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Dual-task interference and brain structural connectivity in people with Parkinson's disease who freeze

Daniel S Peterson^{1,2}, Brett W Fling^{1,2}, Martina Mancini¹, Rajal G Cohen³, John G Nutt¹, and Fay B Horak^{1,2}

¹Department of Neurology, School of Medicine, Oregon Health & Science University, Portland, Oregon, USA

²Portland Veterans Affairs Medical Center, Portland, Oregon, USA

³Department of Psychology & Communication Studies, University of Idaho, Moscow, Idaho, USA

Abstract

Background—Freezing of gait in people with Parkinson's disease (PD) is likely related to attentional control (ie, ability to divide and switch attention). However, the neural pathophysiology of altered attentional control in individuals with PD who freeze is unknown. Structural connectivity of the pedunclopontine nucleus has been related to freezing and may play a role in altered attentional control; however, this relationship has not been investigated. We measured whether dual-task interference, defined as the reduction in gait performance during dual-task walking, is more pronounced in individuals with PD who freeze, and whether dual-task interference is associated with structural connectivity and/or executive function in this population.

Methods—We measured stride length in 13 people with PD with and 12 without freezing of gait during normal and dual-task walking. We also assessed asymmetry of pedunclopontine nucleus structural connectivity via diffusion tensor imaging and performance on cognitive tests assessing inhibition and set-shifting, cognitive domains related to freezing.

Results—Although stride length was not different across groups, change in stride length between normal and dual-task gait (ie, dual-task interference) was more pronounced in people with PD who freeze compared to non-freezers. Further, in people with PD who freeze, dual-task interference was correlated with asymmetry of pedunclopontine nucleus structural connectivity, Go-NoGo target accuracy (ability to release a response) and simple reaction time.

Correspondence to, Dr Daniel Peterson, Oregon, Health & Science University, 3181 SW Sam Jackson Park, Road, Portland, OR 97239, USA; petedani@ohsu.edu.

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Competing interests FBH has an equity/interest in APDM, a company that may have a commercial interest in the results of the study. This potential conflict of interest has been reviewed and managed by the Research & Development Committee at the Portland VA Medical Center.

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Conclusions—These results support the hypothesis that freezing is related to altered attentional control during gait, and suggest that differences in pedunculopontine nucleus connectivity contribute to poorer attentional control in people with PD who freeze.

INTRODUCTION

Gait disturbances in people with Parkinson's disease (PD) are more pronounced during dual-task (DT) walking.¹ This reduction in gait performance during DT walking, known as DT interference, may be related to reduced automatic control of movement.²³ The reduction in automaticity necessitates increased cognitive control of movement, enhancing the interference between primary (locomotion) and secondary (cognitive) tasks. Further, alterations in attentional control (one's ability to divide and switch attention between tasks), likely increase DT interference in this population.⁴ DT walking is particularly challenging in individuals with PD who experience freezing of gait (FoG),⁵ suggesting attentional control and/or automation of locomotion play important roles in FoG. Other cognitive domains are also altered in individuals with PD who experience FoG (FoG+) with respect to those not experiencing FoG (FoG-), and may contribute to FoG or DT interference. Specifically, recent studies show that FoG+ exhibit worse performance in executive function domains including response inhibition⁶⁷ and set-shifting.⁸⁹ In fact, altered executive function, coupled with a loss of automaticity of movement has been suggested to lead to FoG.¹⁰

Although attentional control and automaticity likely play a role in FoG, few investigations have directly studied DT interference in FoG+, and results of these studies are mixed. Two reports showed that during DT walking, FoG+ increased cadence more than FoG-,⁵¹¹ indicating more pronounced DT interference. Conversely, Hackney and Earhart¹² recently reported that in a large group of FoG+ and FoG-, dual-tasking did not have a differential effect on gait across groups. Of these reports, only Hackney and Earhart measured changes in stride length (SL), a measure strongly linked to FoG.¹³ Further, the secondary cognitive tasks completed during walking in these studies were verbal fluency or mental subtraction. DTs that incorporate motor and cognitive function may require additional cognitive resources, thereby increasing DT interference.

The neural pathophysiology underlying altered attentional control during gait in FoG+ is not well understood. Recent research suggests that in addition to cortical areas such as the dorsolateral prefrontal cortex, deep brain structures including the pedunculopontine nucleus (PPN) may play an important role for attention, due to the large number of cholinergic projections from the PPN to the basal ganglia.¹⁴ Indeed, lesion studies in animals support the role of PPN in attention.¹⁵ Perhaps unsurprisingly, FoG+ exhibit altered structural and functional connectivity brain stem and cortical structures.¹⁶⁻²¹ For example, FoG+ exhibit altered activity in the mesencephalic locomotor region (MLR, which includes the PPN) during imaged locomotion and atrophy of this region with respect to FoG-.¹⁷ Further, the volume of white matter tracts emanating from the PPN (measured via diffusion tensor imaging, DTI) are diminished in the right hemisphere in FoG+ relative to FoG-, resulting in higher right-left PPN white matter asymmetry in FoG+. This PPN white matter asymmetry was directly related to measures of inhibition.¹⁶ Given the altered connectivity of the PPN in FoG+, and the possible relationship between the PPN and attention, PPN dysfunction may

play a role in FoG and DT interference. However, the relationship between PPN dysfunction and DT interference (an important manifestation of altered attentional control) has yet to be explored.

Understanding the relationship between DT interference and factors that underlie FoG, including structural connectivity and executive function, can provide insight into the relationship between attentional control and FoG. Therefore, the primary goal of the current study was to better understand how DT interference is altered in FoG+, and whether it is related to abnormal structural connectivity within the PPN. A secondary goal was to understand whether DT interference is related to two domains of executive function previously related to FoG: inhibitory control and set-shifting. We addressed three questions: (1) Are FoG+ and FoG- differentially affected by DT during gait? (2) Is DT interference correlated with PPN structural connectivity? (3) Is DT interference correlated with cognitive measures shown to be related to FoG? We hypothesise that dual-tasking has a more profound effect on FoG+ than FoG-, and that this change correlates with structural and cognitive measures related to FoG.

METHODS

Participants

A convenience sample of 25 participants were recruited through the Parkinson's Center of Oregon at Oregon Health & Science University (OHSU) and Portland Veteran's Affairs Medical Center, and all data were collected at OHSU. All participants signed an informed consent approved by OHSU's Institutional Review Board. Exclusion criteria were: dementia (score <21 on the Montreal Cognitive Assessment, MoCA²²), neurological diseases other than PD, vestibular disorders, musculoskeletal impairment, and inability to stand and walk for 20 min. Individuals with severe resting tremor were excluded to improve quality of MRI and to match FoG+ and FoG- participants on aspects of PD apart from FoG. Testing was carried out in the practical OFF state (12+ hours of PD medication withdrawal). Participants were included in the FoG+ group if they answered 'yes' to question 1 of the New FoG Questionnaire (NFOGQ): "Have you experienced FoG in the past month?" Based on these criteria, 13 FoG+ and 12 FoG- were included in the study (table 1). Age and MoCA scores were similar across groups. Compared to FoG-, FoG+ had more severe PD based on Hoehn & Yahr stage and scores on part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III) and a trend towards longer disease duration.

Procedure

Participants underwent MRI to collect DTI data, followed by normal and DT walking. Participants continuously walked along a 20 m hallway for 2 min, making 180° turns at each end. For both conditions, participants wore headphones. Headphone volume was adjusted so participants could hear 0.33 Hz tones in both ears. During the DT walking session, participants walked while an audio tone was played in the right or left ear (random order) at intervals ranging from 1650 to 4000 ms. Participants were instructed to turn their head quickly in the direction of the tone and then back to centre. Participants then completed the same seated choice reaction head-turning task, providing a control for DT walking, and

allowing calculation of change in head-turning errors between cognitive only and DT conditions. This secondary task was chosen to incorporate both cognitive and motor tasks into the secondary task. In addition, we wished to have a task that was not so challenging as to fully arrest locomotion. Participants then completed nine cognitive tests in a pseudorandom order (for detailed description, see ref.⁶). Previous reports suggest that inhibition⁶⁷ and set-shifting⁸⁹ relate to FoG. Thus, we analysed four cognitive tasks: two tests of inhibition (Stroop, Go-NoGo) and two tests of set-shifting (Trail-Making task, Plus-Minus task). Stroop, Trail-Making and Plus-Minus tasks were administered via pencil and paper. Simple reaction time (SRT) and Go-NoGo tests were administered using online software (Psychology Experiment Building Language; PEBL²³).

Gait analysis

Seven opal inertial sensors (APDM Inc) were worn on the wrists, ankles, sacrum, chest and forehead during walking, and Mobility Lab software (APDM, Inc) automatically analysed gait characteristics. SL and SL variability, calculated as SD of all strides (normalised to height), were primary outcomes because these measures are sensitive to FoG.¹³²⁴ Steps during turns were automatically excluded from the SL and SL variability calculations using an automatic algorithm that identified turns using yaw angular velocity of the trunk.²⁵ Head turns were identified by an automated threshold-based algorithm (yaw angular velocity of the head of 60°/s) and visually inspected to check for possible errors. DT interference was calculated as the difference between SL during normal and DT walking.

Executive function analysis

Variables of interest for cognitive tests have been discussed previously.⁶ Two tests of inhibition (Stroop and Go-NoGo), and two tests of set-shifting (Trail-Making and Plus-Minus) were included due to the relationship between FoG and inhibition and set-shifting. Stroop: time to complete the conflict condition⁶; Go-NoGo: target accuracy (percent accuracy during 'Go' trials)⁶; Trail-Making: time difference between alternating (numbers and letters) and numeric only conditions⁸; Plus-Minus: time difference between the mean of addition and subtraction conditions and the alternating condition.

Structural connectivity analysis

Image acquisition and analysis—Image acquisition and analysis for this cohort have previously been described.¹⁶ Briefly, images were acquired using a 3.0 T Siemens Magnetom Tim Trio scanner with a 12-channel head-coil at the OHSU's Advanced Imaging Research Center. One whole-brain high-resolution structural T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (orientation=sagittal, echo time (TE)=3.58 ms, repetition time (TR)=2300 ms, 256×256 matrix, resolution=1 mm³) was collected. Three sets of diffusion-weighted images were collected using a 30-gradient direction, whole-brain echoplanar imaging sequence (TR=9100 ms, TE=88 ms, field of view=240 mm², b value=1000 s/mm², isotropic voxel dimensions=2 mm³) and three images in which the b value was equal to zero. A static magnetic field map was also acquired using the same parameters as the DTI sequence. Standard diffusion image processing was followed using tools implemented in FMRIB Software Library (FSL; V.4.1.9; <http://>

www.fmrib.ox.ac.uk/fsl), including correction for eddy current distortions and motion artefacts, averaged to improve signal-to-noise ratio and subsequently skull-stripped using FSL's brain extraction tool.

Identification of region of interests /probabilistic tractography—The PPN was chosen as a region of interest (ROI) due to (1) considerable research implicating this structure in FoG,²⁶²⁷ and (2) its projections to cortical and subcortical regions critical for locomotor control and cognition.¹⁶²⁶²⁸ The PPN ROIs (Right/Left) were centred at $x=\pm 7$, $y=-32$, $z=-22$ and ranged $x=\pm 6$ to 9, $y=-30$ to -35 , $z=-17$ to -26 (Montreal Neurological Institute coordinates). To analyse the PPN network we identified unrestricted connectivity maps for ROIs in both hemispheres. Probabilistic fibre tracking (using FDT 1.0) was initiated from every voxel within the binarised ROI sphere in each participant's native diffusion space. Streamline samples (25 000) were sent out from each voxel, with a step length of 0.5 mm and a curvature threshold of 0.2. For group analyses, the probabilistic connectivity distribution maps from individual participants were thresholded at 5% (thus selecting all connections where more than 1250 of 25 000 samples passed).²⁹ 'Tract quantity' was assessed by computing the volume comprising the identified tracts that exceeded an fractional anisotropy (FA) threshold of 0.2, a standardised value used to differentiate between grey and white matter.³⁰ Laterality of PPN white matter volume was calculated as follows: $\text{PPN laterality} = (\text{Left} - \text{Right}) / (\text{Left} + \text{Right})$.¹⁶ This measure was chosen because (1) it inherently normalises projections within each patient and (2) previous work shows laterality is higher (worse) in FoG+ with respect to FoG-.¹⁶

Statistics

Homogeneity of variance across groups was verified using Levene's Test. A two-way (groups $\times$ condition) repeated-measures analysis of covariance (ANCOVA) was used to investigate the difference in SL and SL variability across groups (FoG +/FoG-) and across conditions (normal/DT). Disease duration, UPDRS-III and MoCA score were covariates for ANCOVAs analyses. Non-parametric (Spearman) partial correlations were performed to investigate the associations between DT interference and (1) PPN lateralisation and (2) measures of inhibition and set-shifting (Stroop, Go-NoGo, Trail-Making, Plus-Minus), controlling for the effect of UPDRS-III. Non-parametric correlations were used because some variables (eg, PPN lateralisation, Stroop conflict time) were not normally distributed, as determined by the Shapiro-Wilk Test. For one FoG+ participant, DTI data were not analysed due to excessive head movement in the scanner. Statistical analyses were performed using SPSS (V.22).

RESULTS

No freezing or festination was observed during straight forward walking. Some individuals in the FoG+ group froze during turning; however, turns were excluded from all analyses.

DT effects on primary (gait) and secondary (cognitive) tasks

After correcting for symptom severity (UPDRS-III), disease duration and MoCA, SL was not different across groups; however, a significant condition effect and group $\times$ condition

interaction were observed (table 2, figure 1A). SL variability was higher in FoG+ (significant group effect) and there was a trend towards higher SL variability during dual-tasking within FoG+ (condition-effect). No group $\times$ condition effect was noted for SL variability (table 2).

Owing to equipment malfunction, DT error data were available for nine FoG– and eight FoG+ participants. Errors were not significantly different across groups during sitting (mean (SD); FoG– 0.33 (0.71); FoG+ 0.5 (0.53)) or walking (FoG– 1.89 (1.05); FoG+ 2.75 (2.38); group main effect: $F_{1,15}=0.78$; $p=0.39$). There was a significant condition effect ($F_{1,15}=4.6$; $p=0.049$), but no group by condition effects ($F_{1,15}=0.084$; $p=0.78$; figure 1B).

Correlations among DT interference, PPN connectivity and cognitive tests

Group statistics have been previously reported for the diffusion imaging approach here.¹⁶ Briefly, fibre tracts comprising the locomotor network traversing the PPN were identified within all participants. Tractography for FoG– participants is shown in figure 2. FoG– participants had significantly greater PPN tract quantity within the right hemisphere compared to FoG+. Partial correlation analyses are shown in table 3 and figure 3. DT interference correlated with PPN laterality, Go-NoGo target accuracy and SRT across all participants. When each group was analysed separately, significant correlations remained only for the FoG+ group. Specifically, in the FoG+ group, DT interference showed ‘strong’ or ‘very strong’ correlations with Go-NoGo, SRT and PPN laterality. Means and SDs of cognitive tests for each group have been reported previously.⁶

DISCUSSION

In FoG+, larger DT interference was strongly correlated with more lateralised PPN structural connectivity, linking PPN structural connectivity with an inability of FoG+ to maintain SL under DT conditions. In addition, DT interference was related to worse Go-NoGo target accuracy and longer SRT. Finally, in keeping with previous findings,⁵¹¹ we showed that the ability to maintain SL when attention is divided is more affected in FoG+ than FoG–. SL variability was also higher in FoG+ than FoG–, and dual-tasking tended to increase SL variability (in both groups) over normal walking. Together, these findings support the notion that FoG+ exhibit altered attentional control and reduced automation of locomotion with respect to FoG–, and suggest a possible neural underpinning, that is, altered PPN structural connectivity, for this change.

PPN structural connectivity and DT interference

In FoG+, lateralisation of PPN structural connectivity was strongly related to DT interference, suggesting the PPN may play a role in attentional control in FoG+. In fact, post hoc analyses showed that in addition to the PPN structural connectivity —DT interference correlation, PPN connectivity was also correlated to SL during normal and DT walking; however, the relationship was much stronger during DT walking (normal walking: $r=-0.46$, $p=0.14$; DT walking: $r=-0.83$, $p=0.001$). The relationship between PPN structural connectivity and attentional control is not entirely surprising, given the dense connectivity between the PPN and both locomotor and cognitive hubs, including the basal ganglia,

subthalamic nucleus (STN), supplementary motor area (SMA) and cerebellum (among others).¹⁶²⁶³¹ The PPN comprises a large number of cholinergic cells and may play an important role in attention and gait in healthy adults and individuals with PD.³² Indeed, recent work has related cholinergic function to attentional control during gait in this population¹⁴; however, until now the link between attentional control and PPN structural connectivity has not been shown. Our results are partially consistent with a previous study investigating neural activity during a virtual reality locomotor task and simultaneous high-load and low-load cognitive tasks.³³ Results suggested that complex cognitive tasks result in reduced activity in cortical (eg, insula, pre-SMA) and basal (striatum, STN) regions. Although activity in the PPN was not different across groups, many of the regions exhibiting altered activity have strong structural connectivity to the PPN (eg, STN, pre-SMA¹⁶). Results from the current study are also partially consistent with a study focused on another population that experiences freezing: progressive supranuclear palsy (PSP). Zwergal *et al*³⁴ showed that during walking, patients with PSP exhibited lower activity in supraspinal locomotor centres, including the PPN/MLR. Further, activity within the cerebellum, STN and prefrontal cortex, correlated with SL. Moreover, individuals with PSP (and particularly those who experience a high rate of falls), exhibited marked SL dysfunction during DT walking.³⁵ Together, these reports underscore the importance of the PPN as one of several regions contributing to FoG and attention regardless of disease pathophysiology.

DT interference and FoG

In conjunction with the previous literature, DT interference was more pronounced in FoG+ than FoG−, providing indirect evidence that FoG+ exhibit reduced automaticity and increased compensatory cortical control of locomotion.⁵¹¹ In support of these findings, PD has been associated with increased reliance on cortical control during movement,³ possibly due to dysfunction of the basal ganglia.² Automation of motion may be particularly affected in FoG+.¹⁰³⁶ Recent work from our laboratory shows FoG+ exhibit increased functional connectivity between cortical midline structures (SMA) and deep brain locomotor regions (MLR and cerebellar locomotor region).²¹ Further, increased SMA-MLR connectivity was related to increased freezing severity, suggesting that larger cortical-deep brain connectivity could be maladaptive. Although these data were collected at rest, they provide indirect evidence that FoG+ may have increased cortical control of motion and that this increased control is maladaptive.

Finally, although FoG+ exhibited a larger reduction in SL during dual-tasking than FoG−, the groups made similar numbers of choice reaction time errors (ie, head turning errors) while seated or during DT walking. This suggests that in FoG+ there was a higher prioritisation on the cognitive task than FoG−, resulting in a disproportionate deterioration of gait performance. The tendency for locomotion to be altered more than the cognitive task during DT walking, described as a ‘posture second’ strategy, has been reported previously in PD.³⁷ Our data suggest that a posture second strategy may be even more pronounced in FoG+. The prioritisation of cognitive task over gait could be particularly detrimental to FoG+, increasing fall risk. These data are consistent with Spildooren *et al*,⁵ who noted that during DT turning, FoG+ showed decrements in gait first, followed by alterations in secondary-task performance, suggesting a posture second strategy in FoG+. However, the relatively small

sample size, further reduced for this analysis due to equipment failure (see Methods section), somewhat tempers this conclusion.

DT interference and executive function

Converging evidence suggests that FoG is related to alterations in executive function,⁷³⁸ including alterations in attentional control, inhibition⁶⁷ and shifting.⁸⁹ In the current report, we found that in FoG+, DT interference was related to performance on the Go-NoGo test. Specifically, the target accuracy (ie, errors on 'Go' trials) correlated with DT interference. This result suggests diminished ability to maintain gait during DT conditions is related to an inability to release preplanned programmes. As noted earlier, previous investigations from this laboratory have suggested freezing may be related to an inability to effectively couple the release of wanted motion (ie, stepping) and the inhibition of unwanted motion (ie, weight transfer).⁶³⁹ Indeed, in the same data set used here, Cohen *et al*⁶ found that of nine cognitive tasks spanning inhibition, shifting and updating domains, Go-NoGo target miss rate showed the largest differences between FoG+ and FoG- groups. Results from the current study support this finding, and further suggest automaticity and attentional control may be related to diminished ability to release motor programmes. Finally, in a recent review, Vandenbossche *et al*¹⁰ highlight the importance of both automated and cognitive (ie, voluntary) control of movement in FoG and provide a model of FoG that suggests FoG may be the result of a breakdown of both paths. Our results, along with previous reports,⁶ support this hypothesis; however, future investigations should work to clarify the interaction between cognitive control and automaticity of movement in FoG.

In the current study, more pronounced DT interference was also significantly related to slower SRT. The cause of this correlation is not entirely clear; however, faster reaction times may indicate more movement automaticity, potentially freeing up cognitive resources during walking and reducing the effects of DT interference. Interestingly, we found no significant correlation between DT interference and Stroop conflict time, Trail-Making task (B-A) or Plus-Minus task; although our small sample may have precluded detecting differences.

Limitations

Several limitations should be noted. First, FoG+ and FoG- were not fully matched for disease severity. This difference was due in part to our attempt to match FoG+ and FoG- groups on non-tremor symptoms to allow for neuroimaging collection. However, we statistically accounted for this difference by incorporating both disease duration and UPDRS-III in our statistical models. Second, our sample sizes were small, especially to establish correlations within the FoG+ group (n=13), reducing our ability to draw strong conclusions from these data. Third, the secondary cognitive task was not as challenging to participants as other secondary tasks (eg, auditory Stroop task). However, we did note DT interference in both PD groups and head turning errors were made in both conditions (seated and walking). Finally, for technical reasons we were not able to assess head turning errors in all participants, possibly limiting our ability to detect group by task effects and therefore tempering conclusions regarding the increased 'posture second strategy' observed in FoG+.

CONCLUSION

This is the first study to relate attentional control during gait to structural brain connectivity, showing higher DT interference in people with PD who freeze was strongly related to reduced structural connectivity of the right PPN. Further, FoG+ were less able to maintain SL during DT walking than FoG–; and FoG+ exhibited a posture second strategy with respect to FoG –. These results support the hypothesis that FoG is related to altered locomotor automaticity and attentional control, and suggest that alterations in PPN connectivity may contribute to these changes.

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Figure 1.

(A) Mean and SE of stride length under single and DT conditions. (B) Mean and SE of errors in head-turning direction while seated and during walking. DT, dual-task; FoG +, individuals with Parkinson's disease who experience freeze of gait (FoG); FoG-, individuals with Parkinson's disease who do not experience FoG. *Significant task effect at the $p < 0.05$ level; **Significant task effect at the $p < 0.001$ level; #Significant group by task interaction at the $p < 0.05$ level.

Figure 2.

Regions of interest (ROIs) and probabilistic tractography employed in the current manuscript. (A) Depicts the right hemisphere's pedunculopontine nucleus (PPN; green) utilised for unconstrained fibre tractography (data for left hemisphere not shown). Principal subcortical and cortical regions demonstrating structural connectivity with the PPN can be observed in A–C including the subthalamic nucleus (STN; blue), the primary motor cortex (M1; violet), the supplementary motor area (SMA; cyan) and the preSMA (red). (C) Depicts group fibre tracts from FoG– participants ($n=12$); the colour bar indicates the percentage of participants with identified tracts in each region. Note the majority of fibre tracts connecting the PPN with the cortex are situated medially within the SMA and M1.

Figure 3.

Linear correlation between DT interference and (A) PPN laterality index (B) Go-NoGo target accuracy and (C) simple reaction time. DT, dual-task; FoG, freeze of gait; FoG+, individuals with Parkinson's disease who experience FoG; FoG-, individuals with Parkinson's disease who do not experience FoG; PPN, pedunculopontine nucleus; SL, stride length.

Table 1

Subject characteristics and cognitive test performance

	FoG– (n=12) Mean (SD)	*FoG+ (n=13) Mean (SD)	Group differences (p value)
Age	64.9 (6.9)	66.2 (5.5)	0.60
UPDRS	29.2 (6.9)	36.8 (9.7)	0.03
MOCA	27.8 (1.9)	26.5 (2.1)	0.12
H&Y	1.96 (0.69)	2.62 (0.51)	0.01
Disease duration	6.5 (4.2)	10.8 (6.2)	0.06
Preferred gait velocity (% stature/s)	74.8 (9.01)	70.56 (9.60)	0.26

* FoG+ identified via New FoG Questionnaire.

FoG, freeze of gait; FoG+, individuals with Parkinson's disease who experience FoG; FoG–, individuals with Parkinson's disease who do not experience FoG; H&Y, Hoehn & Yahr Scale; MOCA, Montreal Cognitive Assessment; UPDRS, Unified Movement Disorders Rating Scale.

Table 2

SL and SL variability in people with PD who do not experience FoG (FoG-) and PD who do experience FoG (FoG+)

	FoG- (n=12) Mean (SD)	FoG+ (n=13) Mean (SD)	Condition effect	Group effect	Group×condition interaction
SL (cm)					
Normal	81.3 (7.9)	75.0 (7.5)	p<0.001	p=0.317	
DT	79.7 (7.4)	71.2 (8.5)			
DT interference	1.6 (1.4)	3.8 (2.9)			p=0.020
SL variability (cm)					
Normal	1.53 (0.40)	2.23 (0.56)	p=0.058	p=0.018	
DT	1.64 (0.40)	2.66 (0.43)			
DT interference	0.10 (0.31)	0.43 (0.88)			p=0.323

DT, dual-task; FoG, freeze of gait; PD, Parkinson's disease; SL, stride length.

Table 3

Partial correlation (Spearman's r) between dual-task interference and: (1) pedunclopontine nucleus (PPN) laterality, (2) inhibition and set-shifting tests and (3) simple reaction time in individuals with Parkinson's disease (PD) who do not experience FoG (FoG-), who do experience FoG (FoG+) and all participants combined (All), accounting for Unified Parkinson's Disease Rating Scale (UPDRS)-III

	FoG- (n=12)	FoG+ (n=13)	All (n=25)
Structural connectivity			
PPN laterality	-0.62	-0.91**	-0.82**
Inhibition			
Stroop conflict time	-0.08	-0.40	-0.32
Go-NoGo (target accuracy)	0.02	0.65*	0.44*
Set-shifting			
Plus-Minus Task	0.21	-0.44	-0.10
Trail-Making task B-A	0.40	-0.51	-0.14
Simple reaction time	-0.19	-0.71*	-0.45*

*
p<0.05;

**
p<0.001.