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Neuromodulation targets pathological not physiological beta bursts during gait in Parkinson's disease

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Abstract

Freezing of gait (FOG) is a devastating axial motor symptom in Parkinson's disease (PD) leading to falls, institutionalization, and even death. The response of FOG to dopaminergic medication and deep brain stimulation (DBS) is complex, variable, and yet to be optimized. Fundamental gaps in the knowledge of the underlying neurobiomechanical mechanisms of FOG render this symptom one of the unsolved challenges in the treatment of PD. Subcortical neural mechanisms of gait impairment and FOG in PD are largely unknown due to the challenge of accessing deep brain circuitry and measuring neural signals in real time in freely-moving subjects. Additionally, there is a lack of gait tasks that reliably elicit FOG. Since FOG is episodic, we hypothesized that dynamic features of subthalamic (STN) beta oscillations, or beta bursts, may contribute to the Freezer phenotype in PD during gait tasks that elicit FOG. We also investigated whether STN DBS at 60 Hz or 140 Hz affected beta burst dynamics and gait impairment differently in Freezers and Non-Freezers. Synchronized STN local field potentials, from an implanted, sensing neurostimulator (Activa® PC+S, Medtronic, Inc.), and gait kinematics were recorded in 12 PD subjects, off-medication during forward walking and stepping-in-place tasks under the following randomly presented conditions: NO, 60Hz, and 140Hz DBS. Prolonged movement band beta burst durations differentiated Freezers from Non-Freezers, were a pathological neural feature of FOG and were shortened during DBS which improved gait. Normal gait parameters, accompanied by shorter bursts in Non-Freezers, were unchanged during DBS. The difference between the mean burst duration between hemispheres (STNs) of all individuals strongly correlated with the difference in stride time between their legs but there was no correlation between mean burst duration of each STN and stride time of the contralateral leg, suggesting an interaction between hemispheres influences gait. These results suggest that prolonged STN beta burst durations measured during gait is an important biomarker for FOG and that STN DBS modulated long not short burst durations, thereby acting to restore physiological sensorimotor information processing, while improving gait.

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Declaration of interest

None of the authors have any conflicts of interest.

Supplementary Material

Supplementary data available in 'Supplementary Material' attached.

Keywords

Parkinson's disease; freezing of gait; deep brain stimulation; beta bursts; subthalamic nucleus

Introduction

Axial motor symptoms of Parkinson's disease (PD) such as freezing of gait (FOG) and postural instability are major reasons for loss of autonomy, falls, institutionalization, and death in patients with PD (Giladi *et al.*, 1992, 1997; Bloem *et al.*, 2004; Vervoort *et al.*, 2016). FOG frequently manifests as patients attempt to initiate walking, turning, and while navigating obstacles. It results in life-threatening falls or sudden immobility that renders patients helpless in dangerous situations such as crossing a street. The response of FOG to treatment is complex, variable, and has yet to be optimized. Both dopaminergic medication and subthalamic nucleus (STN) deep brain stimulation (DBS) at low and high frequencies may improve FOG, suggesting that neural mechanisms underlying FOG reside within the sensorimotor networks accessed by both medication and DBS (Moreau *et al.*, 2008; Sidiropoulos *et al.*, 2013; Annic *et al.*, 2014; Khoo *et al.*, 2014; Nantel and Bronte-Stewart, 2014; Vercruyssen *et al.*, 2014; Fasano *et al.*, 2015; Xie *et al.*, 2015). However, PD patients may still develop FOG while on medication and/or DBS even while the other cardinal motor signs of PD (tremor, rigidity, and bradykinesia) are well-treated (Lilleeng *et al.*, 2015). Fundamental gaps in the knowledge of the underlying neurobiomechanical mechanisms of FOG make this symptom one of the unsolved challenges in the treatment of PD.

Subcortical neural mechanisms of gait impairment and FOG in PD are largely unknown due to the challenge of accessing deep brain circuitry and measuring neural signals in freely-moving subjects and in the lack of gait tasks that reliably elicit FOG. Until recently, subcortical local field potentials (LFPs) could only be recorded in the intra- or peri-operative period, when PD subjects were stationary and attached to cables (Thevathasan *et al.*, 2012; Singh *et al.*, 2013; Toledo *et al.*, 2014). Additionally, there is a lack of knowledge concerning the contribution of each hemisphere to an axial task such as gait. Recent clinical reports demonstrated that unilateral STN DBS can be as efficacious as bilateral DBS for treating gait impairment but the neural mechanism underlying this finding remains unknown (Ricciardi *et al.*, 2015; Lizarraga *et al.*, 2017; Rizzone *et al.*, 2017).

Advances in concurrent sensing and stimulating technology from an implanted sensing neurostimulator (Activa® PC+S, Medtronic Inc.) have made it possible to record synchronized subthalamic neural activity and quantitative kinematic data in freely-moving human PD subjects (Quinn *et al.*, 2015; Blumenfeld *et al.*, 2017; Hell *et al.*, 2018). Using such technology we recently demonstrated that Freezers exhibited increased STN sample entropy during periods of FOG suggesting that temporal fluctuations of STN neural activity may play an important role in FOG (Syrkin-Nikolau *et al.*, 2017). Short fluctuations in beta (13–30 Hz) oscillations (beta bursts) are a physiological feature of normal cortical and subcortical motor circuitry and it has been proposed that short duration beta bursts represent normal signal processing in the sensorimotor network (Murthy and Fetz, 1992, 1996; Courtemanche *et al.*, 2003; Feingold *et al.*, 2015). This hypothesis has been supported by

evidence that longer duration beta bursts in the resting-state, correlated with PD motor disability and were reduced in number by therapeutic doses of dopaminergic medication (Tinkhauser, Pogosyan, Little, *et al.*, 2017; Tinkhauser, Pogosyan, Tan, *et al.*, 2017).

To date no study has investigated the nature of STN beta bursts during gait and freezing of gait in freely moving human subjects with PD, nor whether the nature of dynamic fluctuations in beta activity is different in PD subjects with FOG (Freezers) compared to Non-Freezers. Moreover, whether beta burst properties are modulated by STN low or high frequency DBS, during tasks that elicit FOG, has yet to be explored. To optimize therapies for the treatment of FOG, these gaps need to be addressed. Using synchronized neural and kinematic recordings and concurrent sensing and neurostimulation in freely-moving PD subjects, we demonstrate that STN beta burst duration, measured during novel gait tasks that elicited FOG in freely-moving PD subjects, differentiated Freezers from Non-Freezers during gait without freezing and were longer in Freezers during FOG. We also demonstrate that STN DBS, either at 60 Hz or 140 Hz shortened the pathological, longer beta burst durations and improved gait impairment in Freezers but left unchanged the shorter burst durations and normal gait parameters in Non-Freezers.

Materials and Methods

Human subjects

Twelve PD subjects (7 male) 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 (MER) (Bronte-Stewart *et al.*, 2010; Quinn *et al.*, 2015). Dorsal and ventral borders of each STN were determined during MER, and the base of electrode zero was placed at the ventral border of the STN. The two leads were connected to the implanted investigative neurostimulator (Activa® PC+S, Medtronic, Inc. FDA Investigator Device Exemption approved). The preoperative selection criteria, surgical technique, and assessment of subjects have been previously described (Bronte-Stewart *et al.*, 2010; Quinn *et al.*, 2015). All subjects gave their written informed consent 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). 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 were classified as a freezer or non-freezer based on the clinical history of a subject's symptoms and/or if the subject displayed freezing behavior during the tasks.

Experimental Protocol

Recordings were collected in the Stanford Human Motor Control and Balance Laboratory. Experiments were performed off-medication and following at least 21 months of continuous, high frequency DBS. Subjects performed two gait tasks: Stepping in Place (SIP) and Forward Walking (FW). The tasks were performed a mean of 23.42 days (range 1 – 78 days) apart. During the SIP task, subjects began with 30 seconds of standing, at rest, followed by 100 seconds of alternating, self-paced stepping on adjacent dual force plates. For the FW task, subjects walked forward for 10 m, turned around and returned, and repeated this for a

total of 40 m of straight walking. Subjects performed each of the tasks during randomized presentations of no, 60 Hz and 140 Hz DBS and were blinded to each condition. Due to the limitations of sensing capabilities of the Aactiva® PC+S, stimulation was applied in a monopolar configuration through the electrode in between the recording electrode pair (Quinn *et al.*, 2015; Trager *et al.*, 2016; Blumenfeld *et al.*, 2017). The stimulation voltage was determined by a clinician, who optimized the clinical DBS parameters by monitoring the subject for adverse effects but had no other involvement in the research. Voltage was held constant across frequencies for each subject's STN since it has been previously demonstrated that the difference in STN LFPs between 60 and 140 Hz DBS was frequency specific and not power specific (Blumenfeld *et al.*, 2015). At least a five minute break was allotted in between experiments to allow the subjects to rest. Prior to experiments, two minutes were spent with no DBS for the effects of previous stimulation to wash out. We have previously demonstrated that after six months of chronic DBS, the effects of DBS on neural activity would have been washed out after two minutes as there was no statistical difference in the off therapy LFP beta power from recordings taken fifteen seconds after DBS was turned off and one hour later (Trager *et al.*, 2016).

Data Acquisition and Analysis

Ground reaction forces were captured at 1000 Hz with two force plates on the Bertec system (Bertec Corporation, Columbus, OH). The SIP cycle began with the initial contact of one foot with the ground and ended just prior to contact of the same foot with the ground, consistent with the usual definition of a gait cycle. As described in our previous studies, gait cycle parameters were calculated from the force plate data and freezing episodes (FEs) were identified by a validated computerized algorithm (Nantel *et al.*, 2011). Leg or shank angular velocity was measured during the forward walking task using wearable inertial measurement units (IMUs, APDM, Inc., Portland, OR), which were positioned in a standardized manner for all subjects and tasks on the top of the feet, on both shanks, on the lumbar, and chest trunk regions. All 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 zero phase 8th order low pass Butterworth filter with a 9 Hz cut-off frequency and principal component 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 peak angular velocities (first positive peak following the beginning of swing phase) were identified. From these times, swing and stride times (time between consecutive peak angular velocities) were calculated. Swing and stride times were then used to calculate arrhythmicity and asymmetry during periods when the subject was not freezing. Asymmetry and arrhythmicity were defined as: $\text{asymmetry} = 100 \times |\ln(\text{SSWT}/\text{LSWT})|$, where SSWT and LSWT correspond to the leg with the shortest and longest mean swing time over the trials, respectively and arrhythmicity = the mean stride time coefficient of variation (CV) of both legs (Plotnik *et al.*, 2005, 2007; Nantel *et al.*, 2011). A large stride time CV is indicative of a less rhythmic gait. Analysis was performed in MATLAB (version 8.2, The MathWorks Inc. Natick, MA, USA).

STN LFPs were recorded from electrode pair 0–2 or 1–3 of the DBS lead; see Supplementary Table 1 for details for each subject. Pre-amplified LFP signals were high-pass filtered at 0.5 Hz and low pass filtered at 100 Hz. The sampling rate for the LFP data was 422 Hz (10-bit resolution). The gain and center frequency parameters chosen for each LFP recording which was determined using a standardized protocol, further detailed in Blumenfeld et al., (Supplementary Material). This protocol provides a robust method by which the channels from which we record can be configured to produce the most reliable neural data possible, by avoiding channel overload and center frequency mismatch. Only the quality and resolution of the recordings from the sensing components of the device during stimulation are impacted by these parameters and they have no impact on the therapy (Blumenfeld *et al.*, 2017). Uncompressed LFP data were extracted via telemetry using the Activa® PC+S tablet programmer and transferred to a computer for offline analysis in MATLAB. Using the movement state, power spectral density curves were created. A peak detection algorithm was used to identify the peak frequency in the beta band region for each STN. LFP recordings from the Activa® PC+S all feature a distinct 1/f falloff which served as a baseline fit in the power spectral density curves (Connolly *et al.*, 2015). Using this baseline, crossings were identified as the first interpolated 1/f crossings to the left and right of the identified peak in the beta band (13–30 Hz) region. To capture peak activity, we took half of the frequency bandwidth between these two 1/f crossings and centered it on the peak beta frequency. This half width centered about the peak frequency was chosen as the ‘movement band’. The raw LFP signals were then filtered using a zero-phase 8th order Butterworth bandpass filter around this subject-specific frequency band and was squared, Fig. 1A and B.

An amplitude envelope was calculated by linearly connecting consecutive peaks of the filtered and squared LFP cycle to form an outline of the maximum power, Fig. 1B. Bursts were identified as periods, during which the envelope amplitude was greater than a defined baseline. The baseline was determined by finding the troughs in the envelope and was set to two times the median trough power, Fig. 1C. The troughs were the local minima of the envelope and represented the local smallest peak amplitudes of the filtered and squared signal. The estimated noise of the device was calculated based on the bandwidth of the filter (BW) used. This was calculated using:

$$Total\ Noise\ Power = (150\ nV/\sqrt{Hz})^2 \times BW$$

The ‘noise of the device’ refers to the estimated noise floor after the LFP has been filtered and squared. It has been reported in the literature as well as in the manufacturer datasheet that the Activa® PC+S neurostimulator has a nominal noise floor (150 nV/ Hz) which provides a lower limit, above which we can reliably detect LFP signals (Rouse *et al.*, 2011; Stanslaski *et al.*, 2012). The equation represents the calculation for total noise power based on our method of LFP signal processing for our burst analysis in which the raw LFP is bandpass filtered and squared. Troughs that fell below this estimated noise floor of the device were excluded from the baseline analysis. The duration of each burst was determined as the interval between successive crossings over the baseline of the amplitude envelope, Fig. 1C. The average power within each burst was calculated by taking the average power of

the bandpass filtered and squared LFP over the duration of the burst. Since raw signal power can vary by multiple orders of magnitude, normalization of burst power was necessary to allow for comparison across subjects. Relative burst power for an individual burst was calculated by taking each burst's average amplitude and dividing it by the mean of burst amplitudes across the resting-state in the subject's 40–70 Hz band during no DBS. It has been previously reported and seen in this cohort that the LFP spectrum in the 40–70 Hz range in the resting-state (no DBS) was free of any artifact or peaks (Syrkin-Nikolau *et al.*, 2017).

A three-dimensional spectrogram of the squared LFP, see Results, was constructed using a series of overlapping and consecutive envelope power calculations and was performed as follows: the envelope power was calculated in 1 Hz increments from 4 Hz to 34Hz using a 2Hz wide bandpass filter. The overlap has the benefit of capturing spectral events that occur at the edge of the filter but decreases the maximum spectral resolution to 3 Hz. Each envelope was then interpolated in time onto a rectilinear uniformly spaced grid and the power mapped to both the z-axis and the color heat map.

Synchronization of neural and kinematic recordings was achieved offline using internal and external instruments, using a data acquisition interface (Power1401) and Spike software (version 2.7, Cambridge Electronic Design, Ltd., Cambridge, England) (Quinn *et al.*, 2015; Blumenfeld *et al.*, 2017; Syrkin-Nikolau *et al.*, 2017). Prior to the experiment, surface electrodes were attached to the skin. Subjects received a pulse of 20Hz/1.5V neurostimulation for a few seconds through either DBS lead. A signal artifact was detected by the implanted neurostimulator and Spike Software, the latter system using the surface electrode to record the stimulation artifact.

Statistics

Kruskal-Wallis One Way Analysis of Variance on Ranks was used for the comparison of beta burst dynamics between Freezers and Non-Freezers during no DBS. This decision was decided after a Normality Test (Shapiro-Wilk) was failed ($P < 0.050$) for these distributions. The effect of different stimulation frequencies on burst duration, the difference in burst duration during freezing episodes versus non-freezing episodes, and the difference in peak frequency in the spectral profile during movement was evaluated using one-way repeated measure ANOVAs. Following the normalization process, burst power was evaluated using the same statistical tests, as described for burst duration. The relationship between burst duration and power was investigated using a Pearson product moment correlation analysis to compare the distribution of each burst's duration and power during no DBS on all subjects. The same analysis was used to investigate the relationship between stride time and burst duration.

To compare arrhythmicity, asymmetry, or stride time between groups, a one-way ANOVA was used. Paired *t*-tests were used to compare the effects of different stimulation frequencies on arrhythmicity, asymmetry, and stride time within each group for each task. Student's *t*-tests were used for the comparison of demographics between the Freezer and Non-Freezer groups. *Post hoc* analyses were completed to compare between stimulation conditions. All

statistical testing was performed in SigmaPlot (Systat Software, San Jose, CA) using two-tailed tests with significance levels of $P < 0.05$.

Results

Age, disease duration, preoperative off- and on- medication Unified Parkinson's disease Rating Scale III (UPDRS III) scores were not significantly different between Freezers ($N = 8$) and Non-Freezer groups ($N = 4$), see Supplementary Table 2 for demographics. UPDRS III was also performed by the same experienced rater for each patient at each research visit, throughout the duration of the study. There was no significant difference in off medication / off stimulation UPDRS III at the time of the visit between the two groups ($P = 0.103$), see Supplementary Table 2. Out of the 24 hemispheres, 18 STNs were used for the neural analysis for the SIP task and 20 STNs were included in the neural analysis for the FW tasks when comparing the effects of DBS. One subject froze during the entire SIP task during all stimulation conditions. As a result, the subject was unable to complete the gait task and was excluded from the neural and kinematic portion of the analysis for that task. The remaining four hemispheres, from four subjects, were excluded due to either stimulation artifact that interfered with the beta band region of LFP recordings obtained from the respective lead or electrocardiogram (ECG) artifact.

Subject-specific movement band is conserved during different gait tasks

Fig. 2 demonstrates the neural and kinematic signals from a representative subject during the resting-state and during stepping in place and forward walking when no FOG occurred.

For this subject, the LFP spectral profile was different during movement compared to the resting-state, in both STNs, but was similar between the SIP and FW tasks, Fig. 2B, C and E, F. This was representative of all subjects; in all cases, there was a change in the LFP profile from the resting to the movement-state, as we have demonstrated previously (Quinn *et al.*, 2015; Syrkin-Nikolau *et al.*, 2017). While the LFP profile during movement varied among subjects and between STNs, the peak frequency during movement was conserved between gait tasks in each STN ($P > 0.05$). A frequency band surrounding the peak during movement was chosen for each STN; see Methods, Supplementary Table 3 for the subject-specific frequency band for each task. We defined this frequency band as the movement band, which had an average bandwidth of 6.84 ± 2.08 Hz across subjects and was conserved between gait tasks for each STN ($P > 0.05$).

Freezers demonstrate longer duration beta bursts than non-freezers during 'normal' gait

Beta burst duration and power was calculated using movement bands, during both the resting and movement-states. Fig. 3 demonstrates that movement band burst durations and power was greater in a representative freezer compared to a representative non-freezer during 'normal' stepping without freezing episodes.

The group analysis supported this observation; during SIP without FOG, burst durations were significantly longer in Freezers compared to Non-Freezers, ($H(1) = 45.068$, $P < 0.001$). The same result was seen during the FW task without FOG ($H(1) = 69.564$, $P < 0.001$). In contrast, there was no significant difference in burst duration between Freezers and Non-

Freezers during rest. Freezers also had higher relative mean beta burst power than Non-Freezers while stepping without freezing ($H(1) = 212.680$, $P < 0.001$) but mean burst power was not different between the two groups during forward walking. In the entire cohort, a very weak relationship was seen between burst duration and burst power during rest, stepping in place and forward walking ($R^2 = 0.0625$, $P < 0.001$; $R^2 = 0.108$, $P < 0.001$; $R^2 = 0.006$, respectively).

Freezers demonstrate more severe gait impairment during gait without freezing than Non-Freezers

Freezers exhibited longer average stride time ($F(1) = 7.715$, $P = 0.012$) and more arrhythmic stepping during SIP ($F(1) = 6.194$, $P = 0.034$) compared to Non-Freezers. Freezers demonstrated significantly more asymmetric gait during the FW task ($F(1) = 6.640$, $P = 0.013$) when compared to Non-Freezers. No significant difference between the two groups was seen in arrhythmicity or stride time during FW or in asymmetry during SIP.

Freezers exhibit longer burst durations during periods of FOG

The SIP task has provided a mechanism to investigate the difference in behavior between stepping without and with freezing episodes within the same trial (Nantel *et al.*, 2011; Syrkin-Nikolau *et al.*, 2017). Synchronized neural and kinematic recordings allow investigation of neural activity in real-time as the subject performs the task. Fig. 4 shows the envelope of power across the alpha/beta frequency spectrum presented as a three-dimensional spectrogram with the SIP traces, from a representative Freezer and Non-Freezer.

The Non-Freezer exhibited consistent alternating stepping during the task and there was evidence of low power bursts in the beta range that remained consistent throughout the task, Fig. 4A. In contrast the Freezer performed consistent stepping only for the first 20 seconds of the task, after which there was progressive degradation of the motor program leading to freezing episodes of varying durations, interspersed with short cycles of alternating stepping for the remainder of the task. There was evidence of bursting behavior that was variable in beta burst power and duration throughout the freezing behavior. Among the Freezers who froze during SIP ($N = 5$), burst duration was significantly longer during stepping with freezing compared to stepping when not freezing ($F(1,815) = 13.114$, $P < 0.001$), but there was no significant difference in burst power during stepping with compared to without freezing episodes.

Bilateral hemispheric control of alternating stepping

Axial motor programs are influenced by neural activity from both cerebral hemispheres (Wagner *et al.*, 2016; Pizzamiglio *et al.*, 2018). However, Parkinson's disease usually starts on one side of the body, which remains the more affected (MA) side and we have shown that resting-state beta band power is higher in the MA STN (Shreve *et al.*, 2017). We investigated whether movement band burst durations varied between STNs, and whether this was related to gait impairment, during the SIP task.

Fig. 5A and B display the burst durations in the left (MA) and right (LA) STNs, respectively, of a representative Freezer during SIP. The mean (± 2 SD) of the burst durations of the Non-Freezers is shown on Fig. 5A and B (green lines). The mean burst duration in this subject was longer in the MA STN compared to the LA STN (0.85 sec, 0.55 sec respectively) during the periods of stepping without freezing, although both were longer than the mean Non-Freezer burst duration of 0.27 ± 0.04 sec. During the period of regular alternating stepping, 82.4% of the bursts in the MA STN were longer than those of the non-freezer group, Fig. 5A, whereas 66.7% of the burst durations in the LA STN were longer and outside the range of those of Non-Freezers, Fig. 5B. The burst durations in the LA STN increased 23 seconds after the start of the trial, after which the stepping performance became more impaired and freezing episodes occurred, Fig 5C. For the ten subjects, in whom bilateral STN data was available, the difference in the mean burst duration between hemispheres (STNs) of individuals strongly correlated with the difference in stride time between their legs ($r = 0.853$, $P = 0.002$), during SIP without freezing episodes, but there was no correlation between mean burst duration of each STN and mean stride time of the contralateral leg.

Neurostimulation at 60 Hz and 140 Hz improves FOG and shortens beta burst durations

Subjects performed SIP and FW during randomized presentations of no DBS, 60Hz and 140 Hz STNDBS. Fig. 5 demonstrates the effect of 60 Hz and 140 Hz DBS on the gait of a representative Freezer during SIP.

During no DBS the subject exhibited asymmetric and arrhythmic alternating stepping and the algorithm identified three freezing episodes, Fig. 6A. Both 60 Hz and 140 Hz DBS improved the alternating stepping patterns; the subject spent 17.0% of the SIP task freezing during no DBS, 0% during 60 Hz DBS, and 4.5% during 140 Hz DBS. Table 1 summarizes the effects of 60 Hz and 140 Hz DBS on the kinematics of the entire FW and SIP tasks in the Freezer and Non-Freezer groups.

During SIP without freezing, both 60- and 140 Hz DBS improved gait arrhythmicity in Freezers compared to no DBS ($t(6) = -2.366$, $P = 0.016$, $t(6) = 2.994$, $P = 0.024$, respectively). Stride time during SIP was significantly shorter during 140 Hz DBS compared to no DBS and during 60 Hz DBS ($t(13) = 3.747$, $P = 0.002$; $t(13) = 3.727$, $P = 0.003$). During SIP with freezing, 60 Hz DBS significantly improved gait arrhythmicity compared to no DBS ($t(6) = -2.366$, $P = 0.016$). In the FW task, 60 Hz DBS significantly improved gait arrhythmicity compared to both no DBS and to 140 Hz DBS ($t(31) = 2.512$, $P = 0.017$, $t(31) = -2.787$, $P = 0.009$). Among the eight Freezers, five exhibited FEs during no DBS, two during 60 Hz DBS, and two during 140 Hz DBS during SIP; subjects spent a total of 239.4 seconds freezing no DBS, 122 seconds during 60 Hz DBS, and 152.3 seconds during 140 Hz DBS. One subject experienced one FE during the no DBS condition of FW, this FE was excluded from the neural and kinematic analysis. None of the Freezers exhibited FEs during FW during either 60- or 140 Hz DBS. In Non-Freezers, gait parameters were similar to healthy controls (Nantel *et al.*, 2011), DBS had no overall effect. Gait asymmetry during FW was lower during 60 Hz compared to 140 Hz DBS ($t(15) = -2.276$, $p = 0.038$).

STN DBS differentially affects burst duration and power in Freezers compared to Non-Freezers

There was a significant effect of stimulation conditions on burst duration among Freezers during stepping with freezing ($F(2, 3007) = 24.27, P < 0.001$), stepping without freezing ($F(2, 2803) = 22.247, P < 0.001$) and walking without freezing ($F(2, 1202) = 3.376, P = 0.034$). Both 60- and 140 Hz significantly shortened duration of bursts compared to no DBS but there was no significant difference in the effect of either frequency of DBS. Within the Non-Freezer group, there was no significant change in burst duration during no, 60 Hz, and 140 Hz DBS for either task.

Freezers experienced significant but different effects of stimulation conditions on burst power during the SIP ($F(2, 2380) = 245.361, P < 0.001$) and FW tasks ($F(2, 1195) = 136.211, P < 0.001$). During SIP without freezing, both 60 Hz ($P < 0.001$) and 140 Hz DBS ($P < 0.001$) attenuated burst power compared to no DBS and 60 Hz attenuated burst power to a greater degree in comparison to 140 Hz DBS ($P < 0.001$). Freezers during the FW task showed a similar attenuation of burst power during both 60 Hz ($P < 0.001$) and 140 Hz ($P < 0.001$) DBS compared to no DBS. Non-Freezers experienced a significant effect of stimulation on burst power in both SIP ($F(2, 2282) = 89.353, P < 0.001$) and FW ($F(2, 735) = 17.615, P < 0.001$) tasks. During the two gait tasks, 60 Hz ($P < 0.001$) and 140 Hz DBS ($P < 0.001$) attenuated burst power compared to no DBS and 140 Hz DBS significantly attenuated burst power compared to the 60 Hz DBS condition ($P < 0.001$).

Discussion

For the first time, this study has demonstrated that beta burst duration and power, recorded during freely-moving gait, differentiated PD Freezers from Non-Freezers and was differentially modulated during low and high frequency STN DBS. STN beta burst durations were longer in Freezers compared to Non-Freezers during all gait tasks, in which gait was more impaired in Freezers. Within Freezers, burst durations were longer during periods of FOG compared to during gait without freezing. There was no difference in burst duration between the two groups in the resting-state and burst duration and was not correlated with mean power in either the resting or moving-state. DBS at 60- and 140 Hz shortened burst durations and improved FOG in Freezers and had no effect on the already shorter burst durations and normal SIP gait parameters in Non-Freezers.

Beta burst duration and power during gait is relevant to FOG

In this and in previous studies, it has been shown that STN LFP beta band power might attenuate but does not completely disappear during ongoing movement (Quinn *et al.*, 2015; Blumenfeld *et al.*, 2017; Syrkin-Nikolau *et al.*, 2017; Hell *et al.*, 2018). Instead, there is a distinct band of elevated power in the beta band region during both upper extremity movement and gait, which was the movement band. In this study, the movement band peak frequency was similar between the different gait tasks, suggesting conservation of the movement band in similar activity states; similarly, it has been demonstrated that the resting-state band is conserved in different resting-state postures (Quinn *et al.*, 2015).

This is the first study to demonstrate the relevance of movement band beta burst duration and power during gait and FOG in freely-moving PD subjects. Previous studies investigating LFP beta burst durations and power have focused on the resting-state in both PD human subjects and in healthy, non-human primates (Murthy and Fetz, 1992, 1996; Feingold *et al.*, 2015; Tinkhauser, Pogosyan, Little, *et al.*, 2017; Tinkhauser, Pogosyan, Tan, *et al.*, 2017). In those studies, longer resting-state beta burst durations correlated with increased motor disability in PD human subjects and dopaminergic medication shifted the distribution of burst durations toward shorter durations (Tinkhauser, Pogosyan, Little, *et al.*, 2017; Tinkhauser, Pogosyan, Tan, *et al.*, 2017). Longer durations of elevated STN beta band power reflect longer periods of neural oscillations and synchrony in beta frequency bands, which has been previously associated with the pathological Parkinsonian state (Kühn *et al.*, 2006, 2008; Ray *et al.*, 2008). Conversely, it has been proposed that short beta burst durations reflect normal sensorimotor processing (Murthy and Fetz, 1996; Courtemanche *et al.*, 2003; Feingold *et al.*, 2015; Tinkhauser, Pogosyan, Little, *et al.*, 2017).

The state dependent nature of STN LFP beta activity and these findings highlight the value of identifying subject-specific movement bands to investigate the neural features of impaired movement such as FOG in PD, since there was no difference in burst duration between the two groups in the resting state. Previously, it has been shown that Freezers exhibited a lower average STN beta band power and higher beta entropy during gait without FOG than Non-Freezers (Syrkin-Nikolau *et al.*, 2017). In this study, this is confirmed with distinct differences in subthalamic neural activity between Freezers and Non-Freezers using subject-specific dynamic features of the movement band during gait.

Bihemispheric control of gait - Can one hemisphere compensate to avoid FOG?

Parkinson's disease is usually asymmetric as the disturbance of motor control (tremor, bradykinesia, rigidity) starts on one side of the body and that side usually remains the more affected side (Hoehn and Yahr, 1967; Louie *et al.*, 2009). Similarly the pathological features of motor signs in PD, such as striatal dopamine denervation, also tend to be asymmetric and the resting-state alpha/beta band power is shown to be greater in the more affected STN in 112 STNs from 56 PD subjects (Marek *et al.*, 1996; Shreve *et al.*, 2017). Axial signs such as postural instability and FOG tend to occur after motor signs manifest on both sides of the body (Hoehn and Yahr, 1967). In this cohort, the mean movement band burst durations were different between STNs in individuals and the difference in mean burst duration between STNs during SIP without freezing was correlated with the mean difference in stride time between legs during the task. However, there was no correlation between individual STN burst durations and contralateral leg stride time. This suggests that there is bihemispheric influence on axial tasks such as SIP and that gait was more impaired when the difference in burst durations between hemispheres was greater. Our results support a network model of FOG suggesting that episodic-increased 'crosstalk' between frontostriatal circuits overloads the informational processing capacity in the dopamine depleted striatum, which leads to inhibition of brainstem locomotor regions and FOG and other studies proposing that gait asymmetry might be related to asymmetric neural dysfunction in the basal ganglia (Plotnik *et al.*, 2005; Plotnik and Hausdorff, 2008; Peterson and Horak, 2016; Ehgoetz Martens *et al.*, 2018). Burst durations varied during the SIP task, during which there were periods of

relatively normal alternating stepping and periods of FOG. In certain Freezers, periods of SIP without FOG were associated with periods of relatively shorter burst durations in one STN, Fig. 5, and that the gait became more disordered leading to freezing episodes after burst durations became longer in both STNs. This suggests that the number of freezing episodes and severity of FOG could be mitigated by the compensatory influence of the STN with shorter burst durations, which are closer to those associated with normal sensorimotor processing (Feingold *et al.*, 2015; Tinkhauser, Pogosyan, Little, *et al.*, 2017; Tinkhauser, Pogosyan, Tan, *et al.*, 2017).

The hypothesis that one hemisphere can compensate for the other in axial tasks such as gait has been supported by a recent study of unilateral versus bilateral STN DBS for gait, which demonstrated that there appeared to be a ‘dominant’ STN, unilateral stimulation of which was almost as efficacious as bilateral STN stimulation (Rizzone *et al.*, 2017). Other studies have demonstrated that if the stimulation parameters of both STNs are adjusted to minimize the difference in stride times between legs, there was improvement in FOG (Fasano *et al.*, 2011). It has also been demonstrated that the less affected hemisphere can compensate for the greater pathology of the more affected hemisphere in appendicular tasks such as finger tapping (Kishore *et al.*, 2007; Trager *et al.*, 2015). Furthermore, asymmetric therapies targeting the less affected side have been shown to be efficacious and comparable to more symmetrical therapies (Ricciardi *et al.*, 2015; Lizarraga *et al.*, 2017; Rizzone *et al.*, 2017).

Pathological neural features and gait impairment in Freezers improve during STN DBS

Both neural and kinematic features of gait impairment and FOG improved with STN DBS compared to no DBS but there were differences between the effect of 60- and 140 Hz. The mean movement band burst durations of Freezers were shorter and mean burst power was attenuated during both 60- and 140 Hz DBS compared to no DBS. Furthermore, there was greater attenuation of burst power during 60 Hz compared to during 140 Hz. The gait arrhythmicity and stride time in SIP decreased during both 60- and 140 Hz DBS, and with greater improvement in stride time during 140 Hz compared to 60 Hz. The gait arrhythmicity of FW improved during 60 Hz but not during 140 Hz. There were fewer subjects, who exhibited FOG, and less overall time was spent freezing, during either frequency compared to no DBS.

This and our previous study investigating the effect of 60 Hz DBS on neural and kinematic features of progressive bradykinesia demonstrate that 60 Hz DBS promotes more regularity in ongoing movement (Blumenfeld *et al.*, 2017). The irregularity of ongoing movement is the definition of progressive bradykinesia and of gait impairment, and may predict the transition from a Non-Freezer to a Freezer phenotype (Hausdorff *et al.*, 2003; Plotnik and Hausdorff, 2008; Nantel *et al.*, 2011). This provides a mechanism to explain the clinical studies showing that 60 Hz DBS improved FOG more than conventional high frequency DBS in PD subjects (Moreau *et al.*, 2008; Xie *et al.*, 2015).

Non-Freezers with less gait impairment and shorter burst durations exhibit modest changes during STN DBS

Non-Freezers' gait parameters remained largely unchanged during either 60 Hz or 140 Hz DBS compared to no DBS. Similarly, the shorter movement band burst durations of both the SIP and FW tasks were not affected by either frequency of DBS. Mean burst power of both gait tasks was attenuated during 60- and 140 Hz DBS with the greater attenuation occurring during 140 Hz DBS. These results demonstrate that if the neural and kinematic features associated with FOG were not apparent then there was no change during either frequency DBS. Whereas in PD subjects exhibiting FOG, there was shift towards less pathological beta burst durations and gait impairment, during DBS.

A similar 'if it isn't broken, it doesn't need fixing' effect of DBS was seen on aspects of postural instability (Bronte-Stewart *et al.*, 2002; Shivitz *et al.*, 2006). PD subjects with already normal postural sway in sensory deprived conditions showed no change after pallidotomy or during STN DBS. However, those demonstrating postural instability in these conditions improved after pallidotomy and during STN DBS. Gait parameters of the Non-Freezer were already within the range of normal values, as reported in previous studies, resulting in no significant change during DBS (Nantel *et al.*, 2011; De la Casa-Fages *et al.*, 2017). Together with the lack of neuromodulation of bursts, we propose there might be a more precise effect of DBS such that it preferentially modulates only pathological neural and kinematic aspects of behavior.

Significance of Neuromodulation of Beta Bursts

While continuous DBS has been an established therapy for PD, there have been promising studies that have successfully used neural driven adaptive DBS to improve behavioral outcomes (Little *et al.*, 2013; Rosa *et al.*, 2015; Arlotti *et al.*, 2018). Recent studies have shown adaptive DBS shortened long beta bursts which were positively correlated with motor impairment (Tinkhauser, Pogosyan, Little, *et al.*, 2017). By demonstrating for the first time that beta burst durations are relevant to gait impairment including FOG, this suggests that beta burst duration may be an important feature for adaptive DBS. Neural driven adaptive DBS systems that modulate longer beta bursts but not physiological short bursts may be a more efficient and effective therapy for FOG. These results contribute to the further development of control policy algorithms that can potentially use the dominant or more affected hemisphere to drive bihemispheric stimulation. Ultimately, these results bring us closer to optimizing a more patient-specific therapy for FOG.

Limitations

A limited number of Acliva PC+S® investigative neurostimulators are allocated to centers which contributed to the small sample size of this cohort (Quinn *et al.*, 2015; Blumenfeld *et al.*, 2017; Syrkin-Nikolau *et al.*, 2017). Additionally, there was an unequal distribution of subjects in the Freezer group compared to the Non-Freezer group. Despite our previous studies having a relatively even number of subjects in each group, over time some subjects have developed FOG and turned into Freezers (Syrkin-Nikolau *et al.*, 2017). Progression into the freezer phenotype was not investigated in this study. In the future, we hope to further this question with a longitudinal study exploring the development of neural and kinematic

features of FOG. Another limitation stems from the fact that these first-generation devices sometimes develop low-frequency ECG artifact in LFP recordings and/or experience sensing channel overload during stimulation (Blumenfeld *et al.*, 2017); see Supplementary Material. Additionally, a longer habituation period following each stimulation paradigm could have produced alternate results. The interval used between no, 60 Hz and 140Hz DBS has been documented to be long enough for STN LFP power to return to baseline (Trager *et al.*, 2016; Blumenfeld *et al.*, 2017). We did not document that the performance of gait tasks returned to baseline but we randomized the order of the DBS frequencies and the no DBS condition and therefore, we do not believe that this affected the results. Our results reflect the acute effects of stimulation frequency and are congruent to what was reported in previous studies (Moreau *et al.*, 2008; Xie *et al.*, 2012; Vallabhajosula *et al.*, 2015). Lastly, neither 60- nor 140 Hz DBS completely normalized neural or kinematic features of gait in Freezers. To enable concurrent sensing and stimulation through the DBS lead it was only possible to use monopolar stimulation and thus the DBS parameters may not have been optimal in comparison to the patient's clinical stimulation settings.

Conclusion

The study demonstrates that longer duration of beta bursts in the movement band is a defining feature of freezing behavior in freely-moving PD subjects. Our results show that both 60- and 140Hz STN DBS can improve gait impairment in Freezers and shorten pathological beta burst durations. In contrast to Freezers, Non-Freezers exhibited shorter duration beta bursts and normal gait, which were unchanged on versus off DBS. These results support the hypothesis that in PD, pathological prolonged beta synchrony is superimposed upon physiological shorter periods of beta oscillations and synchrony which are critical to sensorimotor processing (Murthy and Fetz, 1992, 1996; Tinkhauser, Pogosyan, Little, *et al.*, 2017). STN DBS acted to restore physiological sensorimotor processing by targeting pathological (longer) not physiological (short) beta burst durations, while improving gait in Freezers. The correlation between the difference in STN beta burst durations and the difference in leg stride times provided evidence that gait became more impaired when there was greater difference in burst duration between STNs. We also suggest that the STN with shorter burst durations may be able to compensate to maintain gait without freezing. With the unique opportunity to investigate the temporal dynamics of neural signals during gait, we have identified a potential biomarker for FOG that can instruct future closed-loop, adaptive DBS algorithms to prevent freezing behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

FOG	freezing of gait
DBS	deep brain stimulation
LFP	local field potential
STN	subthalamic nucleus
SIP	stepping-in-place
FW	forward walking

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Highlights

- First study to investigate STN beta bursts during gait in freely moving PD subjects
- Prolonged movement beta band burst durations were a pathological feature of FOG
- STN DBS shortened pathological burst durations and improved gait in Freezers
- Normal gait parameters, accompanied by shorter bursts, were not modulated by DBS
- Greater difference in burst duration between STNs correlated with more impaired gait

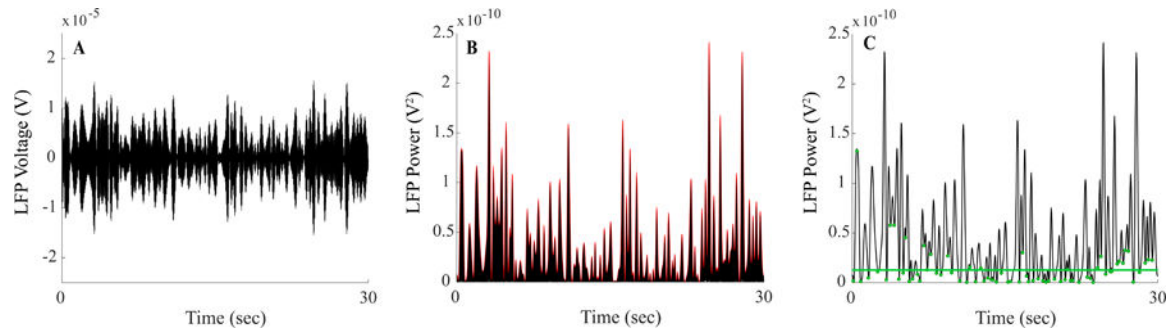


Figure 1:

Beta burst determination process (A) Raw local field potential was band pass filtered around the STN specific frequency band of interest during 30 seconds of the movement state. (B) The filtered local field potential signal was squared and, an envelope, denoted in red, connected consecutive peaks from the squared signal. (C) The envelope of the filtered squared signal; green dots indicate the identified troughs of the envelope signal. The baseline of the envelope power, represented by the green line, was determined by taking two times the median of the trough power.

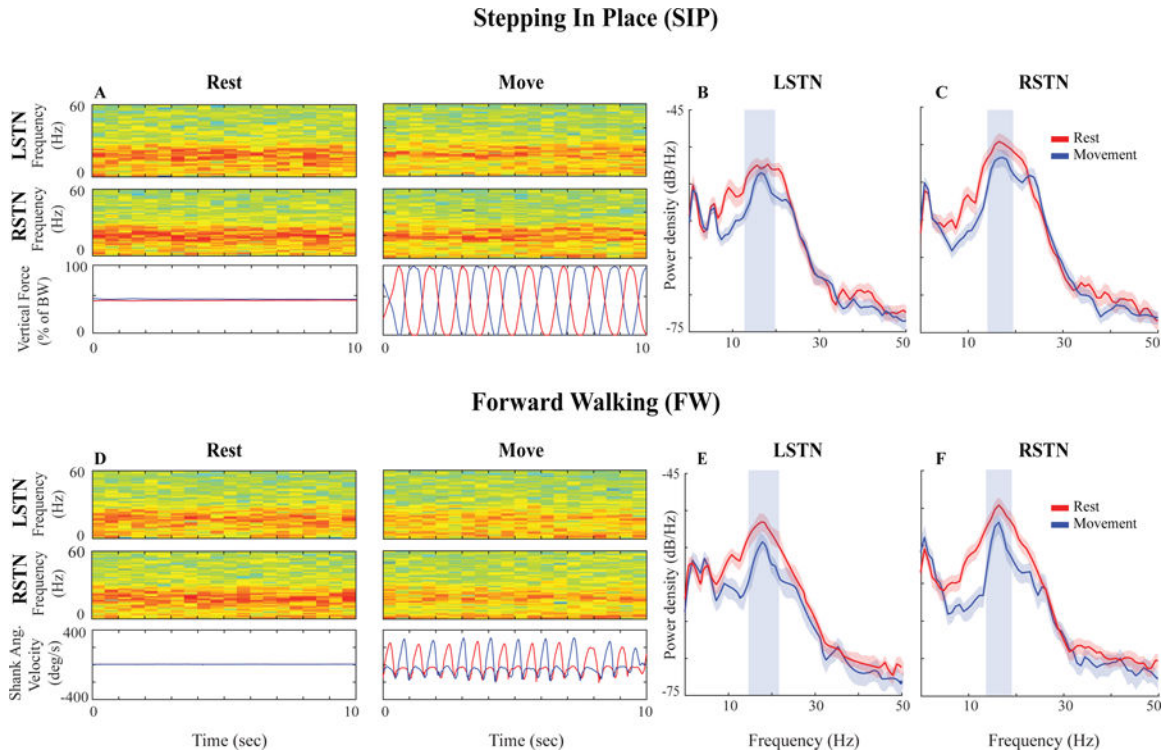


Figure 2: State-dependent beta band profiles. Time frequency spectrograms and synchronized kinematic traces (**A, D**) and power spectral density (PSD) diagrams (**E, F**) from a representative subject during resting and movement states of the stepping in place (SIP) (**A–C**) and forward walking (FW) (**D–F**) tasks. Kinematics from the right and left foot of the subject are represented by the red and blue traces, respectively. Shaded blue region in PSD (**B–C, E–F**) diagram indicates movement band chosen for each STN.

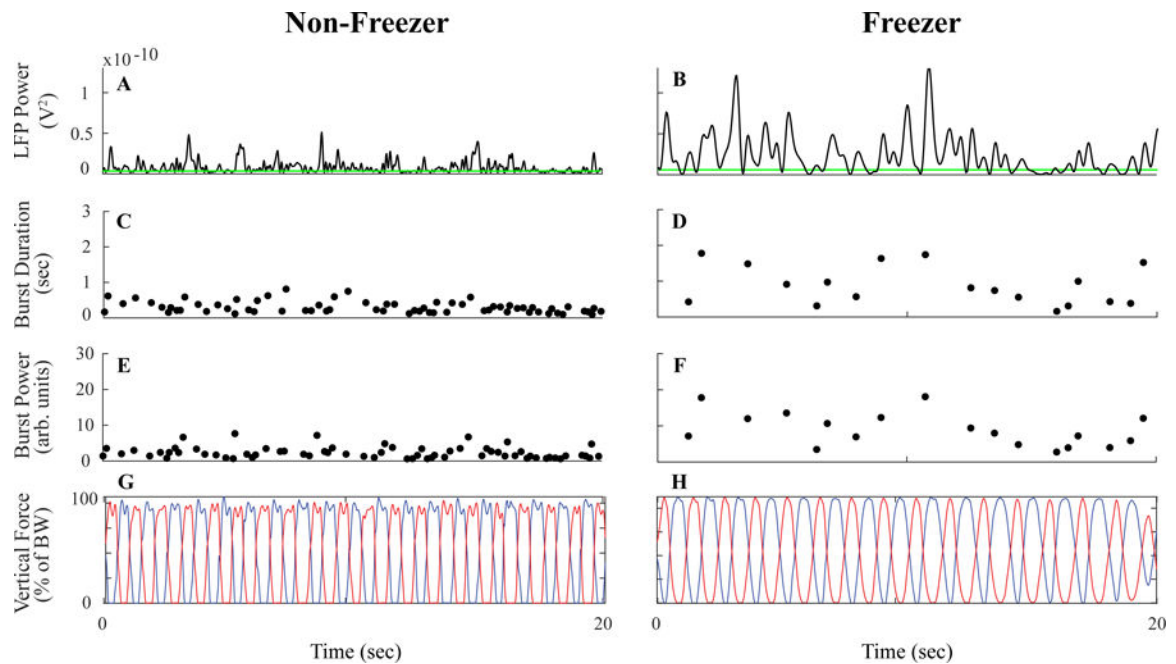


Figure 3: Distribution of envelope power, burst duration and mean burst power with kinematics for Freezer and Non-Freezer. Beta burst distribution of a Non-Freezer and Freezer performing stepping in place (SIP) during no DBS. Envelope power of the squared LFP signal of a representative STN, with the green line indicating the baseline of the signal, is used to determine each individual beta bursts (represented by solid black circles) throughout the task (A, B). The distribution of burst duration (C, D) and relative burst power (E, F) is plotted along with synchronized kinematics (G, H).

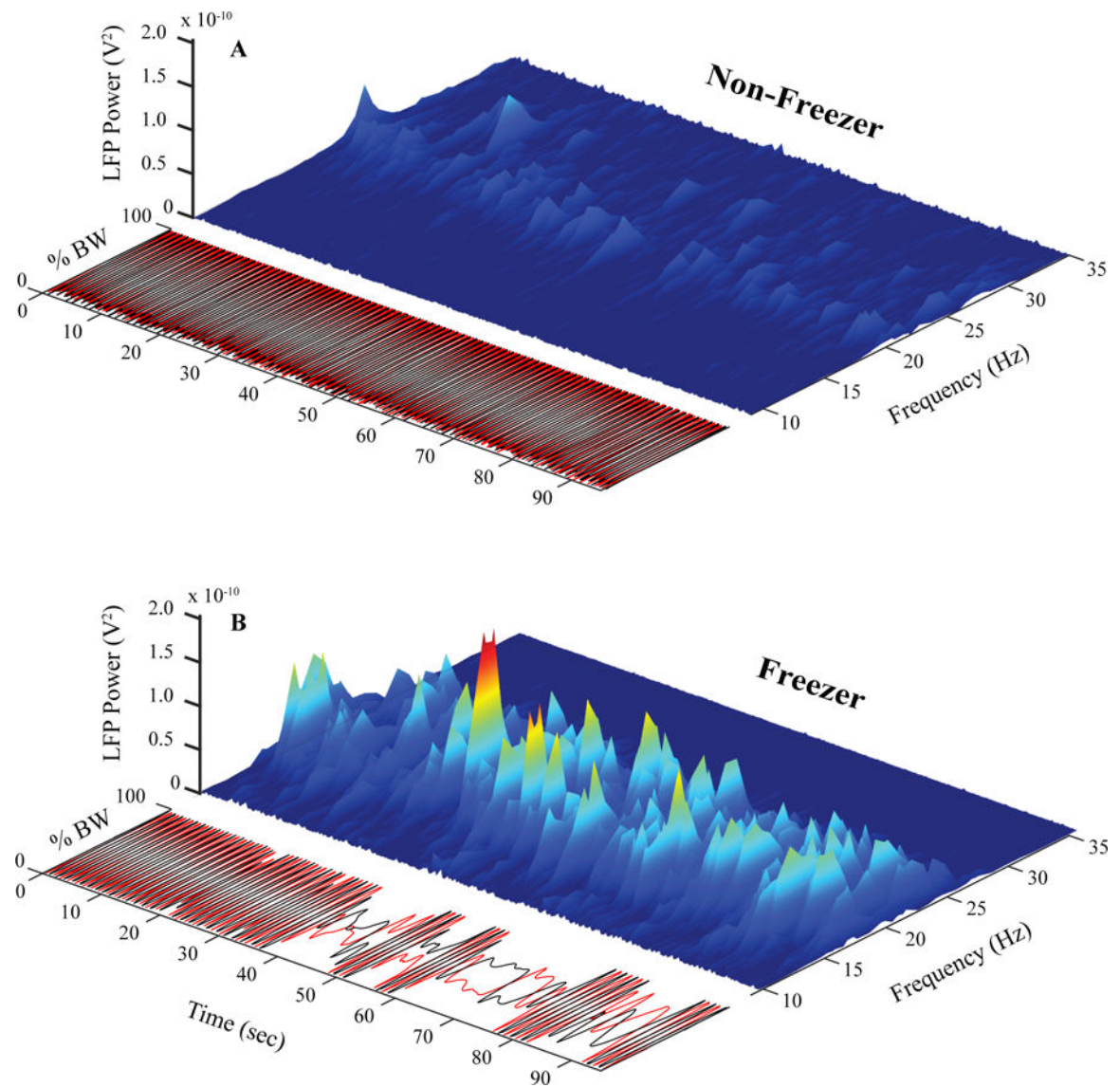


Figure 4: Three-dimensional spectrogram and kinematics during no DBS. Synchronized kinematics and three-dimensional spectrogram plotting time, frequency, and local field potential power for a representative Non-Freezer (A) and Freezer (B) throughout the duration of the stepping in place task during no DBS.

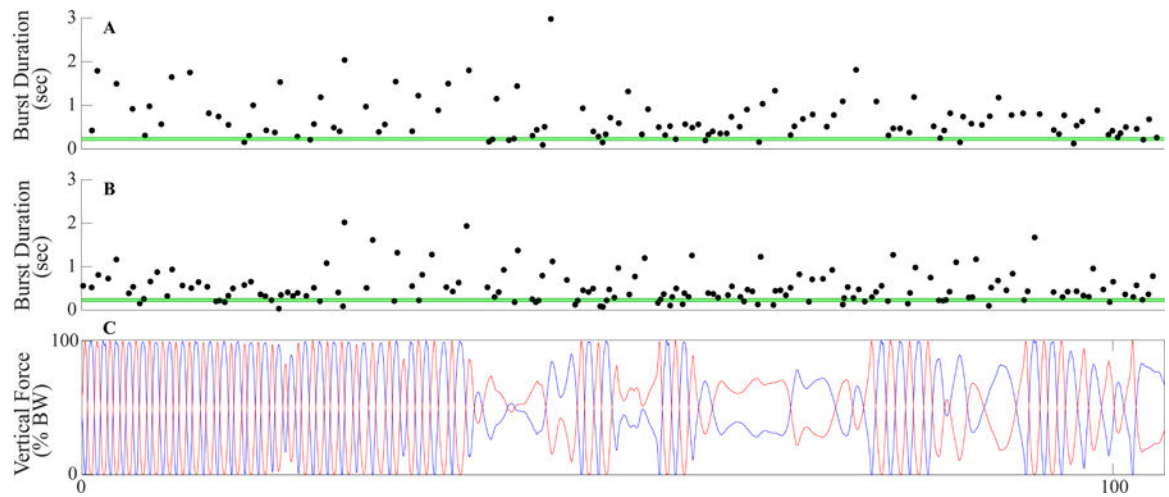


Figure 5: Bilateral beta burst duration distribution. Synchronized beta burst durations in the LSTN (MA) (A) and RSTN (LA) (B) with kinematics of the stepping in place task. The horizontal green lines represent the mean group burst duration for Non-Freezers \pm two standard deviations.

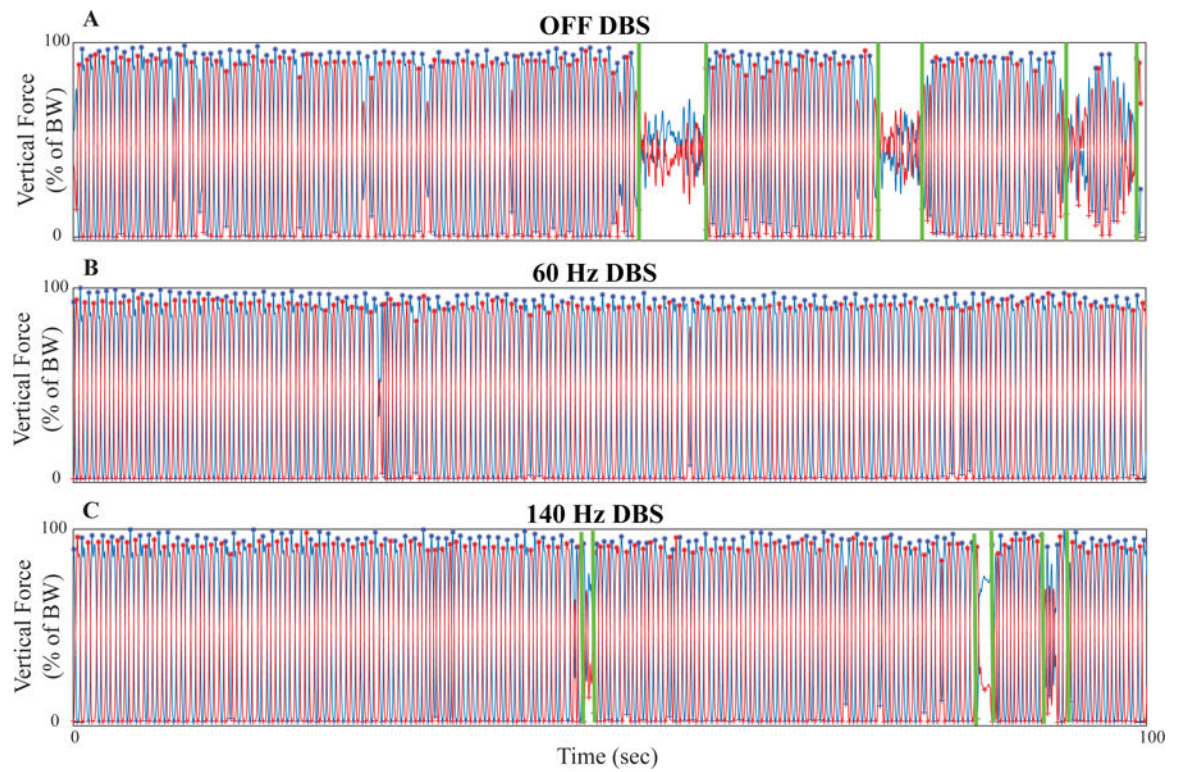


Figure 6: Stepping-in-place kinematics during no, 60 Hz, and 140 Hz STN DBS. Force plate traces from the stepping in place (SIP) task from a representative Freezer during the three stimulation conditions: (A) no DBS, (B) 60 Hz, and (C) 140 Hz DBS.

Table 1:

Kinematic Results for Freezers and Non-Freezers. Asymmetry, arrhythmicity, stride time, and percentage of task spent freezing (mean \pm SD) for Freezers and Non-Freezers during the entire stepping in place (SIP) and forward walking (FW) tasks for the three stimulation conditions: no DBS, 60 Hz DBS, and 140 Hz DBS

		SIP			FW		
		OFF	60 Hz	140 Hz	OFF	60 Hz	140 Hz
Freezer	Asymmetry (%)	26.74 \pm 23.44	27.10 \pm 21.42	15.99 \pm 12.12	6.11 \pm 4.11	5.01 \pm 2.97	4.52 \pm 3.39
	Arrhythmicity (CV %)	54.04 \pm 50.46	27.49 \pm 33.23 *	29.34 \pm 56.18	6.76 \pm 3.29	5.18 \pm 2.25 *^	6.41 \pm 2.68
	Stride Time (sec)	1.71 \pm 0.68	1.44 \pm 0.53 *^	1.21 \pm 0.44 *	1.14 \pm 0.19	1.11 \pm 0.15	1.10 \pm 0.14
	% of Task Freezing	29.37 \pm 38.27	11.01 \pm 29.57	18.13 \pm 34.58	0.17 \pm 0.48	0%	0%
Non-Freezer	Asymmetry (%)	9.54 \pm 6.87	7.86 \pm 7.10	7.25 \pm 9.03	3.32 \pm 1.88 #	2.41 \pm 2.50 ^	4.50 \pm 2.23
	Arrhythmicity (CV)	4.01 \pm 0.81 #	4.10 \pm 1.40	4.00 \pm 0.73	5.98 \pm 4.37	4.96 \pm 1.35	4.94 \pm 1.38
	Stride Time (sec)	1.07 \pm 0.15 #	1.05 \pm 0.14	1.06 \pm 0.17	1.16 \pm 0.06	1.15 \pm 0.07	1.18 \pm 0.10

* Significant difference between OFF during same task ($P < 0.05$)

^ Significant difference between 140 Hz during same task ($P < 0.05$)

Significant difference between Freezers in same task ($P < 0.05$)