Clinical Neurophysiology 128 (2017) 463–471

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Motor preparation rather than decision-making differentiates Parkinson's disease patients with and without freezing of gait

John S. Butler [a,b,c,1], Conor Fearon [a,b,d,1], Isabelle Killane [a,b], Saskia M. Waechter [a,b], Richard B. Reilly [a,b,e,*], Timothy Lynch [d,*]

[a] Trinity Centre for Bioengineering, Trinity College, The University of Dublin, Dublin 2, Ireland
[b] School of Engineering, Trinity College, The University of Dublin, Dublin 2, Ireland
[c] School of Mathematical Sciences, Dublin Institute of Technology, Kevin Street, Dublin, Ireland
[d] Dublin Neurological Institute at the Mater Misericordiae University Hospital, Dublin 7, Ireland
[e] School of Medicine, Trinity College, The University of Dublin, Dublin 2, Ireland

ARTICLE INFO

Article history:
Accepted 18 December 2016
Available online 28 December 2016

Keywords:
Parkinson's disease
Freezing of gait
Decision making
Motor preparation
EEG
Current source density
Event related potentials

HIGHLIGHTS

- Analysis and theoretical framework allowing interpretation of decision and motor preparation signals.
- Differences in motor preparation potentials between PD with and without FOG but not decision signals.
- The amplitude of the motor preparation potential correlates with Frontal Assessment Battery scores.

ABSTRACT

Objective: Freezing of gait (FOG) is a brief, episodic phenomenon affecting over half of people with Parkinson's disease (PD) and leads to significant morbidity. The pathophysiology of FOG remains poorly understood but is associated with deficits in cognitive function and motor preparation.
Method: We studied 20 people with PD (10 with FOG, 10 without FOG) and performed a timed response target detection task while electroencephalographic data were acquired. We analysed the data to detect and examine cortical markers of cognitive decision making (P3b or centroparietal positivity, CPP) and motor readiness potential. We analysed current source density (CSD) to increase spatial resolution and allow identification of distinct signals.
Results: There was no difference in the P3b/CPP response between people with PD with and without FOG, suggesting equivalent cognitive processing with respect to decision-making. However, the FOG group had significant difference with an earlier onset and larger amplitude of the lateralized readiness potential. Furthermore, the amplitude of the lateralised readiness potential correlated strongly with total Frontal Assessment Battery score.
Conclusions: The difference in lateralized readiness potentials may reflect excessive recruitment of lateral premotor areas to compensate for dysfunction of the supplementary motor area and resultant loss of automatic motor control. This early, excessive recruitment of frontal networks occurs in spite of equivalent motor scores and reaction times between groups.
Significance: The saturation of frontal processing mechanisms could help explain deficits in attentional set-shifting, dual-tasking and response inhibition which are frequently reported in FOG.

1. Introduction

Freezing of gait (FOG) 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). This paroxysmal symptom affects over half of people with

* Corresponding authors at: Trinity Centre for Bioengineering, The School of Medicine and the School of Engineering, Trinity College Dublin, Ireland (R.B. Reilly). Dublin Neurological Institute at the Mater Misericordiae University Hospital, 57 Eccles Street, Dublin 7, Ireland (T. Lynch).
E-mail addresses: rbreilly@tcd.ie (R.B. Reilly), tlynch@dni.ie (T. Lynch).
[1] J.S. Butler and C. Fearon contributed equally to the paper.

http://dx.doi.org/10.1016/j.clinph.2016.12.019
1388-2457/

Parkinson's disease (PD) over time (Giladi and Nieuwboer, 2008) and is closely associated with falls and admissions to nursing homes (Bloem et al., 2004). The pathophysiology of FOG remains poorly understood but freezing is closely associated with deficits in motor parameters, such as stride time, gait symmetry and rhythmicity (Killane et al., 2015) and cognitive impairment, especially, executive dysfunction (Maruyama and Yanagisawa, 2006; Amboni et al., 2008). Executive function is impaired in PD with FOG (FOG+) compared to those without FOG (FOG−). There are specific deficits in divided attention (Spildooren et al., 2010; Tard et al., 2014), set-shifting (Shine et al., 2013b), response inhibition (Cohen et al., 2014) and conflict resolution (Vandenbossche et al., 2012). Although cognitive dysfunction probably plays a significant role in its pathogenesis, objective quantitative measures of cognitive dysfunction in FOG are lacking. Neuroimaging studies in FOG cannot directly infer cognitive dysfunction and standard neurocognitive batteries such as the Montreal Cognitive Assessment (MoCA) and Frontal Assessment Battery (FAB) remain a relatively insensitive way to assess cognition. Electroencephalography (EEG) can be helpful in the study of freezing as the high temporal resolution allows accurate detection of brief neural responses detectable during paroxysms of freezing (Handojoseno et al., 2012, 2013; Thevathasan et al., 2012; Singh et al., 2013; Shine et al., 2014; Toledo et al., 2014; Velu et al., 2014). However, no EEG study in FOG has examined decision-making tasks which require motor output.

Event-related potentials (ERPs) are EEG surface potentials generated by a psychophysiological event, often a sensory stimulus, and are electrophysiological indicators of cognitive function. The "classical" P3b potential is a large-amplitude global reference ERP with a positive peak around 300–600 ms following a task-relevant stimulus (Sutton et al., 1965; Polich, 2007). More recently, the equivalent term "centroparietal positive potential" (CPP), generated by different analysis methods, has been used to describe this potential (O'Connell et al., 2012). The precise neural substrates of the P3b/CPP are not understood. However, P3b abnormalities correlate with executive dysfunction (Kindermann et al., 2000), response conflict and response inhibition (Groom and Cragg, 2015). All of which probably have a central role in FOG (Vandenbossche et al., 2012; Cohen et al., 2014). Recently, the P3b has also been shown to be involved in decision making in response to sensory stimuli (Twomey et al., 2015). This signal increases in amplitude as sensory information accumulates before, reaching a threshold at which a response is executed. P3b latency is increased in PD compared with healthy controls and correlates with disease severity and cognitive dysfunction (O'Donnell et al., 1987; Toda et al., 1993; Katsarou et al., 2004; Matsui et al., 2007). No study to date has examined whether differences in these measures exist between FOG+ and FOG− in PD.

ERP analysis can also be used to study the electrical correlates of motor preparation. The readiness potential, also known as the Bereitschaftspotential, is a movement-related cortical potential preceding voluntary or goal-directed movement (for a review of movement potentials in Parkinson's see (Georgiev et al., 2016)). It reflects electrical activity in the motor cortex, premotor area (PMA) and supplementary motor area (SMA) (Shibasaki and Hallett, 2006). This negative potential has to reach a certain threshold before movement or EMG activity is triggered. Readiness potentials for self-initiated, but not externally triggered, movements are attenuated in PD and correlate with reduced regional blood flow in the SMA (Jahanshahi et al., 1995). This SMA dysfunction may be compensated for by lateral premotor activation (Cunnington et al., 1995). Dysfunction of the SMA may be integral to the pathophysiology of FOG (Nutt et al., 2011), however there has been no study of readiness potentials in FOG to date.

Freezing is characterised not only by the arrest of movement but also by the initial intention to move (Nieuwboer and Giladi, 2013). For this reason, we hypothesized that motor initiation in FOG− and FOG+ will be different. Even simple motor tasks require both decision-making and motor preparation. Of note, freezing is associated with both cognitive and motor deficits. We performed an EEG-based analysis on FOG− and FOG+ to simultaneously analyse cognitive ERPs and motor readiness potentials. We hoped to deduce whether impairments in cognitive processing or motor initiation (or both) differentiates FOG− from FOG+. In order to separate the decision making and motor preparation cortical signals, we used a spatial filter known as the current source density (CSD) to increase the spatial resolution of the data. This method employs a local reference point, thus reducing interference from remote sources and current diffusions through the skull, leading to better spatial resolution compared with the global reference used in standard ERP approaches. CSD has been shown to separate these two signals in healthy participants (Kelly and O'Connell, 2013). These methods are described in detail below and we highlight their importance in ERP analysis in PD.

2. Methods

2.1. Participants

We recruited 20 people with PD (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. 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). FOG status was recorded for all patients based on by observation of 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., 2008). All participants had normal corrected vision and were tested in the "on"-state.

2.2. Stimuli and procedure

Participants were seated comfortably and performed a two-stimulus oddball task consisting of a flashing green cross presented randomly on a 55″ LCD monitor. This visual stimulus consisted of either vertical (standard) or 45° rotated (target) green crosses presented for 500 ms on a complex background. 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 with their right hand as soon as the target stimulus was seen. The standard and target stimuli were presented with random interstimulus intervals of between 250 and 750 ms. A single trial of 300 s was performed for each participant. Participants were instructed to minimize head movements during the trial.

2.3. Data acquisition

We recorded synchronous electroencephalographic (EEG) data in all participants using a 128-channel Biosemi Active Two EEG acquisition system during the task. Electrodes were placed using an adapted extension of "10–20" arrangement according to the Biosemi designed equiradial system (http://www.biosemi.com/