Neurobiology of Disease 108 (2017) 288–297

Contents lists available at ScienceDirect

Neurobiology of Disease

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

Subthalamic neural entropy is a feature of freezing of gait in freely moving people with Parkinson's disease

Judy Syrkin-Nikolau[a], Mandy Miller Koop[a], Thomas Prieto[a], Chioma Anidi[a], Muhammad Furqan Afzal[a], Anca Velisar[a], Zack Blumenfeld[a], Talora Martin[a], Megan Trager[a], Helen Bronte-Stewart[a,b,*]

[a] Stanford University, Department of Neurology and Neurological Sciences, Rm H3136, SUMC, 300 Pasteur Drive, Stanford, CA 94305, USA
[b] Stanford University, Department of Neurosurgery, 300 Pasteur Drive, Stanford, CA 94305, USA

ARTICLE INFO

Keywords:
Parkinson's disease
Sample Entropy
Complexity
Deep brain stimulation
Beta band oscillations
Subthalamic nucleus
Freezing of gait

ABSTRACT

The goal of this study was to investigate subthalamic (STN) neural features of Freezers and Non-Freezers with Parkinson's disease (PD), while freely walking without freezing of gait (FOG) and during periods of FOG, which were better elicited during a novel turning and barrier gait task than during forward walking. Methods: Synchronous STN local field potentials (LFPs), shank angular velocities, and ground reaction forces were measured in fourteen PD subjects (eight Freezers) off medication, OFF deep brain stimulation (DBS), using an investigative, implanted, sensing neurostimulator (Activa® PC + S, Medtronic, Inc.). Tasks included standing still, instrumented forward walking, stepping in place on dual forceplates, and instrumented walking through a turning and barrier course. Results: During locomotion without FOG, Freezers showed lower beta (13–30 Hz) power ($P = 0.036$) and greater beta Sample Entropy ($P = 0.032$), than Non-Freezers, as well as greater gait asymmetry and arrhythmicity ($P < 0.05$ for both). No differences in alpha/beta power and/or entropy were evident at rest. During periods of FOG, Freezers showed greater alpha (8–12 Hz) Sample Entropy ($P < 0.001$) than during walking without FOG. Conclusions: A novel turning and barrier course was superior to FW in eliciting FOG. Greater unpredictability in subthalamic beta rhythms was evident during stepping without freezing episodes in Freezers compared to Non-Freezers, whereas greater unpredictability in alpha rhythms was evident in Freezers during FOG. Non-linear analysis of dynamic neural signals during gait in freely moving people with PD may yield greater insight into the pathophysiology of FOG; whether the increases in STN entropy are causative or compensatory remains to be determined. Some beta LFP power may be useful for rhythmic, symmetric gait and DBS parameters, which completely attenuate STN beta power may worsen rather than improve FOG.

1. Introduction

Freezing of gait[1] (FOG) is a common and debilitating symptom of Parkinson's disease[2] (PD), affecting up to 47% of patients (Giladi et al., 1992; Macht et al., 2007). Patients often display FOG while turning, in small spaces, and while walking through doorways (Giladi et al., 1992; Schaafsma et al., 2003), however, the forward walking assessment that is used during the Unified Parkinson's disease Rating Scale[3] (UPDRS) does not include these situations. For this reason, FOG can be a difficult symptom to elicit in a research or clinical setting.

Subthalamic nucleus[4] (STN) local field potential[5] (LFP) recordings demonstrate oscillatory neuronal activity in both the alpha (8–12 Hz) and beta (13–30 Hz) bands in the resting state in PD (Brown et al., 2001; Bronte-Stewart et al., 2009; Hammond et al., 2007; Kühn et al.,

* Corresponding author at: Stanford University, Department of Neurology and Neurological Sciences, Rm H3136, SUMC, 300 Pasteur Drive, Stanford, CA 94305, USA.
E-mail addresses: jsyrkinn@stanford.edu (J. Syrkin-Nikolau), mkoop@stanford.edu (M.M. Koop), tprieto@stanfordhealthcare.org (T. Prieto), canidi@stanford.edu (C. Anidi), furqan@stanford.edu (M.F. Afzal), avelisar@stanford.edu (A. Velisar), zblumenf@usc.edu (Z. Blumenfeld), talora@stanford.edu (T. Martin), mht2132@cumc.columbia.edu (M. Trager), hbs@stanford.edu (H. Bronte-Stewart).

[1] Freezing of gait = FOG.
[2] Parkinson's disease = PD.
[3] Unified Parkinson's disease Rating Scale = UPDRS.
[4] Subthalamic nucleus = STN.
[5] Local field potential = LFP.

http://dx.doi.org/10.1016/j.nbd.2017.09.002
Received 7 June 2017; Received in revised form 24 August 2017; Accepted 5 September 2017
Available online 07 September 2017
0969-9961/

2006; Matzner et al., 2016; Ray et al., 2008; Shreve et al., 2017; Whitmer et al., 2012; Wingeier et al., 2006). Both alpha and beta band oscillations have been linked to a sensorimotor rhythm (Bevan et al., 2002; Chen et al., 2007; Kühn et al., 2005) in the basal ganglia, and the cortical alpha rhythm has also been associated with executive function and attentional tasks (Horn et al., 2017; Jahanshahi, 2013). In addition to changes in neuronal firing rates and oscillatory activity in the basal ganglia in PD, several studies have highlighted the emergence of aperiodic fluctuations in neuronal firing patterns in Parkinsonism that are better quantified by non-linear signal analyses such as entropy, a measure of the predictability of a pattern in a time series (Cruz et al., 2009; Dorval, 2008; Gatev et al., 2006; Rodríguez et al., 2003). Evidence of increased single unit neuronal entropy in basal ganglia nuclei has been demonstrated in animal and computational models of Parkinsonism, and has been supported by similar findings intra-operative studies in PD human subjects. Entropy decreased after therapeutic STN DBS in both Parkinsonian rodents and primates, and after therapeutic doses of apomorphine in PD subjects (Dorval et al., 2008; Dorval and Grill, 2014; Lafreniere-Roula et al., 2010).

Entropy in the electroencephalogram (EEG) may be a useful feature to distinguish the EEG of PD subjects from controls (Liu et al., 2017) and changes in multiscale entropy in the EEG have been associated with an increased risk of developing dementia in PD (Bertrand et al., 2016). Recently changes in beta entropy in the ambulatory EEG have been associated with the transition from walking to freezing in PD subjects with FOG (Handojoseno et al., 2015) but to our knowledge there is no information about how basal ganglia LFP entropy relates to FOG in PD.

The limited knowledge of the role of basal ganglia neural signals in FOG is partly due to the challenge of accessing deep brain circuitry to measure neural signals in freely moving PD subjects, while they perform gait tasks that may elicit FOG. Until recently, STN LFPs could only be recorded in the intra- or peri-operative period when the subjects were stationary and attached to cables and research involving untethered, freely moving subjects was limited (Singh et al., 2013; Thevathasan et al., 2012; Toledo et al., 2014). It is now possible to record neural signals from an implanted sensing neurostimulator (Activa® PC + S, Medtronic Inc., FDA IDE approved) in freely moving human PD subjects (Neumann et al., 2016; Quinn et al., 2015; Rosa et al., 2015; Blumenfeld et al., 2017). In this investigation, synchronized STN LFPs and quantitative kinematics were recorded during the resting state (standing), a forward walking task, a stepping in place task on dual forceplates (Nantel et al., 2011), and during a novel gait task (the Turning and Barrier Course) designed to elicit FOG. The main goals of this study were to determine whether there were linear and/or non-linear neural features that identified Freezers from Non-Freezers at rest, and when walking without freezing, and that identified FOG in Freezers.

2. Materials and methods

2.1. Human subjects

Fourteen PD subjects (9 male) consented to participate in the study, which was approved by the Food and Drug Administration (FDA) and the Stanford School of Medicine Institutional Review Board (IRB). All subjects had bilateral implantation of DBS leads (model 3389, Medtronic, Inc.) in the sensorimotor region of the STN using a standard functional frameless stereotactic technique and multi-pass microelectrode recording (Bronte-Stewart et al., 2010; Quinn et al., 2015; Shreve et al., 2017). The leads were connected to an implanted investigative neurostimulator (Activa® PC + S, Medtronic, Inc. FDA Investigator Device Exemption (IDE) and IRB-approved). The preoperative selection criteria, surgical technique, and assessment of subjects have been previously described (Bronte-Stewart et al., 2010; Quinn et al., 2015). Long-acting dopaminergic medication was withdrawn over 24 h (72 h for extended release dopamine agonists), and short-acting medication was withdrawn over 12 h before all study visits. Subjects had been OFF DBS for at least 87 min. Five out of fourteen subjects were excluded for the neural portion of the analysis. Three were excluded due to intermittent tremor during the resting and movement states of the tasks, which may alter alpha/beta band oscillatory power, and which could alter the LFP analysis for reasons not related to gait (Bronte-Stewart et al., 2009; Qasim et al., 2016; Shreve et al., 2017; Wang et al., 2005); two akinetic rigid subjects had identifiable beta peaks in the resting state at the initial programming visit prior to activating the STN DBS system, but were excluded as beta peaks were not evident at subsequent visits (Trager et al., 2016), see Fig. S1, Supplementary information. Subjects were classified as a Freezer or Non-Freezer by the clinical history of a subject's symptoms and/or if the subject displayed freezing behavior pre-operatively or during the tasks.

2.2. Experimental protocol

Recordings were collected in the Stanford Human Motor Control and Balance Laboratory, off medication. Subjects completed three tasks: (1) Stepping in Place[6] (SIP); (2) Forward Walking[7] (FW); (3) Turning and Barrier Course[8] (TBC), Fig. 1. The SIP task was performed at the time of initial programming before STN DBS was activated in 12/14 subjects. Two subjects performed the SIP task at 6 months post initial programming. The FW and TBC tasks were performed on the same day, after a mean of 14.6 months (range 6–27 months) of STN DBS. All tasks were performed at least 87 min after DBS had been turned off. We have demonstrated that, after 6 and 12 months of DBS there was no statistical difference in the off therapy PSD from recordings taken right after DBS was turned off and 1 h later (Trager et al., 2016).

All three tasks started with 30 s of quiet standing. During the SIP task, which has been validated with the Freezing of Gait Questionnaire (FOG-Q), the subject performed alternating stepping on dual forceplates, at a self-selected pace for 100 s (Nantel et al., 2011). Ground reaction forces were captured at 100 Hz and 1000 Hz with two force places on the Smart Equitest or Bertec system, respectively (NeuroCom Inc., Clackamas, OR, Bertec Corporation, Columbus, OH, USA). For the FW task, subjects walked forwards for 10 m, turned around and returned, and repeated this for a total of 40 m of straight walking. The average duration of the forward walking task was 27.29 s (range 24–58 s). The TBC is a novel forward walking and turning course, around and through a narrow opening formed by room dividers, which were two meters high, Fig. 1B, D. The TBC was enclosed by a row of dividers on one side and a wall on the other, Fig. 1B. After the initial standing resting state period, the subject was instructed to sit on the chair. On the 'Go' command, the subject was instructed to stand up and walk around the dividers in an ellipse twice, and then to walk in a 'figure eight', twice around and through the opening between the dividers, before sitting down again, Fig. 1D. The subject was then instructed to repeat the task in the opposite direction, for a total of four ellipses and four figures of eight. The average total duration of the TBC was 140.08 s (range 90–331 s). During SIP, freezing behavior is described as freezing episodes[9] (FEs), and during FW and TBC, where the patient is performing forward walking, freezing behavior is described as FOG.

2.3. Data acquisition and analysis

Subthalamic LFPs were recorded from electrode pair 0–2 or 1–3 of the DBS lead. The electrode pair, 1–3 was chosen if ECG artifact was present during 0–2 recordings, or if electrode 2 was chosen for clinical

[6] Stepping in place = SIP.
[7] Forward walking = FW.
[8] Turning in barrier course = TBC.
[9] Freezing episodes = FEs.