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Cortico-subthalamic field potentials support classification of the natural gait cycle in Parkinson's disease and reveal individualized spectral signatures

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KHL, DDW, and PAS Designed Research; KHL, DDW, RG, and MSY Performed Research; KHL, MAM, JC, CdH, and SL Analyzed data; KHL and DDW Wrote the paper.

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Abstract

Human's ability to coordinate stereotyped, alternating movements between the two legs during bipedal walking is a complex motor behavior that requires precisely timed activities across multiple nodes of the supraspinal network. Understanding of the neural network dynamics that underlie natural walking in humans is limited. We investigated cortical and subthalamic neural activities during overground walking and evaluated spectral biomarkers to decode the gait cycle in three patients with Parkinson's disease without gait disturbances. Patients were implanted with chronic bilateral deep brain stimulation leads in the subthalamic nucleus (STN) and electrocorticography paddles overlaying the primary motor (M1) and somatosensory (S1) cortices. Local field potentials (LFP) were recorded from these areas while the participants performed overground walking and synchronized to external gait kinematic sensors. We found that the STN displays increased low frequency (4-12 Hz) spectral power during the period prior to contralateral leg swing. Furthermore, STN shows increased theta frequency (4-8 Hz) coherence with the primary motor through the initiation and early phase of contralateral leg swing. Additional analysis revealed that each patient had specific frequency bands which could detect a significant difference between left and right initial leg-swing. Our findings indicate that there is alternating spectral changes between the two hemispheres in accordance with the gait cycle. In addition, we identified patient-specific, gait-related biomarkers in both the STN and cortical areas at discrete frequency bands that may be used to drive adaptive DBS to improve gait dysfunction in patients with Parkinson's disease.

Significance Statement

By recording from chronically implanted electrodes from the subthalamic nucleus and sensorimotor cortex in patients with Parkinson's disease, we found power modulations across multiple frequency bands (4-30 Hz) during specific phases of the gait cycle. The coherence between subthalamic-cortical areas of each brain hemisphere also increases prior to contralateral leg swing. The data supports the hypothesis that the basal ganglia and cortex coordinate alternating power and coherence fluctuations between hemispheres, which may indicate a mechanism to regulate continuous bipedal locomotion in humans. Lastly, we show that these putative biomarkers for gait can decode left and right gait events, implicating a potential use to drive future adaptive DBS algorithms.

Introduction

Human walking is a complex motor task that requires the flexible coordination of reciprocal left and right leg movements. Natural upright walking consists of each leg alternating between the stance phase, when the foot is in contact with the ground, and the swing phase, when the foot is in the air; these two phases make up the “gait cycle,” comprised of a series of stereotyped events such as left and right heel-strikes and toe-offs.

The subthalamic nucleus (STN) and primary motor cortex are likely key nodes of the supraspinal network that regulate human gait, given the STN’s projection to the locomotor regions in the brainstem (Takakusaki, 2017), and its direct connections to the motor cortex via the hyperdirect pathway (Nambu et al., 2002). Understanding of the cortico-subthalamic

network activities that underlie natural walking in humans is, however, limited due to methodological constraints. Scalp electroencephalography (EEG) studies have shown that natural overground walking is associated with fluctuations in the alpha (8-12 Hz), beta (13-30 Hz), and gamma (70-90 Hz) frequency ranges from the sensorimotor regions of healthy subjects (Gwin et al., 2011; Seeber et al., 2015; Wagner et al., 2012). Although, EEG lacks the spatial resolution to discern whether these rhythms originate from the motor cortex or represent sensory feedback during walking, and are prone to movement artifacts. Basal ganglia field potentials recorded from implanted deep brain stimulation (DBS) leads of patients with Parkinson's disease (PD) have also revealed modulation of beta (13-30Hz) oscillations from the STN while stepping in place (Fischer et al., 2018; Hell et al., 2018; Tan et al., 2018) and during overground walking throughout the gait cycle (Arnulfo et al., 2018; Canessa et al., 2020; Hell et al., 2018). However, because aberrant beta oscillatory synchrony in the STN is a hallmark of akinesia in PD (Hammond et al., 2007; Little and Brown, 2014), and beta oscillations decreases with movement planning and execution in general, including those of the upper extremity (Eisinger et al., 2020; Kühn et al., 2004; Wingeier et al., 2006), whether these subthalamic beta modulations represent biomarker of specific gait events is unclear. Finally, little is known about cortical-subthalamic interactions during the natural gait cycle.

Our hypothesis is that the STN interacts with the motor cortex in a temporal-specific manner to coordinate reciprocal leg movements to generate effective bipedal locomotion. We investigated the cortical-subthalamic circuit dynamics of natural walking from three patients with PD without major gait disturbances in the on-mediation state to capture the most

physiological gait possible. Patients were implanted with chronic bilateral STN DBS leads and sensorimotor cortex electrocorticography (ECoG) paddles. Neural oscillatory activities were simultaneously and wirelessly streamed from the bilateral primary motor (M1) and somatosensory (S1) cortices as well as the STN during overground walking, and were synchronized to external gait kinematic sensors. Our aims were: 1) to characterize the oscillatory signatures of natural walking from the STN and sensorimotor cortices, 2) to identify cortico-subthalamic circuit coherence changes throughout the gait cycle, and 3) to determine accuracy of gait event decoding (i.e., heel-strike or toe-off) based on these cortical and subthalamic oscillatory signatures.

Materials and methods

Subjects and electrode reconstruction

Three male subjects with idiopathic PD undergoing evaluation for DBS surgery were enrolled at the University of California - San Francisco. Subjects did not exhibit major gait impairments, with MDS-UPDRS III postural instability and gait sub-scores on medication between 1 (slight) to 2 (mild) (**Table 1**). All subjects provided written informed consent (NCT03582891).

All subjects underwent bilateral implantation of quadripolar DBS leads into the STN (Medtronic model 3389), quadripolar cortical paddle overlying the sensorimotor cortices (Medtronic model 0913025), connected to bilateral investigational sensing pulse generators (Medtronic Summit RC+S model B35300R) as previously described (**Fig. 1**) (Gilron et al., 2021a).

Each RC+S device was connected to an STN DBS electrode and a cortical paddle from the same brain hemisphere.

DBS and cortical electrode localization were performed using 2-month postoperative CT images fused with preoperative T1-weighted MRI images. STN DBS lead reconstruction was performed using the DISTAL atlas and TRAC/CORE algorithm available within LEAD-DBS, an open-source MATLAB toolbox (Ewert et al., 2018; Horn and Kühn, 2015). Intracranial EEG Anatomical Processing and Electrode Reconstruction Pipeline (https://edden-gerber.github.io/ecog_recon/) was used for cortical paddle reconstruction. T1 images were parcellated and converted into a standardized cortical surface mesh using FreeSurfer (Dale et al., 1999) and AFNI's SUMA (Saad et al., 2004). Cortical contacts were then manually identified on the CT images in BioImage Suite (Papademetris et al.) and the electrode coordinates were projected onto the standardized mesh using a gradient descent algorithm in MATLAB. Postoperative lead localization was performed using

Neural recordings and gait kinematic measurements during natural walking

Subjects walked overground at their preferred speed for 2 minutes in a straight path of at least 15 feet before turning around. All subjects were on their typical dose of Parkinsonian medication during the task. In all subjects LFPs were recorded from two STN electrode pairs: *ventral STN* (+2-0) and *dorsal STN* (+3-1), where contact 0 is in the ventral STN, contact 3 just above the dorsal border, and contacts 1 and 2 in the motor territory based on microelectrode mapping (**Fig. 1A**). The two cortical electrode recording configuration were +9-8 (S1) and +11-

10 (M1), based on and imaging reconstruction. LFPs were sampled at 500 Hz and passed through a pre-amplifier high-pass filter of 0.85 Hz and low-pass filter of 450 Hz. Accelerometry data from the Summit RC+S system was sampled at 64 Hz. All data from the RC+S system was extracted and analyzed using open-source code (https://github.com/openmind-consortium/Analysis-rcs-data).

Gait kinematic data was collected using two wireless sensor systems: Delsys Trigno® system (Delsys Inc. Natick, MA) and Xsens MVN Analyze (Xsens Technologies, The Netherlands). The Delsys sensors included two Avanti force sensitive resistor (FSR) adapters, two Avanti goniometer adapters, and two Trigno surface electromyography (EMG) sensors with a built-in accelerometer. The Avanti adapters were placed bilaterally on the shank of the leg, and the EMG sensors were placed on top of both RC+S and used for synchronization (see below). Each FSR adapter was attached to four FSRs (Delsys DC:F01) placed under the calcaneus, hallux, 1st metatarsal (1MT), and 5th metatarsal (5MT). Digital goniometer (SG110/A) was placed next to the lateral malleolus. The Xsens system is comprised of 14 inertial measurement unit sensors placed over the entire body and limbs for wireless motion tracking.

Data analysis

LFP and gait kinematic data was synchronized by aligning the acceleration peaks captured by the RC+S, Delsys Trigno sensors over the RC+S, and Xsens accelerometry. Four signal processing methods were applied to the LFP signals using built in MATLAB functions: continuous wavelet transform (CWT; “cwt” function), wavelet coherence (“wcoherence”

function), short-time Fourier transform (STFT; “spectrogram” function), and power spectral density (PSD; “spectrogram” function with 1 second window, 90% window overlap, and a transform length of 512 data points). We used wavelet transformation because it has greater low-frequency resolution. We also used the Fourier transform because this is the on-board spectral decomposition method used by the RC+S system (Sellers et al., 2021).

Gait kinematic data was used to determine left and right toe-off and heel-strike events using a custom MATLAB script (**Fig. 2**). Heel-strike was defined as the time when the calcaneus or 5MT FSR crosses over a 5% threshold in the positive direction. Toe-off was defined as the time when the hallux or 1MT FSR crosses over the 5% threshold in the negative direction. For the Xsens system, toe-off was defined as the time of peak ankle plantarflexion velocity, while heel-strike was defined as the time of ankle velocity impulse. All gait events were visually inspected, and erroneous events were manually corrected. Turns were excluded from analysis. 40 gait cycles were included for analysis from subject 1, 67 for subject 2, and 106 for subject 3.

Individual gait cycle epochs were extracted from the CWT and wavelet coherence data and divided into time bins representing 1% of the gait cycle. Power and magnitude-square coherence values for each gait cycle were normalized to the average value during the entire walking period by z-score. Z-cored values for gait cycles were then averaged across subjects to obtain the grand average spectrogram and coherogram.

To identify frequency bands where power differed between gait events, instantaneous power at each gait event (left and right toe-off and heel-strike) were extracted. All possible frequency bands were created between 0-50 Hz, and a Kruskal-Wallis test was used to identify

frequency bands where power differed among the gait events. A Kruskal-Wallis test was used because the data sets were not normally distributed (Shapiro-Wilk test), but the variances of the different gait events were equal (Levene's test). P-values were adjusted using Tukey's Honest Significant Difference method. Frequency bands where the multiple comparison test reached p-values < 0.05 were designated as gait-event-modulated frequency bands.

Gait event classification

A classification model was built to predict gait events from LFP power and the STN-cortical coherence. The classification model used an ensemble learning approach to enhance the stability and accuracy (Polikar, 2006; Wolpert, 1992) and consisted of a Random Forest (RF) feature selection model and a linear discriminant analysis (LDA) model. RF has been shown to achieve better performance than other feature selection methods (Chen et al., 2020), and is robust to collinearity (Genuer et al., 2010). The LDA model matched the on-board hardware classifier of the RC+S. The classifier models were built in R with the "Tidymodel" framework (Kuhn and Wickham, 2020) and trained for each subject, brain hemisphere, and recording area.

Features used in the RF model were instantaneous power or magnitude-squared coherence during toe-off events in all possible frequency bands between 2.5-50 Hz. All features were normalized to a mean of 0 and a standard deviation of 1. Prior to feature selection, RF hyperparameters, the number of decision tress and number of features a tree considers during node splitting, were optimized using 10-fold cross-validation with each data set stratified by

toe-off classes. Once optimized, the RF feature selection model was trained on all normalized features using the "ranger" (Wright and Ziegler, 2017) package in RStudio (www.rstudio.com).

The top ten features with the largest variable importance value based on "permutation importance" (Altmann et al., 2010) were used to generate new data sets for each subject and brain hemisphere. Next, the new data sets were split into 75% for training and 25% for testing. The accuracy and receiver operator characteristic area under the curve (AUC) were calculated.

Statistical analysis

Linear repeated-measure mixed model was used to determine power or coherence values that differed from the average during the gait cycle. A single fixed effect was used, and subjects were added to the model as a random to account for individual baseline neural power differences. Significance was tested using F-tests with Satterthwaite's degrees of freedom method. Statistical analysis of classification models were performed only on models that achieved greater than chance accuracy (≥ 50%). Significance was tested by permuting the toe-off class labels 1000 times and calculating the class accuracy on the permuted data. Models were determined to be significant if it correctly classified the event in < 5% of total number of permutations (Herrojo Ruiz et al., 2014).

Results

STN shows coordinated low frequency power modulation during walking

To investigate STN and sensorimotor cortical neural dynamics during the gait cycle, we extracted and averaged spectral power across all gait cycle epochs and tested whether the power significantly changes during the gait cycle. We found that the two hemispheres showed coordinated and reciprocal changes in spectral power within the ventral and dorsal STN during the gait cycle. Significant changes in power were seen in the alpha to low-gamma frequency (10-50 Hz) band power in the ventral STN, and in low frequency (5-15 Hz) band power in the dorsal STN. Increased power occurred during double support phase, the period from ipsilateral heel-strike to contralateral toe-off (0-10% for the left leg and 50-60% for the right leg) (**Fig. 3A and B, top**). The left STN also demonstrated significant alpha-beta (8-30 Hz) power decrease during right leg swing period, and beta band (13-30 Hz) decrease during right heel-strike (**Fig. 3A and B, top**). These changes in LFP power were also seen in individual gait cycles across all subjects (**Extended Data Fig. 3-2 A and B**).

M1 and S1 also demonstrated power changes throughout the gait cycle, though the frequency-specific changes between the left and right hemispheres were not reciprocal. The left M1 showed decreased beta activity during right leg swing (10-30% of gait cycle) and increased beta power during right leg stance (60-80% of gait cycle) **(Fig. 3-1A, top)**. While the right M1 does not show significant beta power modulation, it showed theta power changes during the end of right leg swing and beginning of left leg swing **(Fig. 3-1A, bottom)**. The right S1 shows a similar pattern of theta modulation during transition from right leg swing to left leg swing (**Fig. 3-1B, bottom**).

STN interacts with motor and sensory cortices during different phases of the gait cycle

Because the STN has direct connections with sensorimotor cortices and plays important functions in motor control, we examined whether the STN interacts with the cortex during specific phases of the gait cycle. To determine the nature and degree of this interaction, we compared the averaged magnitude-squared coherence value between the STN and M1/S1 for each brain hemisphere during the gait cycle. We found increased STN-M1 theta band coherence during contralateral toe-off and initial contralateral leg swing, similar to the power modulations seen in the STN (**Fig. 4A**). Interesting, STN-S1 showed greater theta and alpha band coherence during ipsilateral heel-strike (**Fig. 4B**). The two brain hemispheres showed reciprocal coherence modulations.

Patient-specific oscillatory biomarkers of gait

Because our data showed several distinct gait-related frequency bands of modulation during the gait cycle, we used a data-driven approach to determine individual-specific frequency bands that are putative biomarkers for heel-strike and toe-off events. We created frequency bands of varying lengths ranging from 0-50 Hz, extracted power spectral density values at each gait event, and performed an ANOVA test for each band (**Fig. 5-1).** We found that each patient had unique frequency bands where power values differentiated gait events

(**Fig. 5**). Significant gait-event-modulated frequency bands were found within all canonical frequency bands, with a majority in the theta and beta bands (**Fig. 5A**). Frequency ranges of the gait-event-modulated bands varied by electrode location but were typically a sub-range of the canonical bands. By comparing the instantaneous power spectral density during each of the four gait events, we found power differences between gait events that are temporally distinct (**Fig. 5A, inset plots)**, whereas gait events occurring in temporal proximity have a more similar power spectra profile (**Fig. 5A**).

To evaluate how the amplitudes of these gait-specific biomarkers change over the gait cycle, we the averaged their power over a 1 second period around each gait event and found them to fluctuate for the duration of the gait cycle (**Fig. 5B**). Power averages for the left heel-strike and right toe-off events are offset by half a gait cycle to the right heel-strike and left toe-off events. In all subjects, the left and right hemispheres showed reciprocal power modulations across different contacts.

To investigate whether each gait event's instantaneous powers are distinct from each other, a multiple comparison test was performed between all possible pairs of gait events. Significant power differences were found between left and right heel-strikes in subjects 1 and 2 in both hemispheres (**Fig. 5C**). Other significant differences occurred between toe-off events (**Fig. 5C**). Gait events temporally close to each other did not differ in power.

Decoding gait events based on cortical and subcortical LFPs

Based on finding spectral signatures for specific gait events of the gait cycle, we wanted to decode gait events using these personalized "gait biomarkers." Using the linear discriminant analysis (LDA) model, we were able to classify toe-off events with ≥61% accuracy (**Table 2**) in all subjects from at least one of the recorded contacts (**Fig. 6**). Significant above-chance accuracy was achieved from models built using left and right hemisphere data in subjects 2 and 3, but only from left hemisphere trained models in subject 1. No electrode location outperformed others consistently but was subject specific. Overall, the median model accuracies were greater than chance and ranged from 54.4-60.3%. Further analysis of the models showed the maximum discriminatory value achieved, evaluated by calculating the area under the curve (AUC), ranged between 0.585-0.763.

We also explored whether coherence between STN to M1/S1 could classify toe-off events. The subcortical-cortical coherence pair that achieved the highest accuracy was subject specific, and only subject 2 and 3 had models reach significant above-chance accuracy (accuracy: 58.9-68.3%, AUC: 0.602-0.786) (**Fig.6-1**).

Discussion

We used chronic invasive recordings in PD patients to advance our understanding of dynamic subthalamic and sensorimotor oscillatory changes that underlie natural overground walking. First, we demonstrate the novel finding that STN displays increased low frequency (4-12 Hz) activity during the double support period prior to contralateral leg swing. Furthermore,

345 STN shows increased theta frequency coherence with the primary motor during initiation of
346 contralateral leg swing, implicating a potential mechanism for the supraspinal network to scale
347 and fine tune leg muscle activation during stepping. Our findings support the hypothesis that
348 oscillations from the basal ganglia and cortex direct alternating power fluctuations between the
349 two hemispheres in that is offset by half a gait cycle, which may indicate a mechanism to
350 coordinate and maintain continuous bipedal locomotion in humans. In addition, we identified
351 patient-specific, gait-related biomarkers in both subcortical and cortical areas at discrete
352 frequency bands. Exploratory ensemble classification models showed above-chance accuracy in
353 classifying left and right gait events using oscillatory power features.

354

355 Alternating multi-frequency modulations from bilateral STNs during gait

356 Several groups have described beta power modulations within the STN during the gait
357 cycle between the left and right hemispheres during seated stepping (Fischer et al., 2018) and
358 overground walking (Arnulfo et al., 2018; Canessa et al., 2020; Hell et al., 2018) in Parkinson's
359 disease patients. Because elevated beta synchrony within the STN is associated with the
360 akinetic state in Parkinson's disease, it is logical that beta desynchronization is required for
361 movement, including gait. We found that these gait-event related alternating power
362 modulations between the left and right STNs are not limited to the high beta frequency range
363 but also involve other low frequency bands.

What are the roles of subthalamic lower frequency (theta and alpha) modulation during gait? Previous studies on upper extremity movement tasks have shown event-related theta/alpha frequency synchronization within the STN at the onset and throughout the duration of a sustained voluntary muscle contraction task (Kato et al., 2016; Tan et al., 2013). In some cases, the amplitude of these theta/alpha oscillation correlate with the force generated during hand movement (Anzak et al., 2012). STN theta activity has also been shown to have a role in the cognitive control of movement, such as during sensorimotor conflict (Aron et al., 2016; Zavala et al., 2017) and response inhibition (Alegre et al., 2013). We posit that these low frequency oscillations emerge from the STN during periods of gait that require greater cortical engagement. Based on increases in STN theta/alpha power we found during the transition from double support (both feet on the ground) to single support (ipsilateral leg on the ground) period, we postulate that these low frequency modulations engage multiple motor cortical areas to generate the appropriate scale and force required during contralateral leg swing to maintain stable single limb support and bipedal locomotion.

While some suggest that low-frequency modulations during gait may be secondary to movement-related artifacts (Hell et al., 2018), we believe that these low-frequency oscillations reflect physiological signals for several reasons. First, spectral activities that change during the gait cycle are focal in frequency range and are not broadband in nature (**Fig. 3**). Second, the spectral power changes in left and right STNs are offset by half a gait cycle, unlike in a previous study where both STNs showed concurrent spectral power increases during the gait cycle regardless of laterality (Hell et al., 2018). Finally, the dorsal and ventral STN, as well as M1 and

S1 contacts connected to the same RC+S show different time-frequency changes from each other during the gait cycle, and hence less likely to reflect artifacts.

One key question is whether these gait-related oscillatory modulations reflect physiological or pathological gait patterns. While our patients did not have overt gait abnormalities such as shuffling gait or freezing of gait, they performed the walking task on dopaminergic medication, which can affect oscillatory activity (Foffani et al., 2006; Ray et al., 2008). Pallidal LFP recorded from patients with segmental dystonia without gait disorders has shown power modulations in the theta, alpha, and beta frequency during gait (Singh et al., 2011), and demonstrated similar theta/alpha frequency power modulations during early stance and swing phase of the contralateral leg. While we cannot rule out the presence of compensatory signals in the disease state, we speculate that our results are an indicator of physiological gait, rather than pathological. The dynamic changes of oscillations across different frequency bands may provide a mechanism to coordinate and recruit different cortical and subcortical areas in response to changes in posture, balance, and forward momentum during walking.

Cortical-subthalamic interactions during gait

In a study involving simultaneous recording of STN LFPs and scalp EEG during walking in Parkinson's disease patients with freezing of gait, the authors found elevated cortical-STN synchrony in 4-13 Hz during effective gait (Pozzi et al., 2019). The spatiotemporal specificity of

field potentials captures by the permanently implanted cortical electrodes indicate distinct interactions between the STN and different cortical areas during gait. We demonstrated increased STN-S1 coherence in the low frequency ranges (theta-alpha) during the double-support period between ipsilateral heel-strike and contralateral toe-off. We also found increased STN-M1 theta frequency coherence during contralateral toe-off and early contralateral leg swing. These alternations in coherence are offset by half a gait cycle between the left and right hemispheres. To our knowledge, this is the first report of distinct patterns of STN-S1 and STN-M1 synchrony during human gait. We speculate that increased STN-S1 coherence during ipsilateral heel-strike to contralateral toe-off may represent sensory integration during the double support period as one prepares for leg swing. Increases in STN-M1 theta coherence then follows, during initiation of contralateral leg swing, which may allow the motor cortex to regulate the force of leg muscle activation required to drive forward stepping during gait. While these M1-STN interactions may represent normal recruitment of leg muscles during weight acceptance and transfer phase of the gait cycle, they may also represent compensatory mechanisms by which greater cortical activity is required to drive and maintain locomotion in Parkinson's disease.

Gait event decoding and potential clinical significance

A key finding from our study was that for each patient, a unique range of frequencies were significantly differentially modulated corresponding to the various gait events. While these frequency bands often overlap canonical bands, they are usually narrower and span many

different canonical frequencies. The variations among patients may be due to slight differences in electrode placement. While our results show greater than chance median accuracy and acceptable to medium discriminatory ability, the models may be under-optimized for each subject. By constraining the set of possible hyperparameter values, possible values that would result in better accuracy and discriminatory ability for different subjects may have been missed. Additionally, the ratio of features (1770 total) compared to observations during feature selection can over-fit the model, leading to poor feature selection. Nonetheless, our study demonstrates the feasibility of distinguishing gait events based on cortical or STN LFP power.

One of the reasons to identify gait-specific biomarkers is to use them as control signals for closed-loop, also known as adaptive DBS (aDBS). The Summit RC+S system implanted in our subjects allow for aDBS in real time and utilizes LDA to detect different brain states using Fourier transform power within a frequency band (Ansó et al., 2022; Sellers et al., 2021). The aDBS feature of the Summit RC+S device has been successfully tested in PD patients (Gilron et al., 2021a, 2021b) and a cervical dystonia patient (Johnson et al., 2021), with varying timescale for stimulation changes (from 100s of milliseconds to minutes). Therefore, it is feasible to implement real time aDBS to rapidly change stimulation parameters to improve gait function in Parkinson's disease patients.

Limitations

Our sample size is small due to invasive nature of these studies with investigational devices. Patients performed all tasks while on medication, which may affect beta power modulation. Due to variations in patient anatomy and electrode placement, M1 and S1 electrodes may capture different parts of the homunculus. Our event-related power modulation from the cortex may be related to arm rather than leg movement. However, in another study, we have observed that the motor cortex is attuned to different limb movements in different frequency ranges (i.e., greater beta modulation during arm swing vs. greater theta modulation during leg movement; unpublished data). Additionally, there is increasing evidence pointing to the existence of intermixed neural tuning of the whole body, including leg and foot movement, in the "hand knob" area of the precentral gyrus in humans (Willett et al., 2020; Zeharia et al., 2012).

Conclusion

This study provides new insights on the role of subthalamic and sensorimotor oscillations play in human gait. Our data also support the notion that the STN and sensorimotor cortices contain patient-specific, gait-related frequency modulations that can be used to distinguish between left and right gait events. This knowledge has the potential to be integrated into adaptive neuromodulation therapies to improve gait functions in patients with Parkinson's disease.

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Figure and legends

Figure 1 DBS and cortical lead localization. (**A**) 3D reconstructions of all DBS lead locations in the STN (orange). Individual subject's leads are shown in by different colors. (**B**) 3D reconstructions of cortical electrode paddle location. The two most anterior contacts overlie the primary motor cortex (M1), while the two most posterior contacts overlie the somatosensory cortex (S1).

Figure 2 Synchronized gait kinematic data with raw local field potential recordings during natural walking. (**A**) Illustration of gait events and phases during a single gait cycle, aligned to left heel-strike (0% gait cycle). (**B**) Heel-strike (squares) and toe-off (circles) gait events were detected from the left (black) and right (gray) force sensitive resistor data. Heel-strikes were detected when the heel force (solid line) exceeded a threshold (dotted line), and toe-offs were detected when toe force (dashed line) fell below the threshold. (**C**) Example local field potential recordings from both STN and M1 synchronized to a gait cycle.

Figure 3 STN local field potentials show spectral power modulations during the gait cycle. Grand average z-score spectrograms from the dorsal and ventral STNs normalized to a gait cycle. (**A and B**) Significant power increases are seen during weight acceptance of the left leg in

the left hemisphere (~0-10% gait cycle) and right leg in the right hemisphere (~50-60% gait cycle). Power increases was observed in a wide frequency band (10-50 Hz) in the ventral STN and in low frequency band (5-15 Hz) in the dorsal STN. Significant beta (13-30 Hz) desynchronization was also seen during contralateral leg swing and heel-strikes. (**A and B**) Gait cycle percentages and frequencies where power was significantly different compared to the average power during the entire walking task is outlined by the dashed white lines. A linear mixed-effect model was used to determine significance with p-value < 0.05. Extended Data Figure 3-1 shows grand average gait cycles from cortical recorded contacts. Extended Data Figure 3-2 shows a single gait cycle from all recorded areas from all subjects in the study and shows alternating left-right power changes throughout the gait cycle.

Figure 3-1 Cortical local field potentials show spectral power modulations during the gait cycle. (**A**) Left M1 shows alpha (8-10 Hz) and beta desynchronization during right leg heels strike and initial right leg swing, respectively. Right M1 shows increased theta-alpha (5-12 Hz) during initial left leg swing and decreased beta around left heel-strike. (**B**) Significant decreased beta power is seen during left leg weight acceptance and initial right leg swing. Increases in theta-beta power (5-23 Hz) were seen during weight acceptance of the right leg and initial left leg swing.

633 **Figure 3-2 Individual gait cycle spectrograms.** Spectrograms of a single gait cycle from the STN
634 and sensorimotor cortices. All subjects show alternating left and right spectral power changes
635 throughout the gait cycle.

636

637 **Figure 4 Low frequency STN/Cortical coherence increase during the initiation of contralateral**
638 **leg swing.** Grand average z-score coherogram from STN-M1 and -S1 normalized to a gait cycle.
639 Reciprocal coherence modulation was seen in both hemispheres. (**A**) STN-M1 coherence
640 showed significant increases in the theta band (5-8 Hz) during the initiation of contralateral leg
641 swing through mid-swing. Additionally, the left hemisphere showed beta band coherence
642 increases during initial ipsilateral weight acceptance. (**B**) STN-S1 coherence modulation was
643 seen theta/alpha band across both hemispheres during ipsilateral heel-strike. (**A and B**) Gait
644 cycle percentages and frequencies where coherence was significantly different from the
645 average coherence during the entire walking task are outlined by the dashed white lines. A
646 linear mixed-effect model was used to determine significance with p-value < 0.05.

647

648 **Figure 5 Unique frequency bands within each subject can differentiate gait events.** (**A**)
649 Average heel-strike and toe-off PSDs from the STN and M1. Each subject had unique frequency
650 bands where power during heel-strikes (left heel-strike = green, right heel-strike = orange) and
651 toe-off (left toe-off = blue, right toe-off = pink) gait events were significantly different ($p < 0.05$).
652 The unique frequency bands were mainly found within the canonical frequency ranges (color of
653 shaded area), but rarely spanned the entire range (width of shaded area). Inset plots show

power differences between gait events temporally distinct from each other in relation to the gait cycle. (**B**) Average power and standard error ± 1 second around the gait event. Reciprocal power modulation, offset by half a gait cycle, is seen between temporally distinct gait events in all subjects. Furthermore, all left hemisphere data show higher power during left heel-strike/right toe-off and most of the right hemisphere data show higher power during right heel-strike/left toe-off. (**C**) Boxplot of gait event power within the frequency bands from B. Individual gait event powers are shown as transparent colored dots with outliers shown on the dotted line. Multiple comparison tests were performed against each pair of gait event within the same hemisphere. Level of significance is indicated as follows: * = $p<0.05$ and ** = $p<0.005$. Extended Data Figure 5-1 shows a visualization of the arbitrary length frequency bands created and an ANOVA p-value heat-map.

Figure 5-1 Example arbitrary frequency bands and Kruskal-Wallis testing. Related to Figure 5. Varying length frequency bands were created between 0-50 Hz. Each frequency is referenced as a bin. Start and end bin refers to the varying length frequency band's start and end frequency. Power during left and right heel-strike and toe-off events were extracted from each frequency band and an Kruskal-Wallis test was performed. The p-value of the Kruskal-Wallis test was stored and a heat map was created. Example of the resulting heat map is shown from subject 2 M1 recorded area. Significant Kruskal-Wallis test outcomes can be observed to fall within the low gamma band (35-45 Hz) frequency.

Figure 6 Gait event decoding using oscillatory features achieves greater than chance accuracy. LDA ensemble classifiers were trained on left and right toe-off events for each contact and hemisphere across all subjects. All subjects had at least one contact where at least one model's classification accuracy was ≥61.1%. Maximum accuracy achieved across all subjects were between 61.1-69.2%. Maximum discriminatory ability was calculated using the area under the receiver operator characteristic curve and ranged between 0.585-0.763. Each subject's models are shown on each row. The recorded area the LDA model was built from is indicated in color and follows this order (left to right): red – ventral STN, green – dorsal STN, blue – S1, purple – M1. Bar pattern indicates brain hemisphere the model was built from: solid – left hemisphere, striped – right hemisphere. Asterisks ("*") above bar indicates significance: p-val < 0.05 (*), <0.005 ("**"), <0.0005 ("***"). Extended Data Figure 6-1 shows results from classifier models built using coherence values between the STN and M1.

Figure 6-1 Toe-off gait event decoding using STN-M1 coherence. LDA ensemble classifiers were trained using coherence magnitude squared values between the ventral and dorsal STN to M1 and S1. Highest accuracy and discriminatory value achieved were similar to models built from individual recorded areas. The highest accuracy achieved were between 58.9-68.3% and highest discriminatory values were between 0.602-0.786. Each subject's models are shown on each row. The recorded area the LDA model was built from is indicated in color and follows this order (left to right): pink – ventral STN, yellow – dorsal STN, brown – S1, orange – M1. Bar pattern indicates brain hemisphere the model was built from: solid – left hemisphere, striped –

696 right hemisphere. Asterisks ("*") above bar indicates significance: p-val < 0.05 (*), <0.005

697 ("**"), <0.0005 ("***").

698

Tables

Table 1
Subject Demographics

ID	Age/Sex	Disease Duration	DBS Target	UPDRS III Total Off-meds	UPDRS III Total On-meds	UPDRS III PIGD* On-meds
Subject 1	42/M	06	STN	41	14	2
Subject 2	58/M	09	STN	34	09	1
Subject 3	61/M	05	STN	35	12	1

Table 2
Classification Summary

ID	Median Accuracy	Maximum Accuracy	Median AUC	Maximum AUC
Subject 1	55.8%	69.2%	0.592	0.763
Subject 2	60.3%	68.0%	0.635	0.733
Subject 3	54.4%	61.1%	0.574	0.585

AUC = Area Under the Curve