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Subthalamic Neural Entropy is a feature of Freezing of Gait in freely moving people with Parkinson's disease

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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.

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Declaration of interest

None of the authors have any conflicts of interest.

Keywords

Parkinson's disease; Sample Entropy; Complexity; deep brain stimulation; beta band oscillations; subthalamic nucleus; freezing of gait

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 P J Neurosci 2001, Bronte-Stewart et al., 2009; Hammond, Bergman, & Brown, 2007; Kühn, Kupsch, Schneider, & Brown, 2006; Matzner, Moran, Erez, Tischler, & Bar-Gad, 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, Magill, Terman, Bolam, & Wilson, 2002; Chen, Wu, Sheu, Chow, & Lin, 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, Neumann, Degen, Schneider, & Kühn, 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, Mallet, Magill, Brown, & Averbeck, 2009; Dorval, 2008; Gatev, Darbin, & Wichmann, 2006; Rodríguez, Pereda, González, Abdala, & Obeso, 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 & 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 has been associated with the

[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

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 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 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, de Solages, & Bronte-Stewart, 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.

Materials and methods

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, Louie, Batya, & Henderson, 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 minutes. 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, Aziz, Stein, & Liu, 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 Figure 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.

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), Figure 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 minutes 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 hour later (Trager et al., 2016),

All three tasks started with 30 seconds 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 seconds (Nantel et al., 2011). Ground reaction forces were captured at 100Hz with two force places on the Smart Equitest or Bertec system (NeuroCom Inc, Clackamas, OR, Bertec Corporation, Columbus, OH, USA). For the FW task, subjects walked forwards for 10m, turned around and returned, and repeated this for a total of 40m of straight walking. The average duration of the forward walking task was 27.29 seconds (range 24–58 seconds). 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 seconds (range 90–331 seconds). 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.

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 programming (Quinn et al., 2015), see supplementary information and Table S1 for details of the recording electrode pairs for each subject. Pre-amplified LFP signals were high-pass filtered at 0.5 Hz and low-pass filtered at 100 Hz within the device. All LFP data were sampled at 422 Hz (10-bit resolution). Uncompressed LFP data were extracted via telemetry using the Activa® PC+S tablet programmer and transferred to a computer for offline analysis in MATLAB (version 8.2, The Mathworks,

[6]Stepping in Place = SIP
[7]Forward Walking = FW
[8]Turning in Barrier Course = TBC
[9]Freezing Episodes = FEs

Inc., Natick, MA, USA). Leg or shank angular velocity was measured using wearable inertial measurement units[10] (IMUs, APDM, Inc., Portland, OR, USA), which were positioned in a standardized manner for all subjects and all tasks on the top of the feet, on both shanks, and on the lumbar, and chest trunk regions (six IMUs per subject). The angular velocity signals from the IMU tri-axial gyroscope were sampled at 128 Hz. Care was taken to align the sensor on the shank, so that the positive Z-axis was lateral and picked up the gait angular velocity in the sagittal plane. The data were filtered using a 0 phase 8th order low pass Butterworth filter with a 9Hz cut-off frequency and a principal components analysis was used to align the angular velocity with the sagittal plane. Using the aligned Z angular velocity, the beginning of the swing phase (positive slope zero crossing), end of swing phase (subsequent negative slope zero crossing), and heel strike (first negative peak following the end of the swing phase) were identified. From these times, swing and stride times were calculated. The kinematic signals were acquired concurrently, using a data acquisition interface (Power1401) and Spike software (version 2.7, Cambridge Electronic Design, Ltd., Cambridge, England).

The synchronization of neural and kinematic recordings, using internal and external instrumentation, respectively, was achieved by administering a few seconds of 20 Hz/1.5 V neurostimulation through either DBS lead. The signal artifact was detected concurrently by the implanted system and Spike software, the latter system recording the electroencephalography stimulation artifact using surface electrodes attached to the skin (one on the forehead and one above the implanted neurostimulator), which was recorded at 1 kHz. The files were then co-registered in MATLAB during offline analysis (Quinn et al., 2015). Spectrograms were generating using a short-time Fourier transform, with a 1 second Hanning window and a 0.5 second overlap, creating a frequency resolution of 1 Hz. PSDs were calculated using the Welch method with the same window and overlap parameters. Power was summed in the beta and alpha bands. The predictability of the LFPs (band-pass filtered between 8–12 Hz for alpha and 13–30 Hz for beta) was analyzed using Sample Entropy[11] (SampEn), a nonlinear measure suitable for physiological time series. SampEn may be a more consistent measure and more suitable to shorter time series data than approximate entropy, partially due to the elimination of counting self matches (Richman & Moorman, 2000). SampEn is calculated as the negative logarithm of the estimated conditional probability that if consecutive subseries of length m are similar according to some preset tolerance r, the consecutive subseries of length $m+1$ will be similar too. Mathematically, it is defined as:

$$SampEn\,(m, r, N) = -\ln\left[A^{m+1}(r)/A^{m}(r)\right]$$

Where $A^{m+1}(r)$ represents the number of vector pairs (within the time series) of length $m+1$ whose mutual distance is less than r, and $A^{m}(r)$ equals the number of vector pairs (within the time series) of length m whose mutual distance is less than r. Here the length of the vector pairs, m, denotes the embedding dimension. Chebyshev distance was used to get the mutual

[10]Inertial measurement unit = IMU
[11]Sample Entropy = SampEn

distance between the vector pairs. For this study, the parameters m and r were set to 4 and 20 percent of the standard deviation of the data respectively (Bruce, Bruce, & Vennelaganti, 2009; Richman & Moorman, 2000; Yuvaraj & Murugappan, 2016).

Experiments were also monitored by video recordings (30 frames per second). FOG in the FW and TBC tasks were identified in the video recordings by a neurologist as a change from the subject's forward walking pattern that included shortened, faster steps (festination) and periods of no forward motion. The FEs were verified by confirming visual changes in amplitude, wavelength, and/or regularity of the shank angular velocity traces. FEs during SIP were identified using a validated computerized algorithm (Nantel et al., 2011). Arrhythmicity and asymmetry during both FW and SIP were calculated using periods of walking or stepping when the subject was not freezing. According to previous studies, asymmetry and arrhythmicity are defined as (Nantel et al., 2011; Plotnik, Giladi, Balash, Peretz, & Hausdorff, 2005; Plotnik, Giladi, & Hausdorff, 2007).:

$$Asymmetry = 100 \times |ln(SSWT/LSWT)|, \text{(SSWT} - \text{shorter and LSWT} - \text{longer mean swing time)}$$

$$Arrhythmicity = the\ mean\ stride\ time\ coefficient\ of\ variation\ (CV)\ of\ both\ legs$$
(a greater stride time CV implies less rhythmic gait or stepping .)

Statistics

The main outcome variables were alpha/beta power and SampEn. Alpha/beta power varied across subjects sometimes by orders of magnitudes. Relative alpha and beta power was calculated by dividing the summed absolute alpha or beta power by the summed power in the 40–70Hz band during the resting state, and allowed comparison across subjects, whose raw signal magnitude can vary by one or two orders of magnitude, see supplementary information. The FW task was analyzed by excluding the turning periods at the end of the 10m of straight walking. As a result, each FW task had 4 trials. Similarly, as the TBC task had four trials, it was also analyzed as four separate time periods for each patient. The SIP task had one trial per patient. Asymmetry and arrhythmicity were assessed individually using a linear mixed effect model in Freezers and Non-Freezers during FW, while a one-way ANOVA was used in SIP. A one way ANOVA and a Kruskal-Wallis test by ranks was also used to determine if alpha or beta power and SampEn changed significantly between Freezers and Non-Freezers in SIP, while a linear mixed effects model was used for both TBC and FW, in order to account for the four trials. Freezer or Non-Freezer type was a fixed effect and a factor variable with 2 levels (Freezer and Non-Freezer). Subject STN was a random effect, and a random intercept was used in the model. Residuals were assessed for homoscedasticity and normality, and all statistical assumptions were met.

The relationship between power and SampEn was assessed by running an exponential fit on all subjects (Freezers and Non-Freezers) for each task. The equation, F statistic, Adjusted R^2, and P values are reported. For the FW and TBC tasks, trials were averaged into one value so as not to skew the fit towards any one subject's values. Student's t-tests were used

to compare age, disease duration, pre-op and post-op Unified Parkinson's disease Rating Scale (UPDRS).

Results

Gait tasks that elicited freezing behavior

Table 1 outlines the demographic characteristics and kinematic results of the two groups.

Subjects were off medication and OFF DBS for all tasks, see Methods. All fourteen subjects completed the Forward Walking (FW), Stepping in Place (SIP), and Turning and Barrier Course (TBC). Figure 2A–F demonstrates the gait patterns during the three tasks of a representative Freezer and Non-Freezer. The Non-Freezer did not demonstrate FOG in any of the tasks, Fig. 2B, D, F; the Freezer performed the FW task without any FOG, Fig. 2A but exhibited FOG during both the SIP and TBC tasks, Fig. 2C and E.

Table 2 demonstrates that among the eight Freezers, four exhibited freezing episodes (FEs) during FW, five during SIP, and seven during TBC. Among the tasks, the TBC tended to elicit the largest number of FEs per trial with the longest duration of FEs, although this was not powered to perform a statistical comparison. FW elicited the fewest and shortest duration FEs. Fig. 2G demonstrates where in the TBC FEs occurred; these were clustered at the turns and when the subject went through the narrow opening between the barriers. A few FEs occurred at the sit-to-walk, or walk-to-sit transitions. In all but one Freezer, the figure eight section of the TBC task elicited more freezing behavior than the ellipses, Table 3.

Decreased beta power and increased beta sample Entropy distinguish Freezers from Non-Freezers during stepping without FOG

Beta (13 – 30 Hz) LFP power and beta SampEn differentiated Freezers (five subjects) from Non-Freezers (four subjects) while they were stepping in place without evidence of FOG (N=18 STNs). Figure 3 demonstrates resting state, stepping in place, and forward walking kinematics, LFP spectrograms, and power spectral density diagrams (PSDs), from a representative Freezer STN (Fig. 3A, B, C, G, H, I) and representative Non-Freezer STN (Fig. 3D, E, F, J, K, L). The Freezer STN demonstrated a greater attenuation of resting state beta power during stepping than the Non-Freezer STN, Fig. 3C and F.

The group data confirmed these findings, Table 4 and Figure S2 in supplementary information. During the SIP task (without FOG) there was lower relative beta power in the Freezer compared to Non-Freezer groups ($H(1) = 7.17$, $P = 0.036$), which resulted in a greater attenuation of resting state beta power in Freezers ($F(1, 15) = 28.37$, $P < 0.001$). The cadence and shank angular velocity were similar between groups, Table 4. Nonlinear signal analysis demonstrated that SampEn in the beta band was greater during SIP (without FOG) in Freezers compared to Non-Freezers ($H(1) = 4.61$, $P = 0.032$).

There were no differences in beta power or beta SampEn in the resting state or during FW (without FOG) between the Freezer and Non-Freezer groups. Neither alpha (8–12 Hz) band power nor alpha SampEn differentiated Freezers from Non-Freezers when stepping or walking without FOG. There was no difference in alpha power in the resting or movement

state between groups in both SIP and FW. Alpha band SampEn was lower than beta band SampEn in both the resting ($H(1) = 24.77$, $P < 0.001$) and movement ($H(1) = 14.29$, $P < 0.001$) states and was not significantly different between Freezers and Non-Freezers. Assessment of the TBC task revealed that there were not enough gait cycles without FEs in the Freezer group to allow a similar comparison of kinematic and neural signals between the groups during TBC without FOG.

Neural Analysis of Freezing of Gait (FOG)

Among Freezers, beta power was lower during FOG compared to during forward walking without FOG (N = 8 STNs, $F(1,51) = 14.45$, $P < 0.001$, Table 4). Freezers also showed increased alpha SampEn during FOG when compared to walking without FOG ($F(1, 51) = 7.67$, $P = 0.005$). Non-Freezers demonstrated lower alpha and beta power during TBC than during FW, even though they did not freeze (N = 7 STNs, $F(1,48) = 3.83$, $P < 0.05$, and $F(1,48) = 5.84$, $P = 0.02$ respectively) but there was no difference in alpha SampEn. Neither Freezers nor Non-Freezers showed any difference in beta SampEn during TBC compared to FW.

Gait Entropy is inversely correlated with beta, but not alpha band power

In FW, SIP, and TBC, there was an inverse relationship between beta power and beta SampEn across the whole group, Figure 4 ($P <0.001$ for all tasks). This was evident in the FW and SIP tasks when there was no FOG, and during TBC, which included FOG. There was no relationship between alpha power and alpha SampEn.

Freezers display more Arrhythmicity and Asymmetry than Non-Freezers during locomotion without freezing

During the FW task, without FOG, the gait arrhythmicity ($t = -2.19$, $P = 0.037$) and asymmetry ($t = -2.16$ and $P = 0.034$) were greater in the Freezer compared to the Non-Freezer group (Table 4). SIP showed the same trend and was significant in a previous, larger cohort (Nantel et al., 2011). Freezers, when stepping or walking without FEs, tended to exhibit greater asymmetry and arrhythmicity when performing the SIP task compared to the FW task. We did not compare performance of SIP to FW, as they were not performed on the same day.

Discussion

Subthalamic neural and kinematic recordings in freely moving people with Parkinson's disease distinguish Freezers from Non-Freezers

Synchronized neural and kinematic recordings from a fully embedded sensing neurostimulator (Activa® PC+S, Medtronic, Inc) and Bluetooth enabled wearable sensors (IMUs) have allowed this first of its kind investigation into the subthalamic neural features of FOG in freely moving, untethered PD subjects, off medication, OFF DBS. We have previously shown that freezing episodes (FEs) can be objectively measured during a stepping in place (SIP) task on dual forceplates and we validated this metric to the standard assessment of FOG, the FOG-Questionnaire (FOG-Q), (Nantel et al., 2011). In this study we introduced a novel forward walking task that also elicited FOG, a turning and barrier course

(TBC). Both SIP and the TBC elicited more and longer duration FEs than forty meters of forward walking. During the TBC, FOG occurred most commonly during turns and when walking through a narrow opening, which was similar to PD subjects' reports of when they freeze during daily life experiences: when turning, going through doorways, and/or in crowded spaces, (Schaafsma et al., 2003). The SIP task was performed before the DBS system was activated in the majority of subjects, whereas FW and the TBC were performed on the same day, after an average of 14.6 months of STN DBS. Therefore we did not compare metrics between the SIP and forward walking tasks.

During repetitive stepping, when subjects were not freezing, STN beta power was lower and beta sample entropy was higher in Freezers compared to Non-Freezers. There was a greater attenuation of resting state beta power in Freezers, when stepping. There was no difference between Freezers and Non-Freezers in alpha power and alpha entropy when stepping and no difference in any neural feature during the resting state. Among Freezers, STN beta power was lower and alpha sample entropy was higher during FOG compared to during forward walking without FOG. In Non-Freezers STN alpha/beta power was lower during the TBC compared to FW tasks but there was no difference in alpha/beta sample Entropy. Freezers exhibited more asymmetric and arrhythmic gait during forward walking without FOG, which has been demonstrated previously (Nantel et al., 2011; Plotnik et al., 2005, 2007).

Subthalamic neural entropy in local field potentials in freely moving PD subjects

Non-linear analysis of neurophysiological signals is a useful addition to linear analyses due to the non-linear dynamics inherent in neural activity in the brain (Darbin, Jin, Von Wrangel, et al., 2016; Darbin, Dees, Martino, Adams, & Naritoku, 2013; Darbin, Soares, & Wichmann, 2006). Entropy in time series data is a measure of the predictability of a metric over time, the higher the entropy the less predictable the metric (S. Pincus, 1995; S. M. Pincus, 1991; Steven M. Pincus, Gladstone, & Ehrenkranz, 1991; Richman & Moorman, 2000). Neuronal entropy of single unit firing patterns is thought to relate to the ability of neuronal ensembles to communicate information. Lower neuronal entropy reflects a greater predictability of the occurrence of single spikes, and has been hypothesized to be associated with successful information transfer, whereas higher neuronal entropy (less predictable spike occurrence) may be associated with in a lower fidelity of neuronal information transfer (Darbin, Jin, von Wrangel, et al., 2016; Dorval et al., 2008; Dorval, Kuncel, Birdno, Turner, & Grill, 2010; Guo, Rubin, McIntyre, Vitek, & Terman, 2008). Entropy of thermodynamic systems, relates to the number of possible states of a system, and is a measure of disorder (Gyftopoulos & Cubuķcu, 1997). Similarly high entropy of a neuronal ensemble has been related to a network with a large number of different possible patterns, and limited order and organization (Darbin et al., 2013). Neuronal entropy has become a useful metric for the known increase in oscillatory, irregular, and bursting firing patterns that occur in the Parkinsonian state (Bergman, Wichmann, Karmon, & DeLong, 1994; Darbin et al., 2006; Dorval, 2008; Rodríguez et al., 2003; Wichmann & DeLong, 2003), from which Darbin proposed the 'entropy hypothesis:' high entropy in neuronal firing patterns in the globus pallidus interna (GPi) is associated with Parkinsonism motor inhibition, while low GPi neuronal entropy is a feature predisposing increased motor selection (Darbin et al., 2013). This hypothesis was supported by evidence that animal and computational models of

Parkinsonism were associated with increased neuronal entropy in basal ganglia nuclei (Andres, Cerquetti, Merello, & Stoop, 2014; Cruz et al., 2009; Darbin, Jin, Von Wrangel, et al., 2016; Dorval & Grill, 2014; Dorval et al., 2010, 2010; Dorval, Panjwani, Qi, & Grill, 2009; Guo et al., 2008; Mallet et al., 2008; Sanders, Clements, & Wichmann, 2013). Therapeutic DBS in the animal model was associated with a decrease in pallidal entropy, which was not seen with non-therapeutic DBS (Dorval et al., 2008), and therapeutic doses of apomorphine decreased the entropy of STN spike trains in human subjects (Lafreniere-Roula et al., 2010). In human subjects GPi neuronal entropy was higher in PD subjects than in subjects with dystonia (Alam et al., 2016). It has been proposed that the increase in basal ganglia entropy in the Parkinsonian state induces errors in pallido-thalamic information processing (Dorval, Kuncel, Birdno, Turner, & Grill, 2010; Guo, Rubin, McIntyre, Vitek, & Terman, 2008; King, Anderson, & Dorval, 2016). However, in one small intra-operative study single neuronal entropy was lower than that of shuffled data in human PD basal ganglia nuclei (Lim et al., 2010).

To our knowledge this is the first report of changes in LFP power and entropy in the subthalamic LFP in freely moving PD freezers and non-freezers. According to the entropy hypothesis, the increased entropy demonstrated in Freezers compared to non-freezers during normal stepping and in Freezers themselves during periods of FOG may suggest greater errors in subthalamic outflow sensorimotor information processing in Freezers and motor inhibition, which may be reflected in abnormal gait patterns when not freezing, and during FOG.

In contrast to the entropy hypothesis outlined above, an alternate hypothesis has been proposed: high beta power and low beta entropy represent lower information transfer capacity in sensorimotor cortical rhythms and in the STN LFP at the onset and offset of movement (Baker, Kilner, Pinches, & Lemon, 1999; Murthy & Fetz, 1996). Complexity in STN beta band LFPs in PD subjects, was shown to be inversely related to limb akinesia and rigidity, such that greater complexity was related to less akinesia and rigidity (C. C. Chen et al., 2010). This alternative hypothesis would suggest that the low beta power and high beta entropy seen in the current study would lead to higher information transfer in sensorimotor rhythms that may reflect a compensatory attempt to overcome the abnormal gait in Freezers. Ambulatory EEG in PD Freezers has demonstrated an increase in central theta oscillations and a decrease in beta entropy in the transition to FOG, which led to the suggestion that cortical activity was ‘less complex’ when PD subjects transitioned from normal walking to freezing (Handojoseno et al., 2015). Further analysis of STN LFPs during transitions from walking to FOG will help to determine whether this is also seen in subcortical structures.

Subthalamic neural oscillations in Freezers during gait and FOG

In this study Freezers demonstrated decreases in beta power during stepping without freezing compared to Non-Freezers and no difference at rest. These results differ slightly from two previous studies; one demonstrated that resting state power in the high beta band (22–35 Hz) was greater in self-described Freezers compared to Non-Freezers (Toledo et al., 2014), and the other reported that Freezers had increased low beta and (12–22 Hz) power when walking (Singh et al., 2013). Both studies were performed shortly after DBS lead

placement, and it is possible that the micro-lesion effect may have played a role in the differences seen. Additionally, these studies divide beta into high and low beta frequency ranges, which we avoided in order to reduce the number of comparisons in our statistics.

Freezers demonstrated lower beta power and greater alpha SampEn during FOG compared to walking without FOG. Although the exact mechanisms remain to be discovered, alpha band activity has been implicated in freezing of gait in several previous studies. A decrease in alpha activity in attentional networks including the pedunculopontine nucleus, as well as an increase in EEG alpha band activity has been associated with freezing episodes (Shine et al., 2014; Thevathasan et al., 2012).

FOG has been associated with impairment in cognitive domains such as executive function and attention, as well as positively associated with stress (Giladi & Hausdorff, 2006; Lewis & Barker, 2009; Naismith, Shine, & Lewis, 2010; Nantel, McDonald, Tan, & Bronte-Stewart, 2012; Plotnik & Hausdorff, 2008; Yogev, Plotnik, Peretz, Giladi, & Hausdorff, 2007, Dagan, Herman, Mirelman, Giladi, & Hausdorff, 2017). It has also been shown that Freezers perform worse than Non-Freezers on visuospatial perception and reasoning tasks such as Block Design and Matrix Reasoning (Nantel, McDonald, Tan, & Bronte-Stewart, 2012). Alpha power in the STN has also been associated with frontal cortical and premotor areas (Horn et al., 2017), which are linked to attention and executive motor functions, especially those that are not well-rehearsed or are technically challenging (Jahanshahi, 2013). As the TBC is a more challenging task that may make more demands on attention and executive cognitive domains, the increase in alpha entropy during gait with freezing episodes may be a reflection of impaired information

There was an inverse relationship between STN beta power and beta SampEn, which has been demonstrated in single unit firing rats in Parkinsonian rats (Cruz et al., 2009). This was not seen in the alpha band and was not related to the entropy calculation. The two parameters measure different aspects of the LFP, one time invariant and one time variant

Limitations

The sample size in this study was small due to limited number of investigative sensing neurostimulators allocated to centers involved with the Activa® PC+S project (Blumenfeld et al., 2017; Quinn et al., 2015). As sensing neurostimulators become more readily available it will be possible to examine in more detail events such as transitions from normal walking/stepping to freezing and behavior within a freezing episode such as festination and complete stoppage of gait. The SIP task was performed before DBS was activated in the majority of subjects, whereas the FW and TBC tasks were performed on the same day after an average of 14.6 months of STN DBS. The difference in beta SampEn and between freezers and Non-Freezers demonstrated during SIP was not seen during FW, which may be due to differences between the tasks (no forward motion or optic flow in SIP) and/or may be related to changes from long-term STN DBS. Performing the stepping and forward walking tasks on the same day will help to refute or support the former possibility and longitudinal analyses of these tasks will be interesting to investigate the latter possibility.

Conclusions

This study demonstrated that a novel turning and barrier walking task successfully elicited FOG in Freezers and was superior to standard forward walking in this regard. For the first time, using synchronized subthalamic neural and kinematic recordings in freely moving PD subjects, we have demonstrated that neural entropy and lower power in the beta band identified Freezers from Non-Freezers during locomotion without FOG. When Freezers exhibited FOG, beta power was even lower and neural entropy increased in the alpha band. These results support the current neuronal entropy hypothesis and suggest that greater unpredictability in the STN beta rhythm may contribute to more asymmetric and arrhythmic gait and greater unpredictability in alpha rhythms may contribute to FOG. Conversely increased entropy in alpha/beta rhythms may be a compensatory attempt to improve the gait impairment. These results also suggest that deep brain stimulation parameters that result in complete attenuation of STN beta power may worsen rather than improve FOG.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- FOG was elicited with a novel turning and barrier gait task.
- Freezers showed lower beta band power and higher beta entropy than Non-Freezers during locomotion without freezing.
- Freezers showed increased alpha entropy during periods with freezing compared to periods without freezing.

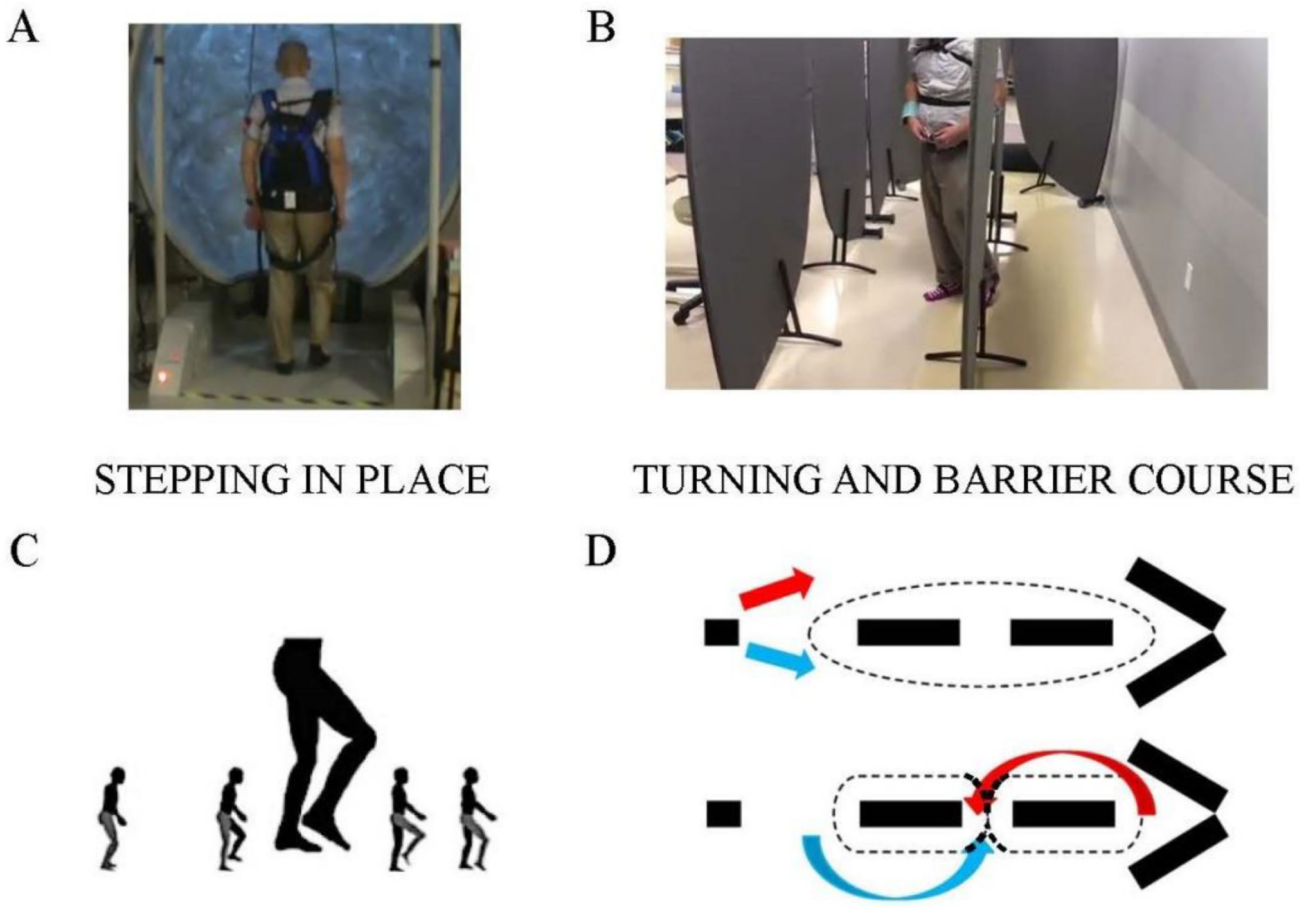

Figure 1.

(A) A subject performing the SIP task on dual force plates (Bertec Inc Columbus, OH) (B) Subject performing the TBC. A row of room dividers and a wall enclosed the course on either side. (C) Schematic diagram of a stepping cycle (D) Aerial view of the TBC showing the path of the subject, starting from either the right or left side. For each direction, the subject first performed two ellipses and then two 'figure eights.'

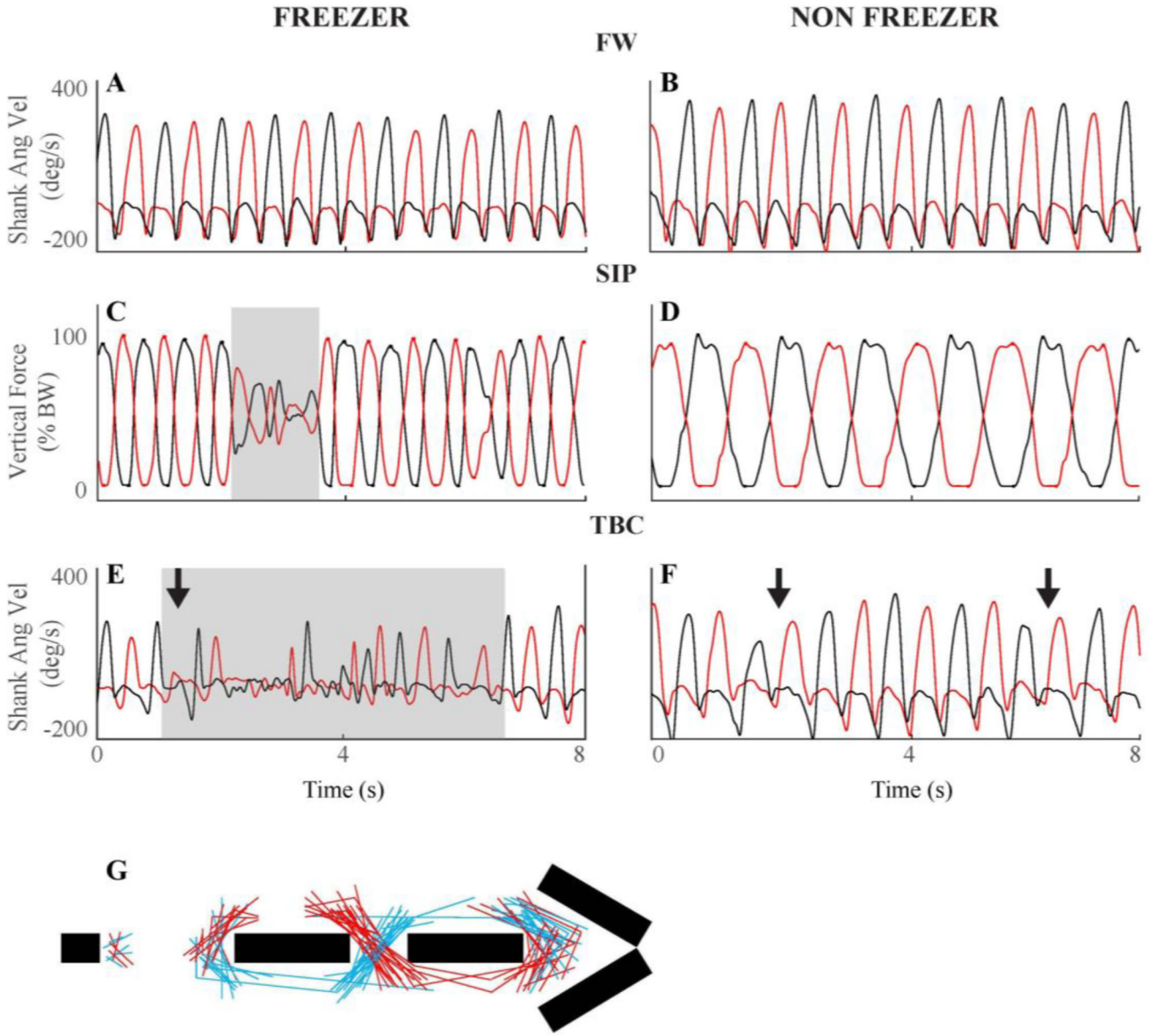

Figure 2.

Representative raw kinematic traces of a Freezer and Non-Freezer during FW (**A, B**), SIP (**C, D**), and TBC (**E, F**). Freezing behavior is shown in grey. Arrows show times where the subjects are turning (without FOG). **G**: aerial view of the TBC and the locations of freezing episodes while turning in the TBC to the left (blue lines) and to the right (red lines).

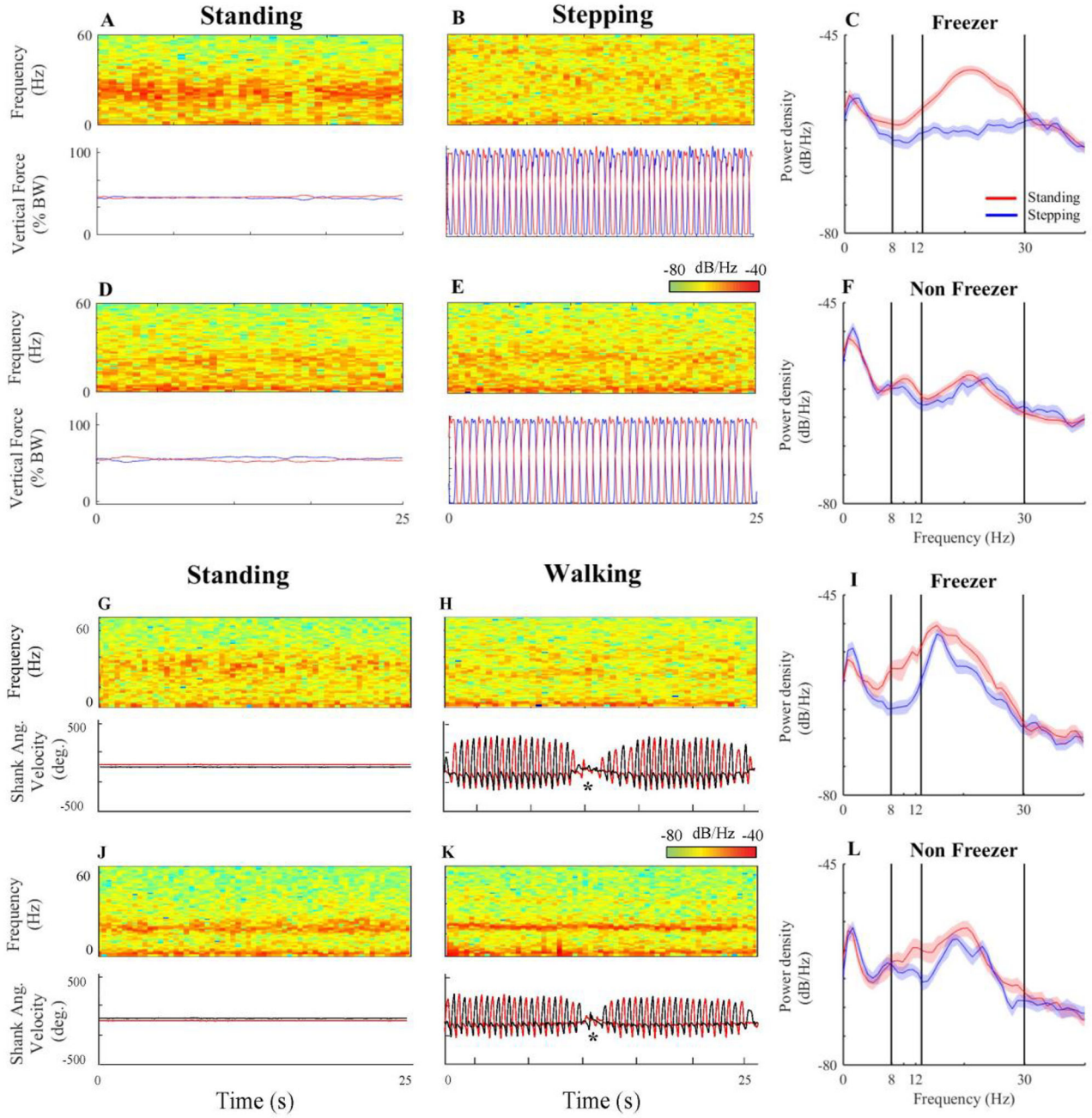

Figure 3.

Representative Freezer (**A, B, C, G, H, I**) and Non-Freezer (**D, E, F, J, K, L**) synchronized time-frequency STN LFP spectrograms, SIP cycles, FW cycles, and power spectral density diagrams (PSDs) during standing (red) and stepping or FW without FEs (blue). %BW = Percentage of bodyweight. * denotes subject turning around, not freezing.

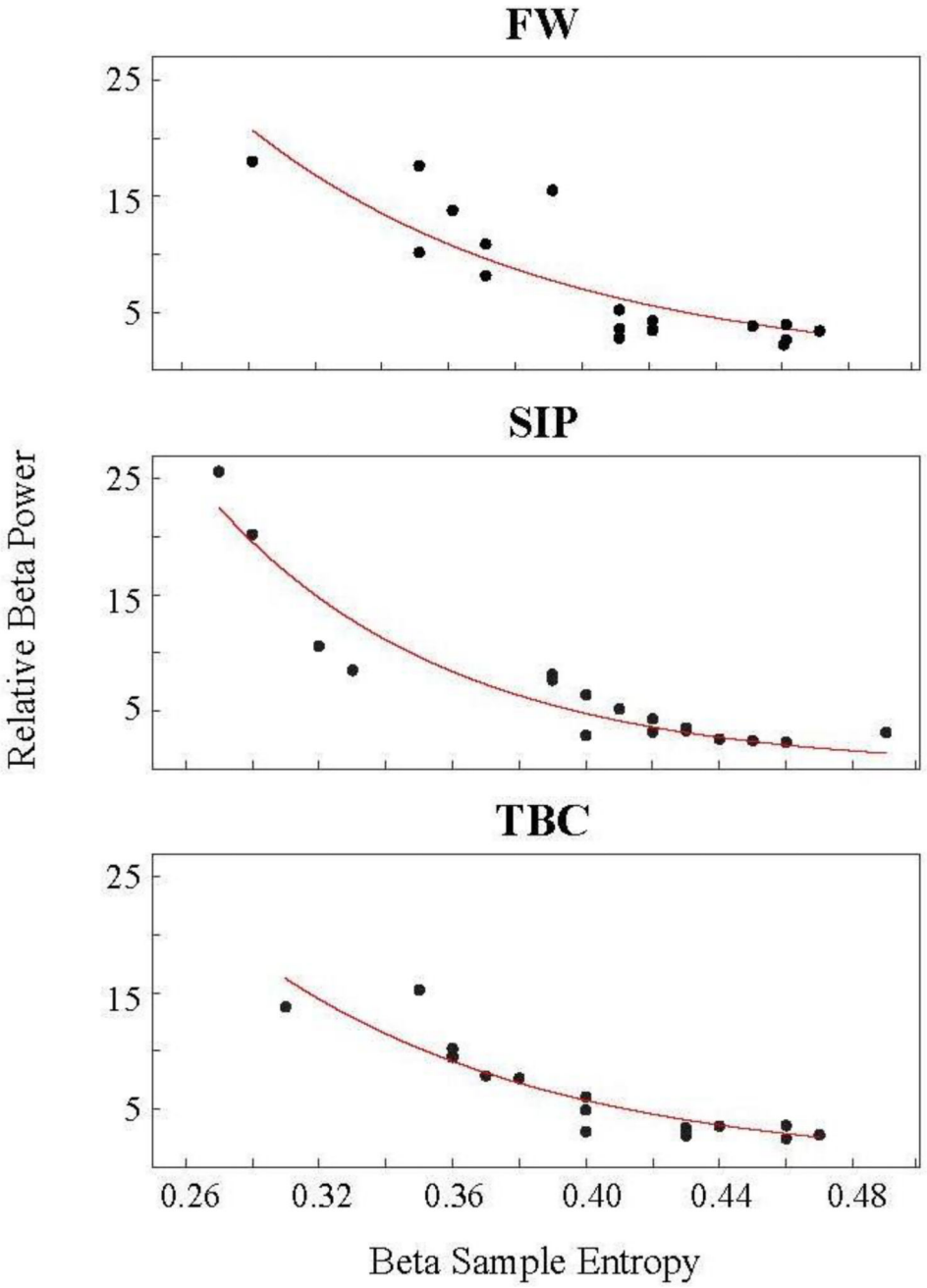

Figure 4.

Beta Sample Entropy (arbitrary units) and relative beta power have a negative exponential relationship during Forward Walking ($y=966.65e^{-13.49x}$, F=42.07, Adj R^2 =0.71, P < 0.001), Stepping in Place ($y=989.79e^{-13.07x}$, F=72.22, Adj R^2 =0.82, P < 0.001), and Turning and Barrier Course ($y=674.65e^{-12.74x}$, F=78.36, Adj R^2 =0.82, P < 0.001).

Table 1

Demographic information for Freezers and Non-Freezers.

	Freezers (n = 8)	**Non-Freezers (n = 6)**
Age	56.85 ± 8.55	62.56 ± 7.00
Disease duration	9.62 ± 3.16	10.91 ± 3.45
Pre-op UPDRS off	48.14 ± 8.55	43.50 ± 6.34
Pre-op UPDRS on	19.86 ± 8.47	15.75 ± 7.89

Table 2

Average number and duration of freezing episodes and percent of time spent freezing during Forward Walking (FW), Stepping in Place (SIP), and Turning and Barrier Course (TBC).

Task	Subjects with FEs/Freezers	Avg. Number of FEs per trial	Avg. Duration of FEs (s)	Avg. % of Task Freezing	Avg. Total Duration Freezing during Task (s)
FW	4/8	2 ± 0.82	1.54 ± 0.42	6.03% ± 2.88	3.25 ± 1.71
SIP	5/8	3 ± 0.71	9.54 ± 6.35	27.05% ± 17.15	28.22 ± 19.53
TBC	7/8	9.07 ± 6.86	5.80 ± 5.29	33.14% ± 29.08	97.52 ± 96.68

Table 3

Average percentage of time subject spent freezing during the ellipses and the ‘figure eights’ in the TBC.

Subject	Avg % Time Freezing during Ellipses	Avg % Time Freezing during Figure Eights
Pt 1	38.99	64.41
Pt 2	32.81	91.55
Pt 3	51.02	66.77
Pt 4	11.36	14.38
Pt 5	2.27	7.14
Pt 6	14.10	12.79
Pt 7	0	8.13

Table 4

Neural and kinematic data for freezers and Non-Freezers during Stepping in Place, Forward Walking, and Turning and Barrier Course.

	Freezers					Non-Freezers				
	SIP		FW		TBC	SIP		FW		TBC
	Stand	Move (w/o FEs)	Stand	Move (w/o FEs)	Move (w/ FEs)	Stand	Move	Stand	Move	Move
Alpha Power (arbitrary unit)	1.788 ± 1.632	0.845 ± 0.543	2.244 ± 1.870	1.710 ± 1.280	1.393 ± 0.901	1.251 ± 0.322	1.051 ± 0.511	4.288 ± 5.937	2.753 ± 3.261 ≠	1.890 ± 1.351 ≠
Alpha Sample Entropy	0.251 ± 0.002 ^	0.251 ± 0.002 ^	0.251 ± 0.003 ^	0.248 ± 0.007 ≠^	0.253 ± 0.003 ≠	0.253 ± 0.002 ^	0.253 ± 0.004 ^	0.251 ± 0.004 ^	0.247 ± 0.007 ^	0.250 ± 0.004
Beta Power (arbitrary unit)	13.783 ± 13.739	4.085 ± 2.077 *	12.672 ± 11.012	9.143 ± 6.835 ≠	7.321 ± 4.429 ≠	10.241 ± 6.216	11.258 ± 8.493 *	10.899 ±3.807	8.400 ± 5.529 ≠	6.993 ± 0.207 ≠
Beta Sample Entropy	0.377 ± 0.040 ^	0.407 ± 0.031 *^	0.373 ± 0.034 ^	0.380 ± 0.050 ^	0.377 ± 0.050	0.361 ± 0.040 ^	0.337 ± 0.062 *^	0.352 ± 0.037 ^	0.376 ± 0.053 ^	0.376 ± 0.052
Asymmetry (%)	14.35 ± 8.21		9.22 ± 6.25 *7		N/A	7.55 ± 6.23		3.63 ± 2.50 *77		N/A
Arrhythmicity (CV)	15.42 ± 11.63		3.91 ± 1.69 *7		N/A	5.44 ± 2.13		2.34 ± 1.04 *77		N/A
Cadence (steps/min)	107.67 ± 39.88		111.86 ± 16.81		N/A	114.46 ± 12.98		112.68 ± 6.84		N/A
Shank Ang. Velocity (deg/sec)	N/A		275.12 ± 58.88		N/A	N/A		294.48 ± 46.14		N/A

* Significant difference between freezers and non-freezers ($P < 0.05$),

^ Significant difference between TBC and FW ($P < 0.05$),

≠ Significant difference between alpha band SampEn and beta band SampEn ($P < 0.05$),

7 n = 32, each Freezer has 4 trials during FW,

77 n = 24, each Non-Freezer has 4 trials during FW

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