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Cerebral metabolic changes related to freezing of gait in Parkinson's disease

Trina Mitchell[1,2] Alexandra Potvin-Desrochers, MSc[1,2] Anne-Louise Lafontaine, MD[3] Oury Monchi, PhD[4] Alexander Thiel, MD, PhD[5,6] & Caroline Paquette, PhD[1,2]

[1] Department of Kinesiology and Physical Education, McGill University, Montréal, Canada
[2] Centre for Interdisciplinary Research in Rehabilitation, Montréal, Canada
[3] Montreal Neurological Institute and Hospital, McGill University, Montréal, Canada; Movement Disorders Unit, McGill University Health Centre, Montréal, Canada
[4] Department of Clinical Neurosciences and Hotchkiss Brain Institute, University of Calgary, Calgary, Canada
[5] Department of Neurology and Neurosurgery, McGill University, Montréal, Canada
[6] Jewish General Hospital, Lady Davis Institute for Medical Research, Montréal, Canada

Corresponding author: Caroline Paquette, PhD, Department of Kinesiology and Physical Education, McGill University, Montreal, Quebec, H2W 1S4, Canada. Email: caroline.paquette@mcgill.ca, Phone: 514-398-4184 x00890.

First Author: Trina Mitchell, Department of Kinesiology and Physical Education, McGill University, Montreal, Quebec, H2W 1S4.

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ABSTRACT

Freezing of gait in Parkinson's disease often occurs during steering of gait (i.e., complex gait) which is thought to arise from executive dysfunction. Our aim was to test whether cognitive cortico-basal ganglia-thalamo cortical circuitry is impaired and whether alternate neural circuits are used for complex gait in Parkinson's disease with freezing of gait. **Methods** Eighteen individuals with idiopathic Parkinson's disease in the OFF medication state, nine with freezing of gait (aged 68 ± 6) and nine without freezing (aged 65 ± 5) were included. Positron emission tomography was used to measure cerebral glucose metabolism during two gait tasks, steering and straight walking, performed during the radiotracer uptake period. **Results** During steering, there was reduced change in cerebral glucose metabolism within the cognitive cortico-thalamic circuit. More specifically, those with freezing of gait had less activation of the posterior parietal cortex, less deactivation of the dorsolateral prefrontal cortex and thalamus, and increased activation in the supplementary motor area. Interestingly, activity in the dorsolateral prefrontal cortex correlated with gait impairment (i.e., reduced stride length) in the freezing of gait group. **Conclusions** These results demonstrate decreased parietal control and an alternate control mechanism mediated by prefrontal and supplementary motor areas in Parkinson's disease with freezing of gait.

Keywords: cerebral glucose metabolism, complex gait, freezing of gait, Parkinson's disease, humans

INTRODUCTION

Freezing of gait (FOG) in Parkinson's disease (PD) is a debilitating symptom characterised by episodic motor blocks during gait (*1*). FOG is most often triggered by steering of gait which composes the majority of steps in daily-life (*2*), and compared to forward walking, requires increased executive control (*3*). Recent efforts have probed the control of more challenging gait in PD with FOG (*4-7*).

Conflict-monitoring and top-down control is an important feature of the cortico-basal ganglia-thalamic structure (*8,9*). It is known that hyper-direct connections between supplementary motor area and subthalamic nucleus subserving these functions are impaired in FOG (*10-12*). Thus, it is hypothesized that impairment of frontostriatal executive circuits contributes to FOG. Another hypothesis suggests that supra-threshold activity of motor and cognitive circuits leads to "cross-talk" of these normally segregated pathways resulting in FOG (*13*). Both hypotheses may be explained by high attentional demands resulting from reduced gait automaticity. It has been proposed that internally driven motor programs are impaired in PD with FOG and ordinarily automatic tasks such as gait require increased attentional control (*10,14*). In such cases, increased activity of frontal and parietal cortices would strongly inhibit subcortical basal ganglia and brainstem nuclei responsible for motor output (i.e., globus pallidus internal segment and pedunculopontine nucleus), requiring increased top-down control during gait (*14,15*).

The most frequent method to quantify gait-related whole-brain activity is functional magnetic resonance imaging (fMRI), where mental imagery of gait is performed while lying supine in the scanner. These paradigms have suggested similar involvement of cortical and subcortical substrates in FOG, however, results are contradicting (*5,16*). An important issue

arising is that mental imagery is unable to accurately capture gait in PD with FOG due to the discrepancy between perceived and actual walking resulting from sensory impairments (*17*). fMRI has been used to study turning in FOG during a virtual reality paradigm with continuous foot pedaling. Here, PD with FOG have increased activity of inferior frontal regions involved in a "stopping" network, and decreased activity of parietal and supplementary motor areas (*18*). These findings were taken as evidence that individuals with FOG have a tendency for hesitation and support hypotheses for reduced gait automaticity. Still, postural control requiring complex cortical processing is absent from these paradigms (*19*). More recently, positron emission tomography (PET) has been used to measure whole-brain cerebral glucose metabolism, a marker of brain activity, during unconstrained motor tasks performed during the radiotracer uptake period (*20*).

We recently used 18F-fluorodeoxy-glucose (18F-FDG) PET in normal healthy individuals to measure regional cerebral glucose metabolism (rCGM) during steering of gait (i.e., complex walking) contrasted with steady-state forward walking (i.e., simple walking reference task). Bilateral frontoparietal regions composing the cognitive cortico-basal ganglia-thalamo circuitry were recruited for steering (*21*). Understanding changes to this type of complex control in PD with FOG could provide a better understanding of its pathophysiology. Therefore, the purpose of this study was to determine if cognitive circuits are limited and whether alternate neural circuits are used for steering of gait. To address this aim, we used 18F-FDG PET and an upright gait paradigm to measure rCGM in PD with and without FOG. We hypothesized that PD with FOG would have deficits in executive control, with limited recruitment of the cognitive cortico-basal ganglia-thalamo cortical circuit and increased activation of compensatory motor circuits.

MATERIALS AND METHODS

Subjects

The study protocol was approved by McGill Faculty of Medicine Institutional Review Board for Human Subjects and written informed consent was obtained.

18 participants with idiopathic PD according to the UK Brain Bank criteria and the ability to walk independently for 30-minutes were recruited through the Quebec Parkinson Network (*22*). A score of > 1 in Part I of the New Freezing of Gait Questionnaire (NFOGQ) was used to confirm nine participants as experiencing FOG (FOG+) (*23*). We recruited nine individuals with PD that were matched for age, sex, disease severity, disease duration, medication dosage, laterality of motor symptoms, and cognitive function that did not experience FOG (FOG-), as confirmed by a score of > 1 in Part I of the NFOGQ (Table 1). All participants were free from cognitive impairment assessed by the Montreal Cognitive Assessment (>25), did not present with any coexisting orthopedic or neurological disorders, and were non-diabetic (*24*).

Experimental Procedure

Participants were screened in their "on" medication state. Disease severity was assessed with the Movement Disorders Society Unified Parkinson's Disease Rating Scale Motor Part III and Hoehn and Yahr scale (*25*) and was repeated in the "off" medication state later. The FOG+ group were further assessed for severity of freezing and its effect on daily life using Parts II and III of the NFOGQ which included 8 additional questions resulting in a total score out of 28, with a higher score indicating increased severity of freezing. The hospital anxiety and depression scale assessed anxiety and depression (*26*). During this session, all participants had brief practice of the two gait tasks.

Two subsequent visits to the laboratory were in the clinically defined "off" medication state (i.e., overnight withdrawal of all anti-Parkinson medication, average time off medication=12 ± 2 hours). Cerebral glucose metabolism was measured during two gait tasks, steering (i.e., complex locomotion) and straight walking (i.e., simple locomotor reference task) using PET imaging with 18F-FDG. Each task was performed continuously for 30 minutes immediately following a 185 MBq bolus injection of 18F-FDG on two separate occasions, at least 48 hours apart (*20*). Participants walked at their self-selected "normal" walking speed and received practice of each gait task approximately 10 minutes immediately prior to the tracer injection. The order of task performed was randomized across testing days. All subjects were fasted overnight for both sessions (at least 6 hours).

For the walking tasks, three lanes (1.2 m width by 28 m length) were delineated by yellow and orange cones in a 6 m by 34 m area (Fig. 1). In the straight walking task, participants were instructed to walk in the middle of each walking lane, making 180 degree turns into the adjacent lane (Fig. 1). In the steering task, the same placement of cone markers was used and participants were instructed to continuously turn around the yellow cones, placed in an unpredictable pattern. A safety harness was worn and a research assistant followed behind to prevent a fall (*27*). No falls occurred during the experiments. Following the walking task, participants were escorted to the PET scanner from the experimental room, approximately a 5-minute walk which was of similar duration for all subjects. Therefore, PET scanning began within 50 minutes of the tracer injection. This walk to the scanner does not change 18F-FDG concentration because it is static following the radiotracer uptake period of ~20 minutes (*20,21*).

Spatiotemporal measures of gait (i.e., stride length normalized to height and stride velocity) were measured using the APDM Mobility Lab System (Opal™, APDM Inc., Portland,

OR). Participants wore six wireless inertial sensors containing a tri-axial accelerometer, tri-axial gyroscope, and a tri-axial magnetometer. Data was sampled at 128 Hz.

The number of freezing episodes and total duration spent in FOG over the entire 30-minutes was evaluated using a stopwatch. Onset was determined when there was (i) shuffling of steps with minimal forward movement, (ii) trembling of the legs with absence of forward movement, or (iii) complete motor arrest (*28*). The same observer measured freezing across all participants. A video recording of the complete walking trial validated number and duration of freezing episodes rated by another researcher blinded to participant group. There was high level of agreement between raters (number of episodes: r = 0.98, $P < 0.001$, total duration: r = 0.91, $P < 0.001$). Video-based analysis was used to determine the total distance walked.

Imaging Protocol

PET images were acquired on a Siemens High Resolution Research Tomograph (HRRT) PET scanner (CTI/Siemens, Knoxville, TN, USA) with spatial resolution 2.3-3.4 mm full-width-at-half-maximum . Eight 3D sonograms consisting of 5-minutes each were generated from list-mode data acquired over 40-minutes. Normalization and correction of motion artefacts, random events, and scatter was applied prior to summation into one single 40-minute duration frame. A 10-minute transmission scan was acquired for attenuation correction.

T1-weighted images were acquired on a Prisma 3T Scanner (Siemens, Knoxville, TN, USA) with 3D magnetization prepared rapid gradient echo. T1 images were acquired as $1mm^3$ voxel sizes (ET=2.96 ms; TR=2.3 s; flip angle=9°). 192 contiguous sagittal slices (thickness = 1mm) were obtained using an echo-planar imaging sequence (FOV=$256mm^2$).

Image Analysis

Statistical parametric mapping software SPM12 (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB R2015a (MathWorks, Natick, MA, USA) was used for image processing and statistical analysis. Processing was consistent with previously described methods (*21*). Briefly, reconstructed PET images were co-registered to each subjects' anatomical image and spatially normalized to the Montreal Neurological Institute template. Images were smoothed with a Gaussian filter (FWHM= 8mm) and each voxel was scaled in proportion to the global mean activity thus yielding estimates of relative rCGM.

rCGM during steering was directly compared with rCGM during straight walking to determine task-related activations for both groups. To test a priori hypothesis of FOG within the cortical-basal ganglia-thalamo cortical circuitry, statistical analysis was performed on regions of interest within the cognitive, motor, and limbic cortical-basal ganglia-thalamo cortical circuits (Supplemental Table 1) (*6,13,15*). The MarsBar toolbox in SPM was used to extract parameter estimates for each region of interest which were then imported to IBM SPSS (version 21.0, IBM, Armonk, NY, USA) for further analysis by a two-way ANOVA to determine the effect of task (repeated measures) and group. Secondly, whole-brain voxel-wise analysis were performed using a flexible factorial design including factors: subject, group, and task. Main effects of task (steering vs. straight walking) and group (FOG+ vs. FOG-) and their interaction were determined at $P < 0.005$ (uncorrected) and a cluster extent threshold of 30 voxels (*21,29*).

Statistical Analysis

A two-way ANOVA implemented in SPSS assessed the effect of task (repeated measures) and group (FOG+ vs. FOG-) on stride length and stride velocity. Post-hoc tests were performed whenever a significant interaction occurred. Independent t-tests were used to assess

group differences in clinical variables. Where variables did not meet the assumption of normality assessed by a Shapiro-Wilk test, non-parametric Man-Whitney U tests were used. For the FOG+ group, Pearson correlation coefficients (r) were used to determine the relationship between peak activation in significant regions of interest with freezing severity and stride length, significant at the $P < 0.05$ level (two-tailed). Spearman's rank order correlation coefficient (r_s) were used for non-parametric data as indicated.

RESULTS

Behavioural Outcomes

Eight of nine participants in the FOG+ group experienced at least one freezing episode during the steering task, whereas only three participants experienced a freezing episode during straight walking. During steering, the median and interquartile range of the number of freezing episodes was 5 ± 1, total time freezing was 5.22 ± 31.60 seconds, and the percentage of time spent freezing was 2.9 ± 1.7%. There were no freezing episodes observed in the FOG- group for either task.

FOG+ walked a shorter total distance compared to FOG- in both tasks ($P < 0.01$). Across tasks (main effect of group), FOG+ had reduced stride length (FOG+: 61.6 ± 2.3 % height, FOG-: 70.7 ± 2.5 % height, $P < 0.05$) and stride velocity (FOG+: 0.93 ± 0.04 m/s, FOG-: 1.2 ± 0.05 m/s, $P < 0.01$) compared to FOG-. During steering (main effect of task), both groups similarly decreased their stride length (FOG+: 26.0 ± 0.09 %, FOG-: 26.9 ± 0.06 %) and stride velocity (FOG+: 32.4 ± 0.12 %, FOG-: 28.8 ± 0.04 %) compared to straight walking ($P < 0.001$).

Region of Interest Analysis

The region of interest analysis demonstrated different task-related changes in metabolism between groups in the cognitive cortico-thalamic circuit only (i.e., left posterior parietal cortex,

right dorsolateral prefrontal cortex, and left thalamus) (group x task: $P < 0.05$) (Supplemental Table 2). More specifically, FOG- increased activity in the posterior parietal cortex, decreased activity in the dorsolateral prefrontal cortex and thalamus for steering, whereas there was no significant change in FOG+.

Whole-brain rCGM during Steering

During steering, the most prominent activation (steering>straight) in both groups was in the left superior parietal lobule, inferior parietal lobule (Supplemental Table 3). The prominent deactivations (steering<straight) were in the inferior frontal gyrus and thalamus. Task-related metabolic differences were observed between groups in several regions (Fig. 2, Supplemental Table 4). FOG+ had increased activity during steering (steering>straight) in the right cerebellum (Crus 2), supplementary motor area, and left superior medial gyrus, posterior-medial frontal, and temporal gyri (middle and superior) compared to FOG-. FOG+ also demonstrated more deactivation (steering<straight) in the inferior frontal gyrus. In comparison, FOG+ had reduced activation (steering>straight) of the left superior and inferior parietal lobule, as well as the superior frontal gyrus compared to FOG-. FOG+ had less deactivation (steering<straight) in the right frontal gyri (middle and inferior), and left posterior medial frontal gyrus, precentral gyrus, superior frontal gyrus, and thalamus.

Relationship between rCGM, Disease Severity, and Gait Outcomes

Increased metabolic activity in the right dorsolateral prefrontal cortex during steering (steering>straight) was associated with reduced stride length in FOG+ ($r = -0.71$, $P = 0.033$). This activity was not associated with clinical ($r_s = -0.08$, $P = 0.831$) or objective (number of episodes: $r_s = -0.03$, $P = 0.931$; total duration: $r_s = 0.17$, $P = 0.668$) measures of freezing severity. Activity in the posterior parietal cortex, thalamus, and supplementary motor area did

not correlate with gait impairments or freezing severity. In the FOG- group, there were no correlations between rCGM and stride length for any regions of interest.

DISCUSSION

Changes in cerebral glucose metabolism associated with complex walking were measured in PD with and without FOG. In line with the hypothesis for executive dysfunction, we observed that FOG+ had reduced modulation of metabolic activity in the cognitive cortico-thalamic circuit during steering of gait compared to straight walking (Fig. 3). More specifically, FOG+ had less activation of the posterior parietal cortex and less deactivation of the dorsolateral prefrontal cortex and thalamus compared to FOG-. In addition, FOG+ had increased activation in the supplementary motor area (medial superior frontal gyrus) and less deactivation in mesial frontal (inferior, superior, posterior-medial) gyri during steering. Activity in dorsolateral prefrontal cortex correlated with gait impairment (i.e., reduced stride length) in FOG+.

The frontal and parietal regions with changed glucose metabolism during steering in FOG+ compose the cognitive cortical-thalamic circuitry and are importantly involved in mediating executive function (*30*) and visuomotor integration (*31*). It has recently been demonstrated that this network is active during lower limb motor arrests, thought to serve a positive compensatory strategy to break a freezing episode as individuals with severe freezing limit recruitment of this network (*6*). Structural (*32*) and functional (*5,33*) neuroimaging findings also demonstrate that this network is globally impaired in individuals with FOG. Therefore, our results, which illustrate reduced activation of parietal regions and reduced deactivation of prefrontal regions within this network, could indicate that FOG+ ineffectively activated parietal regions for steering of gait and employed more prefrontal control compared to FOG-. Increased activation of the dorsolateral prefrontal cortex correlated with gait impairment (i.e., reduced

stride length) in FOG+. This finding is interesting because during real freezing episodes there is increased activity of both prefrontal and parietal regions (*6*). Therefore, this shift from parietal to prefrontal control within the cognitive circuit illustrates a unique control mechanism employed by FOG+ during complex walking that may fail in a freezing event.

The supplementary motor area was increased in FOG+ for steering of gait. Notably, the supplementary motor area has direct projections to the subthalamic nucleus (i.e., 'hyper-direct' pathway) responsible for strong inhibition of a planned action (*8,9*) and is strongly activated during real freezing episodes (*34*). In these events, excitation of the subthalamic nucleus by the supplementary motor area leads to inhibition of basal ganglia and brainstem output nuclei believed to result in a lack of locomotor output for successful gait. Thus, during steering, FOG+ have increased activity within the hyper-direct pathway, known to result in inhibition of subcortical nuclei during freezing episodes. Taken together, these results provide evidence for a freezing mechanism that is active during increased cognitive and motor demands associated with complex walking in FOG+. The aforementioned parietal to prefrontal control shift observed in the present study could represent a compensatory strategy used during complex walking to prevent freezing episodes, which may become inefficient during motor arrest.

fMRI virtual reality used to study turning during continuous pedalling in FOG (i.e., between freezing episodes) reveal increased activity of inferior frontal regions, and decreased activity of parietal and supplementary motor areas (*18*). During steering, we also observe increased inferior frontal and reduced parietal metabolism in FOG+, however, our results demonstrate activation of the supplementary motor area. The present study measures global activation during complex gait relative to straight walking and illustrates how individuals with FOG recruit different circuitry during upright gait compared to those without FOG.

Both groups reduced metabolic activity of the thalamus during steering, however, FOG+ demonstrated less deactivation. Indeed, the thalamus along with other subcortical nuclei subserve automatic motor output (*10,35*). Furthermore, it has been suggested that there is reduced automaticity in PD with FOG, evoking increased cortical control (*14*). Indeed, steering of gait requires increased top-down control due to the integration of internal and external movement goals and high degree of motor planning required compared to simple steady-state walking (*21*). Therefore, reduced thalamic deactivation could demonstrate a poor ability to shift between automatic and voluntary control across simple and complex gait tasks in PD with FOG.

In contrast with our findings, a previous study in PD with and without FOG showed increased metabolic activity of parietal regions and subcortical nuclei, as well as reduced activity of frontal regions during an upright complex gait task (i.e., combined dual-tasking, passing through a narrow space, and 360-degree turning) compared to supine rest (*36*). Notably, participants spent approximately 40% in motor arrest. Moreover, the poor temporal resolution of PET and the combined gait task used in this study render the results difficult to interpret with respect to locomotor control. In comparison, our paradigm isolated complex gait from upright stance and steady-state gait and resulted in a small percentage of the total trial in motor arrest (average of 2.5%). Therefore, our findings can be interpreted to better reflect mechanisms underlying complex walking, although they do not completely dissect these phenomena apart. Furthermore, our results do not demonstrate a significant role for the mesencephalic locomotor region in control of complex gait in PD with FOG. The mesencephalic locomotor region has previously been proposed as an integral structure in the pathophysiology of FOG due to its role in initiation and modulation of gait (*37*) and impairment in FOG+ (*5*). Previous evidence using fMRI during continuous foot pedalling reports decreased activity of the mesencephalic

297 locomotor region during freezing episodes, thought to occur from strong inhibition from the
298 globus pallidus internus (*6*). In comparison, investigation of imagined gait using fMRI has
299 shown conflicting results regarding the mesencephalic locomotor region's role in FOG likely due
300 to the discrepancy between actual and perceived gait in PD with FOG (*5,16*). Moreover, our
301 results suggest the mesencephalic locomotor region may not directly be implicated in PD with
302 FOG during upright complex walking as compared to straight walking. Although this result must
303 be interpreted carefully because it is possible the present paradigm is unable to detect 18F-FDG
304 uptake in these brainstem nuclei.

305 **CONCLUSION**

306 This is the first investigation of complex locomotor control in PD with FOG during real
307 gait. Our findings demonstrate that PD with FOG has reduced parietal control and alternate
308 control via prefrontal and supplementary motor cortices compared to PD without FOG during
309 complex walking. Our results provide novel information about the neural mechanisms involved
310 in FOG.

311

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317 **Conflict of Interest Disclosures:** The authors declare no conflict of interest.

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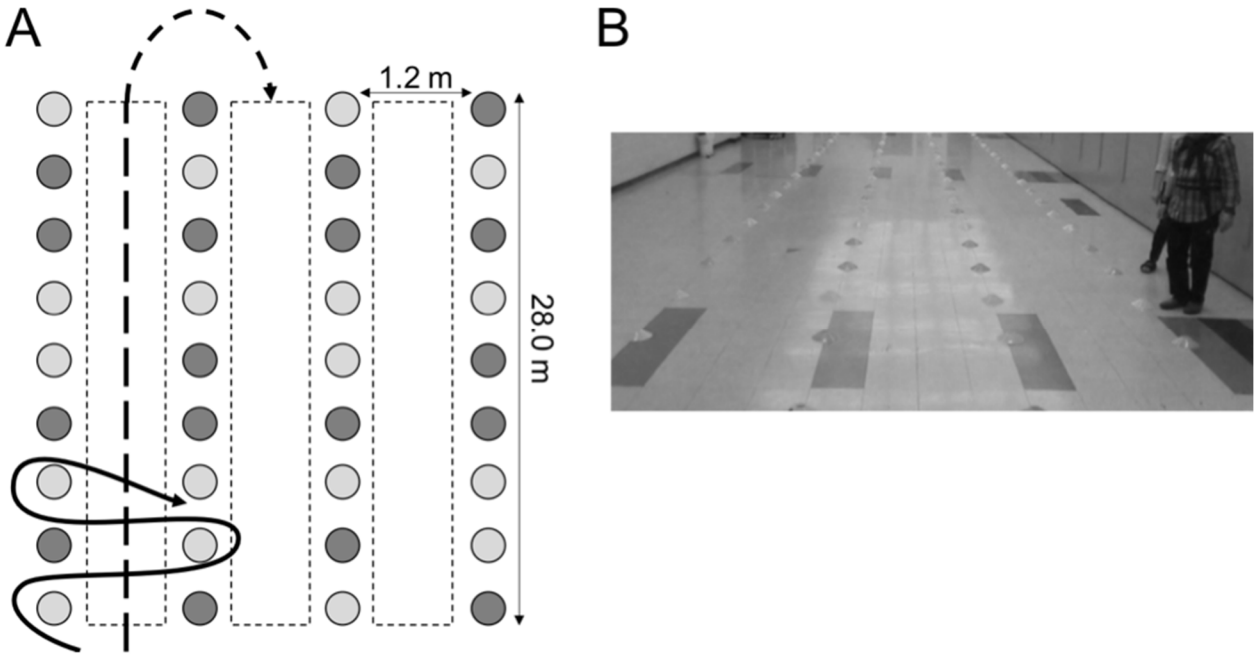

FIGURE 1. Experimental Setup
(A) The solid line illustrates the steering trajectory and the dashed line depicts straight walking. Light grey circles represent yellow cones and dark grey circles represent orange cones. The complete experimental setup had 30 cones spanning the entire length. (B) A participant performing the steering task with the experimenter following behind.

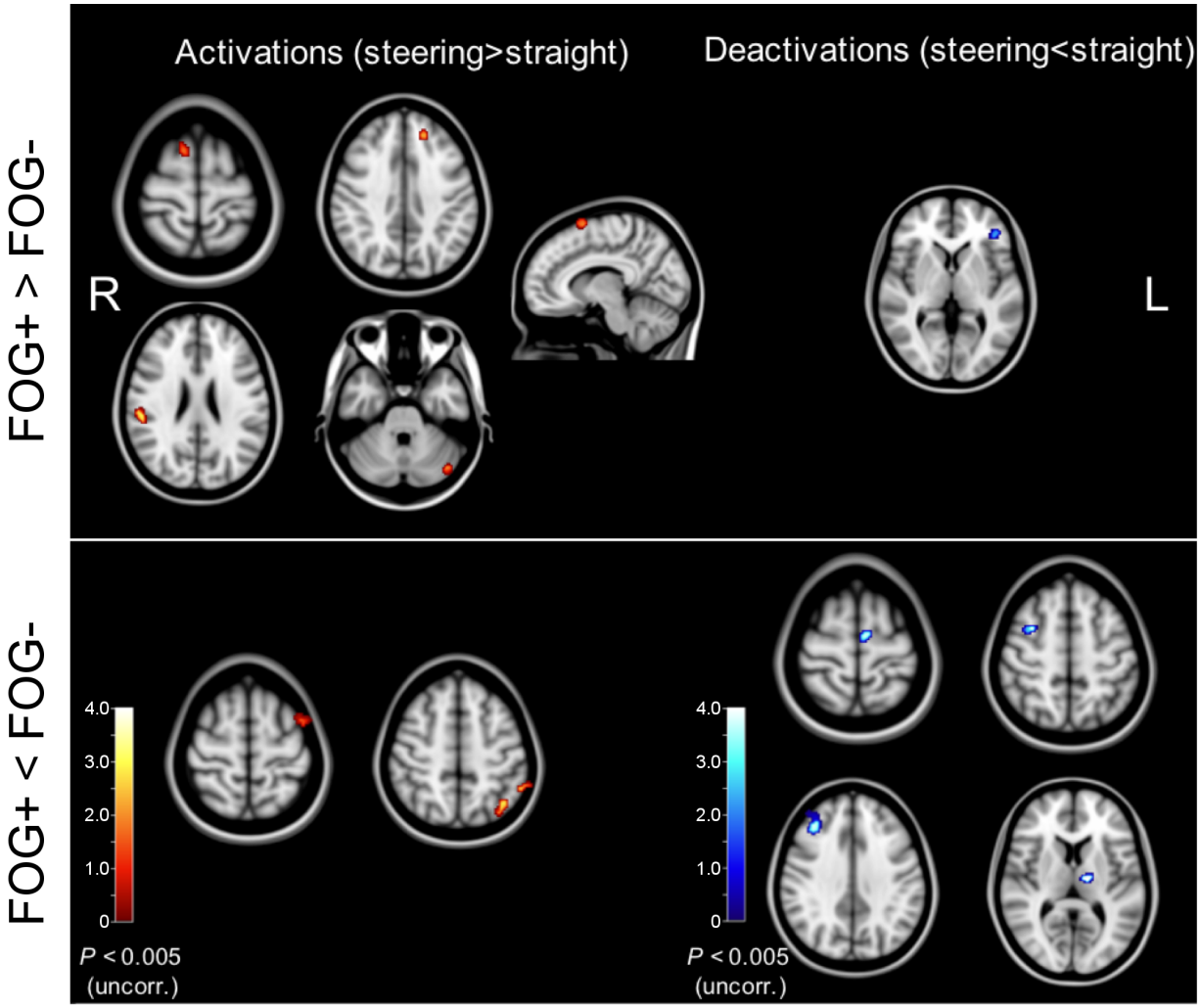

FIGURE 2. Steering related rCGM Group Differences

Statistical parametric maps showing group differences for steering-related activity Activations and deactivations are represented by warm and cool colors, respectively. *P<0.005* (uncorrected), cluster extent threshold=30.

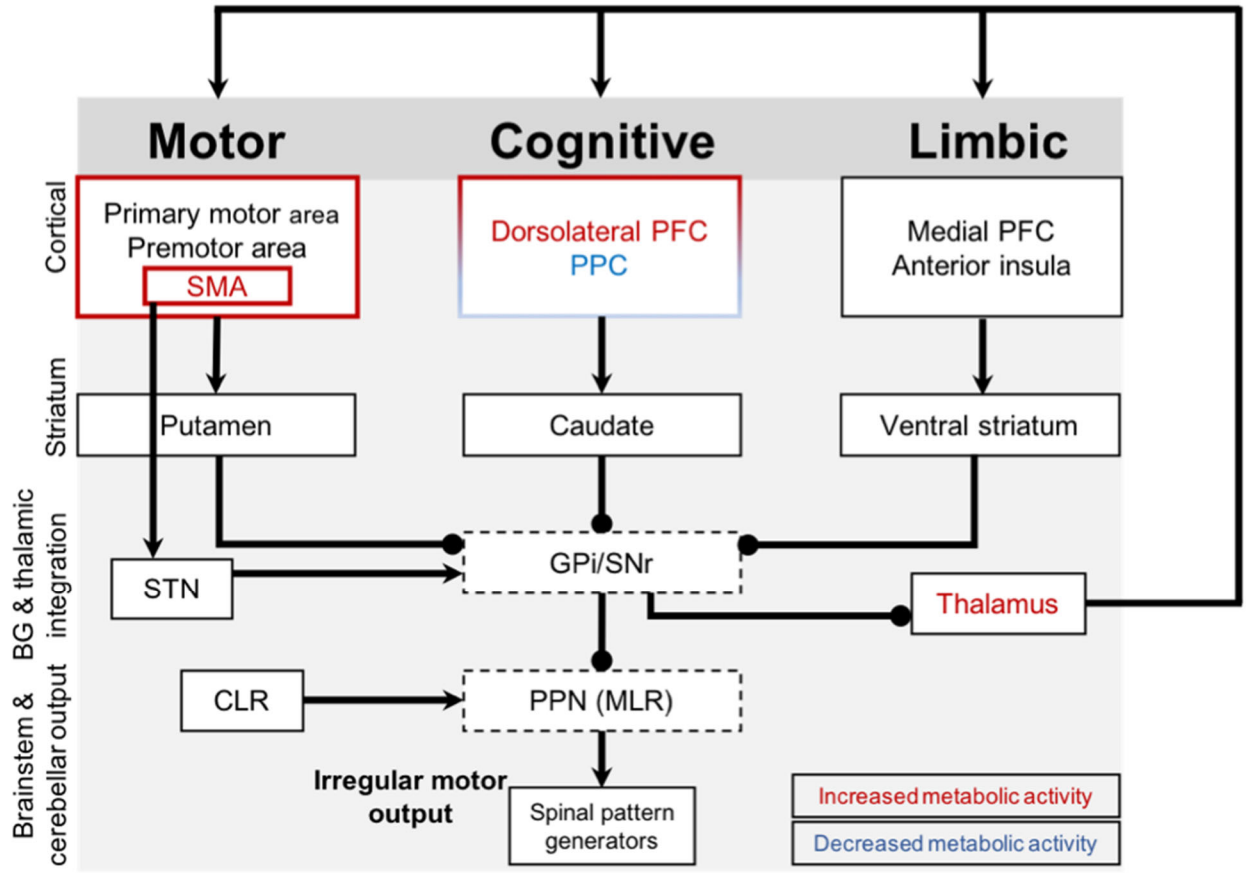

FIGURE 3. Complex Locomotor Control in Freezing of Gait
Arrows indicate excitatory connections and spherical ends denote inhibitory connections. Red and blue labels are regions with increased and decreased cerebral glucose metabolism, respectively, in FOG+ compared to FOG-. FOG+ demonstrates changed metabolic activity in the cognitive cortico-basal ganglia-thalamo cortical circuitry (less activation of parietal and less deactivation of prefrontal cortices). At the same time, there is less deactivation of the thalamus during steering and increased activity of the supplementary motor area, known to have hyper-direct connections with the subthalamic nucleus, with an overall inhibitory effect on already impaired basal ganglia outputs (i.e., globus pallidus internal segment and substantia nigra) and brainstem locomotor nuclei (i.e., pedunculopontine nucleus). SMA: supplementary motor area; STN: subthalamic nucleus; PPC: posterior parietal cortex; PFC: prefrontal cortex; GPi: globus pallidus internal segment; SNr: substantia nigra; PPN (MLR): mesencephalic locomotor region; CLR: cerebellar locomotor region (CLR).

Table 1. Subject demographics

Variables	**FOG+ (n=9)**		**FOG- (n=9)**		**P**
Sex (male/female)	5/4		8/1		0.066
Age (years)	67.7	(5.9)	64.6	(4.9)	0.235
Time since disease onset (years)*	8.7	(6.4)	8.4	(3.4)	0.863
Laterality of predominant motor symptoms (right/left)	3/6		2/7		0.500
Hoehn & Yahr Scale*	2.6	(0.5)	2.2	(0.4)	0.258
MDS-UPDRSIII† score (off-drug)	48.3	(7.6)	41.4	(7.0)	0.064
Dopa equivalent dose	893	(617)	751	(272)	0.557
NFOG – Questionnaire score*	**12.7**	**(8.2)**	**0**	**(0)**	**<0.001**
Montreal Cognitive Assessment	28.0	(1.7)	28.8	(1.6)	0.321
HADS‡ Anxiety	6.2	(3.3)	3.8	(1.6)	0.067
HADS‡ Depression	6.7	(3.7)	4.2	(2.0)	0.103

Mean (standard deviation) presented for all variables except sex, and laterality, which are presented as proportions.
*Non-parametric tests used
† Movement Disorders Society Unified Parkinson's Disease Rating Scale (Part III)
‡ Hospital Anxiety and Depression Scale
Significant group differences indicated in bold type, $p<0.05$.