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

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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),

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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 $0.6 \times 0.6$ 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