Pallidal deep brain stimulation disrupts pallidal beta oscillations and coherence with primary motor cortex in Parkinson's disease

Doris D. Wang, MD, PhD, Coralie de Hemptinne, PhD, Svjetlana Miocinovic, MD, PhD, Jill L. Ostrem, MD, Nicholas B. Galifianakis, MD, Marta San Luciano, MD, and Philip A. Starr, MD, PhD

1Department of Neurological Surgery
2Department of Neurology, University of California San Francisco, San Francisco, CA, USA
3Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA

DOI: 10.1523/JNEUROSCI.0431-18.2018

Received: 16 February 2018
Revised: 27 March 2018
Accepted: 5 April 2018
Published: 16 April 2018


Conflict of Interest: The authors declare no competing financial interests.

This work was supported by NIH R25 PAR-13-384 NINDS grant and R01 NS090913-01.

Corresponding author: Doris D. Wang, doris.wang@cusf.edu, 505 Parnassus, M779, Department of Neurological Surgery, University of California San Francisco, Box 0112, San Francisco, CA 94143-0112

Cite as: J. Neurosci ; 10.1523/JNEUROSCI.0431-18.2018

Alerts: Sign up at www.jneurosci.org/cgi/alerts to receive customized email alerts when the fully formatted version of this article is published.

Accepted manuscripts are peer-reviewed but have not been through the copyediting, formatting, or proofreading process.

Copyright © 2018 the authors
Pallidal deep brain stimulation disrupts pallidal beta oscillations and coherence with primary motor cortex in Parkinson’s disease

Doris D. Wang, MD, PhD1, Coralie de Hemptinne, PhD1, Svjetlana Miocinovic, MD, PhD3, Jill L. Ostrem, MD2, Nicholas B. Galifianakis, MD2, Marta San Luciano, MD2, Philip A. Starr, MD, PhD1

1Department of Neurological Surgery, 2Department of Neurology, University of California San Francisco, San Francisco, CA, USA
3Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA

Corresponding author

Doris D. Wang
doris.wang@cusf.edu
505 Parnassus, M779
Department of Neurological Surgery
University of California San Francisco
Box 0112
San Francisco, CA 94143-0112

Keywords: dystonia, beta oscillation, local field potential, electrocorticography, movement disorders, cross frequency interaction, phase coherence, amplitude coherence, synchronization, basal ganglia thalamocortical network

Authors’ contributions and conflict of interest disclosures: Authors report no conflict of interest.

Acknowledgement: This work was supported by NIH R25 PAR-13-384 NINDS grant and R01 NS090913-01.
ABSTRACT

In Parkinson’s disease (PD), subthalamic nucleus beta band oscillations are decreased by therapeutic deep brain stimulation (DBS) and this has been proposed as important to the mechanism of therapy. The globus pallidus is a common alternative target for PD with similar motor benefits as subthalamic DBS, but effects of pallidal stimulation in PD are not well studied, and effects of pallidal DBS on cortical function in PD are unknown. Here, in 20 PD and 14 isolated dystonia human patients of both genders undergoing pallidal DBS lead implantation, we recorded local field potentials (LFPs) from the globus pallidus and in a subset of these, recorded simultaneous sensorimotor cortex electrocorticography (ECoG) potentials. PD patients had elevated resting pallidal low beta band (13-20 Hz) power compared to dystonia patients, whereas dystonia patients had elevated resting pallidal theta band (4-8 Hz) power compared to PD. We show that this results in disease-specific patterns of interaction between the pallidum and motor cortex: PD patients demonstrated relatively elevated phase coherence with the motor cortex in the beta band and this was reduced by therapeutic pallidal DBS. Dystonia patients had greater theta band phase coherence. Our results support the hypothesis that specific motor phenomenology observed in movement disorders are associated with elevated network oscillations in specific frequency bands, and that DBS in movement disorders acts in general by disrupting elevated synchronization between basal ganglia output and motor cortex.
SIGNIFICANCE STATEMENT

Perturbations in synchronized oscillatory activity in brain networks are increasingly recognized as important features in movement disorders. The globus pallidus is a commonly used target for deep brain stimulation (DBS) in Parkinson’s disease (PD), however, the effects of pallidal DBS on basal ganglia and cortical oscillations are unknown. Using invasive intraoperative recordings in patients with PD and isolated dystonia, we found disease-specific patterns of elevated oscillatory synchronization within the pallidum and in coherence between pallidum and motor cortex. Therapeutic pallidal DBS in PD suppresses these elevated synchronizations, reducing the influence of diseased basal ganglia on cortical physiology. We propose a general mechanism for DBS therapy in movement disorders: functional disconnection of basal ganglia output and motor cortex by coherence suppression.
INTRODUCTION

Alterations in synchronized oscillatory activity in brain networks are increasingly recognized as important in neurological disease (Voytek and Knight, 2015). In movement disorders such as Parkinson’s disease (PD), much has been learned about oscillatory activity from invasive recordings of field potentials in humans undergoing deep brain stimulator (DBS) implantation surgery. In PD, dopamine replacement and DBS therapy reduce the resting state amplitude of beta band (13-30 Hz) oscillatory activity in the subthalamic nucleus (STN), and these reductions correlate with improvements in bradykinesia and rigidity (Brown et al., 2001; Priori et al., 2004; Kuhn et al., 2008; Bronte-Stewart et al., 2009). Further, dopamine replacement and STN DBS both reduce cortical synchronization, as manifested by the entrainment of high frequency activity to beta phase (de Hemptinne et al., 2015; Swann et al., 2015). These findings support the theory that excessive beta oscillatory synchronization throughout the basal ganglia-thalamocortical (BGTC) motor circuit is a key component of the circuit abnormality underlying the motor signs of PD (Weinberger et al., 2006; Hammond et al., 2007; Giannicola et al., 2010; Oswal et al., 2013).

Most invasive studies of human physiology in PD have focused on the STN alone or on subthalamic-cortical interactions. However, there is increasing interest in targeting the globus pallidus (GP) for DBS therapy in PD, based on equivalent motor benefits in three of four randomized trials of STN versus GP DBS (Anderson et al., 2005; Okun et al., 2009; Follett et al., 2010; Odekerken et al., 2013; Ramirez-Zamora and Ostrem, 2018) and increased safety in patients with pre-existing mild cognitive decline or mood disorders (Okun et al., 2009; Follett et al., 2010). Consistent with the evolving theory of excessive beta oscillatory activity in PD, several studies have shown higher resting state beta band oscillatory activity in the GP of PD compared to non-parkinsonian conditions (Silberstein et al., 2003; Weinberger et al., 2012; Jimenez-Shahed et al., 2016). However, no studies have investigated interactions between the pallidum and the sensorimotor cortex in PD at high spatial and temporal resolution, compared such interaction with non-PD conditions, or studied the network effects of therapeutic pallidal DBS.
Here, using combined local field potential (LFP) and electrocorticography (ECoG) recordings in patients undergoing DBS in the awake state, we evaluate pallidal and cortical oscillatory activity in akinetic-rigid PD and in a nonparkinsonian disorder, isolated dystonia. We confirm in this large series that PD patients have relatively elevated resting pallidal oscillatory synchronization in the beta range, while dystonia patients have relatively higher theta oscillations (Silberstein et al., 2003; Weinberger et al., 2012). We show that these patterns of oscillatory synchronization in basal ganglia output influence primary motor cortex through disease specific patterns of phase coherence, and that therapeutic pallidal stimulation disrupts elevated pallido-cortical beta coherence in PD. We propose that this disruption of synchronization between basal ganglia output and motor cortex represents a general mechanism for the therapeutic effect of basal ganglia DBS in movement disorders.
METHODS:

Patients:
Patients with PD and isolated dystonia were recruited from the movement disorders surgery clinics at the University of California San Francisco or the San Francisco Veteran Affairs Medical Center. Our study included 20 PD patients (18 male, 2 female) and 14 isolated dystonia patients (8 male, 6 female). All patients were scheduled to undergo implantation of deep brain stimulator electrodes into the GP, and underwent evaluation for motor impairments within 3 months prior to surgery using the Unified Parkinson’s Disease Rating Scale motor subscale (UPDRS-III) in the off- and on-medication states (for PD patients), or the Toronto Western Spasmodic Torticollis Rating Scale and Burke-Fahn-Marsden Dystonia Rating Scale (for dystonia patients). Inclusion criteria were the following: for PD patients, akinesia and rigidity as the most prominent symptoms with UPDRS-III ≥ 30 in the off state and absent observed tremor during the resting state intraoperative recording, since tremor can have a confounding effect on beta band activity (Qasim et al., 2016). Note that PD patient #14 only had tremors during the DBS ON/OFF recordings and not during resting state recordings. Significant tremor was detected based on an accelerometer attached to the contralateral wrist, rhythmic EMG activity, and/or review of the intraoperative video. For isolated dystonia patients, those with focal cervical dystonia, segmental craniocervical dystonia or generalized dystonia without evidence for acquired etiology were included in the study. Informed consent was obtained prior to surgery under a protocol approved by the Institutional Review Board.

DBS electrode implantation in PD and dystonia patients:
Surgery and recording was performed at least 12 h after stopping all dopaminergic medications (PD group), and oral benzodiazepines and baclofen (dystonia group). Surgical planning and placement of DBS electrodes in the GP were performed using methods previously described (Starr, 2002). Briefly, the intended target location in the posterior internal pallidum is identified on T2 or inversion-recovery (IR) fast spin echo sequence, approximately 17.5 mm lateral to the wall of the third ventricle, 2 mm anterior, and 5 mm inferior to the mid commissural point (the midpoint of the line connecting the...
anterior and posterior commissures) (Figure 1A). All surgeries were performed in the awake resting state after discontinuation of propofol for at least 30 minutes. Microelectrode recordings (MER) were performed to map movement-related single units, and borders of the Gpi and GPe were defined based on the MER map. A DBS lead (Medtronic model 3387 for all patients) was then placed. All DBS electrodes were placed with contact 0 at the base of GP, at the border with optic tract, contact 1 in the Gpi, and contact 2 and/or 3 in the GPe. LFPs were recorded from the motor territory in the bipolar configuration with contact 1 as the active electrode and either contact 0 or 2 as reference. Targeting was confirmed by electrical stimulation-induced symptom improvement and side effect thresholds obtained by DBS stimulation. Postoperative MRI was used to confirm correct lead location.

Subdural electrode placement and localization

LFP were recorded in all patients. In addition, a subset of patients underwent placement of a temporary subdural electrode to record signals from the motor cortex (13 PD patients and 12 dystonia patients). A 6-contact subdural ECoG strip (all except PD patients #18 and #20, who had a high-density 28-contact ECoG strip) was placed on the surface of the brain through the same burr hole used for the DBS implantation. Signals recorded using the 6-contact ECoG electrodes (11 PD patients and 12 dystonia patients) were used for all M1 spectral power and coherence comparisons across PD and dystonia patients to keep our methodology consistent. Data collected from the 28-contact ECoG electrode were only used for within subject comparisons during DBS OFF/ON/OFF experiments for PD patients (see below).

The intended target location was the arm area of primary motor cortex (M1), approximately 3 cm from the mid-line and slightly medial to the hand knob (Figure 1B). The ECoG contact locations were confirmed anatomically using intraoperative computed tomography (iCT) fused to the preoperative planning magnetic resonance imaging with standard surgical planning software (Framelink, version 5.1; Medtronic, Inc, Minneapolis MN). Median nerve somatosensory-evoked potentials (SSEPs) were recorded, and reversal of the first negative component of the cortical SSEP (N20) waveform indicated the M1 contact location (Figure 1C) (Crowell et al., 2012; de
Hemptinne et al., 2013; Miocinovic et al., 2015). We found high concordance between anatomical and physiologic determinations of contact position with respect to the central sulcus (CS) in 20 of 25 patients, but in case of discrepancy (5 patients), the SSEP location was used. M1 spectral power and coherence analysis were performed using the signal recorded from contact pairs spanning M1 (as specified by SSEP reversal and anatomical localization).

**Intracranial recording**

All pallidal LFP recordings were performed intraoperatively within 5-30 min after DBS electrode implantation. The LFPs and ECoG potentials were recorded using the Alpha Omega Microguide Pro (Alpha Omega, Inc, Nazareth, Israel n = 19, 9 PD and 10 dystonia patients), the Neuro Omega (Alpha Omega, Inc, Nazareth, Israel n = 12, 8 PD and 4 dystonia patients), or the PZ5 Neurodigitizer (Tucker-David Technologies, Inc, Alachua, FL; n=3 PD patients) and sampled at 3000, 22,000, or 3052 Hz, respectively. Signals were highpass-filtered at 1Hz. Bipolar GP LFPs were recorded from the physiologically identified motor territory between either contacts 1 (active) and 0 (reference) or contacts 1 (active) and 2 (reference) of the DBS electrode. Because the electrode array spans both the internal and external pallidum, we refer to the recording site using the more general term “globus pallidus” rather than “globus pallidus internus”.

All ECoG potentials were recorded in bipolar configuration with either the most anterior contact of a 6-contact electrode (contact 6) used as reference (when using the Alpha Omega system) or a scalp needle as reference (when using the Neuro Omega and TDT systems). All recorded signals were then re-referenced offline by subtracting signals from adjacent contacts (1-2, 2-3, etc) for the 6-contact ECoG strip (23 patients) or by subtracting the common average from all electrodes for the 28-contact strip electrodes (2 patients).

**During DBS stimulation:** Four PD patients (patients #3, #8, #18, and #20) underwent simultaneous recording of pallidal LFP and motor ECoG potential during therapeutic pallidal DBS stimulation through the DBS lead (monopolar stimulating using contact 1 as the active electrode and shoulder pad as reference) using either the Neuro Omega.
(patient #3, 130 Hz, 90 μS, 2-4 mA) or an analog neurostimulator (Medtronic model 3625; patients #8, #18, and #20, 180 Hz, 60-90 μS, 4-6V). Pallidal LFP were recorded from contacts 0 and 2. Changes in clinical symptoms were determined in contralateral limb rigidity, bradykinesia, and tremor using the UPDRS III motor subscale by an unblinded neurologist.

**Behavioral Tasks**

Recordings were performed in two conditions. 1) During rest: patients were instructed to keep their eyes open and refrain from any voluntary movements. 2) During a movement task: patients performed flexion-extension of the elbow (3- to 5-second movement epoch and 3- to 5-second hold epoch repeated for one minute; 5 PD and 7 dystonia patients) or an iPad (Apple Inc., Cupertino, CA) tapping task where the patient lifted his or her arm from the resting position and touched dots on the screen on cue (~5 seconds of movement with 5 seconds of hold epoch repeated 10 times; 2 PD and 3 dystonia patients) (de Hemptinne et al., 2015; Rowland et al., 2015). All patients had recordings performed at rest, and seven patients with PD and ten patients with dystonia underwent the movement task. We distinguish “rest” from “hold” as patients were engaged in a task and prepared to move during the “hold” epochs. Muscle activity was recorded using surface electromyography from the deltoid, biceps brachii, and extensor carpi radialis muscles. Movement was detected by a wrist accelerometer.

**Signal processing and data analysis:**

LFP and ECoG potential data were processed and analyzed offline in MATLAB (Mathworks, Inc). Data were down sampled to 1 KHz and notch filtered for power line noise (60 Hz) and its harmonics (at 120, 180, 240 Hz) using a Butterworth filter. For data recorded at rest, the first 30 seconds of data without obvious electrical noise or movement were selected for the analyses. For data recorded during DBS ON, stimulation artifact was rejected by removing 30 sample data points (22,000 Hz sampling rate) around the stimulation artifact peak, and interpolating the data points at the beginning and end of artifact using a straight line (patient #3). For patients #8, #18, and #20, there was less high frequency stimulation artifact such that notch filtering alone was sufficient for artifact removal. Data recorded during stimulation was notch-
filtered for stimulation frequency (130 or 180 Hz) and its first and second order
harmonics using a Butterworth filter. For data recorded during the movement task, hold
and movement epochs were defined using EMG data and each epoch >1 second were
included for PSD analyses (see below).

**Spectral Power:** Power spectral density (PSD) was calculated using the Welch
periodogram method (Matlab function pwelch). For PSD calculations, we used a fast
Fourier transform of 1024 points (for a frequency resolution of 0.95 Hz) and 50%
overlap using a Hann window to reduce edge effects. Power was normalized as
percentage of total power between 4-100 Hz excluding 55-65 Hz line noise (Silberstein
et al., 2003). Percent total power of the resulting normalization was averaged across the
following frequency bands: theta (4-8 Hz), alpha (8-12 Hz), low beta (13-20 Hz), high
beta (20-30 Hz), beta (13-30 Hz), broadband gamma (50-200 Hz), and high frequency
oscillations (HFO, 200-400Hz).

Spectrograms during DBS OFF/ON/OFF recording were performed using the short time
Fourier transform (Matlab function spectrogram) with a 1024-point window and 50-ms
frame advance. Spectral power across the entire recording is plotted on a log power
color scale.

**Beta Burst:** To quantify bursts of LFP or ECoG potential beta activity, we used
methods previously described (Tinkhauser et al., 2017b; Tinkhauser et al., 2017a). Beta
band peaks were individually visually identified on log spectral power density plots.
Each LFP or ECoG potential signal was bandpass filtered (± 4 Hz) around individual
beta peak frequency, and the amplitude envelope of the beta activity envelope was
obtained. A threshold was then set at the 75\(^{th}\) percentile of the beta amplitude. The
onset of a burst was defined as when the filtered signal crossed the threshold amplitude
and the end of the burst defined as when the amplitude fell below threshold (Figure
4A). An example of a scatter plot showing the distribution of burst amplitudes and
lengths is demonstrated in Figure 4B. Bursts lasting <100ms were discarded from
analysis. Bursts were then categorized according to their duration into nine time
windows and compared across disease states. Mean amplitudes, mean durations of
bursts, and burst frequencies (number of bursts per second) were calculated for each individual recording and compared across disease states.

**Coherence:** Coherence (magnitude-squared coherence) was calculated using Welch's averaged modified periodogram method with a 1 s window and a frequency resolution of 1 Hz (MATLAB function mscohere). Coherence was analyzed along a spectrum of frequencies, and averaged across the aforementioned frequency bands. Comparisons were made between averaged coherence in a given frequency band.

Phase coherence, was measured by bandpass filtering each signal around the frequency band of interest using a two way, least squares FIR filter (eegfilt from EEGLAB toolbox). Phase information was extracted from each filtered signal using the Hilbert transform, and was used to calculate the phase difference, $\phi$. The angular phase difference distribution was obtained by transforming $\phi$ onto the unit circle in the complex plane using Euler's formula (Qasim et al., 2016).

Amplitude coherence was performed by taking the amplitude envelope for each bandpass-filtered signal and calculating the Pearson's correlation coefficient between the amplitude envelopes over the course of recording. This correlation coefficient was squared in order to make it more comparable to magnitude-squared coherence (Qasim et al., 2016).

**Phase-amplitude coupling:** We calculated phase-amplitude coupling (PAC) between the phase of low frequencies (4-50 Hz) and the amplitude of high frequencies (50-200 Hz) from M1 ECoG potentials using the Tort method (Tort et al., 2010). Mean beta phase-gamma amplitude PAC value was calculated by averaging PAC indices from 13 to 30 Hz in the phase frequency range and from 50 to 200 Hz in the amplitude frequency range (de Hemptinne et al., 2015; Miocinovic et al., 2015).

**Statistical Analysis**
The nonparametric Wilcoxon rank sum test (Matlab function ranksum) was used to evaluate differences between PD and dystonia patients for all variables studied. Two-
way ANOVA was used to compare beta burst distribution and disease state (Tinkhauser et al., 2017a). Repeated measure ANOVA with post-hoc Tukey’s test was used for within-subject comparisons during different DBS stimulation conditions. All statistics with multiple comparisons were false discovery rate (FDR) corrected and only adjusted p-values are presented (Hochberg and Benjamini, 1990).
RESULTS

Study subjects
We recorded simultaneous pallidal and motor cortex recordings in 13 PD patients and 12 dystonia patients. In an additional seven PD and one dystonia patients, we recorded only pallidal LFPs. Clinical characteristics, including lead contact locations, for PD and dystonia patients are summarized in Tables 1 and 2, respectively. Mean age was 63.3 ± 7.7 years for PD and 44.7 ± 11.8 years for dystonia. For PD patients, mean UPDRS-III off medication score was 46 ± 11 and on medication was 24 ± 8. For dystonia patients, the mean TWSTRS score was 18 ± 10 and BFMDRS score was 19 ± 12. Seven of the dystonia patients had focal cervical, or segmental craniocervical forms, without any limb or trunk involvement, and seven had generalized dystonia. Example lead location in the GP and cortex, and examples of resting recordings in PD and dystonia are shown in Figure 1.

Pallidal, and not M1, beta and theta oscillations distinguish PD and dystonia in the resting state
First, we utilized all pallidal recordings (pooling those with and without simultaneous cortical recordings) to confirm disease specific patterns of pallidal oscillatory activity. Representative GP LFP recordings for a PD and dystonia patient are shown in Figure 1D. Average LFP RMS voltage was 19.3 ± 14.4 μV for PD and 16.3 ± 13.6 μV for dystonia (p=0.2554; Wilcoxon rank sum test). Log transformed power spectral densities for a PD patient and a dystonia patient are plotted in Figure 2A, and group comparisons showed that PD patients had higher resting beta power than dystonia (PD vs. dystonia: low beta: p=0.0039, high beta: p=0.0224; post-hoc FDR-ADJUSTED Wilcoxon rank sum). To account for intersubject variability in signal amplitude, we normalized each power spectrum as percent of total power between 4-100 Hz excluding line noise around 55-65 Hz (Silberstein et al., 2003) (Figure 2C). Normalized spectral power was averaged for physiologically relevant frequency bands theta (4-8 Hz), alpha (8-12 Hz), low beta (13-20 Hz), high beta (20-30 Hz), broadband gamma (50-200 Hz), and high frequency oscillation (HFO, 200-400 Hz). We found that dystonia patients had higher theta power than PD, and PD patients had higher low beta
band power than dystonia (PD vs. dystonia: theta: $p=0.0223$, alpha: $p=1.0$, low beta: $p=0.0132$, high beta: $p=0.7342$, broadband gamma: $p=0.1323$, HFO: $p=0.7342$; post-hoc FDR-adjusted Wilcoxon rank sum; Figure 2C).

We also compared resting oscillatory activity recorded from M1 in a subset of 11 PD and 12 dystonia patients with a temporarily placed 6-contact electrocorticography (ECoG) strip electrode placed over the sensorimotor area (Figure 1B). Representative M1 ECoG potentials and log spectral powers from a PD and dystonia patient are shown in Figure 1D and Figure 2B, respectively. Normalized M1 spectral power showed no difference in any oscillatory bands measured (PD vs. dystonia: theta: $p=0.9755$, alpha: $p=0.6903$, low beta: $p=0.9382$, high beta: $p=0.6903$, broadband gamma: $p=0.8834$, HFO: $p=0.9382$; post-hoc FDR-adjusted Wilcoxon rank sum test; Figure 2D).

Pallidal movement-related desynchronization is more pronounced in PD

Since beta band desynchronization in the motor system is a critical feature of normal movement (Crone et al., 1998; Taniguchi et al., 2000), and beta band activity in PD in the pallidum is elevated at rest, we hypothesized that movement initiation might require a more pronounced decrease in pallidal beta band activity, compared to nonparkinsonian conditions. We therefore investigated how pallidal and M1 oscillatory activity changes with movement. Seven PD patients and ten dystonia patients participated in either an elbow movement task or an iPad arm-reaching task which showed similar levels of movement-related power changes. We separated each recording into hold and movement epochs based on surface electromyography recordings (Figure 3A). Spectral power for each hold and movement epochs >1 second were calculated and averaged for the pallidum (Figure 3B) and M1. These values were also compared to those recorded during rest, when the patient is not engaged in a task (Figure 3B). Movement-related power changes were measured by subtracting the averaged power spectra during movement from the averaged power spectra during hold phase and calculating the percent power change from the hold phase power. PD patients had greater alpha and beta band desynchronization with movement compared to those of dystonia patients, and this difference was evident in individual recordings (PD vs. dystonia: theta: $p=0.1613$, alpha: $p=0.0226$, low beta: $p=0.0413$, high beta: $p=0.0073$; post-hoc FDR-adjusted Wilcoxon rank sum test; Figure 3C).

We also investigated whether movement-related desynchronization could be measured using a single electrode placed over the sensorimotor area to remove intersubject variability. Spectral power was calculated and averaged across the hold and movement phases for each patient. Movement-related power changes were measured by subtracting the averaged power spectra during movement from the averaged power spectra during hold phase and calculating the percent power change from the hold phase power. PD patients had greater alpha and beta band desynchronization with movement compared to those of dystonia patients, and this difference was evident in individual recordings (PD vs. dystonia: theta: $p=0.1613$, alpha: $p=0.0226$, low beta: $p=0.0413$, high beta: $p=0.0073$; post-hoc FDR-adjusted Wilcoxon rank sum test; Figure 3C).
p=0.0062; post-hoc FDR-adjusted Wilcoxon rank sum test; Figure 3C). Thus, voluntary movement suppresses elevated pallidal beta band synchronization. Movement is often associated with increases in gamma band activity in the basal ganglia (Cassidy et al., 2002), but the movement related increase in pallidal low gamma (30-70 Hz) activity in PD was less pronounced than in dystonia (p=0.0170). In M1, differences in movement related changes between PD and dystonia did not reach significance (data not shown).

Disease specific differences in pallidal beta oscillations are driven by the amplitude of beta bursts

Beta band oscillations in the motor system are often studied by computing averaged power spectra over many oscillatory cycles, but examination of time series data shows that beta oscillations tend to be packaged in bursts whose amplitude and duration may encode information germane to movement kinematics and to therapeutic mechanisms in movement disorders (Tinkhauser et al., 2017b; Tinkhauser et al., 2017a). Bursts in beta band oscillatory activity were characterized using these recently published methods (Tinkhauser et al., 2017b; Tinkhauser et al., 2017a) (Figure 4A and 4B). We found higher mean pallidal beta burst amplitude in PD than dystonia (p=0.0060; post-hoc FDR-adjusted Wilcoxon rank sum test; Figure 4C, right), but no difference in the mean beta burst duration (PD vs. dystonia: p=0.0772; Wilcoxon rank sum test; Figure 4C, middle) or in the distribution of beta burst durations (PD vs. dystonia for all bin durations: F(1,8)=0.1140, p=0.9987; two-way ANOVA; Figure 4C, left). There was also no difference in burst frequency between disease states (PD vs. dystonia: p=0.0741; Wilcoxon rank sum test; data not shown). Thus, the observed disease specific differences in beta pallidal spectral power averaged over time (Figure 2A and C), were driven by differences in the amplitude but not the duration or frequency of individual bursts. These differences in beta bursts were specific to the pallidum, as M1 recordings showed similar distribution of beta burst duration (PD vs. dystonia for all bin durations: F(1,8)=0.3513, p=0.9443; two-way ANOVA; Figure 4D, left), mean burst duration (PD vs. dystonia: p=0.9264; Wilcoxon rank sum test; Figure 4D, middle), mean burst amplitudes between the two disease groups (PD vs. dystonia: p=0.1985;
Greater pallido-cortical beta coherence in PD compared with dystonia

In humans, the internal pallidum is the major output structure of the basal ganglia, and strongly modulates cortical function (via synaptic connections in the motor thalamus) (DeLong, 1990). We therefore evaluated disease-specific differences in pallido-cortical functional connectivity using simultaneous field potential recordings from subdural ECoG strips and pallidal DBS lead in 11 PD and 12 dystonia patients. PD patients had elevated low beta band coherence between GP and primary motor cortex compared to dystonia patients (PD vs. dystonia: theta: p=0.6724, alpha: p=0.6724, low beta: p=0.0248, high beta: p=0.6724, broadband gamma: p=1.0, HFO: p= p=0.6724; post-hoc FDR-adjusted Wilcoxon rank sum; Figure 5A). This difference was specific to the primary motor area, as coherence between the pallidum and primary somatosensory cortex did not differ between disease groups (data not shown).

To determine whether disease-specific patterns of pallido-cortical coherence were driven primarily by phase effects or amplitude effects, we analyzed phase coherence and amplitude coherence for each patient population separately. PD and dystonia patients did not differ in theta or low-beta GP-M1 amplitude coherence (PD vs. dystonia: theta: p=0.1858, low-beta: p=0.1858; post-hoc FDR-adjusted Wilcoxon rank sum; Figure 5B). However, dystonia patients had higher theta frequency phase coherence than PD, whereas PD had higher low-beta phase coherence than dystonia (PD vs. dystonia: theta: p=0.0148, low-beta: p=0.0289; post-hoc FDR-adjusted Wilcoxon rank sum; Figure 5D).

GP DBS stimulation reduces pallidal beta power and pallido-cortical beta coherence in PD

To investigate whether therapeutic DBS in PD corrects exaggerated beta oscillatory activity in GP and in GP-motor cortex coherence, we recorded from M1 and pallidal LFP signals from contacts immediately above and below the active GP contact in four PD patients. An example of a continuous pallidal LFP recording in the DBS.
OFF/ON/OFF condition is shown in Figure 6A. The corresponding pallidal LFP time-frequency spectrogram demonstrated suppression of beta power during periods of GPi DBS stimulation as well during UPDRS clinical testing (Figure 6B). To quantify the effects of DBS on pallidal resting power, log spectral power calculated during DBS OFF, 2mA DBS ON, 4mA DBS ON, and DBS OFF washout showed decreased beta frequency power during DBS stimulation, which returned to baseline after a 30-second washout period (Figure 6C). Clinical assessment of contralateral arm UPDRS III subscores demonstrated improvement of tremor and bradykinesia during DBS, which returned to baseline after stimulation was off (Figure 6C, insets). Group comparison of four PD patients during DBS OFF/ON/OFF recordings showed decreased total beta power in the DBS ON and compared to pre-DBS and post-DBS states ($F(2)=13.42$, $p=0.0061$, repeated measure ANOVA; Pre-DBS vs. DBS ON: $p=0.0109$; DBS ON vs. Post-DBS: $p=0.0090$; repeated post-hoc Tukey's test; Figure 6D). The effect of DBS on beta power was specific to the pallidum as DBS had no effect on M1 beta power ($F(2)=1.3773$, $p=0.3219$, repeated measure ANOVA; Pre-DBS vs. DBS ON: $p=0.3239$; DBS ON vs. Post-DBS: $p=0.4791$; post-hoc Tukey's test; Figure 6E).

We further explored changes in pallido-M1 interactions during pallidal DBS stimulation in PD patients (Figure 6F). DBS stimulation reduced both pallido-cortical beta phase synchrony ($F(2)=5.98$, $p=0.0312$, repeated measure ANOVA; Pre-DBS vs. DBS ON: $p=0.0055$; DBS ON vs. Post-DBS: $p=0.2758$; post-hoc Tukey's test; Figure 6G) and pallido-cortical beta amplitude coupling ($F(2)=8.7126$, $p=0.0168$, repeated measure ANOVA; Pre-DBS vs. DBS ON: $p=0.0151$; DBS ON vs. Post-DBS: $p=0.0740$; post-hoc Tukey's test; Figure 6H).

Because DBS at the STN has been shown to reduce cortical phase-amplitude coupling (PAC) (de Hemptinne et al., 2015), we tested whether acute pallidal DBS reduced PAC in the primary motor cortex. We found a trend toward reduction of beta phase to broadband gamma amplitude coupling in PD that did not reach significance (data not shown). Resting state motor cortex PAC in PD was less than in isolated dystonia, consistent with prior reports (de Hemptinne et al., 2013).
DISCUSSION

We recorded pallidal LFPs and motor cortex ECoG potentials in patients undergoing DBS surgery for akinetic-rigid PD or isolated dystonia, to evaluate disease specific differences in pallidal and pallido-cortical oscillatory phenomena, and to investigate mechanisms of pallidal DBS. We found that in the resting state, beta power at 13-20 Hz is relatively elevated in PD, whereas theta power is relatively elevated in dystonia. This elevation in beta band oscillations in PD is driven largely by the amplitude and not the duration or frequency of individual “bursts” of beta activity, and it is reduced by voluntary movement, consistent with prior studies (Gillies et al., 2017; Tsiokos et al., 2017). Resting state low beta pallido-cortical coherence is elevated in PD and is reduced by therapeutic pallidal DBS. Our findings support the theory that elevated beta oscillatory synchronization in the basal ganglia-thalamocortical-motor network is a hallmark of the parkinsonian state, point to the importance of the globus pallidus as a critical site for this elevated synchrony, and suggest a mechanism for stimulation-mediated suppression of the influence of basal ganglia output on cortical function.

Oscillatory signature of rigid-akinetic PD

Analysis of invasive recordings in humans have led to the hypothesis that bradykinesia arises from excessively synchronized oscillatory activity in the basal ganglia thalamocortical motor loop (Brown, 2003; Oswal et al., 2013). The initial evidence for this was derived from STN LFP recordings in PD patients on and off dopamine, or on and off DBS, showing that effective therapy reduces the amplitude of the dominant motor beta rhythm (Priori et al., 2004; Kuhn et al., 2008; Bronte-Stewart et al., 2009). Subsequently, other metrics of beta synchronization, such as the entrainment of high frequency activity to the phase of the beta rhythm in STN (Lopez-Azcarate et al., 2010) and cortex (de Hemptinne et al., 2013), have been found to be prominent in PD patients off medication, and reduced by medications (Swann et al., 2015) and STN DBS (de Hemptinne et al., 2015).

While many forms of neuronal synchronization in the motor network are modulated by therapy, it has been difficult to identify a simple measurement based on
field potential recording at a single brain site, such as spectral power at beta frequency in the resting state, that is clearly elevated in PD compared to nonparkinsonian conditions. In motor cortex, ECoG studies of movement disorders patients compared with those without movement disorders have not shown resting differences in spectral power (Crowell et al., 2012; Kondylis et al., 2016). Likewise, a comparison of resting STN LFP recording in PD and isolated dystonia showed no apparent differences (Wang et al., 2016), although a smaller study did suggest increased beta band LFP power in PD (Geng et al., 2017). Here, in a large series of human recordings, we add to the evidence from three prior smaller series (Silberstein et al., 2003; Weinberger et al., 2012; Jimenez-Shahed et al., 2016) pointing to the GP as site in the motor circuit with resting state elevation in LFP beta band oscillations compared to nonparkinsonian movement disorders. Thus, conceptual or computation models of bradykinesia in PD should incorporate elevated pallidal beta band activity as a critical component. Globus pallidus may provide a more robust site for detection of a disease specific biomarker of the parkinsonian state, compared with other structures in the motor network. Since LFP beta band spectral power is readily detected by currently available totally implantable neural interfaces (Quinn et al., 2015; Swann et al., 2017), this finding suggests a strategy for “adaptive” (feedback controlled) DBS in PD utilizing pallidal beta oscillations, a strategy currently under exploration for STN-DBS (Meidahl et al., 2017).

Pallidal oscillations entrain primary motor cortex at frequencies specific to abnormal motor signs

The internal pallidum, as the primary site of basal ganglia outflow in primates, is positioned to exert a strong modulatory effect on motor cortex, via the thalamus. While the original “rate model” postulated this influence to be expressed by rates of neuronal firing (DeLong, 1990), here we propose that it is based on coherence. Through combined pallidal and ECoG studies, we showed that specific patterns of oscillatory activity in the pallidum are reflected in coherence between GP and primary motor cortex, and that this elevated coherence is primarily based on phase relationship between these structures. The critical role of phase coherence between functionally
related structures of the nervous system is underscored by the “communication through coherence” hypothesis, which posits that structures that oscillate together become functionally connected by increasing the probability that action potentials from one structure arrive at the related one (in this case, via a thalamic synapse) at a phase of transmembrane voltage fluctuations that is most likely to trigger suprathreshold depolarization (Fries, 2005).

The present work adds to the growing evidence that specific manifestations of movement disorders are related to elevated phase coherence between basal ganglia and motor cortex, at characteristic frequencies. Consistent with our work, a study that combined pallidal LFP recording with scalp EEG in PD (Williams et al., 2002) showed high beta coherence between pallidum and cortex in akinetic-rigid PD which was reduced as symptoms were ameliorated by levodopa. A combined LFP and EEG study of isolated dystonia likewise showed prominent pallido-cortical theta coherence which was reduced by therapeutic DBS (Barow et al., 2014).

A unifying hypothesis for the efficacy of DBS in movement disorders

One mystery of the efficacy of DBS in movement disorders is that both STN and pallidal DBS have remarkably similar motor benefits for PD in most randomized comparisons (Burchiel et al., 1999; Anderson et al., 2005; Okun et al., 2009; Follett et al., 2010; Weaver et al., 2012). Further, DBS at both targets have similar benefits in isolated dystonia, a movement disorder that does not usually involve dopamine loss (Ostrem et al., 2011; Ostrem et al., 2017). This suggests a common mechanism for DBS at both targets in both disorder. One contemporary theory of the mechanism of STN DBS in PD focuses on retrograde entrainment of the “hyperdirect” cortico-subththalamic pathway (Gradinaru et al., 2009; Li et al., 2012), but that proposed mechanism is unlikely to apply to pallidal stimulation as a “hyperdirect” cortical input to the pallidum has not been demonstrated.

Here we show that pallidal DBS strongly reduces pallidal beta oscillations and pallido-cortical beta coherence. It has previously been established that STN DBS in PD results in pallidal beta desynchronization (Brown et al., 2004) and that in isolated dystonia, pallidal DBS suppresses theta-alpha oscillations in the GPi and pallido-cortical
theta-alpha coherence in dystonia (Barow et al., 2014). Taking these results together, we suggest a unifying hypothesis for the mechanism of basal ganglia DBS (both STN and GP targets) in movement disorders (both PD and dystonia): suppression of exaggerated coherence between basal ganglia output and cortex. Computational studies support the view that basal ganglia DBS at >100 Hz could suppress inter-structure coherence across a broad frequency range of oscillatory rhythms (Holt and Netoff, 2014; Cagnan et al., 2015), encompassing rhythms that drive diverse motor signs: theta for dystonia (Liu et al., 2002), alpha or “double tremor frequency” for PD tremor (Timmermann et al., 2003), beta for bradykinesia (Oswal et al., 2013), and gamma for dyskinesia/chorea (Swann et al., 2016; Miocinovic et al., 2018). The resulting “functional disconnection” between basal ganglia and cortex might then release cortical neuronal pools from pathological entrainment to the phase of network oscillations (de Hemptinne et al., 2015; Malekmohammadi et al., 2018).

Study Limitations

Data were collected on macroelectrodes after MER recording, which can lead to microlesional effects that result in symptom improvement (Koop et al., 2006). Between-subject comparisons of spectral power typically entail a normalization method, which may affect the results. Here we utilized normalization by total spectral power, a standard in the literature, but disease-specific differences in pallidal spectral power are also apparent without normalization (Figure 2A). The effects of therapeutic DBS in dystonia are typically seen after several weeks or months of stimulation, therefore we did not record the effects of acute DBS stimulation in the intraoperative setting on pallidal oscillations or pallidal-cortical coherence, which was recently reported (Barow et al., 2014). The chronic network effects of pallidal stimulation in PD and dystonia would need to be validated using stimulators with sensing capabilities (Swann et al., 2017). Finally, both in our study and in prior ones (Silberstein et al., 2003; Weinberger et al., 2012; Jimenez-Shahed et al., 2016), quadripolar pallidal DBS leads are placed with ventral contacts in the internal pallidum and dorsal contacts in the external pallidum. Thus, it is likely that neuronal activity in both structures contribute to pallidal recordings.
Conclusions

Akinetic-rigid PD and isolated dystonia are associated with disease specific patterns of elevated oscillatory synchronization in the pallidum and in the phase relationship between pallidum and cortex. Therapeutic DBS in PD suppresses pallidal oscillatory activity and pallido-cortical coherence, reducing the influence of diseased basal ganglia on cortical neuronal activity. This mechanism could account for the therapeutic effect of DBS at multiple basal ganglia targets in multiple disease states.
REFERENCES:


Hochberg Y, Benjamini Y (1990) More powerful procedures for multiple significance

Holt AB, Netoff TI (2014) Origins and suppression of oscillations in a computational

Differentiates Tics from the Resting State, Voluntary Movements, and the
Unmedicated Parkinsonian State. Front Neurosci 10:436.

AS, Turner RS, Crammond DJ, Richardson RM (2016) Movement-related
dynamics of cortical oscillations in Parkinson’s disease and essential tremor.
Brain 139:2211-2223.

quantitative measure of bradykinesia after microelectrode recording in patients
with Parkinson’s disease during deep brain stimulation surgery. Mov Disord
21:673-678.

Kuhn AA, Kempf F, Brucke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A,
Trottenberg T, Kupsch A, Schneider GH, Hariz MI, Vandenbergh W, Nuttin B,
suppresses oscillatory beta activity in patients with Parkinson’s disease in parallel

Li Q, Ke Y, Chan DC, Qian ZM, Yung KK, Ko H, Arbuthnott GW, Yung WH (2012)
Therapeutic deep brain stimulation in Parkinsonian rats directly influences motor

Liu X, Griffin IC, Parkin SG, Miall RC, Rowe JG, Gregory RP, Scott RB, Aziz TZ, Stein
JF (2002) Involvement of the medial pallidum in focal myoclonic dystonia: A
clinical and neurophysiological case study. Mov Disord 17:346-353.

Lopez-Azcarate J, Tainta M, Rodriguez-Oroz MC, Valencia M, Gonzalez R, Guridi J,
Iriarte J, Obeso JA, Artieda J, Alegre M (2010) Coupling between beta and high-
frequency activity in the human subthalamic nucleus may be a

Pallidal deep brain stimulation modulates excessive cortical high beta phase


LEGENDS

Figure 1: Pallidal lead and cortical electrode locations and field potential recordings.

A) Axial T2-weighted magnetic resonance images (MRI) showing pallidal DBS lead locations in the anterior and posterior commissural (AC-PC) plane. Arrows indicate lead artifact. B) 3D-reconstruction of preoperative MRI fused with intraoperative CT showing location of the temporary subdural 6-contact M1 ECoG strip in a PD patient. White dotted line indicates the central sulcus (CS). M1 = primary motor cortex; S1 = primary sensory cortex. B) Median nerve somatosensory-evoked potential (SSEP) shows reversal of the N20 potential at the electrode contact pair spanning M1 (C4-5). Arrow indicate the time of stimulation, and downward direction is negative. The most posterior contact pair with a negative N20 waveform is the C4-5 pair, localizing contact 4 to M1, which is immediately anterior to the central sulcus. C) One second sample resting state pallidal LFP signals (left) and M1 ECoG signals recorded from a PD patient (top) and a dystonia patient (bottom).

Figure 2: Pallidal and M1 spectral power in the resting state for PD and dystonia.

A) Log-transformed resting pallidal spectral power density graphs from a PD patient (blue) and a dystonia patient (red) showing differences in beta frequency power peak. B) Log-transformed resting M1 spectral power density graphs from a PD patient (blue) and a dystonia patient (red) showing similar power spectra. All signals were notch-filtered at 60 Hz. C) Averages of normalized resting pallidal spectral power for 20 PD (blue line) and 14 dystonia (red line) with their respective SEM (shaded). Asterisks indicate frequency bands showing significant difference between the two groups in theta and low beta bands (* p<0.05; post-hoc FDR-adjusted Wilcoxon rank sum test). D) Averages of normalized resting M1 spectral power for 11 PD (blue line) and 12 dystonia (red line) with their respective SEM (shaded) demonstrating no differences in spectral power.
Figure 3: Movement-modulated power changes in pallidal LFP and M1 ECoG potential of PD and dystonia patients.

A) An example of surface electromyography (EMG, top) recorded from the biceps and pallidal LFP (bottom) muscle during a voluntary elbow movement task. Start of each movement epoch is marked by green lines and end of movement is marked by red lines. Time stamps of movement start and end were used to parse the recording into "hold" epochs and "movement" epochs. B) Comparison of mean pallidal LFP log spectral powers ± SEM for all seven PD patient (left) and all ten dystonia patient (right) during rest (blue line) and hold epochs (green line) or movement epochs (red line) during an arm movement task. C) Grouped analysis for averages ± SEM of movement-modulated power changes in the pallidal LFP for seven PD patients (blue line) and ten dystonia patients (red line) who underwent an arm movement task. Movement related power changes were calculated by subtracting mean "hold" power from mean "movement" power and normalizing the power change to "hold" power (* p<0.05, **p<0.01; post-hoc FDR-adjusted Wilcoxon rank sum test).

Figure 4: Beta burst activity in pallidal LFP and M1 ECoG potential in PD and dystonia.

A) Each LFP or ECoG potential signal was bandpass filtered (± 4 Hz) around individual beta peak frequency, and the amplitude envelope of the beta activity envelope was obtained. A threshold was set at the 75th percentile of the beta amplitude. The onset of a burst was defined as when the filtered signal crossed the threshold amplitude and the end of the burst defined as when the amplitude fell below threshold. B) An example of a scatter plot showing the distribution of burst amplitudes and lengths from (A). C) (Left) Distribution of pallidal LFP beta burst durations in PD (black bars) and dystonia (white bars) (F(1,8)=0.1140, p=0.9987; two-way ANOVA). (Middle) Box plot showing distribution of mean pallidal LFP beta burst duration for 20 PD and 14 dystonia patients (p=0.0772; Wilcoxon rank sum test; red line indicates median and box shows 25th-75th percentile values). (Right) Box plot showing distribution of mean pallial LFP beta burst amplitude for 20 PD and 14 dystonia patients (p=0.0060; **p<0.01; Wilcoxon rank sum test; red line indicates median and box shows 25th-75th percentile values). D) (Left) Distribution
of M1 ECoG potential beta burst durations in PD (black bars) and dystonia (white bars)
(F(1,8)=0.3513, p=0.9443; two-way ANOVA). (Middle) Box plot showing mean M1 beta
burst duration for 10 PD and 12 dystonia patients (p=0.9264; Wilcoxon rank sum test;
red line indicates median and box shows 25th-75th percentile values). (Right) Box plot
showing distribution of mean M1 beta burst amplitude for 10 PD and 12 dystonia
patients (p=0.1985; Wilcoxon rank sum test; red line indicates median and box shows
25th-75th percentile values).

Figure 5: Pallidal to M1 coherence in PD and dystonia.
A) Averages of M1-pallidal coherence for 11 PD (blue line) and 12 dystonia (red line)
patients demonstrating greater low beta frequency coherence in PD compared to
dystonia (PD vs. dystonia: theta: p=0.6724, alpha: p=0.6724, low beta: p=0.0248, high
beta: p=0.6724, broadband gamma: p=1.0, HFO: p= p=0.6724; * p<0.05; post-hoc FDR-
adjusted Wilcoxon rank sum test). B) Box plots of M1-pallidal amplitude coherence for
PD and dystonia patients showing no difference across theta or beta frequency bands
(PD vs. dystonia: theta: p=0.1858, low-beta: p=0.1858; post-hoc FDR-adjusted
Wilcoxon rank sum test; red line indicates median and box shows 25th-75th percentile
values). C) Box plots of M1-pallidal phase coherence for PD and dystonia patients
showing greater phase synchrony in theta frequency in dystonia and low beta frequency
in PD (PD vs. dystonia: theta: p=0.0148, low-beta: p=0.0289; * p<0.05; post-hoc FDR-
adjusted Wilcoxon rank sum test; red line indicates median and box shows 25th-75th
percentile values).

Figure 6: Effect of therapeutic high frequency globus pallidum internus (GPI) DBS
on pallidal beta power and pallido-M1 beta coherence
A) Pallidal LFP recorded from contacts 0-2 pre-, during-, and post-DBS stimulation
(monopolar using contact 1, 130 Hz, 90 μS, 2-4 mA). Stimulation conditions
correspond to schematic timeline shown in (B). Insets represent magnified areas
indicated by the green box. Scale bars are on the right of traces. B) Time-frequency
spectrogram showing power changes in the DBS OFF/ON conditions indicated by the
schematic timeline above. UPDRS boxes indicated periods when clinical testing was
performed to assess patient symptoms. Warmer colors indicate higher power. Time access is the same as in (A). C) Log power spectral densities of 30s pallidal LFPs recorded during the following conditions: leftmost: DBS OFF, 2nd from left: DBS ON (2mA), 2nd from right: DBS ON (4mA), and rightmost: DBS washout during the first 30 seconds (dotted line) and last 30 seconds (solid line). UPDRS scores during each condition is shown. T=Tremor; B=bradykinesia; R=rigidity. D) Group comparison of four PD patients during DBS OFF/ON/OFF recordings showed decreased total beta power in the DBS ON and compared to pre-DBS and post-DBS states (F=13.42, p=0.0061, repeated measure ANOVA; Pre-DBS vs. DBS ON: p=0.0109; DBS ON vs. Post-DBS: p=0.0090; post-hoc Tukey’s test; *p<0.05). E) GPi DBS had no effect on M1 beta power (F=1.3773, p=0.3219, repeated measure ANOVA; Pre-DBS vs. DBS ON: p=0.3239; DBS ON vs. Post-DBS: p=0.4791; post-hoc Tukey’s test). F) Averages of M1-pallidal coherence for four PD patients pre- (blue line), during- (red line), and post- (green) GPi DBS demonstrating reduction of beta coherence during GPi DBS. G) Box plots of average beta phase coherence pre-, during-, and post-DBS showing reduction of beta phase synchrony during GPi stimulation (F=5.98, p=0.0312, repeated measure ANOVA; Pre-DBS vs. DBS ON: p=0.0055; DBS ON vs. Post-DBS: p=0.2758; post-hoc Tukey’s test; *p<0.05; red line indicates median and box shows 25th-75th percentile values). H) Box plots of average beta amplitude coherence pre-, during-, and post-DBS showing difference between DBS ON and DBS washout period (F=8.7126, p=0.0168, repeated measure ANOVA; Pre-DBS vs. DBS ON: p=0.0151; DBS ON vs. Post-DBS: p=0.0740; post-hoc Tukey’s test, *p<0.05; red line indicates median and box shows 25th-75th percentile values).

Table 1: 1 location of the midpoint of the recording contact pair in anterior commissure and post commissure plane. Lat: lateral distance from mid-commissural point; AP: anterior-posterior distance from mid-comissural point; Vert: vertical distance from mid-commissural point. 2The preoperative levodopa equivalent dose (LEED) was calculated using the following conversion factors: ropinirole x 20; pramipexole x 100; levodopa with decarboxylase inhibitor x 1; controlled release levodopa with decarboxylase inhibitor x 0.7; levodopa with decarboxylase and catechol-O-methyltransferase inhibitor x 1.3
(Wenzelburger et al., 2002). All doses are daily totals. * This patient was intolerant of levodopa and only took rasagiline. UPDRS: Unified Parkinson’s Disease Rating Scale.

Table 2: Dyt medication: medications for dystonia; 1 location of the recording contact in anterior commissure and post commissure plane. TWSTERS: Toronto Western Spasmodic Torticollis Rating Scale (motor severity score); BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale (movement subscale); Lat: lateral distance from mid-commissural point; AP: anterior-posterior distance from mid-commissural point; Vert: vertical distance from mid-commissural point. *medication for patient 9 was held 2 days prior to surgery. na: not available.
Figure 1

A

B

C

D

Pallidal LFP

M1 ECoG potential

PD

Dystonia

50μV

200ms
Figure 2

A) Pallidal Power at Rest

B) M1 Power at Rest

C) Normalized Pallidal Resting Power

D) Normalized M1 Resting Power
Figure 3

A

EMG

LFP

10mV

10s

50μV

10s

B

PD Pallidal Power

Dystonia Pallidal Power

log (Power) (μV^2/Hz)

log (Power) (μV^2/Hz)

Frequency (Hz)

Frequency (Hz)

C

Movement-Modulated Power Change in Pallidum

% Power Change

Frequency (Hz)
Figure 4

A

Raw LFP

Filtered LFP

B

75th Percentile

Burst Amplitude (a.u.)

0 10 20 30 40 50 60 70 80

Burst Length (sec)

0 0.1 0.2 0.3 0.4

C

GPI LFP: Beta Burst Length

% Amount of bursts

0.1-0.2 0.2-0.3 0.3-0.4 0.4-0.5 0.5-0.6 0.6-0.7 0.7-0.8 0.8-0.9 >0.9

Time Windows (s)

[Graph showing distribution of burst percentage for PD and Dyt]

Duration

Amplitude

Mean Burst Duration (s)

0.1 0.12 0.14 0.16 0.18 0.2

PD Dyt

Mean Burst Amplitude (μV)

0 20 40 60 80 100 120 140 160 180 200

PD Dyt

D

M1: Beta Burst Length

% Amount of bursts

0.1-0.2 0.2-0.3 0.3-0.4 0.4-0.5 0.5-0.6 0.6-0.7 0.7-0.8 0.8-0.9 >0.9

Time Windows (s)

[Graph showing distribution of burst percentage for PD and Dyt]

Duration

Amplitude

Mean Burst Duration (s)

0.1 0.12 0.14 0.16 0.18 0.2

PD Dyt

Mean Burst Amplitude (μV)

0 20 40 60 80 100 120 140 160 180 200

PD Dyt
Figure 5

A  M1-GP LFP Coherence

B  M1-GP Amplitude Coherence
   Theta
   Low Beta

C  M1-GP LFP Phase Coherence
   Theta
   Low Beta
## Table 1: Clinical characteristics of PD patients

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Age</th>
<th>Sex</th>
<th>Side</th>
<th>Disease duration (years)</th>
<th>Levodopa equivalent dose (mg)</th>
<th>Off UPDRS-III</th>
<th>On UPDRS-III</th>
<th>Lead location (mm)</th>
<th>Movement Task</th>
<th>Motor ECoG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lat -2.0</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>1</td>
<td>53</td>
<td>M</td>
<td>L</td>
<td>8</td>
<td>640</td>
<td>55</td>
<td>29</td>
<td>22.3</td>
<td>2.8</td>
<td>-2.0</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>R</td>
<td>10</td>
<td>None*</td>
<td>64</td>
<td>31</td>
<td>-22.2</td>
<td>3.8</td>
<td>-3.1</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>M</td>
<td>R</td>
<td>7</td>
<td>300-450</td>
<td>58</td>
<td>39</td>
<td>-20.7</td>
<td>4.2</td>
<td>-3.8</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>M</td>
<td>R</td>
<td>12</td>
<td>845</td>
<td>47</td>
<td>39</td>
<td>20.5</td>
<td>2.5</td>
<td>-1.9</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>M</td>
<td>L</td>
<td>14</td>
<td>1778</td>
<td>50</td>
<td>31</td>
<td>21.9</td>
<td>1.1</td>
<td>-3.8</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>M</td>
<td>R</td>
<td>7</td>
<td>724</td>
<td>41</td>
<td>22</td>
<td>-26.2</td>
<td>8.3</td>
<td>-0.1</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>M</td>
<td>R</td>
<td>13</td>
<td>640</td>
<td>38</td>
<td>20</td>
<td>22.1</td>
<td>5.2</td>
<td>0.0</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>M</td>
<td>R</td>
<td>8</td>
<td>1620</td>
<td>31</td>
<td>20</td>
<td>22.9</td>
<td>1.2</td>
<td>-5.3</td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>M</td>
<td>R</td>
<td>7</td>
<td>750</td>
<td>42</td>
<td>23</td>
<td>20.4</td>
<td>3.9</td>
<td>-3.3</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>M</td>
<td>R</td>
<td>5</td>
<td>940</td>
<td>39</td>
<td>21</td>
<td>22.8</td>
<td>5.2</td>
<td>-0.6</td>
</tr>
<tr>
<td>11</td>
<td>59</td>
<td>M</td>
<td>R</td>
<td>5</td>
<td>790</td>
<td>53</td>
<td>16</td>
<td>-23.1</td>
<td>5.9</td>
<td>-4.6</td>
</tr>
<tr>
<td>12</td>
<td>72</td>
<td>M</td>
<td>R</td>
<td>10</td>
<td>1755</td>
<td>34</td>
<td>27</td>
<td>21.6</td>
<td>2.5</td>
<td>-3.6</td>
</tr>
<tr>
<td>13</td>
<td>65</td>
<td>F</td>
<td>L</td>
<td>11</td>
<td>720</td>
<td>73</td>
<td>32</td>
<td>22.4</td>
<td>3.4</td>
<td>-0.5</td>
</tr>
<tr>
<td>14</td>
<td>61</td>
<td>M</td>
<td>L</td>
<td>7</td>
<td>325</td>
<td>39</td>
<td>20</td>
<td>21.9</td>
<td>7.1</td>
<td>-0.2</td>
</tr>
<tr>
<td>15</td>
<td>50</td>
<td>M</td>
<td>R</td>
<td>15</td>
<td>1260</td>
<td>39</td>
<td>18</td>
<td>-20.3</td>
<td>2.9</td>
<td>-0.8</td>
</tr>
<tr>
<td>16</td>
<td>63</td>
<td>M</td>
<td>L</td>
<td>11</td>
<td>1840-2340</td>
<td>32</td>
<td>15</td>
<td>-22.9</td>
<td>4.0</td>
<td>-1.5</td>
</tr>
<tr>
<td>17</td>
<td>78</td>
<td>M</td>
<td>L</td>
<td>8</td>
<td>540</td>
<td>48</td>
<td>12</td>
<td>-22.9</td>
<td>4.9</td>
<td>-2.5</td>
</tr>
<tr>
<td>18</td>
<td>65</td>
<td>M</td>
<td>L</td>
<td>28</td>
<td>780</td>
<td>65</td>
<td>28</td>
<td>-23.6</td>
<td>6.0</td>
<td>-0.7</td>
</tr>
<tr>
<td>19</td>
<td>58</td>
<td>M</td>
<td>L</td>
<td>13</td>
<td>1640</td>
<td>42</td>
<td>15</td>
<td>-19.0</td>
<td>4.0</td>
<td>-1.1</td>
</tr>
<tr>
<td>20</td>
<td>58</td>
<td>F</td>
<td>L</td>
<td>10</td>
<td>1300</td>
<td>37</td>
<td>22</td>
<td>-19.0</td>
<td>3.8</td>
<td>-6.6</td>
</tr>
</tbody>
</table>
Table 2: Clinical characteristics of dystonia patients

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Age</th>
<th>Sex</th>
<th>Side</th>
<th>Dystonia Type</th>
<th>Disease duration (years)</th>
<th>Medication (mg)</th>
<th>TWSTRS/BFMDRS</th>
<th>Lead location $^a$</th>
<th>Movement Task</th>
<th>Motor ECoG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>M</td>
<td>R</td>
<td>Cervical</td>
<td>6</td>
<td>baclofen 60, diazepam 20, trihexyphenidyl 6</td>
<td>33.75 / 6</td>
<td>19.5</td>
<td>3.5</td>
<td>-1.1</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>F</td>
<td>R</td>
<td>Craniocervical</td>
<td>10</td>
<td>cyclobenzaprine 10</td>
<td>na / 11</td>
<td>21.2</td>
<td>4.0</td>
<td>-0.7</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>M</td>
<td>R</td>
<td>Craniocervical</td>
<td>23</td>
<td>clonazepam 1</td>
<td>18 / 20</td>
<td>21.4</td>
<td>4.7</td>
<td>-1.6</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>F</td>
<td>R</td>
<td>Craniocervical</td>
<td>14</td>
<td>clonazepam 2</td>
<td>28 / 9</td>
<td>18.7</td>
<td>4.5</td>
<td>-1.1</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>F</td>
<td>R</td>
<td>Craniocervical</td>
<td>2</td>
<td>cetirizine 10</td>
<td>20 / 7</td>
<td>18.6</td>
<td>3.5</td>
<td>-0.4</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>M</td>
<td>R</td>
<td>Cervical</td>
<td>5</td>
<td>lorazepam 6</td>
<td>23 / 12</td>
<td>22.2</td>
<td>4.5</td>
<td>-2.6</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>M</td>
<td>R</td>
<td>Cervical</td>
<td>4</td>
<td>clonazepam 1, baclofen 20</td>
<td>25 / 8</td>
<td>18.2</td>
<td>4.4</td>
<td>-2.0</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>F</td>
<td>L</td>
<td>DYT1+</td>
<td>37</td>
<td>trihexyphenidyl 4</td>
<td>0 / 24</td>
<td>-19.3</td>
<td>7.5</td>
<td>-1.6</td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td>F</td>
<td>L</td>
<td>Generalized</td>
<td>11</td>
<td>clonazepam 1</td>
<td>12 / 51.5</td>
<td>-19.6</td>
<td>5.3</td>
<td>-1.2</td>
</tr>
<tr>
<td>10</td>
<td>37</td>
<td>M</td>
<td>R</td>
<td>DYT1+</td>
<td>29</td>
<td>clonazepam 1</td>
<td>0 / 23</td>
<td>21.6</td>
<td>6.8</td>
<td>-0.2</td>
</tr>
<tr>
<td>11</td>
<td>57</td>
<td>F</td>
<td>R</td>
<td>Generalized</td>
<td>40</td>
<td>clonazepam 1,5, diazepam 40</td>
<td>25 / 26</td>
<td>19.7</td>
<td>2.4</td>
<td>-1.9</td>
</tr>
<tr>
<td>12</td>
<td>26</td>
<td>M</td>
<td>L</td>
<td>Generalized</td>
<td>7</td>
<td>LEED 450², trihexyphenidyl 6</td>
<td>13 / 29</td>
<td>-20.3</td>
<td>6.3</td>
<td>-2.7</td>
</tr>
<tr>
<td>13</td>
<td>22</td>
<td>M</td>
<td>L</td>
<td>DYT1+</td>
<td>14</td>
<td>baclofen 50, trihexyphenidyl 15</td>
<td>na / 30.5</td>
<td>-23.1</td>
<td>1.5</td>
<td>-4.2</td>
</tr>
<tr>
<td>14</td>
<td>35</td>
<td>M</td>
<td>R</td>
<td>Generalized</td>
<td>1</td>
<td>baclofen 30, LED 600; cetirizine 10</td>
<td>18 / 11</td>
<td>21.2</td>
<td>4.7</td>
<td>-2.1</td>
</tr>
</tbody>
</table>