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Neurophysiological Measures of Dual Tasking while Stepping in People with Parkinson's disease and Freezing of Gait

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Abstract

Freezing of gait in people with Parkinson's disease (PwP) is associated with executive dysfunction and motor preparation deficits. We have recently shown that electrophysiological markers of motor preparation, rather than decision-making, differentiate PwP with freezing of gait (FOG+) and without (FOG-) while sitting. To examine the effect of locomotion on these results, we measured behavioural and electrophysiological responses in PwP with and without FOG during a target response time task while sitting (single-task) and stepping-in-place (dual-task).

Behavioural and electroencephalographic data were acquired from 18 PwP (eight FOG+) and seven young controls performing the task while sitting and stepping in place. FOG+ had slower response times while stepping. However, response-times were faster while stepping for FOG- and controls. Electrophysiological responses showed no difference in decision-making potentials (Centroparietal Positivity) between groups or conditions but there were differences in neurophysiological markers of response inhibition (N2) and motor preparation (Lateralized Readiness Potential, LRP) in FOG+ while performing a dual-task. This suggests that the addition of a second complex motor task (stepping-in-place) impacts automatic allocation of resources in FOG+, resulting in delayed response times. The impact of locomotion on the generation of the N2 and LRP potentials, particularly in freezers, indirectly implies that these functions compete with locomotion for resources. In the setting of multiple complex tasks or cognitive impairment, severe motor dysfunction may result, leading to freezing of gait.

Introduction

The basal ganglia play an important role in the selection of actions in response to stimuli (Friend & Kravitz, 2014). Dopamine modulates these neural dynamics for stimulus-response (Vo *et al.*, 2017). The loss of automatic motor control in Parkinson's disease (due to loss of dopaminergic innervation of the basal ganglia) means that even simple motor tasks require greater reliance on deliberate, cognitively effortful (goal-directed) movement and increased recruitment of cortical areas involved in cognitive control (Wu *et al.*, 2015; Butler *et al.*, 2017). People with Parkinson's disease (PwP) are vulnerable to interference from other goal-directed tasks which utilize similar neural substrates (Redgrave *et al.*, 2010). This is further exacerbated in PwP with freezing of gait , which is a brief episodic phenomenon, characterised by the "absence or marked reduction in forward progression of the feet despite the intention to walk" (Nutt *et al.*, 2011). Freezing of gait is associated with both executive dysfunction and motor preparations deficits (Amboni *et al.*, 2008; Jacobs *et al.*, 2009; Tard *et al.*, 2014) and leads to an increased risk of falls (Bloem *et al.*, 2004).

Dual-tasking deficits are associated with falls in PwP (Hausdorff *et al.*, 2003; Beck *et al.*, 2015; Heinzel *et al.*, 2016). Problems with dual-tasking are particularly prominent in patients with freezing of gait (FOG+), highlighting difficulties with dividing attention (Spildooren *et al.*, 2010; Pieruccini-Faria *et al.*, 2014). During dual-tasking, FOG+ are more influenced by a second cognitive task (dual-task interference) than patients without freezing of gait (FOG-) (Camicioli *et al.*, 1998). Furthermore, gait parameters in freezing of gait deteriorate when adaptation of movement is required during walking, suggesting that motor planning and preparation is also impaired (Knobl *et al.*, 2012). To date, only diffusion tensor imaging and functional MRI studies have examined the neural substrates of dual-tasking in freezing of gait (Shine *et al.*, 2013a; Shine *et al.*, 2013b; Peterson *et al.*, 2015; Vervoort *et al.*, 2016). These neuroimaging modalities lack the temporal resolution to interrogate the dynamics of processes involved in performing additional cognitive tasks while walking.

Recent studies in younger adults have shown that electroencephalography (EEG) is well suited for the investigation of neural correlates of walking while performing a second response task due to its high temporal (millisecond) resolution (De Sanctis *et al.*, 2012; De Sanctis *et al.*, 2014; De Vos *et al.*, 2014; Malcolm *et al.*, 2017; Malcolm *et al.*, 2018). Malcolm *et al.*, (2015) showed in healthy older adults that, while behavioural measures can remain stable between single- and dual-tasking, analysis of electrophysiological markers revealed differences in decision making and response conflict processes between single- and dual-task conditions.

In this study, we examine the behavioural impact of stepping-in-place on a simple response time task and the underlying electrophysiological markers for decision-making (CPP/P3 potentials (Twomey *et al.*, 2015)), response conflict (N2 potential (Eimer, 1993)) and motor preparation (Lateralized Readiness Potential, LRP (Shibasaki & Hallett, 2006)) in PwP with Freezing of Gait (FOG+), PwP without Freezing of Gait (FOG-) and young controls, to gain insight into the mechanisms of dual-task impairment in FOG.

Methods

Participants

We recruited 20 PwP (as defined by the UK Brain Bank Criteria (Hughes *et al.*, 1992), Hoehn and Yahr stage II-III) from the Movement Disorder clinic at the Dublin Neurological Institute at the Mater Misericordiae University Hospital and seven control participants. Ethical approval was granted from the hospital ethics committee and informed consent was obtained from all participants. All patients underwent clinical and neuropsychological testing including Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB) and Unified Parkinson's Disease Rating Scale III (UPDRS III). Freezing of gait status was recorded for all patients based on observation by a movement disorder specialist and Question 1 of the New Freezing of Gait Questionnaire ("Did you experience a freezing episode over the past month?") (Nieuwboer *et al.*, 2009). All participants had normal or corrected-to-normal vision and were tested in the "on"-state.

Task

Participants performed a two-stimulus oddball task in which they watched repeated presentations of a green cross in order to detect 45° rotated targets among vertically-oriented standard stimuli, on a corridor background. Each stimulus was presented for 500 ms on a complex background, in random order on a 55" LCD monitor at eye height. The standard stimulus was presented 80% of the time and the participant was instructed not to respond to this stimulus. For the remaining 20%, the target stimulus was presented and participants were instructed to press the button (Wii remote) with their right hand as soon as they saw the target stimulus. The standard and target stimuli were presented with random interstimulus intervals between 250 and 750 milliseconds. The task was performed both sitting and stepping-in-place (Waechter *et al.*, 2015). The sitting condition was run as a single block of 300 seconds consisting of approximately 60 target trials and 240 standard trials. In the stepping condition participants held on to a walker frame and stepped in place. To minimize fatigue the condition was divided into three blocks of 20 target and 80 standard trials. Participants were instructed to minimize head movements during the trials.

Data Acquisition

Synchronous electroencephalographic (EEG) and button press data were acquired for all participants using a 128-channel BioSemi ActiveTwo EEG acquisition system during the task. Electrodes were placed using a 10-20 montage and amplified at source by an internal pre-amplifier. Data were recorded at a digitization rate of 2048 Hz using DC amplifiers with a low-pass cutoff of 150 Hz.   A subset of the sitting data was published previously (Butler *et al.*, 2017). Two FOG+ participant's data could not be used for analysis due to a technical error resulting in incorrect trigger (button press) labeling during recording.

Behavioural Data

Button press responses were processed offline using MATLAB (Mathworks, Natick, MA). Mean response times (time between stimulus presentation and button press response, RT) were calculated for each participant in both conditions. Only target trials with response times falling within 200ms and 1200ms of target presentation were considered valid (Figure 1). The response time data were submitted to mixed-groups factorial ANOVA with the factors condition (STEP, SIT) and group (FOG+, FOG-, controls). Follow up statistical t-tests were also performed.

EEG Data

Using custom-MATLAB scripts, EEGLAB (Delorme & Makeig, 2004) and CSD toolbox functions (Kayser & Tenke, 2006b; a), the continuous data was downsampled to 512Hz and band-pass filtered offline between 0.1 and 30Hz (6 dB/octave). Epochs of 800ms with 100ms pre-stimulus were extracted from the data for standard and correct target trials. An automatic artifact rejection criterion of ±80μV was applied across all electrodes in the array, and suspected "flat" channels with a standard deviation of <0.5μV were rejected. We rejected trials with more than 12 artifact channels. In trials with less than 12 such channels, any remaining bad channels were interpolated using the nearest neighbour spline. Target trials were rejected if there was no response within 1200ms of the stimulus presentation. The epochs were baseline corrected with respect to 100ms pre-stimulus period. Average standard and target-locked responses were calculated as amplitude of the potentials for each group and the presence of between-group differences was assessed.

To increase spatial resolution and minimize volume conduction, these data were converted using a Laplacian transformation to calculate the second spatial derivative of the potentials known as the current source density (CSD) (Perrin *et al.*, 1989). We have previously shown that this method improves spatial resolution in order to better discriminate between frontocentral motor preparation signals and centroparietal decision-making signals (CPP, equivalent to the P3b) (Butler *et al.*, 2017).

The subtraction of the Target and Standard evoked activity over central parietal (CPz) area indicated by the three electrode locations (highlighted dots) in the head schematic in Figure 2 was chosen to investigate response inhibition potentials from 250-350ms (N2) (Malcolm *et al.*, 2015) and decision making responses from 450-650 (CPP) (O'Connell *et al.*, 2012; Kelly & O'Connell, 2013; Twomey *et al.*, 2015; Loughnane *et al.*, 2016). To illustrate the relationship between the response times and the evoked potentials within groups, individual target trials were sorted by response time and presented as a surface plot (Figure 2C). To investigate unimanual motor preparation, the lateralized readiness potential (LRP) was calculated by subtracting left frontocentral (FC4) scalp from the right frontocentral (FC3) scalp EEG activity. LRP is indicated by the electrode locations in highlighted dots in the head schematic shown in Figure 3 (Shibasaki & Hallett, 2006). Each site of interest was represented by an average of the three nearest electrodes to increase the signal-to-noise ratio.

Three mixed-group factorial ANOVAs were performed to examine the effects of group (FOG+, FOG-, controls) and condition (SIT, STEP) on:

1) the average CPP amplitude from 450 to 650ms (Twomey *et al.*, 2015),

2) the average N2 amplitude from 250 to 350ms (Eimer, 1993) and

3) the average LRP amplitude from 400-600ms (Shibasaki & Hallett, 2006).

ANOVAs were performed in Rstudio version 1.1.456 (Rstudio, 2016) using R version 3.3.3 (R Development Core Team, 2017). Follow up t-tests were also conducted where appropriate. R markdown analysis script and data are provided as supplementary materials. Unpaired t-tests at each time point were calculated for each condition to test for significant differences in the LRP between FOG- and FOG+ groups (suggesting group differences in motor preparation). To control for Type I errors a period of statistical significance was only considered if an alpha criterion of 0.05 or less was obtained for at least 21ms (11 consecutive time points) (Guthrie & Buchwald, 1991).

Bayes Factor Analysis

Bayes factor analysis provides a measure of evidence for one model versus another (Dienes, 2016). Here it is used to investigate evidence for the null hypothesis (that there is no difference in PwP with and without freezing of gait) or the alternative hypothesis (that there is a difference in Parkinson's disease with and without freezing of gait). The JZS Bayes factor was computed using the function BayesFactor as part of the R Suite for Statistical Computing using the default effect size of 0.707 (Rouder *et al.*, 2009). A JZS Bayes factor can be interpreted such that a factor less than 1 favours the null hypothesis over the alternative hypothesis, while a JZS Bayes factor greater than 1 favours the alternative hypothesis.

Results

Demographics

The demographic and neurocognitive data for the participants with Parkinson's disease cohort categorized by freezing status is given in Table 1 below. There were significant differences between groups with respect to sex, disease duration and Frontal Assessment Battery scores between FOG+ and FOG- but no significant differences in age, Hoehn and Yahr stage, UPDRS III or Montreal Cognitive Assessment scores. The controls were significantly younger than the disease cohorts.

	FOG+	FOG-	Controls
N	8	10	7
Age (years)	65.7 (6.9)	62.5 (7.9)	25(4.9)
Gender (M:F)*	7:1	4:6	3:4
H&Y stage (median)	2.6 (0.32)	2.3 (0.35)	
Disease Duration (years)*	12.3 (8.36)	7.0 (3.6)	
UPDRS III	28.6 (10.9)	29.1 (14.1)	
MOCA	24.0 (1.9)	26.1 (2.9)	
FAB*	14.9 (2.7)	17.3 (1.3)	

Table 1. *Participant demographics. Means shown with standard deviation in parentheses. * indicates statistically significant difference between groups on an unpaired t-test. FOG+ = People with Parkinson's disease with freezing of gait, FOG- = People with Parkinson's disease without; H&Y stage = Modified Hoehn & Yahr stage; UPDRS III = Unified Parkinson's Disease*

Rating Scale III total; MOCA = Montreal Cognitive Assessment total; FAB = Frontal Assessment Battery total

Behavioural Data

Participants performed a target response time task, responding with a button press to target stimuli while sitting (SIT) or stepping-in-place (STEP).

	FOG+	FOG-	Controls
N	8	10	7
STEP*	665.2 (107.38)	530.2(67.6)	448.25(48.8)
SIT	571.3 (55.5)	550.0 (81.8)	471.0 (48.4)
Relative RT (STEP-SIT)	93(81.5)*	-20.8 (34.3)	-22.7 (14.8)*

Table 2. *Behavioural data. Group mean with standard deviation in parentheses Response Times (RT) in milliseconds by freezing of gait status and condition. * indicates statistically significant difference between groups on an unpaired t-test.*

Figure 1 illustrates individual participant mean RT data for the STEP and SIT (line). The FOG+ (circles) participants are on the left side and the FOG- participants (squares) are in the middle and the Control participants (triangles) are on the right of the figure. Table 2 shows the group mean and standard deviation RTs, which were submitted to a repeated measures ANOVA which showed a significant main effect of group ($F(2,22)=9.675$, MSE=91376 , $p<0.001$, JZS Bayes Factor= 33.84), and a significant interaction, ($F(2, 22) = 14.96$, MSE=166681 , $p < 0.005$, JZS Bayes Factor= 1105) with no effect of experimental condition ($F(1, 22) = 1.786$, MSE=2386 ,

p =0.195, JZS Bayes Factor= 0.627). Follow up paired t-tests comparison within groups were conducted. For the control group there was a significant difference in RTs between conditions ($t(6)=4.03$, $p<0.01$, JZS Bayes Factor= 6.837), with faster RTs in the STEP condition. For the FOG- group there was a no significant difference in RT between conditions ($t(9)=1.968$, $p=0.0806$, JZS Bayes Factor= 1.23), but the group average response time in the STEP condition was faster than the RT in the SIT condition, which was in line with the control group. For the FOG+ group there was a significant difference between conditions ($t(7)=-3.0638$, $p<0.025$, JZS Bayes Factor= 3.66) with slower RTs in the STEP compared to the SIT condition. These analyses point to the interaction differences being driven by this significantly slower RTs for the FOG+ group in the STEP condition. This is illustrated by the individual data plotted in Figure 1 showing 100% of participants in the control group had a faster RT for STEP than SIT indicating by the downward lines from SIT to STEP. The opposite was the case for the FOG+ group, 100% of participants had slower RT for STEP than SIT indicating by the upward lines from SIT to STEP. While in the FOG- group only four of the ten participants were slower in the STEP condition than the SIT condition.

INSERT FIGURE 1 AROUND HERE

EEG Analysis: cognitive decision making (P3/CPP)

Figure 2A shows the mean and standard error of the mean (SEM) of the standard (green) and red (target) current source density (CSD) response for both FOG+ (top row) and FOG- (bottom row) for the STEP (left column) and SIT (middle column) over central parietal scalp. The right column of Figure 2B shows the mean and SEM of the subtraction of the target and standard CSD responses for the SIT (orange) and STEP (blue) conditions, the dashed vertical lines indicate response times. To assess differences in the amplitude of the P3/CPP, the mean amplitude of the subtraction (Target-Standard) from 450-650ms were submitted to a mixed repeated measures ANOVA with the factors group (FOG+, FOG-, controls) and condition (STEP, SIT). The analysis revealed no main effect of group ($F(2,22)= 0.807$, $MSE=393.6$, $p=0.42$, JZS Bayes factor=0.414), condition ($F(1,22)= 0.03$, $MSE=5.6$, $p=0.865$, JZS Bayes factor=0.28), or interaction of group and condition ($F(2,22)= 2.311$, $MSE=434.4$, $p=0.123$, JZS Bayes factor=0.11).

INSERT FIGURE 2 AROUND HERE

EEG Analysis: automatic response conflict (N2)

The N2 response is the deflection in the subtraction wave between 250 and 350ms in Figure 2B. To assess differences in the amplitude of the N2, the mean amplitude of the subtraction (Target-Standard) waveform from 275-325ms were submitted to a mixed repeated measures ANOVA with the factors group (FOG+, FOG-, controls) and condition (STEP, SIT). This revealed a significant main effect of group ($F(2,22)= 3.638$, $MSE=686.3$, $p<0.05$, JZS Bayes factor=1.59), and a no effect of condition ($F(1,22)= 3.778$, $MSE=389.5$, $p=0.051$, JZS Bayes factor=1.4) but no significant interaction effect ($F(2,22)= 2.049$, $MSE=187.8$, $p=0.1527$, JZS Bayes factor=2.2). Follow up paired t-test comparisons within groups were conducted. For the control group there was no significant difference in N2 amplitude between conditions ($t(6)=-0.19706$, $p=0.8503$, JZS Bayes Factor= 0.379). For the FOG- group there was no significant difference in N2 amplitude between conditions ($t(9)=-0.4887$, $p=0.6367$, JZS Bayes Factor= 0.356). For the FOG+ group there was a significant difference in N2 amplitude between conditions ($t(7)=-3.5712$, $p<0.001$, JZS Bayes Factor= 5.92).

EEG Analysis: motor preparation potentials (LRP)

Figure 3 shows lateralized readiness potential (LRP) CSD waveforms, the subtraction target response over left and right frontal areas indicated by the dots for the FOG+ (dark grey) and FOG- (grey) and control (light grey) group and the SIT (top panel) and STEP (bottom panel) conditions. To assess differences in the amplitude of the LRP, the mean amplitude of the subtraction (Target-Standard) from 400-600ms were submitted to a mixed repeated measures ANOVA with the factors group (FOG+, FOG-, Control) and condition (STEP, SIT). The analysis revealed a main effect of group ($F(2,22)= 7.889$, MSE=4137, $p<0.005$, JZS Bayes factor=17.22), with no significant effect of condition ($F(1,22)= 0.090$, MSE=119.8, $p=0.343$, JZS Bayes factor=0.38) and no interaction effect of group and condition ($F(2,22)= 1.987$, MSE=253.4, $p=0.161$, JZS Bayes factor=5.12).

To investigate the onset of differences between PwP groups in the LRP for each time point an unpaired t-test was performed. Time points of statistical differences in the LRP between the FOG+ group and the FOG- group are depicted as markers running along the bottom of the plots in Figure 3. The group difference occur just after ~400ms and continues until the mean response time (indicated by the dashed vertical lines).

INSERT FIGURE 1 AROUND HERE

Discussion:

In the current study, we examined the effect of stepping on these results by measuring behavioral and electrophysiological responses in PwP with and without freezing of gait while they performed the same target response time task (oddball task) both sitting (single-task) and stepping-in-place (dual-task). The behavioural results showed slower response times while stepping-in-place (STEP) compared to seated (SIT) for FOG+. However, FOG- had faster response times in the STEP condition compared to the SIT condition. There was no significant difference in response times between the PwP groups while seated but slower response times were seen in the FOG+ group compared to FOG- and control during stepping-in-place, suggesting a dual-task interference which occurs in the freezing group only.

The electrophysiological data enabled the simultaneous analysis of parameters which can contribute to the delayed response times: i) decision making processing (CPP), ii) "automatic" response conflict processing (N2), and iii) motor preparation (LRP). The CPP potential correlates with executive function (Kindermann *et al.*, 2000) and decision making in response to sensory stimuli (Twomey *et al.*, 2015). In line with our previous finding there was no significant difference in CPP amplitude (Butler *et al.*, 2017) between FOG+ and FOG- for the SIT and STEP conditions, suggesting that decision making processes are not the source of the response delay (reduced RT). The N2 potential is present for the sitting condition for both groups which implies that response conflict processing occurs to help perform the task. In the stepping condition FOG+ display a reduction of the N2 potential which suggests reduced allocation of automatic processing resources which could contribute to a delayed response time. The LRP, our measure of motor preparation, is present in the FOG+ group but not in the FOG- group (or control group) for the SIT and STEP conditions. In the FOG+ group the LRP is maintained longer for the STEP condition (dual-task) than the SIT condition (single-task). Overall our findings show that the addition of a second complex motor task (stepping-in-place) impacts the automatic allocation of electrophysiological markers of response conflict and motor preparation (but not decision making) in people with Parkinson's with freezing of gait, resulting in a delayed response time. Response inhibition and motor preparation have close associations with FOG. These will be dealt with separately below.

Response Inhibition

The N2 potential has a role in monitoring sensory information and selecting relevant information in order to select a response (Malcolm *et al.*, 2015), ultimately determining response time (Loughnane *et al.*, 2016). The reduction of the N2 potential in the FOG+ group for the dual task is remarkable as it points to inflexibility in allocation of automatic resources (Malcolm *et al.*, 2015). The clear presence of an intact N2 potential in the SIT condition for the FOG+ group implies that this is specific to the dual-task condition. On the other hand, there is no significant difference in the N2 potential in the FOG- group across conditions. The N2 potential has been associated with appropriate inhibition of a distracting secondary task or the prioritisation of the primary task (Mazza *et al.*, 2009; Malcolm *et al.*, 2015). Inability to select relevant stimuli (and by extension, suppress irrelevant stimuli) would result in loss or attenuation of the N2 potential. Our findings would suggest that the N2 process is related to an enhancement of the target detection as it is present in single task condition but disappears in the dual task condition, coinciding with a slower response time. This concept is very closely linked with dual tasking as, to decide which task to prioritize and which task to suppress, the unwanted response has to be inhibited. Areas associated with response inhibition in functional imaging studies include the right inferior frontal gyrus (an area central to resolution of dual task interference (Herath *et al.*, 2001), the premotor area and the primary motor cortex. Involvement of the right inferior frontal gyrus is notable as this area is selectively atrophied in volumetric MRI studies in patients with freezing of gait (Kostic *et al.*, 2012; Canu *et al.*, 2015).

Poor inhibitory control is proposed to be central to freezing of gait via a generalized impairment in conflict resolution and response inhibition (Vandenbossche *et al.*, 2011; Vandenbossche *et al.*, 2012). These tasks require suppression of irrelevant information that could interfere with the relevant stimulus. The right inferior frontal gyrus inhibits responses via the hyperdirect pathway to the subthalamic nucleus. Structural and functional neuroimaging has shown that this hyperdirect pathway is deficient in all PwP compared with controls (Shine *et al.*, 2013c; Fling *et al.*, 2014). The reduction of the N2 potential in the current study suggests that dysfunction in this pathway is associated with freezing. The current study provides electrophysiological evidence of impairment in response inhibition in FOG.

Motor preparation

There is a clear LRP in FOG+ which is remarkable for such a simple motor task (Figure 3). The presence of the LRP in both conditions for the FOG+ group, but not the FOG- and control groups, suggests that FOG+ require additional resources in order to initiate movement for simple motor tasks (possibly via lateral premotor areas (Wu & Hallett, 2008)). As these frontal networks become overloaded during a second task such as locomotion, FOG+ compensate by recruiting more resources and initiating movement even earlier. Indeed, there is some evidence to support this idea: functional MRI studies have shown extensive cortical activation both during freezing episodes and normal locomotion in patients with freezing of gait (Shine *et al.*, 2013a).

The differential impact of locomotion on the generation of the N2 and LRP potentials may be the result of differences in cognitive reserve between FOG+ and FOG-/controls or a greater use of cognitive resources in FOG+, even for simple motor tasks, resulting in earlier depletion of these resources. When stress is placed on these resources (in terms of cognitive and motor loads), these premotor differences are amplified in FOG+, ultimately resulting in clinically detectable deterioration of task performance. This suggests a maladaptive system which is prone to overload in stressful situations, which could result in motor breakdown and freezing of gait.

Future Directions and Limitations

Since 2010 there have been a number of studies investigating ambulatory ERP analysis in healthy controls (Gramann *et al.*, 2010; Gwin *et al.*, 2010; Debener *et al.*, 2012; De Vos *et al.*, 2014) and a number of studies looking at power spectral density in people with Parkinson's while walking (Handojoseno *et al.*, 2012; 2013; Shine *et al.*, 2014; Handojoseno *et al.*, 2015). This is the first study to examine evoked response in people with Parkinson's disease while stepping. In future studies, a larger sample size would allow correlation of electrophysiological measures with clinical markers of the disease (such as disease duration and severity) and standard neurocognitive tests. Another avenue of interest would be to examine the impact of dopaminergic therapy (or deep brain stimulation) on the above findings, as all patients were tested in the "on"-medication state. Although there were no differences in medication doses or timings between groups, it would be necessary to confirm that these findings can be replicated off medication and in patients with deep brain stimulators. There were differences in baseline characteristics between FOG+ and FOG- (including gender, disease duration and FAB scores) which may have impacted on the results here. While the FOG- group and young control group exhibited similar behavioural and electrophysiological results, future studies with an age-matched control group would enable the distinction between age-related response delays and those related to Parkinson's disease (Fearon *et al.*, 2015). Finally, since dual-tasking has been shown to have an effect on gait parameters as well as secondary task performance (Killane *et al.*, 2015), investigating the interaction between electrophysiological correlates of the gait cycle with clinical gait parameters would allow a more ecological study of these processes on gait itself, rather than a simple motor task during stepping shown here.

Conclusion

In this study event-related potentials were recorded from PwP with and without freeing of gait while sitting and stepping. FOG+ had slower response times while stepping, however response times were faster while stepping for FOG- and controls. The FOG+ showed evidence of premotor cortical dysfunction (reduction of the N2 potential and prominence of the lateralized readiness potential) while performing the dual-task. In contrast, our measure of executive function, the CPP response, is robust in the face of dual-task interference for all groups. This suggests that the behavioural differences seen in response times between FOG+ and the FOG-/controls is primarily due to motor and response conflict impairments rather than decision making impairments. The impact of stepping on the generation of the N2 and LRP potentials indirectly implies that these functions compete with stepping for resources. In the setting of multiple complex tasks or cognitive impairment, severe motor dysfunction may result, leading to freezing of gait (Lewis & Shine, 2016).

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Author contributions

CF, JSB, IK, RBR, TL designed the research project. CF and SMK organized and executed the research. CF and JSB designed the analysis. JSB and SNW analysed the data. CF JSB, SPK, RBR and TL reviewed and critiqued the analysis. CF and JSB wrote the first draft. All authors critically reviewed and edited the manuscript, and TL and RBR obtained the funding. All authors approved the final version of the manuscript.

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Legends

Figure 1 Response times for the people with Parkinson's disease with freezing of gait (FOG+) (circles), people with Parkinson's disease without freezing of gait (FOG-) (squares) and controls (triangles). The lines link each individual response times for the sitting (SIT) (left) and stepping in place (STEP) (right) conditions.

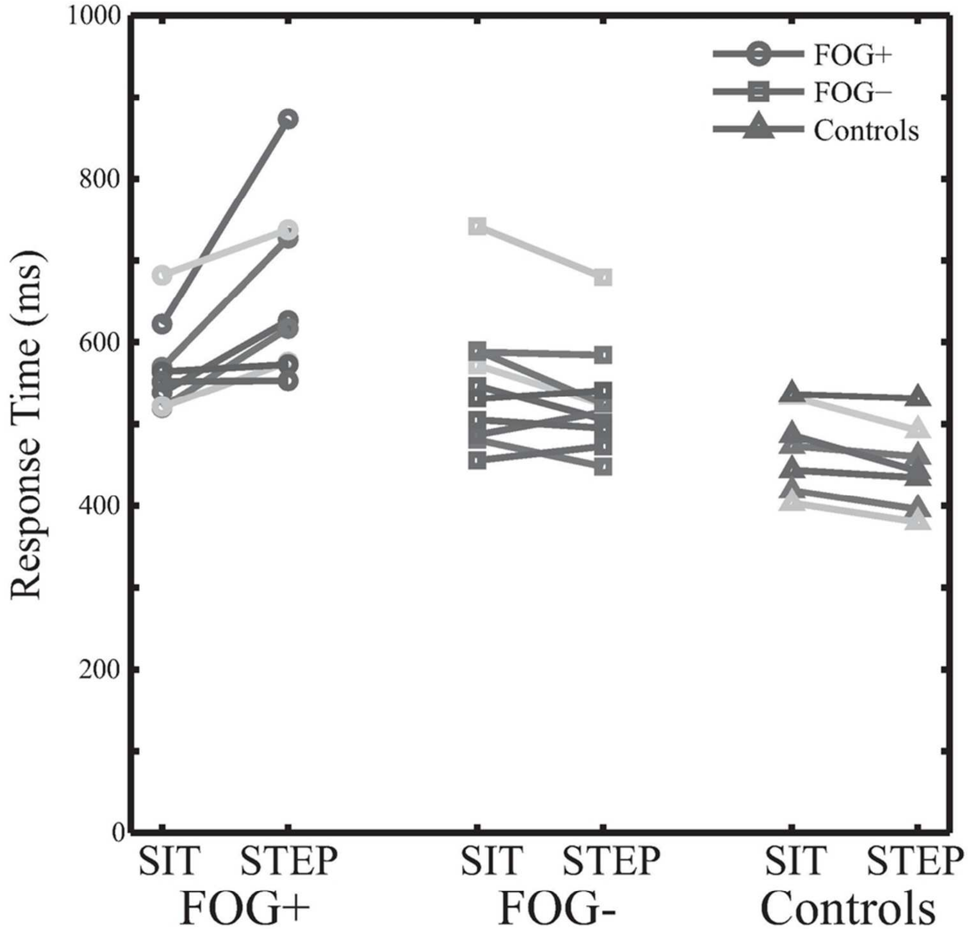
Figure 2 A) The mean and standard error of the mean of the target (red) and standard (green) average CSD response of three electrodes over central parietal scalp (indicated by the large dots in the top down head schematic) for the FOG+ group (top row), the FOG- group (second row) and the control group (bottom row) for the sitting (SIT) condition left column and the stepping-in-place (STEP) condition.

B) Mean and standard error of the mean of the difference between the CSD waveform for the target stimulus and standard stimulus over central parietal scalp for the FOG+ group and FOG- group for the STEP (orange) condition and SIT (blue) condition. The solid black line indicates the stimulus onset, the dashed vertical lines indicate the mean response time for the stepping-in-place (orange) condition and sitting (blue) condition.

C) Mean scalp Topographic distributions of the difference waveform averaged over the N2 component (top row) and CPP component (bottom row) for each group and the SIT condition (left) and STEP condition (right).

D) Surface plots of the CPP pooled across participants for each group and sorted in ascending order according to response time for each condition SIT (left) and STEP (right), smoothed using a Gaussian moving window of 100 trials. Curved black line represents response times.

Figure 3 Mean and standard error of the mean of the lateralized readiness potential(LRP) current source density (CSD) calculated by subtracting the average activity of three electrodes over the left frontocentral area (three large electrodes corresponding to D3, D4 and D5 in the 128 Biosemi ABC electrode layout) from the right frontocentral (three large electrodes corresponding to C3, C4 and C5 in the 128 Biosemi ABC electrode layout) area for the FOG+ (dark grey), FOG- (grey) and control (light grey) groups for the SIT (top panel) and STEP (bottom panel) conditions. The solid black line indicates the stimulus onset, the dashed vertical lines indicate the mean response time, the dots along the time axis indicate significant differences between the People with Parkinson's disease without freezing of gait (FOG-) and People with Parkinson's disease with freezing of gait (FOG+) at each time point.



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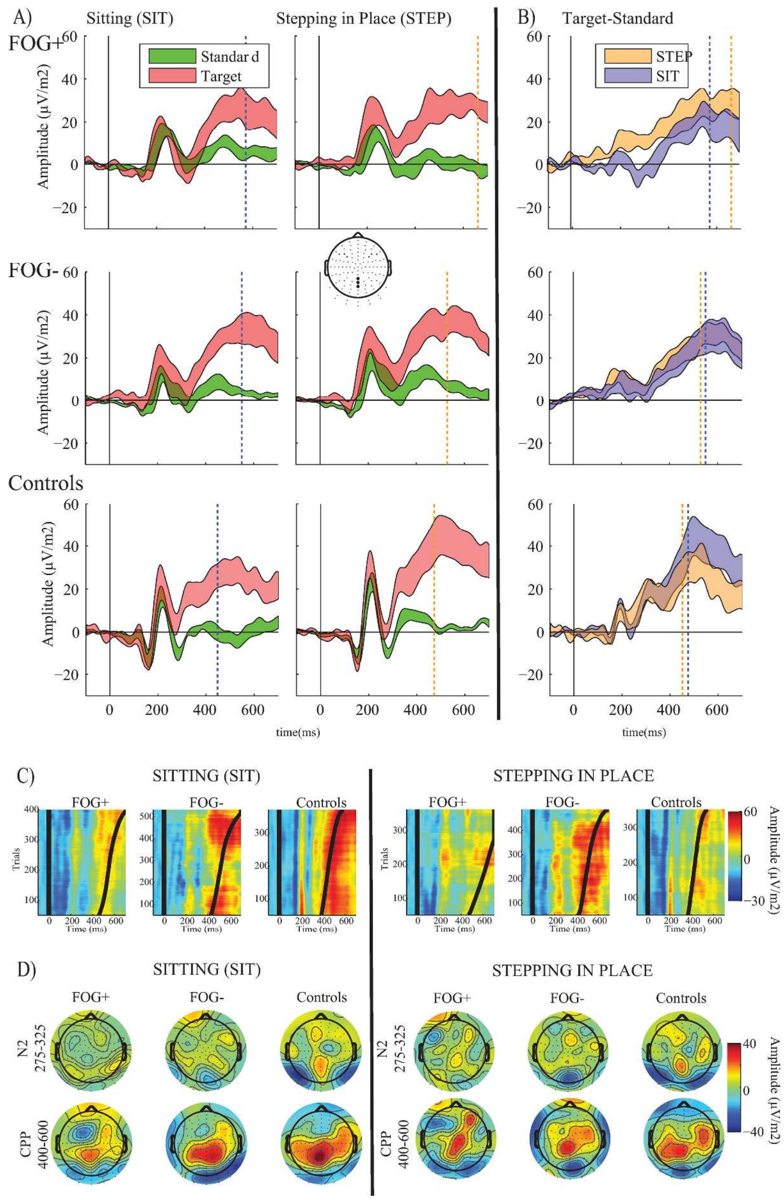

Figure 2 A) The mean and standard error of the mean of the target (red) and standard (green) average CSD response of three electrodes over central parietal scalp (indicated by the large dots in the top down head schematic) for the FOG+ group (top row), the FOG- group (second row) and the control group (bottom row) for the sitting (SIT) condition left column and the stepping-in-place (STEP) condition. B) Mean and standard error of the mean of the difference between the CSD waveform for the target stimulus and standard stimulus over central parietal scalp for the FOG+ group and FOG- group for the STEP (orange) condition and SIT (blue) condition. The solid black line indicates the stimulus onset, the dashed vertical lines indicate the mean response time for the stepping-in-place (orange) condition and sitting (blue) condition. FOG- = People with Parkinson's disease without FOG; FOG+ = People with Parkinson's disease with FOG. C) Mean scalp Topographic distributions of the difference waveform averaged over the N2 component (top row) and CPP component (bottom row) for each group and the SIT condition (left) and STEP condition (right). D) Surface plots of the CPP pooled across participants for each group and sorted in ascending order according to response time for each condition SIT (left) and STEP (right), smoothed using a Gaussian moving window of

100 trials. Curved black line represents response times.

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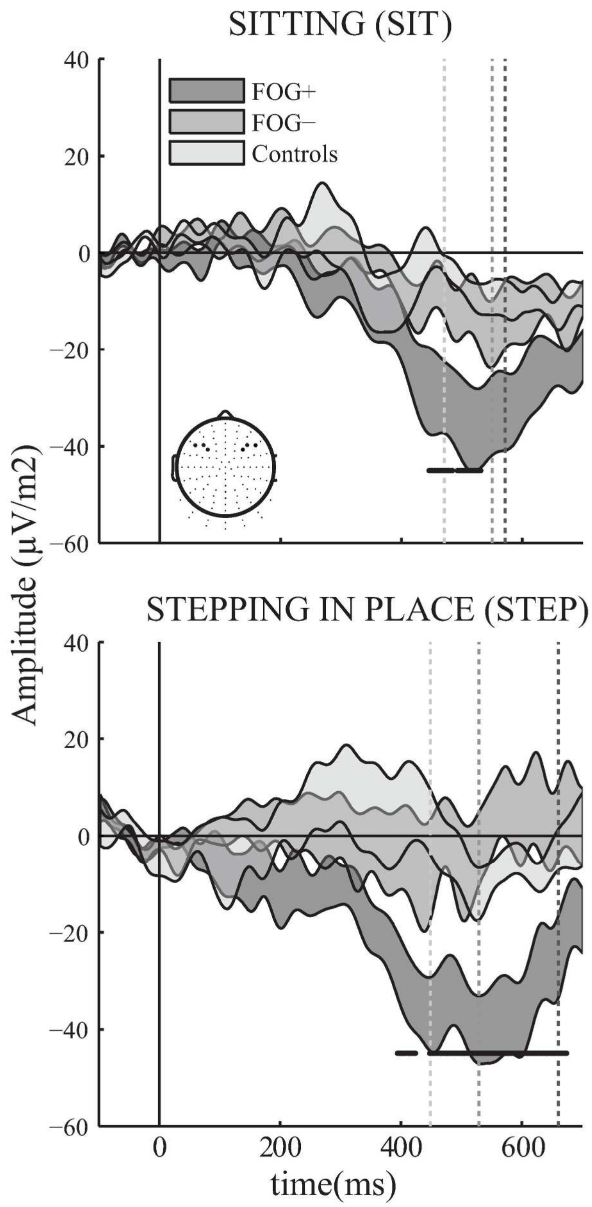

Mean and standard error of the mean of the lateralized readiness potential(LRP) current source density (CSD) calculated by subtracting the average activity of three electrodes over the left frontocentral area (three large electrodes corresponding to D3, D4 and D5 in the 128 Biosemi ABC electrode layout) from the right frontocentral (three large electrodes corresponding to C3, C4 and C5 in the 128 Biosemi ABC electrode layout) area for the FOG+ (dark grey), FOG- (grey) and control (light grey) groups for the SIT (top panel) and STEP (bottom panel) conditions. The solid black line indicates the stimulus onset, the dashed vertical lines indicate the mean response time, the dots along the time axis indicate significant differences between the People with Parkinson's disease without freezing of gait (FOG-) and People with Parkinson's disease with freezing of gait (FOG+) at each time point.

168x346mm (300 x 300 DPI)