RESEARCH ARTICLE

Neurophysiological correlates of dual tasking 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 compared with sitting. However, response times were significantly faster while stepping compared with sitting for 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.

Keywords Parkinson's disease · Event related potentials · Motor control · Executive function

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Introduction

The basal ganglia play an important role in the selection of actions in response to stimuli (Friend and 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, b; Peterson et al. 2015; Vervoort et al. 2016). The major limitation of these methods they require immobilization of the participant's head, precluding the study of natural gait. The majority of MRI studies are, therefore, performed in the resting state (Maidan et al. 2019; Potvin-Desrochers et al. 2019), using motor imagery or using a surrogate tasks (e.g., stepping or other lower limb movements) (Shine et al. 2013b; Piramide et al. 2020). Furthermore, 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 (ms) resolution

(De Sanctis et al. 2012, 2014; De Vos et al. 2014; Malcolm et al. 2017, 2018). Malcolm et al. 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 (Malcolm et al. 2015). Few EEG-based studies in FOG exist to date (Handojoseno et al. 2012, 2013, 2015; Velu et al. 2014; Shine et al. 2014; Toledo et al. 2014; Ly et al. 2017; Maidan et al. 2019). Many of the EEG studies to date have focused on identifying a signature of FOG from EEG recordings during motor activity (normal walking and freezing episodes). Recently, the first study examining P3 in PwP during ambulation showed prolongation and attenuation of the P3 in PwP when walking compared with sitting (Maidan et al. 2019). This suggests impaired recruitment of attentional networks during dual-tasking in PwP. However, we have previously shown that standard ERP analysis can erroneously underestimate a P3 signal in PwP due to interference from a frontal lateralized readiness potential (Butler et al. 2017). By employing current source density analysis [CSD, (Kayser and Tenke 2006a, b)], which increases spatial resolution, identification of these discrete potentials demonstrated that the attenuations seen were due to differences in movement-related potentials, rather than cognitive potentials (i.e., P3) (Salisbury et al. 2001). We demonstrated differences in lateralized readiness potentials between PwP with and without freezing of gait (FOG) during a simple response task while seated in spite of similar response times.

In this study, using a CSD approach, 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 and Hallett 2006)] in PwP with Freezing of Gait (FOG+), PwP without Freezing of Gait (FOG −) and young controls. The aim of this study is to replicate our previous findings using ambulatory EEG while stepping-in-place. We hypothesized that performing a response time task while stepping may exaggerated the differences in movement-related potentials we had previously demonstrated while seated as well as leading to differences in response times while dual-tasking.

Materials and 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 people with Parkinson's disease 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 to detect 45° rotated targets among vertically-oriented standard stimuli, on a corridor background. Each stimulus was presented for 500 ms on a corridor 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 ms. The task was performed both sitting and stepping-in-place (Waechter et al. 2015). A subset of the sitting data (i.e., the FOG + and FOG − sitting data) was published previously (Butler et al. 2017). The sitting condition was run as a single block of 300 s consisting of ~ 60 target trials and 240 standard trials. In the stepping condition participants held on to a walker frame and stepped in place. Sitting and stepping conditions were randomized. To minimize fatigue the 60 target trials and 240 standard trials for the stepping condition were 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. Two FOG + participant's data could not be used for analysis due

to a technical error resulting in incorrect trigger (button press) labelling during recording.
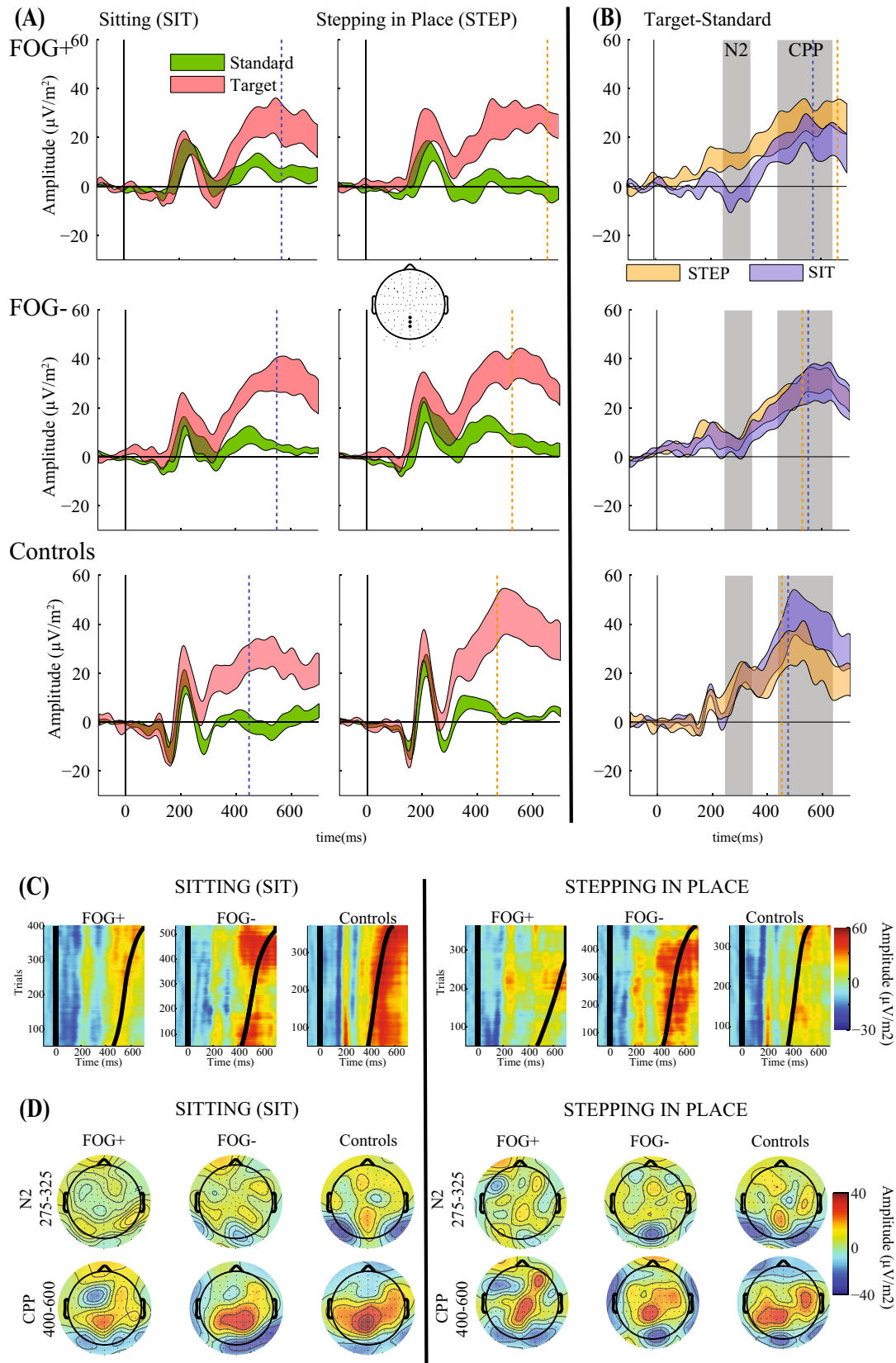
Behavioural data

Button press responses were processed offline using MATLAB (Mathworks, Natick, MA, USA). Mean response times (time between stimulus presentation and button press response, RT) were calculated for each participant in both conditions (Fig. 1). Only target trials with response times falling within 200 ms and 1200 ms of target presentation were considered valid. 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. Chi-squared tests were employed to test sex differences.

EEG data

Using custom-MATLAB scripts, EEGLAB (Delorme and Makeig 2004) and CSD toolbox functions (Kayser and Tenke 2006a, b), the continuous data was downsampled to 512 Hz and band-pass filtered offline between 0.1 and 30 Hz (6 dB/octave). Epochs of 800 ms with 100 ms pre-stimulus were extracted from the data for standard and correct target trials. An automatic artefact rejection criterion of ± 80 μV was applied across all electrodes in the array, and suspected
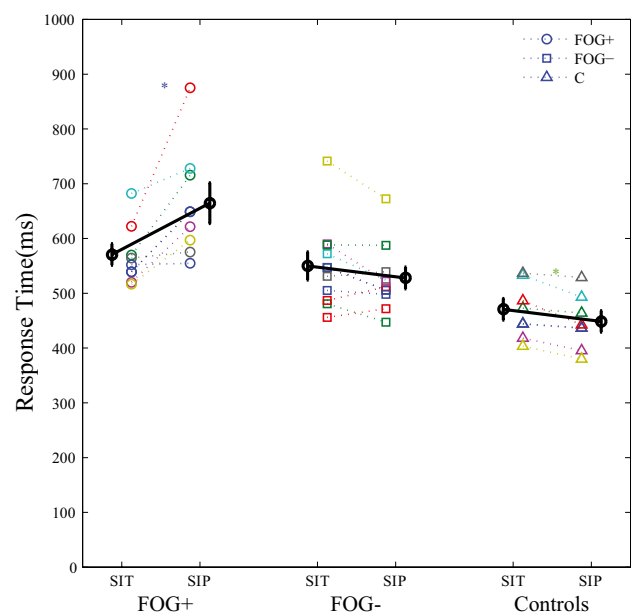
Fig. 1 Response times for the FOG + participants (circles), FOG − participants (squares) and controls (triangles). The dashed lines link each individual response times for the SIT (left) and STEP (right) conditions. The black symbols are the means the error bars are the standard error of the mean

(A)

Sitting (SIT)   Stepping in Place (STEP)

(B) Target-Standard

FOG+

FOG-

Controls

(C)   SITTING (SIT)   STEPPING IN PLACE

FOG+   FOG-   Controls   FOG+   FOG-   Controls

(D)   SITTING (SIT)   STEPPING IN PLACE

FOG+   FOG-   Controls   FOG+   FOG-   Controls

N2
275-325

CPP
400-600

◀**Fig. 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 times 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. The boxes indicate time periods which were averaged across for statistical analysis of the N2 and CPP. **c** Surface plots of the CPP for participants for each group averaged over 50 trials and sorted in ascending order according to response times for each condition SIT (left) and STEP (right), smoothed using a Gaussian moving window of 100 trials. Curved black line represents response times.

"flat" channels with a standard deviation of < 0.5 µV were rejected. We rejected trials with more than 12 artefact 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 between 200 and 1200 ms of the stimulus presentation. The epochs were baseline corrected with respect to 100 ms pre-stimulus period. Average standard and target-locked responses were calculated as the 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 to better discriminate between frontocentral motor preparation signals and centroparietal decision-making signals (CPP, equivalent to the P3b) (Butler et al. 2017).

Activity over the central parietal (CPz) area indicated by the three electrode locations (highlighted dots) in the head schematic in Fig. 2 was chosen to investigate the decision-making responses (CPP) (O'Connell et al. 2012; Kelly and O'Connell 2013; Twomey et al. 2015; Loughnane et al. 2016) and response inhibition potentials (N2) (Malcolm et al. 2015). 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 Fig. 3 (Shibasaki and 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 650 ms (Twomey et al. 2015),
2. the average N2 amplitude from 250 to 350 ms (Eimer 1993) and
3. the average LRP amplitude from 400 to 600 ms (Shibasaki and Hallett 2006).

The amplitudes submitted for CPP and N2 analysis were the mean amplitude of the subtraction (Target-Standard trials) to analyse signals relevant to decision making and response inhibition, normalized for standard sensory processing. The LRP amplitudes submitted were for Target trials (left–right) only since only these trials required a button press and hence, generate an LRP.

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. To control for Type I errors the Benjamimi and Hochberg control was applied to the follow-up tests (Benjamini and Hochberg 1995). To control for Type I errors in the pre-planned analysis of the N2 response, the alpha criterion was set to 0.01.

To test for significant differences for LRP between FOG − and FOG + groups unpaired *t* tests at each time point were calculated for each condition. 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 21 ms (11 consecutive time points) (Guthrie and Buchwald 1991).

Bayes factor analysis

For the pre-planned analysis Bayes factor provided a measure of evidence for one model versus another (Dienes 2016). Here it is used to investigate evidence for the null hypothesis or the alternative hypothesis. The JZS Bayes factor was computed using the function Bayes Factor 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.
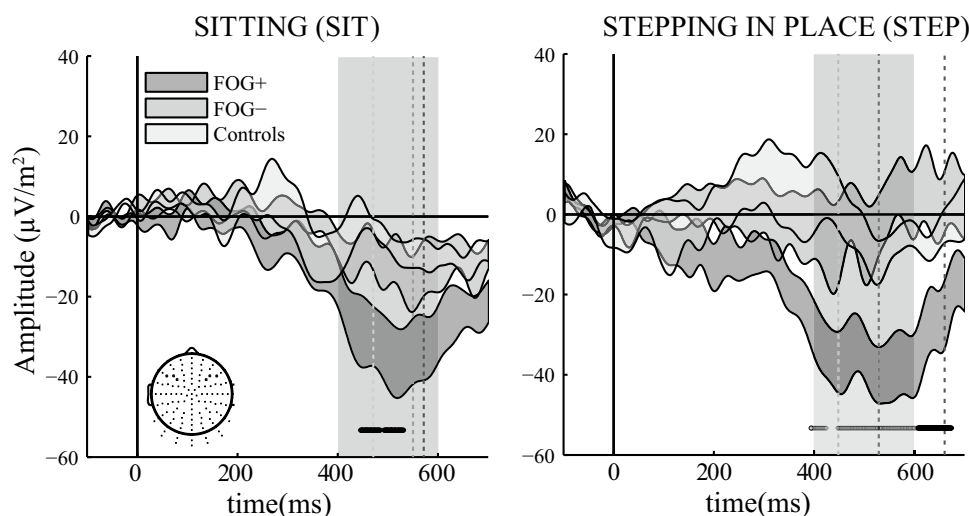
Fig. 3 Mean and standard error of the mean of the lateralized readiness potential (LRP) current source density (CSD) calculated by subtracting the average activity of three electrodes over the left frontocentral area (three large electrodes corresponding to D3, D4 and D5 in the 128 Biosemi ABC electrode 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 (left panel) and STEP (right panel) conditions. The solid black line indicates the stimulus onset, the dashed vertical lines indicate the mean response times, the horizontal dots along the time axis indicate significant differences between the FOG + and FOG − at each time point. The shaded box indicates the time period of LRP that was submitted to statistical analysis

Table 1 Participant demographics

	FOG −	FOG +	t value	p value
N	10	8		
Male	4	7		0.117
Age	62.5 (7.9)	65.0 (6.9)	− 0.718	0.48
NFOGQ	0	19.4 (5.1)		
H & Y	2.25 (0.35)	2.5 (0.32)	− 1.963	0.0678
UPDRS III	29.1 (14.1)	28.63 (10.1)	0.08	0.9372
MOCA	26.1 (2.9)	24.0 (1.9)	1.788	0.0939
FAB[a]	17.3 (1.3)	14.9 (2.75)	2.31	0.045
Disease duration (years)	7.0 (3.55)	12.3 (8.4)	− 1.67	0.12
Total levodopa dose (mg)	289 (248)	488 (260)	− 1.64	0.12

Means shown with standard deviation in parentheses

FOG + people with Parkinson's disease with freezing of gait, *FOG −* people with Parkinson's disease without, *H&Y* modified Hoehn & Yahr stage, *UPDRS III* unified Parkinson's disease rating scale III total, *MOCA* montreal cognitive assessment total, *FAB* frontal assessment battery total

[a]Statistically significant difference between groups on an unpaired t test

Table 2 Behavioural data

	FOG +	FOG −	Controls
N	8	10	7
STEP	665.2 (107.38) ms	530.2 (67.6) ms	448.25 (48.8) ms
SIT	571.3 (55.5) ms	550.0 (81.8) ms	471.0 (48.4) ms

Group mean with standard deviation in parentheses response times (RT) in ms by freezing of gait status and condition

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 and Frontal Assessment Battery scores between FOG + and FOG − but no significant differences in age, Hoehn and Yahr stage, UPDRS III, Montreal Cognitive Assessment scores or disease duration. The controls were significantly younger than the disease cohorts (mean age 25 ± 4.9 years, with 4 males).

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).

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 = 91,376, $p < 0.001$, $\eta_p^2 = 0.401$), and a significant interaction of group and condition, ($F(2, 22) = 14.96$, MSE = 166,681, $p < 0.005$, $\eta_p^2 = 0.073$) with no main effect of experimental condition ($F(1, 22) = 1.786$, MSE = 2386, $p = 0.195$, $\eta_p^2 = 0.005$).

To investigate the effect of the interaction of group and condition on response times, follow-up unpaired t test comparisons between groups of SIT and STEP conditions were conducted. The analysis for the SIT condition revealed a significant difference between the controls and the FOG + group ($p < 0.001$), a significant difference between the controls and the FOG − group ($p < 0.005$) but no significant difference between the FOG + and FOG − groups ($p = 0.505$). The analysis for the STEP condition revealed a significant difference between the controls and the FOG + group ($p < 0.001$), a significant difference between the FOG − and the FOG + groups ($p < 0.005$) but no significant difference between the controls and FOG − group ($p = 0.0509$). To further investigate the interaction effect, follow-up paired t tests between SIT and STEP conditions comparison within groups were conducted. The analysis showed a significant difference in RTs between conditions ($p < 0.01$) for the control group, with faster RTs in the STEP condition. For the FOG − group there was a no significant difference in RT between conditions ($p = 0.0806$), 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 ($p < 0.05$) 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 Fig. 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.

EEG analysis: cognitive decision making (CPP)

Figure 2a and Table 3 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 − (middle row) and controls (bottom row) for the STEP (left column) and SIT (middle column) over central parietal scalp. The right column of Fig. 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 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.

The ANOVA analysis of the mean amplitude of the subtraction (target-standard) CPP from 450 to 650 ms revealed no main effect of group ($F(2,22) = 0.807$, MSE = 393.6, $p = 0.42$, $\eta_p^2 = 0.048$), condition ($F(1,22) = 0.03$, MSE = 5.6, $p = 0.865$, $\eta_p^2 = 0.00$), or interaction of group and condition ($F(2,22) = 2.311$, MSE = 434.4, $p = 0.123$, $\eta_p^2 = 0.053$). 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 (Fig. 2c).

EEG analysis: automatic response conflict (N2)

The N2 response, is the deflection in the subtraction wave between 250 and 350 ms in Fig. 2b. The ANOVA analysis of the mean amplitude of the subtraction (target-standard) N2 from 250 to 350 ms revealed a significant main effect of

Table 3 EEG analysis data

	FOG +		FOG −		Controls	
	SIT	STEP	SIT	STEP	SIT	STEP
CPP	18.43 (16.7)	26.52 (17.5)	27.4 (20.5)	28.5 (14.4)	39.28 (22.4)	26.12 (18.8)
N2	− 2.61 (8.9)	10.88 (8.7)	3.53 (16.74)	6.11 (10.1)	15.76 (9.41)	16.57 (13.6)
LRP	− 30.75 (21.4)	− 36.04 (19.7)	− 11.58 (15.7)	− 1.77 (24.5)	− 6.271 (4.0)	− 3.17 (10.6)

Group mean with standard deviation in parentheses CSD amplitude ($\mu V/m^2$) for the CPP, N2 and LRP by group and condition

group ($F(2,22) = 3.638$, MSE $= 686.3$, $p < 0.05$, $\eta_p^2 = 0.165$), with no significant effect of condition ($F(2,22) = 3.778$, MSE $= 389.5$, $p = 0.051$, $\eta_p^2 = 0.047$) or significant interaction effect ($F(1,22) = 2.049$, MSE $= 187.8$, $p = 0.1527$, $\eta_p^2 = 0.045$).

To investigate the effect of group on the N2 amplitudes, follow-up unpaired t test comparisons were conducted, the analysis revealed a significantly larger amplitude for the controls compared the FOG + groups ($p < 0.05$) and a similar significant difference between the controls and the FOG − groups ($p < 0.05$) but no significant difference between the FOG + and FOG − groups ($p = 0.866$).

Pre-planned analysis of the N2 amplitude within each group, motivated by the significant interaction in the behavioural results and the work by (Loughnane et al. 2016) which showed a relationship with response and the N2 amplitude. For the control group there was no significant difference in N2 amplitude between conditions ($t(6) = - 0.19706$, $p = 0.8503$, JZS Bayes factor $= 0.379$), similarly 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 ($t(7) = - 3.5712$, $p < 0.01$, JZS Bayes factor $= 5.92$), with a larger amplitude in the STEP condition.

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 (left panel) and STEP (right panel) conditions. The ANOVA analysis of the mean amplitude of the Target LRP trials (left–right) from 400 to 600 ms revealed a main effect of group ($F(2,22) = 7.889$, MSE $= 4137$, $p < 0.005$, $\eta_p^2 = 0.356$), with no significant effect of condition ($F(2,22) = 0.090$, MSE $= 119.8$, $p = 0.343$, $\eta_p^2 = 0.005$) and no interaction effect of group and condition ($F(2,22) = 1.987$, MSE $= 253.4$, $p = 0.161$, $\eta_p^2 = 0.022$). Follow up unpaired t tests between groups to investigate the main effect of group were conducted. There was a statistically significant difference in the LRP amplitude between the FOG + and the FOG − groups ($p < 0.001$), the FOG + groups had a more negative LRP amplitude. Similarly, there was a statistically significant difference in the LRP amplitude between the FOG + and the control groups ($p < 0.001$). There was no statistically significant difference between the LRP amplitude for the controls and the FOG − groups ($p = 0.75$).

To investigate the onset of differences in the LRP between the PwP groups the LRP data for each time point was submitted to an unpaired t test. 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 Fig. 3. The difference in onset between groups occurs just after ~ 400 ms and continues until the mean response time (indicated by the dashed vertical lines).

Discussion

We have recently shown that electrophysiological markers of motor preparation rather than decision-making differentiate PwP with (FOG +) and without FOG (FOG −) while sitting (Butler et al. 2017). In the current study, we examined the effect of stepping on these results by measuring behavioural and electrophysiological responses in PwP with and without freezing of gait and young healthy controls 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 + . There was no significant difference between SIT and STEP conditions for FOG − but this group displayed a similar pattern to the healthy control group which were significantly faster during the STEP condition. Faster response time while walking has been shown before in older adults (Malcolm et al. 2015). One possible explanation for this improvement could be due to more reliable evoked responses. In a recent study, rodents showed a less variable evoked response in the superior colliculus and primary visual cortex (V1) in rodents during locomotion (Savier et al. 2019). The similarity of the responses of the FOG − group and the healthy controls suggests that this response time effect may be a phenomenon which is closely linked with the development of FOG.

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 + , FOG − and healthy controls for the SIT and STEP conditions, suggesting that decision-making processes are not the source of the response delay (prolonged 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 significantly larger in the FOG + group than 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 PwP 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 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). While there was no significant interaction between group and condition, the pre-planned analysis showed that the presence of an a clear N2 potential in the SIT condition that was reduced in the STEP condition, suggesting that this is specific to the dual-task condition in the FOG + group. On the other hand, there is no significant difference in the N2 potential in the FOG − group or controls 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, 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

The LRP is generated in preparation of a unimanual motor task (in this study, a button press). Figure 3 shows a significant larger LRP for this task in FOG + . This is remarkable for such a simple motor task. The presence of a significantly larger LRP in both conditions for the FOG + group compared to the FOG − group or controls, suggests that FOG + require additional resources to initiate movement for simple motor tasks [possibly via lateral premotor areas (Wu and 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) and EEG spectral power during transitions between normal walking and freezing show a significant increase in theta band power within the central and frontal leads suggesting that the phenomenon seen in the current study may also underpin the intiation of a freezing episode (Shine et al. 2014). Similar cortical activation is seen during during ambulatory EEG in PwP and older adults (Stuart et al. 2018).

The main effect of group seen in the N2 and LRP potential analysis and the emergence of slower response times in the FOG + group while stepping 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, 2015; Shine et al. 2014).

Maidan et al. were the first group to examine ERPs in PwP while walking. In particular, they demonstrated prolongation and attenuation of the P3 in PwP when walking compared with sitting (Maidan et al. 2019). They therefore hypothesised impaired recruitment of attentional networks during dual-tasking in PwP. As mentioned above, we have previously shown that standard ERP analysis can erroneously underestimate a P3 signal in PwP due to interference from the lateralized readiness potential. The higher spatial resolution of the CSD approach utilized here allows separation of the P3/CPP and LRP facilitating simultaneous analysis of these discrete potentials. We demonstrate group-specific response time differences which emerge during stepping and are associated with changes in response inhibition and movement-related potentials between groups.

This is, therefore, the first study to employ a CSD analysis to simultaneously examine evoked response related to decision making, response inhibition and motor preparation in people with Parkinson's disease while stepping. The number of participants in our study is small with a gender imbalance. 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. 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).

Dual-tasking has been shown to have an effect on gait parameters as well as secondary task performance (Killane et al. 2015). It was not possible to analysis gait parameters due to technical issues and is a limitation of the current study. It would be an avenue for future studies to investigate of gait parameters 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. We did not conduct independent component analysis on the data as the evoked response were had similar baseline and early evoked responses across conditions. We also focused our analysis on specific electrode sites that were re-referenced using the CSD which would minimize possible muscle movement artefacts on peripheral electrodes. The use of more classical EEG methods illustrates that these kind of studies can be conducted using a only a handful of electrodes and could pave the way forward for this kind of experiment being applied in a clinical setting. That being said, ICA has been very useful in mobile brain imaging studies (Castermans et al. 2014; Oliveira et al. 2017) in future studies it would be essential when investigating the electrophysiological correlates of the gait cycle to reduce the impact of motion related artefacts.

Conclusion

This is the first study to analyse ambulatory event-related potentials in PwP with and without FOG and the first study to employ a CSD analysis to simultaneously examine evoked response related to decision making, response inhibition and motor preparation in people with Parkinson's disease while stepping. The behavioural results showed that FOG + had slower response times while stepping, however response times were significantly faster while stepping in controls and, while not significant, the FOG − group had on average faster response times while stepping. In association with this, FOG + displayed neurophysiological 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 FOG − by motor and response conflict impairments rather than decision-making impairments. The impact of locomotion on the generation of the N2 and LRP potentials 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 (Lewis and Shine 2016).

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