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Pallidal stimulation in Parkinson disease differentially modulates local and network β activity

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Abstract

Background: β hypersynchrony within the basal ganglia-thalamocortical (BGTC) network has been suggested as a hallmark of Parkinson disease (PD) pathophysiology. Subthalamic nucleus (STN)-DBS has been shown to alter cortical-subcortical synchronization. It is unclear whether this is a generalizable phenomenon of therapeutic stimulation across targets.

Objectives: We aimed to evaluate whether DBS of the globus pallidus internus (GPi) results in cortical-subcortical desynchronization, despite the lack of monosynaptic connections between GPi and sensorimotor cortex.

Methods: We recorded local field potentials (LFP) from the GPi and electrocorticographic (ECoG) signals from the ipsilateral sensorimotor cortex, off medications in nine PD patients, undergoing DBS implantation. We analyzed both local oscillatory power and functional connectivity (coherence and debiased weighted phase lag index (dWPLI)) with and without stimulation while subjects were resting with eyes open.

Results: DBS significantly suppressed low β power within the GPi ($-26.98 \pm 15.14\%$, $p < 0.05$) without modulation of sensorimotor cortical β power (low or high). In contrast, stimulation suppressed pallidocortical high β coherence ($-38.89 \pm 6.19\%$, $p = 0.02$) and dWPLI ($-61.40 \pm 8.75\%$, $p = 0.02$). Changes in cortical-subcortical functional connectivity were spatially specific to the motor cortex.

Conclusions: We highlight the role of DBS in desynchronizing network activity, particularly in the high β band. The current study of GPi-DBS suggests these network-level effects are not necessarily dependent and potentially may be independent of the hyperdirect pathway.

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Conflicts of interest

Authors report no conflicts of interest associated with this publication.

Importantly, these results draw a sharp distinction between the potential significance of low β oscillations locally within the basal ganglia and high β oscillations across the BGTC motor circuit.

Keywords

Parkinson disease; Deep brain stimulation; Globus pallidus internus; β oscillations; functional connectivity

Introduction

β oscillations (13-35 Hz) play an important role throughout the basal ganglia-thalamocortical (BGTC) circuit in normal motor control [1-3]. In addition, pathologically excessive β oscillations have been reported in Parkinson disease (PD) [4-6] in the subthalamic nucleus (STN) and globus pallidus internus (GPi), as well as motor cortices [7-12]. Besides increased power, β oscillations have been associated with an excessive phase-amplitude coupling (PAC) both in basal ganglia and motor cortices [10, 12-16] and cortical-subcortical coupling [17-20]. All of these signal characteristics have been suggested as potential biomarkers of PD [3, 14].

Several studies have shown that dopaminergic medication and therapeutic DBS of the STN suppresses excessive β oscillations not only locally within the STN but also inter-regionally between STN and motor cortex [17, 21-24]. While STN-DBS has been reported to suppress cortical β power (with some inconsistency) [14, 21], recent studies suggest DBS at both STN and GPi reduces excessive PAC within the motor cortex [14, 25] as does dopaminergic therapy [26]. Modulation of local phase-amplitude coupling has also been reported in the STN with dopaminergic therapy [16, 27]. Despite extensive investigations, a clear picture has not emerged of mechanisms of DBS or dopaminergic medications.

Previous studies often consider the β band as one functional unit. However, there is accumulating evidence that this band may, in fact, consist of two functionally discrete sub-bands, including low β (13-20 Hz) and high β (21-35 Hz). Each sub-band exhibits dissociable characteristics in mediating function within and across regions in the BGTC motor circuit [27]. Medication and STN-DBS modulate low β signals locally in the STN [17, 20]. Moreover, phase-amplitude coupling within the STN is maximal at the low β range [27]. We have also shown that similar subcortical PAC exists in the GPi with a preferred phase encoding rhythm in the low β range [9] and that this pallidal PAC is inversely correlated to the disease severity and most likely a surrogate of normal motor control [9]. Another study has recently reported that modulation of low β pallidocortical coherence may be similarly important for normal motor control [28]. The high β band, however, has been implicated in the inter-regional coupling (e.g., STN-cortex) and is modulated by STN-DBS [29]. Likewise, we have recently shown that motor cortical PAC only at the high β is related to the disease severity and significantly suppressed by GPi-DBS. On the other hand, cortical low β power changes in response to contralateral body movement and not stimulation [25]. The aggregation of these β sub-bands may have introduced some confusion and inconsistency in analyses and results in the literature.

We hypothesized that high β cortical-subcortical coherence, at least in part, underlies the pathophysiological basis of PD. This long-range hypersynchrony within the BGTC circuit may serve as an “information block” preventing normal information flow and motor control [18]. Moreover, we hypothesized that therapeutic interventions alter this coupling. Ultimately, these hypotheses will require demonstration of excess cortical-subcortical coupling compared to non-diseased subjects, but such data will be difficult, if not impossible, to attain. Therefore, to begin to evaluate these hypotheses, we simultaneously evaluated cortical and subcortical LFP during GPi-DBS implantation surgery both off and on therapeutic DBS, with attention to the spatial- and frequency-specific effects of DBS on BGTC coupling. Clarification of the effect of DBS, both locally and across regions, is necessary for elucidating the pathophysiological mechanisms of PD and identifying novel avenues for improving therapy based on potential symptom biomarkers. Although clinical trials demonstrate the equal motor efficacy of STN- and GPi-DBS [30-32], most studies have focused on understanding the therapeutic mechanism of STN-DBS. By specifically evaluating the effect of GPi-DBS, we aim to uncover the generalized principles of therapeutic stimulation in PD, particularly those that may not be directly mediated by hyperdirect pathway.

Materials and methods

Patients and surgical procedure

Nine right-handed patients with idiopathic PD underwent stereotactic implantation of DBS leads targeting the motor region of GPi (bilateral N=7, or unilateral N=2). All patients provided written informed consent approved by the Institutional Review Board at the University of California, Los Angeles. All subjects had a detailed pre-operative clinical evaluation which included the UPDRS motor (part III) performed off medication (Table 1). Surgical implantation was performed in the awake state and all medications were held at least 12 hours prior to the surgery. The DBS lead was targeted to the motor (ventral posterolateral) GPi using image-guided targeting, 2-4 mm anterior, 19-24 mm lateral and 4-6 mm inferior to the mid-commissural point (depending on individual anatomy). All trajectories were confirmed with intraoperative microelectrode recordings and awake macrostimulation testing.

All subjects had clinical pre- and post-operative imaging protocol. Pre-operative imaging included T1-weighted magnetization-prepared rapid acquisition gradient echo image (slice thickness = 1 mm, 3T, Siemens Skyra). A Leksell stereotactic head frame (Elekta Instruments) was first applied to the skull and a full head CT scan was obtained using 1-mm slice thickness (Siemens Sensation 64). Prior to right-sided DBS lead implantation (Medtronic, Model 3387, length 1.5 mm, inter-contact distance 1.5 mm, Medtronic Inc, MN), an eight-contact ECoG strip (platinum-iridium 4 mm contacts with 1 cm spacing, AdTech Medical) was implanted subdurally via the right frontal burr hole. Following implantation of the DBS electrode in each hemisphere, a single view lateral fluoroscopy image was acquired to confirm DBS electrode placement. After ECoG recordings were acquired, the subdural strip was removed, the DBS electrode was anchored into place and a burr hole was sealed. Following the procedure, a post-operative CT scan was obtained for

additional confirmation of DBS electrode position. Anatomical localization of ECoG strip was done using a technique previously described [33, 34] (Figure 1 A). The central sulcus was identified and marked on the reconstructed cortical surface. The two overlying bipolar contacts were used for analysis across the cohort: S1 (sensory cortex) and M1/PM (motor/premotor cortices).

We used CranialVault Cloud-based system [35] to confirm the anatomical localization of the DBS leads in the right GPi after the surgery. For each subject, the implanted DBS leads were extracted from the postoperative CT scan and manually checked for accuracy. Subsequently, the postoperative CT scan was co-registered to the pre-operative high-resolution structural MRI, using fully automated intensity-based rigidity body transformation in CranialVault CRAVE toolset [36]. To produce a group-level image demonstrating the lead positioning, pre-operative structural MRIs were transformed into the CranialVault atlas using non-linear intensity based registration technique available in CRAVE (Figure 1B).

Experimental design

Signal acquisition was performed using BCI2000 v3 using g.USBamp 2.0 amplifiers (g.Tec, Austria) with a sampling frequency of 2400 Hz and a 0.1Hz-1000Hz online band-pass filtering. A ground scalp electrode was placed in all subjects. Likewise, a scalp reference was used for electrocorticographic recordings. LFP recordings from the right GPi were obtained using four ring macroelectrode contacts (numbered zero to three ventral to dorsal) with the lead in final implant position as shown in Figure 1B [9]. Concomitant cortical recordings were acquired using an eight-contact ECoG strip covering the sensorimotor cortex in the right hemisphere as shown in Figure 1A.

DBS lead contact one was used to deliver cathodic stimulation (Medtronic analog neurostimulator, model 3625) with either a scalp (N=3) or shoulder (N=6) anode. Contacts zero and two were used for bipolar recording of local GPi activity. Beginning at least 15 minutes after intraoperative clinical macrostimulation testing (to ensure washout of any stimulation effects), each subject performed two sets of alternating 30-second blocks of rest and left hand cued finger tapping. The first block was always acquired without stimulation (i.e. DBS-OFF condition) and the second block was recorded with concurrent high-frequency GPi stimulation (i.e. DBS-ON condition.) After the DBS-ON block, an additional 30 seconds of DBS-OFF data was collected. Only data during rest periods were analysed here to address the specific hypothesis postulated. Prior to the start of the experimental data recording, the attending neurologist (author Y.B.) performed clinical assessment of tremor (item 3.17), rigidity (item 3.3) and bradykinesia (item 3.4) from the MDS-UPDRS examination. During recordings in the DBS-ON condition, stimulation voltage was increased to the value presented in Table 1, the similar clinical examination was performed to reassess therapeutic effects of stimulation.

Data pre-processing

All the analyses were performed offline using Matlab (Mathworks Inc. NA. USA) using Chronux [37] and Fieldtrip toolbox [38]. Kinematic data were carefully parsed into rest periods using automated gross finger movement envelope detection. ECoG signals were re-

referenced to the bipolar configuration (Figure 1A) to enhance spatial specificity and reduce stimulation artifact. LFP and cortical data were then z-score normalized, resulting in zero means and unit variance for all the channels. We excluded all data segments containing electrical or movement artifact using methods previously described [8]. Removed segments primarily featured power spectra with abnormally high values, excessive harmonics and time series with high rates of voltage change. After exclusion of electrical or movement artifacts, we had various lengths of usable data across the cohort. We also excluded 1 second from the beginning and end of the recordings to avoid filtering edge artifacts. After these analyses were performed, the shortest available continuous time segment was 17 seconds long. To maintain the similar share of data across the cohort we used the first 17 seconds of artifact-free signal for each subject for each condition. Previous reports indicate that this timing is sufficient for stimulation to affect and to detect modulation of β activity within the BGTC network [39].

Due to extensive contamination of pallidal signals by stimulation artifact at frequencies >150 Hz and that our focus on β oscillations, we only analyzed the frequencies less than 100 Hz. Using a zero phase Butterworth filter (Filter order = 3, 2-100 Hz), data were bandpass filtered and line noise was removed with a notch filter. (Filter order = 3, bandwidth = 4 Hz). Due to differences in current return (anode selection), the three patients (for whom a scalp anode was used) had sub-harmonic stimulation artifact profiles at 23 Hz in the bipolar GPi LFP signal. All the stimulation-related artifacts were removed from further analysis using zero-phase Butterworth filter (filter order = 3, Bandwidth 4 Hz).

Power Spectral Density (PSD) analysis

PSD for DBS-ON and DBS-OFF conditions were calculated using the Thomson's multitaper method in 1 second consecutive time windows with no overlap for frequencies of 6 to 100 Hz with ± 2 Hz frequency bandwidth (3 tapers) [37]. Group average PSDs for both conditions were then calculated for each cohort at each cortical location and in GPi. To account for inter-subject variability in baseline power, each segmented spectra were normalized to the total power of the signal during each condition (frequencies 6-100 Hz excluding the line noise and its multiples as well as stimulus-related artifacts). We derived change percentage in power for low β (13-20 Hz) and high β (21-35 Hz) frequency bands during the DBS-ON relative to the baseline (i.e. DBS-OFF).

Coherence analysis

We used magnitude squared coherence to explore the cortical-subcortical synchrony. The magnitude squared coherence was calculated between ipsilateral GPi and sensory and motor/premotor cortical signals, using Thomson's multitaper method with similar parameters as the PSD analysis. For each subject, band average coherence was calculated separately for low high β bands and used for further comparison between DBS-ON and DBS-OFF. Similar to the power spectral density analysis we calculated the relative percent change in coherence of the DBS-ON condition relative to DBS-OFF.

De-biased Weighted Phase lag index (dWPLI) analysis

To confirm that coherence results do not represent spurious volume conduction, we employed a measure of phase connectivity. We calculated cross-spectral density (for GPi-S1 and GPi-M1/PM separately) using similar time and frequency resolution as spectral and coherence analysis. The dWPLI was then calculated for all of the frequency values of interest (6-100 Hz) [40, 41]. The dWPLI measures the non-equiprobability of phase leads and lags between the two signals and has been shown to be insensitive to the effects of volume conduction from independent sources or active reference. We calculated the percent change in dWPLI of the DBS-ON condition relative to the DBS-OFF.

The “preferred phase difference” of coupling for each frequency bin was calculated as the circular mean [42] of the phase difference values across all time windows for each condition separately. The average of dWPLI values and the preferred phase difference were calculated for low and high β frequency bands for each subject and used for further statistical comparison between DBS-OFF and DBS-ON conditions.

Statistical analyses

Statistical analysis was performed using SPSS statistical software (IBM Corp) and Matlab. The statistical properties of asymptotic distributions for power spectra and coherence are well characterized [43]. Therefore, a univariate (i.e. frequency-by-frequency) approach was used to examine the significance of spectral power/coherence changes between conditions at each frequency. The two-group test of spectrum/coherence was used to test the null hypothesis that two conditions have equal spectra [34, 43]. We calculated the mean group spectra and corresponding Z statistics using asymptotic probability distribution. The 95% confidence intervals were then calculated based on Jackknife estimation of variance as previously described [43]. To correct for multiple comparisons, we note that differences in spectra due to chance are likely to be at isolated frequencies, while neurophysiological differences are likely to occur across contiguous frequency bands. Since spectral/coherence estimates at two different frequencies by less than the bandwidth of the multitaper method (4 Hz) are correlated, we rejected the null hypothesis for all candidate frequencies constituting bands whose width was larger than 4 Hz [34].

To assess the statistical significance of changes in the group average dWPLI, we used non-parametric permutation testing (N=1000). At each permutation, a random subset of the pool was selected for which the labels of the conditions were swapped, creating a null distribution of the group difference. Since the difference values at each frequency bin were bound between -1 and 1, we used Fisher Z-transform to construct an approximately normal distribution of the condition difference under the null hypothesis [44]. The significance of the condition difference was then assessed at $P=0.05$ and corrected for multiple comparisons in a similar fashion to the spectral and coherence analysis.

Following the results of the univariate analysis, we compared band averaged values (in low and high β) for power and connectivity measures using paired statistical tests. To guide the selection of appropriate statistical test, we used Shapiro-Wilk test and examined normality of distributions. Such analysis revealed a significant deviation from normal distributions

($P < 0.05$). Therefore, we used Wilcoxon signed-rank test (non-parametric). All statistical analyses were performed for low and high β frequency bands. Similarly, the effect of GPi stimulation on clinical symptoms was confirmed by comparing DBS-OFF and DBS-ON clinical scores using the Wilcoxon signed-rank test (selection of the test was guided by Shapiro-Wilk test). For all of these paired tests, the significance level was set to 0.05 and Bonferroni method was further used to adjust the p-values for multiple comparisons.

Finally, we used linear mixed-effect modeling (LMEM) to examine the spatial specificity of coherence in two β sub-bands, between GPi and each cortical signal. By the study design, every subject contributed multiple samples (from different locations in the brain) in a repeated measures design which are not completely independent. LMEM is a robust statistical technique for repeated measures study design and accounts for the inherent correlation between repeated measures from each subject [45, 46]. A mixed model was constructed with two grouping factors including cortical contacts and β subbands. The average values of the coherence between GPi and these cortical signals as a function of the grouping variables were used as response variables. Main effects for each factor and interactions between effects were studied as part of the model and assessed for statistical significance ($P < 0.05$).

Results

Patient Demographics and Acute Response to GPi-DBS

Nine subjects (six men) were included in this study, typical for invasive studies such as this due to the unique nature of these recordings [21, 28, 47, 48]. Median and average ($\pm$ standard deviation) age were 61 and 61.7 (± 6.7) years. When tested before surgery, average total UPDRS-III off medication was 38.29 (± 7.28). During surgery, a subset of UPDRS-III scores for left hand was assessed to investigate effects of acute GPi-DBS on disease symptoms (see the “Materials and Methods” section and Table 1 for more details). Acute GPi-DBS significantly reduced lateralized symptoms from 2.44 (± 0.18) to 0.11 (± 0.11) and from 2.11 (± 0.20) to zero for rigidity and bradykinesia respectively ($P = 0.012$ and 0.012 , Wilcoxon signed-rank test, corrected). Although tremor score was also reduced with GPi-DBS from 0.56 (± 0.29) to 0.22 (± 0.15), this change was not statistically significant ($P = 0.25$, Wilcoxon signed-rank test, corrected).

Confirmation of lead placement in the GPi

CranialVault cloud was used to reconstruct the DBS lead and project them onto an atlas (Figure 1B). Contact one was used to deliver cathodic stimulation, Figure 1B shows contact 1 (red dots) within GPi (dark green) in 8 subjects for whom standard preoperative high resolution imaging was available. In the final subject, due to a previously implanted DBS lead, a low specific absorption rate (SAR) imaging protocol was used, providing lower effective spatial resolution and lower signal-to-noise resulting in inaccurate segmentation and appearance of a slightly lateralized lead. Subject-specific fusion of the preoperative MRI and post-operative CT (BrainLab, Munich, Germany) confirmed this lead was indeed in GPi.

Pallidal DBS modulates local but not cortical low β power

GPI-DBS resulted in statistically significant suppression of local spectral power in the low β range (13-18 Hz, -26.98 ± 15.14 % change) in the GPi as tested by the two-group test of spectra and corrected for multiple comparisons (Figure 2A), but not at other frequencies examined. Furthermore, GPI-DBS did not result in significant spectral power change in the sensorimotor cortices for other frequencies (Figure 2A). We further used paired statistical tests to compare average band powers in low and high β at each location between conditions. Wilcoxon signed-rank test indicated that only changes in pallidal low β power were statistically significant ($P=0.03$), as indicated in the boxplots (Figure 2B) all subject but one showed consistent suppression of this low β power. However, this change did not survive the correction for multiple comparisons.

High β GPI-M1/PM coherence decreases with GPI-DBS

At baseline (rest, DBS-OFF), significant pallidocortical coherence was observed across both low and high β sub-bands (Figure 3A). Pallidal DBS significantly suppressed high β coherence (19-29 Hz) between GPi and M1/PM (two group test of the coherence, Figure 3A). On average, high β GPI-M1/PM coherence reduction was $-38.09 \pm 6.19\%$ ($P=0.02$, Wilcoxon signed-rank test, corrected, Figure 3B); this decrease in coherence was observed in every subject (Figure 3B). This DBS-related change in high β cortical-subcortical coherence was specific to the M1/PM and not observed in S1 ($P=0.11$, Wilcoxon signed-rank test, corrected), for which inspection of individual subject coherence results in a very mixed picture of coherence changes with pallidal stimulation (Figure 3B). GPI-DBS did not alter low β pallidocortical coherence for either GPI-M1/PM ($P=0.10$, Wilcoxon signed-rank test, corrected) or GPI-S1 ($P = 0.34$, Wilcoxon signed-rank test, corrected) at the group level. Inspection of individual results (Figure 3B) again demonstrates very inconsistent results across subjects for low β pallidocortical coherence reduction, in contrast to very consistent results seen for high β GPI-M1/PM coherence reduction.

Furthermore, we have studied PSD curves for each subject and compared peak frequency in the pallidal spectra and peak frequency of the coherence between pallidum and motor/premotor cortex. Pallidal spectral peaks were centered at $15.43 (\pm 0.68)$ Hz and $25.07 (\pm 2.99)$ Hz in low and high β range respectively. Pallidocortical coherence peak frequencies were centered at $15.68 (\pm 1.37)$ Hz and $25.39 (\pm 2.79)$ Hz. There was no significant difference in the peak frequencies between coherence and power spectra ($P=0.21$ and 0.36 for low and high β respectively, Wilcoxon signed-rank test).

High β GPI-PM/M1 phase synchronization decreases with GPI-DBS

Similar to coherence, analysis of pallidocortical phase lag index showed that GPI-DBS suppresses dWPLI between GPI-M1/PM in the β band. Permutation test showed the suppression of dWPLI was significant for frequencies between 18-25 Hz (Figure 4A). On further analysis of β sub-bands, this reduction was only significant in the high β frequency band ($-61.40 \pm 8.75\%$ reduction, $P=0.02$, Wilcoxon signed-rank test, Figure 4B), again with a consistent reduction in all subjects. The reduction in low β dWPLI between GPi and M1/PM was not statistically significant ($P=0.08$, Wilcoxon signed-rank test, corrected).

Likewise, suppression of average dWPLI between GPi and S1 was not significant at either low or high β sub-bands ($P>0.3$, Wilcoxon signed-rank test, corrected).

DBS-dependent changes in dWPLI and coherence in the high β band were significantly correlated (Spearman correlation, $Rho=0.80$, $P=0.01$, Figure 4C) indicating that changes in coherence are related to the changes in the phase synchrony between the signals. Average phase difference for dWPLI in the high β band between GPi and M1/PM changed from $-0.14 (\pm 1.23)$ to $0.88 (\pm 1.21)$ radians for DBS-OFF and DBS-ON respectively, but this was not statistically significantly different between the two conditions ($P=0.13$, Wilcoxon signed-rank test, Figure 4D).

Neurophysiological profiles are restored after cessation of high-frequency GPi-DBS

Pallidal PSD and pallidocortical coherence and dWPLI during DBS-OFF conditions before and after high-frequency stimulation demonstrated no significant change in pallidal power or long-range pallidocortical functional connectivity (Figure 5).

Pallidal signals are more strongly coherent to the motor and premotor cortices

After spatial normalization across subjects, we analyzed (resting state, DBS-OFF) pairwise coherence between pallidal signal and 5 cortical signals spanning the central sulcus and ± 2 cm anterior and posterior. We modeled average band coherence as a full-factor combination of contact (5 levels: S1-1cm, S1, CS (contact pair spanning the central sulcus), M1/PM and M1/PM+1cm) and frequency band (2 levels: low and high beta). This model was found to be statistically significant ($\chi^2=34.33$, $P=0.0001$). Both contact and frequency band were found to have significant main effects in the prediction of coherence values ($\chi^2=19.27$, $P=0.0007$ and $\chi^2=7.45$, $P=0.0064$, respectively). These significant main effects suggest that (1) spatial location (ie sensory vs motor/frontal vs parietal) affects the amount of beta coherence and (2) there are differences between low and high beta coherence across the fronto-parietal contacts. The interaction between the two main effects was not statistically significant ($\chi^2=6.76$, $P=0.105$). Posthoc pairwise comparisons of beta coherence between different spatial locations showed that coherence is significantly higher in M1/PM relative to the parietal signals: S1 ($Z=3.26$, $P=0.011$, corrected) and S1-1cm ($Z=3.68$, $P=0.002$, corrected). Therefore, the data indicates that pallidal signals are more strongly coherent to the motor and premotor areas compared to the sensory and parietal cortex.

We also compared the magnitude of low and high β coherence at each of the five cortical sources and the pallidal signal. Doing the paired posthoc test, high β coherence is greater than low β coherence in frontal contacts: CS ($Z=2.38$, $P=0.018$, corrected) and M1/PM+1cm ($Z=2.22$, $P=0.026$, corrected), Figure 6.

Discussion

Excessive β activity throughout the BGTC motor network has been linked to PD symptomatology [3, 11, 17, 22, 29, 49-55]. Several studies have shown that in the untreated state, STN β power correlates with severity of rigidity and bradykinesia and decreases in proportion to clinical improvement with therapy [22, 49, 51, 55, 56]. Thus, STN β power has

been suggested as a biomarker of PD symptom severity and used as a control signal in the realization of closed-loop DBS [57-59]. A recent study has shown that DBS-dependent STN local β power suppression is specific to low β [17]. Interestingly, at the cortical level, there are conflicting reports on DBS and medication-related changes in β oscillatory power [14, 17, 21, 25, 60].

It has been posited that not only local β activity within STN is part of the pathophysiology of disease, but that excessive coupling of these signals across the BGTC motor network is also related to the disease [14, 18, 21]. Studies of interregional connectivity likewise have shown that STN-DBS reduces STN-cortical connectivity [17, 21]. This coupling is maximal in high β frequencies and has been attributed to the hyperdirect pathway because it provides monosynaptic connectivity between the two regions [17]. Likewise, we have recently shown GPi-DBS preferentially modulates motor cortical PAC in the high β range [25]. Although it is plausible that the high β rhythm propagates through the hyperdirect pathway and GPi-DBS blocks its flow, we have also observed high β oscillations in the GPe [9]. Therefore it is more likely that this rhythm, in fact, reverberates through the entire BGTC motor network and is not specific to the hyperdirect pathway.

Despite that randomized clinical trials have shown that GPi-DBS is clinically equally efficacious to STN-DBS [32] (allowing for differential effects on medication requirement [30, 31]), most studies only examine the effects of STN-DBS. The GPi is the common final output of the basal ganglia, sending inhibitory projections to the cortical projecting areas of the thalamus [61]. It remains unclear if the previously described effects of STN-DBS on the basal ganglia-motor cortical functional connectivity are generalizable effects of DBS therapy or are indeed specific and attributable to modulation of the hyperdirect pathway.

Our findings highlight that GPi-DBS (similar to the STN-DBS) modulates local β activity within the basal ganglia without significant modulation of cortical β power. Moreover, pallidal stimulation results in significant suppression of pallidocortical functional connectivity in β frequencies. Furthermore, our results provide new evidence of the functional dissociation between low and high β frequencies by showing that effects of pallidal stimulation on the local basal ganglia β power are only significant in low β range whereas suppression of pallidocortical connectivity occurs in the high β range. Similar to Oswal et al [17], high β functional connectivity dominates in frontal regions where it is selectively modulated by GPi DBS.

The potentially distinct roles of high β activity in motor control and the pathophysiology of PD remain unclear. The modulation of low β pallidocortical coherence may be important for normal motor control [28]. Moreover, studies of hemiparkinsonian animals have shown that low β power is reduced with motor activity while high β activity is increased in the motor cortex and basal ganglia in the dopamine-depleted hemisphere [62-65]. High β activity is most pronounced when animals are engaged in the on-going motor activity and significantly reduced with dopamine [62-65]. In PD patients, clinical improvement with therapy corresponds with a reduction in local STN low β power while cross-site cortico-STN coupling within the high β range is most responsive to therapeutic interventions [17, 29]. Non-linear correlations between low and high β oscillations have been reported in PD

subjects during the off medication state as well. Levodopa administration significantly decreases these correlations and separates these two β sub-bands [66]. All in all, the current study and the literature support functional segregation of low and high β bands, in which low β represents a local signal where high β is more likely a disease-related network-wide oscillation mediating hypersynchrony across the BGTC circuit.

The attenuation of pallidocortical coupling with GPi-DBS occurs without significant cortical or pallidal high β power suppression. This indicates that changes in the coupling are not reflective of the changes in the amplitude of the underlying signals and are directly affected by changes in the phase-based connectivity. Given GPi connectivity, our important finding on the similar effect of the GPi-DBS on the suppression of cortical-subcortical coupling suggests that direct stimulation of hyperdirect pathway is not required for DBS-mediated modulation of network activity. Still, a causal relationship between network modulation and therapeutic effect of DBS remains to be demonstrated.

Our work was limited by our sample size and that no control group was available to contrast our findings, but the number of subjects used is not atypical for this type of study [21, 28, 47, 48]. Moreover, given the consistency of the significant results across all subjects, it is unlikely the current findings are random. We were also limited in our recording time due to the nature of these experiments and the intra-operative constraints. Although we aimed to avoid the post-stimulation effects and kept the order of experiments consistent across our cohort, randomizing the order between DBS-ON and DBS-OFF will provide further insight into the robustness of our findings. Restoration of pre-stimulus neurophysiological profiles after cessation of GPi DBS suggests the observed changes were in fact stimulation-related. Finally, we note that our experimental design was limited by our recording technique. This method mitigates the effects of stimulation artifact by providing two recording channels that are equidistant from the stimulation site. This technique provides signals from a relatively large span of the GPi (3 mm). However as evident in Figure 1B, for the majority of the subjects this recording site was almost entirely within the GPi and minimally dorsal to the nucleus for a few subjects.

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Figure 1.

DBS and ECoG Lead Localization. (A) 2D/3D fusion of intra-operative lateral fluoroscopic image and cortical surface reconstruction, using DBS leads (red and blue straight lines) and tips of the stereotactic frame (+ signs). Two bipolar pairs spanning pre- and post-central gyri (M1/PM and S1 respectively) were used. (B) Group figure demonstrating the contacts of the reconstructed DBS leads (red circles) in the right hemisphere. All images were normalized to the CraniVault atlas and the relative position of the DBS contacts (red dots) with respect to the GPi (dark green) is illustrated.

Figure 2.

Changes in local spectral power in the GPi and sensorimotor cortices with GPi-DBS. (A) Group average PSD for DBS-OFF (black) and DBS-ON (blue), indicating significant suppression of local pallidal power at frequencies (13–18 Hz, low β) without significant modulation of local cortical power. (B) Boxplots showing changes in group average power for low and high β frequencies for two modes of DBS-OFF and DBS-ON. An asterisk (*) indicates a statistically significant change at $P < 0.05$ level as tested by Wilcoxon signed-rank test.

Figure 3.

Changes in pallidocortical coherence with GPi-DBS. (A) Group average coherence between GPi and cortical signals from S1 and M1/PM (left to right) for DBS-OFF (black) and DBS-ON (red). Black dotted line shows 95% confidence level for baseline coherence. Shades around each average coherence curve indicate 95% CI of the mean value at each frequency bin and yellow shade indicate statistically significant difference as tested by two group test of coherence (B) Boxplots showing changes in group average coherence for low and high β frequencies for two modes of DBS-OFF and DBS-ON. An asterisk (*) indicates a statistically significant change at $P < 0.05$ level as tested by Wilcoxon on signed-rank test.

Figure 4.

Changes in GPi-M1/PM phase connectivity by GPi-DBS (A) Group average dWPLI between GPi and M1/PM showing significant suppression of pallidocortical phase connectivity for 18-24 Hz (yellow shade). Shades around each average dWPLI curve indicate 95% CI of the mean at each frequency. (B) Boxplots showing that high β dWPLI is significantly suppressed by GPi-DBS (*, Asterisk indicate statistical significant at $P < 0.05$ level). (C) Scatter plot between percent change in baseline high β coherence and dWPLI across the cohort. (D) The preferred phase difference in high β frequencies for each subject (single dot) across two conditions (DBS-OFF, black) and (DBS-ON, red). Solid arrows show average preferred phase difference across the cohort indicating a positive phase lag between GPi and M1/PM signals.

Figure 5.

Local spectral power in the GPi and pallidocortical coherence before and after cessation of high-frequency GPi DBS. (A) Group average PSD before stimulation, DBS-OFF pre (black) and after cessation of high frequency stimulation DBS-OFF post (blue) (B) Group average coherence between pallidal and motor/premotor cortical recording before stimulation, DBS-OFF pre (black) and after cessation of high frequency stimulation DBS-OFF post (blue) (C) Group average dWPLI between pallidal and motor/premotor cortical recording before stimulation, DBS-OFF pre (black) and after cessation of high frequency stimulation DBS-OFF post (blue)

Figure 6.

Boxplots showing differences in group average coherence for low and high β frequencies (during resting state and DBS-OFF). Asterisk (*) indicates a statistically significant change at $P < 0.05$ level as tested by Wilcoxon signed-rank test.

Table 1:

Demographic and clinical information

Patient	Age Gender	UPDRS III (OFF-DBS/ON-DBS)			ON-DBS stimulation parameters		
		Tremor	Rigidity	Bradykinesia	Voltage (V)	Frequency (Hz)	Pulse Width (µs)
P1 *	64/F	0/0	2/0	2/0	3.4	185	90
P2	61/M	2/1	3/0	2/0	3.4	185	90
P3	72/M	0/0	3/0	3/0	3.4	185	90
P4	61/M	2/1	2/1	1/0	3.4	185	90
P5	73/F	0/0	3/0	3/0	2.5	185	90
P6	57/F	0/0	2/0	2/0	3	185	90
P7	55/M	0/0	3/0	2/0	3	185	90
P8	52/M	0/0	2/0	2/0	4	160	90
P9	61/M	1/0	2/0	2/0	3	185	90

*. This patient had mild dyskinesias that were still present during DBS-ON recordings