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Abnormal patterns of theta frequency oscillations during the temporal evolution of freezing of gait in Parkinson's disease

Shine J.M. [a], Handojoseno A.M.A. [b], Nguyen T.N. [b], Tran Y. [b], Naismith S.L. [a], Nguyen H. [b,1], Lewis S.J.G. [a,*,1]

[a] Parkinson's Disease Research Clinic, Brain and Mind Research Institute, The University of Sydney, NSW, Australia
[b] Centre for Health Technologies, University of Technology Sydney, NSW, Australia

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HIGHLIGHTS

- Electrophysiology can offer novel insights into the spatiotemporal dynamics underlying episodes of freezing of gait.
- Episodes of freezing of gait display a unique signature of abnormal oscillatory activity in theta band power spectral density.
- The results provide a potential means for therapeutic prediction and alleviation of freezing episodes in susceptible patients.

ABSTRACT

Objective: We sought to characterize the electrophysiological signature of Freezing of gait in Parkinson's disease.
Methods: We examined 24 patients with idiopathic Parkinson's disease and significant freezing of gait as they performed a series of timed up-and-go tasks in their 'off' state while electroencephalographic data was collected from four scalp leads. Fast Fourier Transformation was utilized to explore the power spectral density between periods of normal walking and periods of freezing, as well as during the transition between the two states. In addition, Cross Spectrum and Cross Frequency analyses were used to explore the role of impaired temporal and spatial connectivity.
Results: When compared to walking, episodes of freezing were associated with a significant increase in theta band power within the central and frontal leads. The transition from normal walking to freezing of gait was also associated with increased theta frequency coupling between the central and frontal leads, along with an increase in cross-frequency coupling in the central lead.
Conclusions: Episodes of freezing of gait in Parkinson's disease are associated with abnormal oscillatory activity in the brain.
Significance: These results provide novel insights into the pattern of spatiotemporal dynamics underlying freezing of gait and may provide a potential means for therapeutic prediction and alleviation of freezing episodes in susceptible patients.

1. Introduction

Freezing of gait (FOG) is a devastating symptom of Parkinson's disease (PD) in which patients suddenly feel as though their feet have become "stuck to the ground" (Giladi et al., 1997; Weinberger et al., 2006). In combination with impaired balance, FOG often precipitates falls leading to high morbidity and the need for nursing home placement (Aarsland et al., 2000; Singh et al., 2012). Although the freezing phenomenon is well described clinically, its pathophysiology is not well understood (Nutt et al., 2011; Shine et al., 2011b; Niu et al., 2012). It has been proposed that FOG is related to impaired communication within and between competing, yet complimentary neural networks (Chee et al., 2009; Lewis and Barker, 2009). Indeed, recent functional neuroimaging studies have shown that disturbances between frontoparietal cortical regions and key subcortical structures are responsible for the manifestation FOG (Bartels et al., 2006; Thevathasan et al., 2012; Singh et al., 2012; Vandenbossche et al., 2012a,b; Shine et al., 2013a),

* Corresponding author. Address: Parkinson's Disease Research Clinic, 94 Mallett Street, Camperdown, Sydney, NSW 2050, Australia. Tel.: +612 9351 0702.
E-mail addresses: mac.shine@sydney.edu.au (J.M. Shine), simon.lewis@sydney.edu.au (S.J.G. Lewis).
[1] Dual senior authorship.

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The mechanism underlying this disruption remains unclear. This is due in part to the fact that neuroimaging tools such as PET and fMRI lack the temporal resolution required to capture the neural processes determining a freezing event.

Electroencephalography (EEG) represents a potential approach for analyzing dynamic temporal relationships across widespread regions of the brain. Previous work in PD has shown that changes in the power of low frequency bands within the EEG signal are associated with the abnormalities in motor function (Brown, 2002, 2006; Shine et al., 2013b; Cavanagh and Frank, 2013), possibly mediated via synchronous output from the basal ganglia (Brown and Williams, 2005; Marceglia et al., 2007; Lewis and Barker, 2009; Menon, 2011; Shine et al., 2011b; Nutt et al., 2011). Indeed, multiple studies have suggested specific roles for activity within unique frequency bands in the completion of ongoing motor tasks (Salamone and Correa, 2002; Alegre et al., 2013), including roles for beta activity in motor preparation, gamma activity in motor commission and gating (Kühn et al., 2004; Androulidakis et al., 2007; Nachev et al., 2008; Haynes and Haber, 2013; Cavanagh and Frank, 2013) and theta activity in the processing conflict-related signals (Fumagalli et al., 2011; Cavanagh et al., 2012a,b).

While estimates of frequency band power provide limited spatial information about the specific neural regions involved in the production of the signals, the major benefit of EEG technology is the capacity to explore the relative coherence of different frequency bands across cortical regions as a function of time (e.g. comparing the coherence between different frequency bands within the same electrode location). This approach allows for the estimation of the relative 'cross-talk' between two regions over time, which represents the amount of shared information between differing neural hubs (Nachev et al., 2008; Steinke and Galán, 2011). An appreciation of these relationships therefore allows insights into the neural dynamics underlying normal and impaired processes.

In this study, we analyzed the electrophysiological signature associated with the transition from normal walking to freezing. To do so, we explored the Power Spectral Density within four scalp electrodes, chosen to reflect their role in motor planning and execution as well as conflict resolution. In addition, we also explored the data for the presence of abnormalities in 'cross talk' both within and between these four electrode hubs. We predicted that episodes of freezing would be associated with a distinct electroencephalographic signature, likely involving alterations in power within the low frequency EEG bands. Furthermore, we also hypothesized that FOG would be related to impaired 'cross talk' between neural regions.

2. Methods

2.1. Demographic details

24 patients who self-reported significant FOG were recruited from the Parkinson's Disease Research Clinic at the Brain and Mind Research Institute, University of Sydney. They represented a convenience sample who were recruited to take part in a separate study validating the utility of FOG questionnaires (Giladi et al., 2009; Spildooren et al., 2010). All patients satisfied UKPDS Brain Bank criteria. Patients also undertook the Mini-Mental State Examination (MMSE) as a measure of global cognition (Folstein et al., 1975; Almeida and Lebold, 2010; Ehgoetz Martens et al., 2013). The University of Sydney Human Research and Ethics Committee approved the study and written informed consent was obtained. Table 1 contains demographic details for the group of patients.

All patients were tested in the practically defined 'off' state having withdrawn from dopaminergic medications overnight. Of the 24 patients, 20 were on levodopa medication, with a subset of eight taking additional entacapone and 12 on an additional dopamine agonist. Three patients were on dopaminergic agonists alone and one was untreated at the time of assessment. Six of the patients were also fitted with deep brain stimulators (five in the subthalamic nuclei and one in the pedunculopontine nuclei) that were switched off at least 60 min prior to testing.

2.2. Timed up-and-go (TUG) tasks

As described in detail elsewhere (Shine et al., 2011a; Ehgoetz Martens et al., 2013), all patients underwent a structured series of video-recorded timed up-and-go tasks while being video recorded. All TUG tasks started from a sitting position and patients walked five meters to a 0.6×0.6 m target box marked on the floor with yellow tape. In the target box, participants were asked to make a series of 180° and 540° turns (counterbalanced left and right). Patients also navigated a narrow doorway (1.2 m wide) four times. Freezing episodes were defined as the paroxysmal cessation of a patient's footsteps during a TUG task and were analyzed by two independent clinicians (inter-rater reliability > 0.9) (Shine et al., 2011a; Vandenbossche et al., 2012b).

Four separate conditions were identified for each patient:

i) Normal walking – identified as a 1 s epoch of time in which a patient was walking normally with no cessation of normal stride within 2 s of the epoch.
ii) Freezing – identified as a period of time in which a patient suffered from a paroxysmal cessation of their normal stride.
iii) Transition to freezing – identified as a 1 s epoch in the 2 s prior to a freezing episode.
iv) Stationary – identified as a period following a voluntary termination of gait at the end of a TUG trial in which a patient was stationary with no overt gait-related movements within 2 s.

2.3. Electroencephalography

Electroencephalography recording was performed with a 4-channel wireless EEG system with four electrodes recording from the following active lead sites: occipital one (O_1), parietal four (P_4), central zero (C_z) and frontal zero (F_z). Gold cup electrodes were placed on the scalp and the EEG channels were recorded with a sampling rate of 500 Hz, and the hardware filters consisted of a high-pass filter at 0.15 Hz and a low-pass filter at 100 Hz. Data were acquired using bipolar EEG leads at occipital one (O1, with the reference electrode at T4), parietal four (P4, with the reference electrode at T3), and monopolar leads at central zero (Cz) and frontal zero (Fz), both having a common ground at FCz.

The precise location of the scalp electrodes was determined by their role in the general control movement, with the Fz lead representing the pre-supplementary motor area (pSMA), the Cz lead representing precentral gyrus, the P4 lead representing parieto-occipital junction and the O1 reflecting occipital cortex. Raw EEG data was acquired at sampling rate of 500 Hz and a common-mode rejection ratio of >95 dB was employed to improve signal to noise ratio.

2.4. Data preprocessing

The data from the EEG system were processed with custom written scripts in C and MATLAB (v.7.14.0, R2012a). 575 samples of data were taken for each of the three conditions, amounting to total 1725 samples from 24 patients. Low frequency noise, high

frequency noise and 50 Hz line frequency noise were eliminated using band-pass and band-stop Butterworth IIR filters (BPF 0.5–60 Hz and BSF 50 Hz). To eliminate ocular and muscular artifacts, we applied Stein's unbiased risk estimate (SURE) thresholding based on wavelet transforms using Coiflet (Coif5) in all electrode locations (Frank, 2006; Geetha and Geethalakshmi, 2011). EEG data was synchronized with video-recordings of the TUG assessments by filming the precise onset of the EEG program.

2.5. Power spectral density

In the first stage of analysis, pre-processed data were imported into a Power Spectral Density analysis. One second epochs from each condition were filtered from 50 Hz power-line noise using a Butterworth Infinite Impulse Response Band Stop Filter and subsequently entered into the Fourier Transform analysis using Welch periodogram. Window of 500 data sample (1 s) were divided into eight segments of 110 samples (50% overlap). Each segment was multiplied by a smoothing Hamming window function and a Welch periodogram was calculated using the discrete Fourier Transform. The power spectra were subsequently estimated as the average of 8 periodograms to reduce variance. The amplitude spectra were then divided into five frequency bands; delta (δ; 0.5–4 Hz), theta (θ; 4–8 Hz), alpha (α; 8–13 Hz), beta (β; 13–30 Hz) and gamma (γ; 30–60 Hz) for further analysis (see Fig. 1). For example, the power level in the alpha band represents the area under the curve accounting for total power (taken as the square of the amplitude) within the frequency band between 8 and 13 Hz (12).

2.6. Cross talk

To explore the role of synchrony both within and between the separate EEG leads, two further outcome measures were calculated: (i) Cross Spectrum analysis (Mallet et al., 2012; Varshney et al., 2012), which measures the strength of a relationship between pairs of locations and can be interpreted as an indicator of functional relationship between different brain regions; and (ii) Cross Frequency Power Ratio, which is a measure of the degree of relationship between the temporal dynamics of the different frequency bands within one electrode location (Buzsáki and Draguhn, 2004; Schutter et al., 2006; Frank, 2006; Lewis and Barker, 2009). In this study, we analyzed two pairs of cross frequency power ratios: (δ:β) and (θ:β), as these three frequency bands have previously been shown to play a functional role in movement (Brown, 2002; Tsang et al., 2010). For each pairing, we calculated the mean and standard deviation during each EEG epoch.

Table 1
Demographic characteristics of the sample.

	Range	Mean	SD
N = 24			
Age, years	56–84	69.00	8.4
Hoehn and Yahr	2–4	2.66	0.5
Disease duration	1–26	6.56	6.2
UPDRS III	19–65	40.24	11.1
Mini-Mental State Examination	24–30	28.57	1.6
Clinical assessment			
Frequency of freezing episodes	1–63	21.71	17.6
Percentage of time freezing	0.3–75.7	23.70	23.0

2.7. Statistical analysis

The Power Spectral Density analyses were performed using a three-Way ANOVA (Condition × Frequency Band × Electrode Location) followed by two ways ANOVA to analyze interaction between Condition and Frequency Band in each Electrode location. In the 'cross talk' analyses, a non-parametric Wilcoxon sum rank test with continuity correction of 0.5 was implemented since the extracted feature data were not normally distributed. Alpha levels for both analyses were set at 0.05 and were corrected for multiple comparisons using Bonferroni's correction if the Levene's test shows the homogeneity of variance. Otherwise, The Games–Howell test was used as it does not assume equal variance between conditions. Finally, due to the large number of data points sampled

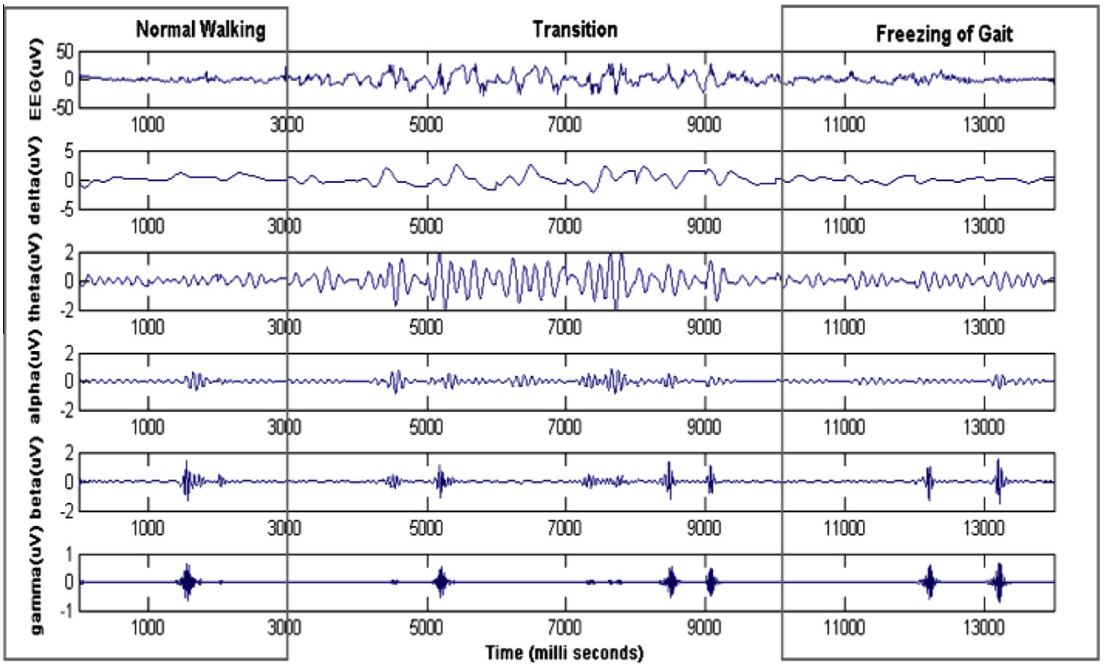

Fig. 1. Example of the raw data of the electroencephalographic frequency bands in the Cz–FCz lead when comparing normal walking with the transition to an episode of freezing of gait in a single subject.

in our experiment, we only interpreted results that were both significant at the corrected p value level and also displayed a Cohen's d effect size of greater than 0.4 (Kenny, 1987; Snijders et al., 2010). In doing so, we were able to constrain our large dataset into results that were likely to be reproducible in a separate cohort.

To ensure that the electroencephalographic signal associated with freezing was not simply related to a lack of movement, we also compared the Power Spectral Density of episodes of freezing with periods when patients were coming to an effective stop. That is, they transitioned from walking to stopping without any evidence of freezing behavior.

3. Results

3.1. Timed up-and-go tasks

There were 530 events of FOG recorded during the TUG tasks, with an average of 21.7 (SD 17.6) per subject (range 1–63). The mean percentage of time spent with freezing was 23.7% (SD 23.0), ranging from 0.3% to 75.7%. Freezing was most likely to occur during turning (48.4%), but also occurred during straight-line walking (26.3%) and during the navigation of narrow doorways (9.9%).

3.2. Power spectral density

All factors from the three-way ANOVA were statistically significant, including: Condition – $F_{3,45921} = 28.901$, $p < 0.0005$; Frequency band – $F_{4,45921} = 5521.012$, $p < 0.0005$; and Electrode location – $F_{3,45921} = 36672.177$, $p < 0.0005$. The interaction between the three factors was also found to be statistically significant ($F_{36,45921} = 22.612$, $p < 0.0005$), indicating that the PSD of the various conditions were clearly different in the five frequency sub-bands and four electrode locations under consideration.

When comparing freezing to walking, there were significant increases in the power within the theta frequency band in the central ($t = 8.6$, $p < 0.0001$) lead (see Fig. 2 and Table 2). In addition, there were significant increases in alpha power in the central ($t = 11.6$, $p < 0.0001$) and frontal leads ($t = 11.6$, $p < 0.0001$), along with increased beta activity in the frontal lead ($t = 13.8$, $p < 0.0001$). During the transition from normal walking to freezing, there was a large increase in low frequency activity in the central (delta: $t = 48.91$, $p < 0.0001$; theta: $t = 51.45$, $p < 0.0001$; and alpha bands: $t = 27.85$, $p < 0.0001$) and frontal leads (theta: $t = 24.06$, $p < 0.0001$; alpha: $t = 35.01$, $p < 0.0001$), along with decreased activity in these bands within the parietal lead (delta: $t = 14.21$, $p < 0.0001$; theta: $t = 15.81$, $p < 0.0001$; and alpha: $t = 9.81$, $p < 0.0001$). When compared to the transition period, episodes of freezing were associated with a large increase in beta power in the parietal lead ($t = 18.16$, $p < 0.0001$), with a concomitant decrease in the delta ($t = 20.91$, $p < 0.0001$) and theta ($t = 15.65$, $p < 0.0001$) bands. Although there were some similarities between freezing and periods when patients were stopping, there was a significant increase in the central ($t = 13.91$, $p < 0.0001$) theta activity during freezing, along with a decrease in alpha activity in the parietal ($t = 14.81$, $p < 0.0001$) and frontal leads ($t = 29.33$, $p < 0.0001$).

3.3. Cross talk

The Cross Spectrum analysis revealed multiple significant differences in the cross-band coherence between normal walking and freezing. During the comparison from walking to the transition, there was an increased coupling between the central and frontal leads in the α ($t = 3.75$, $p < 0.0001$), β ($t = 15.40$, $p < 0.0001$) and γ ($t = 12.98$, $p < 0.0001$) frequency bands. There was also significant increased γ coherence between the posterior and central leads during the transition to freezing ($t = 9.84$, $p < 0.0001$), along with increased δ ($t = 8.71$, $p < 0.0001$). During the comparison of the transition state to freezing, there was an increase in the coherence in the θ band between the central and frontal leads ($t = 3.31$, $p < 0.0001$), along with a decrease in β cross talk ($t = 11.4$, $p < 0.0001$) between the posterior and frontal leads.

The Cross Frequency analysis showed increased temporal coherence between the delta and beta bands in the central lead between normal walking and the transition to freezing ($t = 12.82$, $p < 0.0001$), however the cross-frequency coherence diminished at the onset of freezing behavior ($t = 7.50$, $p < 0.0001$). There was

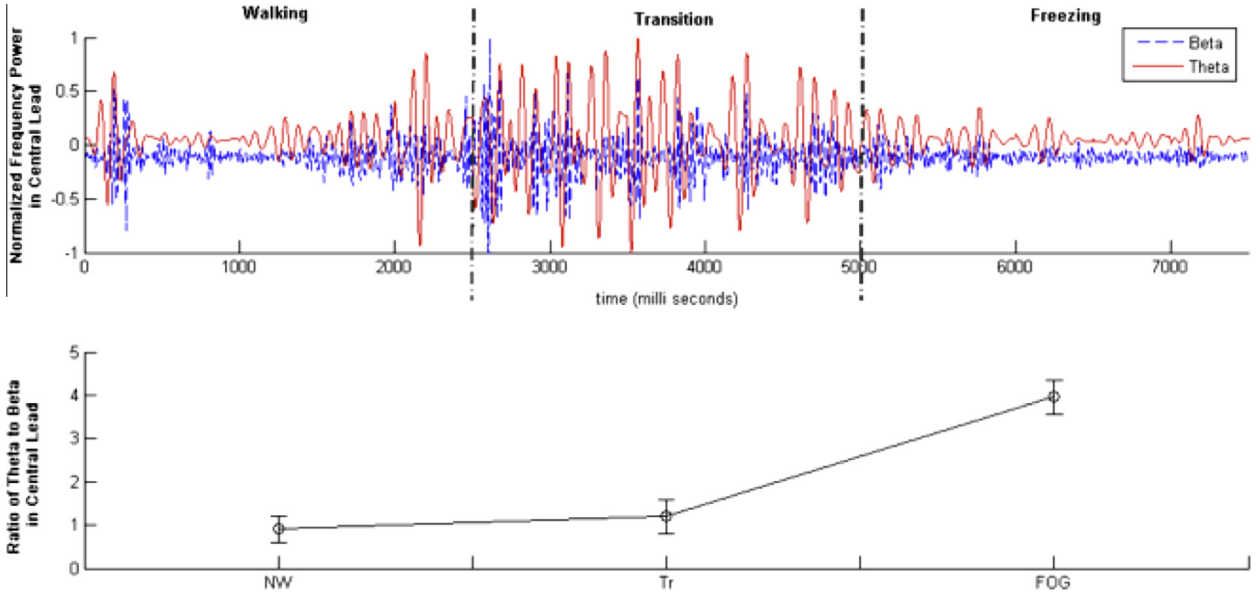

Fig. 2. Example of the Cross Frequency analysis in a single patient. The figure shows the normalized values of activity within the beta (blue dashed line) and the theta (red line) frequency bands through periods of walking, transition and freezing. Although there were large increases in power within the theta band during the transition period, the synchrony between the theta and beta bands was significantly increased in the freezing period (see bottom panel) ($p < 0.001$ and Cohen's $d \geqslant 0.4$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Results from the electroencephalographic analyses comparing normal walking (NW) and the transition (Tr) to a freezing of gait event (FOG). Values represent the Power Spectral Density at each electrode lead (O1 – occipital 1; P4 – Parietal 4; Cz – Central and Fz – Frontal) within each frequency (Freq) band (δ – delta: 0.5–4 Hz; θ – theta: 4–8 Hz; α – alpha: 8–13 Hz; β –beta: 13–30 Hz; and γ – gamma: 30–60 Hz).

Lead	Freq	NW	Tr	FOG	NW vs. Tr	Tr vs. FOG
	δ	0.161 ± 0.13	0.143 ± 0.13	0.136 ± 0.11	*	
	θ	0.079 ± 0.05	0.073 ± 0.06	0.069 ± 0.05	*	
O_1	α	0.041 ± 0.03	0.031 ± 0.03	0.035 ± 0.03	**	*
	β	0.063 ± 0.05	0.038 ± 0.04	0.048 ± 0.04	***	*
	γ	0.036 ± 0.06	0.022 ± 0.04	0.034 ± 0.06	*	*
	δ	0.221 ± 0.15	0.159 ± 0.13	0.197 ± 0.14	***	
	θ	0.107 ± 0.06	0.081 ± 0.05	0.100 ± 0.05	***	**
P_4	α	0.072 ± 0.05	0.058 ± 0.05	0.080 ± 0.06	*	***
	β	0.117 ± 0.07	0.095 ± 0.07	0.134 ± 0.08	**	***
	γ	0.084 ± 0.08	0.071 ± 0.08	0.097 ± 0.07	*	**
	δ	0.070 ± 0.09	0.203 ± 0.19	0.088 ± 0.10	***	***
	θ	0.036 ± 0.05	0.106 ± 0.10	0.061 ± 0.08	***	***
C_Z	α	0.015 ± 0.02	0.028 ± 0.03	0.024 ± 0.03	***	*
	β	0.015 ± 0.01	0.016 ± 0.01	0.014 ± 0.01	*	*
	γ	0.002 ± 0.00	0.004 ± 0.00	0.003 ± 0.00	**	*
	δ	0.004 ± 0.00	0.005 ± 0.01	0.004 ± 0.01	*	
	θ	0.001 ± 0.00	0.002 ± 0.00	0.002 ± 0.00	**	*
F_Z	α	0.000 ± 0.00	0.000 ± 0.00	0.000 ± 0.00	***	
	β	0.000 ± 0.00	0.000 ± 0.00	0.000 ± 0.00	*	*
	γ	0.000 ± 0.00	0.000 ± 0.00	0.000 ± 0.00	*	

Key:
* Significant at $p < 0.001$ and Cohen's $d < 0.3$.
** Significant at $p < 0.001$ and Cohen's $d > 0.3$.
*** Significant at $p < 0.001$ and Cohen's $d \geqslant 0.4$.

also an increase in the θ:β coherence in the central lead during the conversion to freezing ($t = 13.95$, $p < 0.0001$) (see Fig. 2). Finally, both posterior leads showed an initial increase in δ:β coherence ($t = 14.4$, $p < 0.0001$), however the communication dissipated by the onset of the freezing episode ($t = 5.83$, $p < 0.0001$).

4. Discussion

In this study, direct comparison of EEG frequency band power during normal walking and freezing revealed a significant increase in the activity within the theta frequency band in the central electrode (see Fig. 3). Furthermore, this theta activity was significantly increased when compared to periods when patients were stationary, suggesting that this activity was not simply associated with stopping. In addition, the transition from walking to freezing was associated with an increase in beta band activity in the parietal lead. Together, these abnormal patterns of EEG activity may help to inform our understanding of the neural mechanisms underlying freezing behavior in PD.

Activity within the theta frequency band in frontal and central cortical regions has been previously described as the frontal midline theta rhythm (fmθ) (Iramina et al., 1995; Aron and Poldrack, 2006; Frank, 2006; Mitchell et al., 2008; Wiecki and Frank, 2010) and is thought to arise from dynamic coupling between the dorsal anterior cingulate (dACC) and the pre-supplementary motor area (pSMA) (Asada et al., 1999; Sauseng et al., 2006; Aron et al., 2007; Haynes and Haber, 2013). Power within fmθ is regularly elevated during the performance of cognitive tasks (Başar et al., 2001; Nachev et al., 2008), particularly those that require the processing of conflict (Shine et al., 2012; Cavanagh et al., 2012a,b) and cognitive interference (Buzsáki and Draguhn, 2004; Lewis and Barker, 2009; Nigbur et al., 2011), however fmθ may also reflect working memory manipulations (Itthipuripat et al., 2012; Shine et al., 2013a) or the neural activity required to 'over-ride' Pavlovian learning biases (Takakusaki et al., 2003; Cavanagh et al., 2013). In any event, our results suggest that freezing of gait is related to the processing of conflict-related signals in a network of frontoparietal regions underlying cognitive control, a finding that is strongly aligned with previous neuroimaging studies of freezing of gait (Bartels and Leenders, 2008; Moore et al., 2012; Shine et al., 2013b; Shine et al., 2013a), along with the known association between FOG and cognitive impairment (Frank, 2006; Amboni et al., 2008; Naismith et al., 2010; Shine et al., 2012), as well as

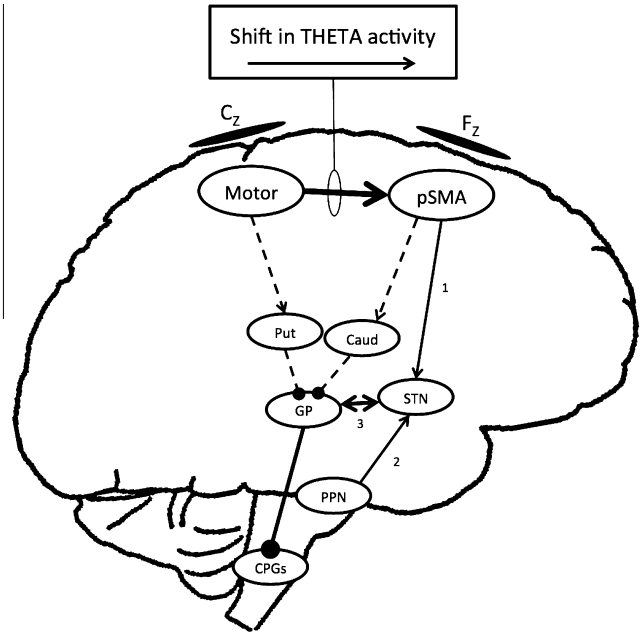

Fig. 3. Graphical depiction of the predicted mechanism underlying freezing of gait. During the evolution of a freezing episode, there is a large increase in theta activity in the C_Z electrode, which lies above the Motor cortex. The theta activity then spreads to the FZ electrode during the cessation of the patient's footsteps, possibly reflecting increased theta activity in the pSMA and connected regions. The shift in theta activity may reflect: 1 – abnormal connections between the pSMA and the subthalamic nucleus (STN); 2 – increased influence from the pedunculopontine nucleus (PPN); or 3 – activity associated with the oscillatory coupling between the STN and the globus pallidus (GP). Ultimately, these alterations in signaling are proposed to manifest as overwhelming inhibitory output onto the central pattern generators (CPGs) controlling gait (see Shine et al., 2013a,b for further details). Put – putamen; Caud – caudate nucleus.

deficits in conflict resolution (Pahapill and Lozano, 2000; Vandenbossche et al., 2011).

The examination of the dynamic changes underlying the transition from normal walking to an episode of freezing of gait revealed a number of other patterns of abnormal neuronal synchronization. For instance, we observed a substantial increase in beta activity in the parietal lead during the transition to a freezing episode. The cross spectrum analysis also revealed significant impairments in fronto-central cross-electrode coherence in the beta frequency band leading into a freezing episode. As decreases in beta activity have been related to motor preparation (Brown, 2006; Weinberger et al., 2006; Jacobs and Horak, 2007), these results could suggest that the frontally generated motor plans were not effectively communicated to the motor cortex, leading to impairments in gait. In addition, increased beta activity has been correlated with worse motor severity in PD (Rye and DeLong, 2003; Silberstein et al., 2005), suggesting that the motor regions of the cortex may have been temporarily impaired during the duration of each freezing episode. There is evidence to suggest that this mechanism may also be driven by increased oscillatory activity within the STN (Levy, 2002; Xiang et al., 2005), which is consistent with recent findings in functional neuroimaging studies that utilize virtual reality paradigms to invoke freezing episodes (Oades and Halliday, 1987; Shine et al., 2013a).

Interestingly, the transition from walking to freezing was also associated with increased and θ:β and δ:β coherence in the central lead, along with an increase in delta, theta and gamma coherence between the frontal and central leads. The strong increases in coherence across multiple frequency bands could reflect an increase in functional interactions amongst neural networks embedded across the cortex (Pahapill and Lozano, 2000; Hogan et al., 2003). Alternatively, the cross-frequency coherence may be mediated by underlying subcortical structures, such as the subthalamic nucleus (STN), as frequency band activity within the STN has been shown to correlate strongly with power within scalp electrodes (Pahapill and Lozano, 2000; Marceglia et al., 2007; Cavanagh and Frank, 2013).

Numerous clinical studies have shown that freezing behavior in PD is associated with a paroxysmal increase in 5–7 Hz (i.e. θ) oscillations, known clinically as 'trembling in place' (Gatev et al., 2006; Follett and Torres-Russotto, 2012). As such, the changes seen in the power and coherence in the theta frequency band during freezing may be due to mechanical oscillations transmitted into the scalp electrodes. However, as we only observed significant increases in theta power in the central and frontal leads, it is unlikely that these increases were due to global motor interference. An alternative explanation is that a dysfunctional neuronal circuit in the subcortical structures of the brain drives the creation of the theta oscillations during a freezing episode (see Fig. 3), ultimately manifesting as 'trembling in place' in the peripheral musculature. Computational modeling experiments have proposed the 5–7 Hz oscillations seen in Parkinsonian tremor are due to increased oscillatory communication between the STN and the globus pallidus (Frank, 2006; Schweder et al., 2010; Fling et al., 2013) and a similar mechanism has recently been proposed to underlie the oscillations seen in freezing (Nachev et al., 2008; Shine et al., 2013a). As such, these results are strongly aligned with the notion that the output structures of the basal ganglia play an integral role in the pathophysiology of FOG. In order to clarify these predictions, further experiments with higher spatial precision, such as direct cell recording, may be required. The direct comparison of lower limb oscillations during freezing of gait, as measured by accelerometry technology, would also help to test this prediction.

These results are strongly aligned with the recent proposal that abnormal excitatory activity from the STN is factor that links the provocation and manifestation of freezing behavior in PD (Shine et al., accepted for publication). In this model, increased response conflict leads to excitation of the 'hyper-direct' pathway of the basal ganglia, driving an overwhelming increase in the inhibitory output of the basal ganglia through the globus pallidus internus nucleus (see Fig. 3). This model is supported by the alleviation of freezing behavior through deep brain stimulation of the STN, which has been shown to lead to decreased freezing behavior, along with a subsequent reduction of dopaminergic medication requirements (Moreau et al., 2008), particularly with low-frequency (~60 Hz) stimulation (Fasano et al., 2011; Xie et al., 2011). Furthermore, cortical fmθ signals associated with successful response inhibition have been shown to directly relate to local field potentials within the STN (Nachev et al., 2008; Cavanagh et al., 2011). Future studies should seek to determine the precise role of abnormal oscillatory activity within the STN and other brainstem structures, such as the pedunculopontine nucleus, in the pathophysiological mechanism of FOG (Shine et al., accepted for publication).

The results presented here are consistent with the suggestions that many of the clinical features of PD result from pathological oscillatory synchronization in the human sensorimotor system (Gatev et al., 2006; Timmermann et al., 2007; Hikosaka and Isoda, 2010). However despite strong alignment with a wide range of neuroimaging and computational modeling studies, the results remain speculative and will require further confirmation. Further studies would benefit from characterizing the electrographic signal associated with freezing across more scalp locations, helping to determine with more precision the precise spatiotemporal dynamics underlying freezing behavior. It would also be interesting to determine whether freezing that occurs in the clinical 'on' state (Almeida et al., 2002) shares similar EEG characteristics with FOG that occurs in the 'off' state. Furthermore, the spectral analysis of the dynamic process underlying the transition from walking to freezing may also contain clinical utility. The discovery of consistent underlying neural signature of FOG could lead to the utilization of EEG technology to predict episodes of FOG before they occur, offering a much-needed therapeutic intervention for this troubling symptom of PD.

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