functional connectivity in freezers compared with nonfreezers. P, posterior; A, anterior; L (l), left; R (r), right; DLPFC, dorsolateral prefrontal cortex; MLR, mesencephalic locomotor region. [Color figure can be viewed at wileyonlinelibrary.com]

the left DLPFC showed no commonalities between nonfreezers and freezers (Pp = 0; Fig. 3A2 vs. 3B2). They were the best discriminative parameters in freezers compared to nonfreezers (group differences; Fig. 3B3). Specifically, the excitatory influence of the left DLPFC to the bilateral MLR and the self-inhibitory connectivity within the left DLPFC were increased in freezers compared to nonfreezers (Pp > 0.99 for the identified connections; Fig. 3B3). The right DLPFC had no significant influence on any regions identified using BMR for the between-group effect.

Accuracy of DCM Model Estimation

The estimation of DCM models for individual participants in nonfreezers and freezers was good to excellent: the average percentage variance explained using DCM estimation was 88.0% (range: 70.2%–96.3%).

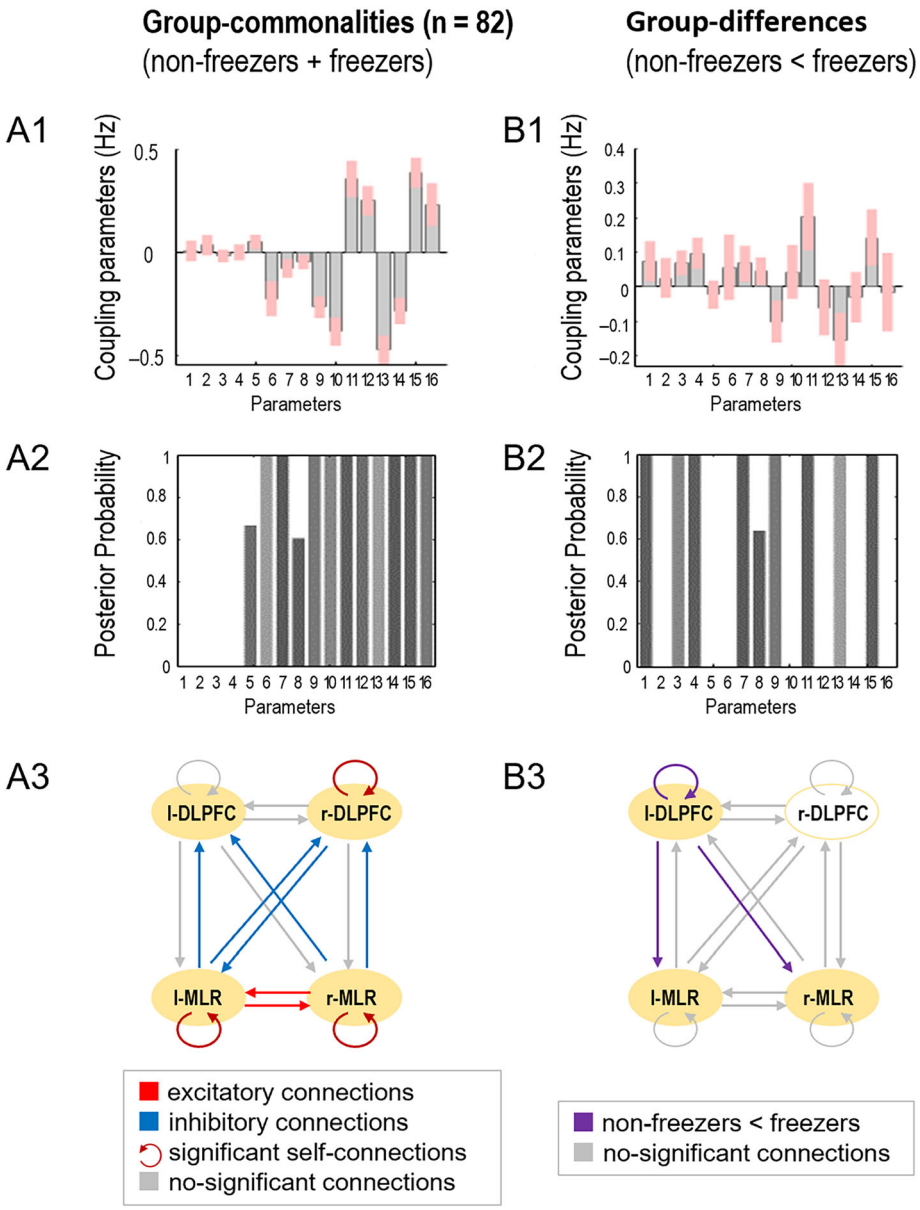

FIG. 3. Results of the Bayesian dynamic model comparison (nonfreezers vs. freezers). The left panels show (**A1**) the commonalities for the coupling parameters of each of the parameters in the model after Bayesian model averaging, (**A2**) the corresponding posterior probabilities, and (**A3**) a schematic representation of the significant excitatory connections (red arrows), inhibitory connections (blue arrows), and nonsignificant connections (gray arrows). The right panels show (**B1**) the strength of the connections that differed significantly between the nonfreezers and freezers regarding the coupling parameters and (**B2**) the corresponding posterior probabilities. Between-group significant connections (purple arrows) and nonsignificant connections (gray arrows) (**B3**). Filled yellow regions show significant connectivity effects that survived Bayesian model reduction (**A3** and **B3**). The number of parameters (*x*-axis; **A1** and **A2**, **B1** and **B2**) indicates patterns of effective connectivity as shown in Table S3. The *y*-axis of **A1** and **B1** indicates the mean coupling parameters in effective connectivity (gray bars, Hz) with 90% Bayesian credible intervals (pink bars), whereas the *y*-axis of **A2** and **B2** indicates posterior probability. DLPFC, dorsolateral prefrontal cortex; MLR, mesencephalic locomotor region. [Color figure can be viewed at wileyonlinelibrary.com]

Associations between Identified Effective Connectivity and Severity of Freezing of Gait Correlation Analysis

Table 2 presents the exploratory partial correlation between FOG severity and effective connectivity in nonfreezers and freezers, while correcting for disease duration, H&Y stage, LEDD, and MDS-UPDRS, Part 3, total score. Among the freezers, significant inverse correlations were found between increased excitatory effective connectivity from the left DLPFC to the left MLR ($r = -0.397$, $P = 0.036$) and right MLR ($r = -0.478$, $P = 0.010$) and lower self-reported FOG severity (both scores in the total FOG-Q and FOG-Q item 3). Similarly, increased self-inhibitory connectivity within the left DLPFC was associated with lower clinically rated FOG severity of the MDS-UPDRS item 3.11

TABLE 2 *Partial correlation coefficient between the measures in FOG severity and effective connectivity*

	Effective connectivity								
	All participants (n = 82)			Nonfreezers (n = 41)			Freezers (n = 41)		
FOG measures	l-DLPFC to l-MLR	l-DLPFC to r-MLR	l-DLPFC self-connect	l-DLPFC to l-MLR	l-DLPFC to r-MLR	l-DLPFC self-connect	l-DLPFC to l-MLR	l-DLPFC to r-MLR	l-DLPFC self-connect
FOG-Q total (0–24)	−0.038	−0.063	−0.057	−0.035	−0.004	0.009	−0.397*	−0.478*	−0.259
FOG-Q item-3[a] (0–4)	−0.075	−0.012	−0.017	−0.027	−0.027	0.230	−0.133	−0.237	−0.411*
MDS-UPDRS item 3.11[a] (0–4)	0.168	0.151	−0.059	NaN	NaN	NaN	0.019	−0.004	−0.480*

Disease duration, H&Y stage, head-movement parameter, LEDD, and MDS-UPDRS, Part 3, total score were added as covariates.
[a]The scores for FOG-Q item-3 and MDS-UPDRS item 3.11 were transformed into a normal distribution using a Box–Cox transformation.
*$P < 0.05$.
Abbreviations: FOG-Q, freezing of gait questionnaire, and FOG-Q item-3 that specifically questions the frequency of FOG; l, left; DLPFC, dorsolateral prefrontal cortex; r, right; MLR, mesencephalic locomotor region; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale, and MDS-UPDRS item 3.11 that clinically rated FOG severity; self-connect, self-inhibitory connectivity; H&Y, Hoehn and Yahr; LEDD, levodopa equivalent daily dose; NaN, no result because all non-freezers had a score of zero in MDS-UPDRS item 3.11.

($r = -0.480$, $P = 0.010$); freezers with more severe freezing (score >1) as rated by the FOG severity item 3.11 of the MDS-UPDRS, Part 3, showed negative values in the self-inhibitory connectivity within the left DLPFC (73.7%; Fig. S4G3). There was no relationship between increased effective connectivity from the left DLPFC to the bilateral MLR and self-inhibitory connectivity within the left DLPFC. Furthermore, these increased effective connectivity and self-inhibitory connectivity had no association with any cognitive score on the MMSE or FAB, or also the MDS-UPDRS, Part 3, total score (correcting for disease duration, H&Y stage, and LEDD).

Global and Local Gray Matter Volume Differences

There were no between-group differences in the mean global and mean local gray matter volumes in the four ROIs (Table S1), nor any significant relationships between the volumes and measures of FOG severity in the PD group and subgroups.

Subgroup Spectral DCM with PEB Analyses

There were within-group imbalances in the laterality of dopaminergic deficits such that 15 of 41 nonfreezers and 14 of 41 freezers showed more striatal dopaminergic deficits in the right hemisphere despite no between-group differences (Table S2). None of the participants exhibited completely symmetrical patterns. To assess whether our results were driven by laterality of the dopamine transmission, further DCM with PEB analysis was performed by enrolling those who had more striatal dopaminergic deficits on the right hemisphere with the same protocol. Importantly, the same connectivity patterns and group differences were found in this subsample as for the whole sample (Fig. S3D3).

Discussion

This study is the first to identify effective connectivity underlying FOG in dedicated ROIs determined using a data-driven approach. We demonstrated the following: (1) presence of abnormally increased functional connectivity between the bilateral DLPFC and the bilateral MLR in freezers compared to nonfreezers; (2) increased top-down excitatory effective connectivity from the left DLPFC to the bilateral MLR, and an independent self-inhibitory connectivity within the left DLPFC in freezers versus nonfreezers, all of which were inversely associated with the severity of FOG; (3) lateralization of these findings was not attributable to the laterality of the dopaminergic deficit; and (4) effective connectivity differences were not accompanied by structural gray matter changes in the DLPFC and MLR regions.

A number of neuroimaging studies have previously shown that PD patients with FOG had increased activation in the DLPFC,[10,42,43] MLR,[9] or both regions.[11] The combined activation changes in the MLR and DLPFC are also in line with earlier fMRI work,[11,44,45] demonstrating higher DLPFC-related connectivity[46] and increased functional connectivity between the MLR and frontal and temporal cortical regions,[12,13] which were related to worse FOG severity. Additionally, a longitudinal study showed that PD patients who developed FOG after 2 years had stronger connectivity between the left DLPFC and the mediodorsal thalamus and a marked reduction in connectivity strength over the 2 years as FOG emerged.[47] These findings were often interpreted as compensatory prefrontal recruitment in response to a loss of motor automaticity rather than as the primary pathological process underlying FOG[44,48,49] especially in the early stages.[47] However, these studies did

not determine the direction of regional connectivity in freezers, hampering a mechanistic interpretation.

Here, we identified increased top-down excitatory effective connectivity from the left DLPFC to the bilateral MLR (directional influence from the DLPFC to the MLR), and increased self-inhibitory connectivity within the left DLPFC, which were associated with milder FOG and an absence of structural differences in any of these regions. The lack of structural deficits is consistent with the idea that FOG represents a breakdown of functional networks, rather than discrete lesions causing FOG.[50] Our findings also support the hypothesis that the DLPFC is engaged in controlling gait through the MLR in freezers. As the greater DLPFC–MLR connectivity was associated with lower FOG severity, it seems that the DLPFC's influence is adaptive and tends to improve FOG, indicating a potential compensatory mechanism. As previous reviews proposed, this mechanism could also signify a shift from posterior to anterior cortico-striatal processing.[18,51,52] Taken together, although further study is needed to conclude whether it is the involvement of aberrant or adaptive processing in FOG, our results, showing that worsening FOG was correlated with decreased effective connectivity and the lack of structural deficits, suggest that the notion of compensatory mechanism is more plausible.

Despite this potential compensatory mechanism, as the DLPFC is not typically involved in regulating gait, its involvement may not always result in effective locomotor output from the MLR, and patients thereby still experience episodic FOG, especially during challenging situations.[1,53] Indeed, it is known that despite its episodic nature, gait tasks with a high motor, cognitive, sensory, and/or limbic demand frequently elicit FOG.[15,54,55] The DLPFC is a major component of the frontostriatal circuitry that is involved in the processing of secondary cognitive and limbic task demands when walking.[45] The reliance on the DLPFC therefore puts freezers at risk of a processing conflict (ie, neural bottleneck),[42] resulting in a failure to recruit compensatory pathways. To make matters worse, people with PD typically prioritize secondary cognitive tasks over motor tasks, further increasing a risk of gait breakdown.[56]

The DLPFC remains relatively spared for a long time in PD, making it a likely area to take over gait control via the anterior frontal–striatal circuit when the automatic processing of gait via the affected posterior motor circuit becomes heavily affected.[10,11,42,43] In contrast, Fling et al showed higher functional connectivity between the SMA, which is part of the posterior motor network, and the bilateral MLR in freezers than in nonfreezers and healthy controls. It therefore seems that FOG can result when either primary motor control (SMA-MLR) or compensatory cognitive control (DLPFC-MLR) fails.

Given the role of the DLPFC in cognitive tasks, it was surprising that we did not find significant associations between effective DLPFC-MLR connectivity and cognitive scores in our sample. This finding, however, is in keeping with a recent study enrolling a large cohort, which showed that cognition or executive function was not associated with FOG severity, when controlling for covariates.[57] Therefore, the exact role of cognitive compensation in the etiology of FOG needs further clarification.[58] Future task-based studies are needed to provide an in-depth understanding of DLPFC-related adaptive functions in FOG.

Another important result in the current study is the self-inhibitory connectivity within the left DLPFC. Because there was no relationship between the increased excitatory connectivity from the left DLPFC to the bilateral MLR and the self-inhibitory connectivity within the left DLPFC, these functions could play distinct functional roles and should be interpreted separately. We found that patients with severe FOG (scores >1) also tended to exhibit more negative self-inhibitory connectivity values within DLPFC, possibly indicating an increased preparedness for involvement from other networks.[36] This suggests that the left DLPFC is more sensitive to the surrounding input, as if ready to engage in supporting the movement (gait) at hand and play a compensatory role. In more advanced freezers, the progressive loss of segregation among motor, cognitive, sensory, and limbic networks[55] may explain the reason for this increased sensitivity within the left DLPFC. Interestingly, a recent task-based fMRI study showed that threatening situations had a similar effect on the transitioning of brain networks into a more integrated state, which was also associated with worse freezing of leg movements.[59] Thus, hypothetically, in mild FOG, a relatively preserved functional segregation of the cognitive networks from the influence of other networks (eg, motor and limbic) could still allow processing of multiple inputs with little interference. In contrast, a highly integrated state could increase the risk of interference, resulting in worsened FOG.[59] Therefore, future studies should investigate connectivity across multiple networks to determine system-level impairments in FOG[60] rather than focus on a single network or pairs of regions.

Besides the network systems underlying FOG, several studies suggest that cholinergic dysfunction is linked to the presence of FOG.[61,62] Both the DLPFC and the MLR are thought to include major cholinergic projections.[63] Therefore, a future study direction is to add nuclear imaging to capture these cholinergic changes and investigate the relationship with the identified effective connectivity in this study.

Interestingly, we found dominantly left-hemisphere lateralization for effective connectivity even when controlling for PD patients with more striatal dopaminergic deficits in the right hemisphere in a sensitivity analysis. This is consistent with previous findings showing that the left-hemisphere circuitry may be less affected in patients with FOG.[13,64-66]

Clinical Implication

Previous pilot studies using noninvasive brain stimulation for improving FOG targeted the left DLPFC and showed a positive impact on gait measures.[67-69] Our findings provide a rationale of why modulating the left DLPFC could benefit gait by normalizing functions of the distant bilateral MLR, implicated in FOG. More prospective studies are now needed to verify if the modulation of DLPFC activity and connectivity could improve gait and FOG.

Study Strengths and Limitations

This study is the first to examine effective connectivity underlying FOG in dedicated ROIs determined using a data-driven approach. First we used a sufficiently large PD imaging cohort that allowed us to obtain equal sample sizes for the nonfreezer and freezer groups after age- and sex matching. Second, nonfreezer and freezer classifications were determined by self-report and expert clinical raters. Third, FP-CIT imaging was used to take asymmetric dopaminergic deficits into account. However, this was a retrospective study, and freezer and nonfreezer groups were not matched for disease severity although we controlled for this difference. Future studies are needed to determine whether the connectivity markers found are predictive of the onset of FOG and can be modulated by an intervention to reduce FOG. Furthermore, we applied predefined symmetrical ROIs based on prior neuroimaging knowledge. At present, there is no specific guideline available for defining the boundaries of the MLR, precluding the creation of individual MLR ROIs based on nonnormalized structural imaging data. Moreover, although we used globally recognized FOG rating scales that have demonstrated validity and reliability,[70-72] their clinimetric properties are not fully established.[73,74] Therefore, future prospective studies should consider the possibility of bilateral asymmetry of MLR ROIs and incorporate objective FOG measures with validated clinimetric properties. Finally, due to clinical feasibility, fMRI was acquired with a resolution of $3.31 \times 3.31 \times 4$ mm and nonisotropic voxels (Supplementary Material 2), which might have impacted the spatial accuracy of the MLR ROI. However, similar parameters have been applied in other imaging studies reporting on the MLR in PD.[10,75] Future imaging studies should aim for optimal parameters (eg, isotropic and smaller voxels).

Conclusion

We found abnormally increased functional connectivity between the bilateral DLPFC and MLR in freezers compared to nonfreezers at rest, which represented a top-down excitatory effective connectivity between the left DLPFC and the bilateral MLR. We also observed independent self-inhibitory connectivity within the left DLPFC. These changes were inversely associated with the severity of FOG. The lateralization of these findings was not attributable to the initial dopaminergic deficit nor to structural changes in these regions. These results imply that modulating the effective connectivity between the left DLPFC and MLR using neurostimulation or other intervention could be a target for reducing FOG in PD.

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Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available because of ethical restrictions but are available from the corresponding author on reasonable request within the limits of participant' consent. The resource codes of MATLAB, CONN toolbox, and Python are available: SPM12 r7771 (https://www.fil.ion.ucl.ac.uk/spm/software/), CONN toolbox version 22.a (https://web.conn-toolbox.org/resources/source-code), and Python version 3.9.7 (https://www.python.org/). Software packages such as MatchIt and PhysIO Toolbox were also utilized.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique. S.T.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B. Y.K.: 1B, 1C, 2C, 3A, 3B. T.K.: 2A, 2C, 3B. G.R.: 1B, 3B. K.O.: 1B, 1C. E.S.: 1B, 1C. K.A.: 1B, 1C. C.S.: 1B, 1C. T.O.: 1B, 1C. Y.K.: 1B, 1C, 2C, 3A, 3B. K.I.: 1B, 1C, 2C, 3A, 3B. N.D.: 2A, 2C, 3A, 3B. M. G.:2C, 3A, 3B. A.N.: 2C, 3A, 3B. H.M.: 1A, 1B, 3B.

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