Effects of Contralateral Deep Brain Stimulation and Levodopa on Subthalamic Nucleus Oscillatory Activity and Phase-Amplitude Coupling

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ABSTRACT

Background: The modulatory effects of medication and deep brain stimulation (DBS) on subthalamic nucleus (STN) neural activity in Parkinson's disease have been widely studied. However, effects on the contralateral side to the stimulated STN, in particular, changes in local field potential (LFP) oscillatory activity and phase-amplitude coupling (PAC), have not yet been reported.

Objective: The aim of this study was to examine changes in STN LFP activity across a range of frequency bands and STN PAC for different combinations of DBS and medication on/off on the side contralateral to the applied stimulation.

Materials and Methods: We examined STN LFPs that were recorded using externalized leads from eight parkinsonian patients during unilateral DBS from the side contralateral to the stimulation. LFP spectral power in alpha (5 to ~13 Hz), low beta (13 to ~20 Hz), high beta (20–30 Hz), and high gamma plus high-frequency oscillation (high gamma+HFO) (100–400 Hz) bands were estimated for different combinations of medication and unilateral stimulation (off/on). PAC between beta and high gamma+HFO in the STN LFPs was also investigated. The effect of the condition was examined using linear mixed models.

Results: PAC in the STN LFP was reduced by DBS when compared to the baseline condition (no medication and stimulation). Medication had no significant effect on PAC. Alpha power decreased with DBS, both alone and when combined with medication. Beta power decreased with DBS, medication, and DBS and medication combined. High gamma+HFO power increased during the application of contralateral DBS and was unaltered by medication.

Conclusions: The results provide new insights into the effects of DBS and levodopa on STN LFP PAC and oscillatory activity on the side contralateral to stimulation. These may have important implications in understanding mechanisms underlying motor improvements with DBS, including changes on both contralateral and ipsilateral sides, while suggesting a possible role for contralateral sensing during unilateral DBS.

Keywords: Deep brain stimulation, levodopa, Parkinson's disease, phase-amplitude coupling, subthalamic nucleus

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) at high frequencies (> 100 Hz) is an established clinical treatment for patients with Parkinson's disease (PD). Simultaneous recording of local field potentials (LFP) during DBS provides a measure of STN and basal ganglia local neuronal activities that reflect oscillatory rhythms in different frequency bands within the target nuclei.[1–4] Among these rhythms, beta band oscillations (~13–30 Hz) have received particular attention[5–7] as they have been shown to correlate with motor impairment and symptoms of rigidity and bradykinesia in PD,[8–10] and are decreased with medication and during DBS.[11,12] Giannicola et al[13] showed a decrease in the power of the beta band rhythm with medications that contain levodopa while DBS was ON. However, they observed that while stimulation effectiveness was demonstrated in all patients, DBS suppressed

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Table 1. Clinical Information for the Patient Participants.

Patient	Age (years)	Gender	Disease duration (years)	Levodopa equivalent dose before surgery (mg/day)	Available signals (Med/Stim conditions)	UPDRS III before surgery	
						Off	On
1	48	M	8	925	All conditions	25/108	2/108
2	49	F	7	900	All conditions	20/108	4/108
3	63	F	13	1512	Baseline only	19/108	0/108
4	61	F	9	1150	All conditions	18/108	2/108
5	61	F	5	1300	All conditions except "Med: On, Stim: Off"	22/108	5/108
6	55	M	7	1305	All conditions except "Med: On, Stim: Off"	22/108	3/108
7	62	M	16	900	Baseline and "Med: On, Stim: Off"	27/108	4/108
8	61	M	10	1200	All conditions	18/108	2/108

F, female; M, male; UPDRS, unified Parkinson disease rating scale.

beta band activity only in a subgroup of patients with higher beta activity at baseline (without medication or DBS). In addition to documented changes in beta activity, modulation of neural activity at lower and higher frequency bands with DBS and medication has also been observed. DBS and levodopa have been reported to increase STN low-frequency (2–7 Hz) activity in patients with PD.[2,14,15] Gamma (40–90 Hz) activity, and high-frequency oscillations (HFO) (200–400 Hz) have also been reported to increase with medication and DBS in a number of studies.[16–19] An overview of STN LFP oscillatory activity and the influence of medication and DBS are provided in a recent review article by Yin et al.[20]

While the focus of most previous studies has been primarily on spectro-temporal analysis, recently, modulation and coupling between different spectral rhythms through cross-frequency coupling (CFC) have also been investigated. CFC provides a measure of the interaction between rhythms in different bands, which can be assessed using intracellular recordings such as LFPs,[21] electrocorticography (ECoG),[22] and electroencephalography.[23] Phase amplitude coupling (PAC) is a special case of CFC in which oscillations are coupled so that the amplitude of a high-frequency band activity occurs at a particular phase of a low-frequency rhythm. The existence of PAC has been demonstrated in animals and humans across different ranges of oscillatory rhythms and brain regions, including modulation of high gamma (80–150 Hz) oscillations by theta (4–8 Hz) and alpha (8–12 Hz) rhythms in epilepsy patients during ECoG recordings,[24] exaggerated coupling between the phase of beta band and amplitude of broadband gamma rhythms between primary motor cortex ECoG and STN LFP recordings in PD and dystonic patients[22,25] and other studies in different pathologies and oscillatory bands.[26–29]

PAC within the STN in PD has been examined using LFP recordings at rest and during movement tasks[18,22,25,30–33] with an effect of both DBS,[25] and medication (mainly levodopa)[18] observed. Although the previous studies reported PAC in parkinsonian STN LFPs and analyzed the effects of DBS and levodopa separately,[18,22,25] the effects of levodopa medication and DBS on PAC in individuals with PD have not been examined.

In this paper, we investigated the effects of contralateral stimulation (Stim) and medication (Med) on PAC between STN LFP beta activity and combined high gamma and high-frequency (100–400 Hz) oscillations (high gamma+HFO) in eight patients with PD. We also analyzed the effects of contralateral DBS and medication, both separately and simultaneously, on the distribution of LFP power across different oscillatory bands, specifically broadband alpha (5–13 Hz), low beta (L-beta) (13–20 Hz), high beta (H-beta) (20–30 Hz), beta and high gamma+HFO bands. Unilateral STN high-frequency DBS has previously been shown to increase neuronal activity and reduce beta band oscillations in the contralateral STN,[34–36] suggesting a modulation of neural activity throughout the basal ganglia-thalamo-cortical network. This study builds upon these findings to explore DBS-medication-induced contralateral modulation of STN LFP activity, utilizing PAC and spectral analysis.

MATERIAL AND METHODS

Experimental Protocol

STN LFPs recorded in eight patients (four female) with idiopathic PD, bilaterally implanted with macro-electrodes for DBS in the STN (model 3389 Medtronic, Minneapolis, MN, USA), were analyzed. Demographic and clinical information for each of the patient participants is summarized in Table 1. The experimental protocol has been reported in a previous study by Giannicola et al,[13] along with details of the DBS surgery and the electrode position. Patients were studied after written informed consent and local ethical committee approval, as fully disclosed in Giannicola et al[13] conformed to the Declaration of Helsinki.

To summarize, LFPs were recorded from the STN both ipsilateral and contralateral to the DBS electrode three days after DBS electrode implantation. Data were amplified by a factor of 50,000 and recorded with a sampling frequency of 2,500 Hz. The nucleus contralateral to the most affected body side was chosen for monopolar stimulation (pulse duration = 60 μs and DBS frequency = 130 Hz) using a constant voltage stimulator (Dual Screen, Medtronic) through contact one (out of four contacts 0-1-2-3) placed at the optimal functional target detailed in Table 2 of the previous work by Giannicola et al.[13] The stimulation intensity was clinically assessed and set by the experienced neurologist at the contralateral body side to the stimulated nucleus. Participants attended the experiment following overnight withdrawal of medication. Signals were then recorded during each combination of medication (levodopa) and stimulation (DBS) on and off: first with no medication and no stimulation (Med: off, Stim: off), following no medication and stimulation on (Med: off, Stim: on), and then both medication and stimulation on (Med: on, Stim: on) and finally no stimulation while medication is on (Med: on, Stim: off). Each session lasted approximately one hour. The experimental protocol included the six steps summarized in Figure 1 (detailed along with the surgical procedure in Giannicola et al[13]).

Data Preprocessing

Signals recorded contralateral to the nucleus stimulated by DBS were chosen for analysis. Among these contralateral signals, for each of the four different medication and stimulation conditions, data for some conditions were missing. Data segments that were highly contaminated by noise and that did not show LFP activity were removed prior to analysis. This was done by visual inspection of the time series, spectrograms, and power spectral densities (PSDs), simultaneously for each of the recordings. After discarding the contaminated recordings (17 out of 44 available signals), the number of patients and available signals varied between different conditions (summarized in Table 1, "Available signals"). Epochs of 100 s duration were extracted from each data set, and PAC and spectral power were computed from a randomly selected 30-second window. This was repeated 100 times with overlapping windows. The data were high-pass filtered at 5 Hz (f_{stop}= 5 Hz, f_{pass}= 8 Hz, A_{stop}= 80, and A_{pass}= 1), and a notch filter was applied at 50 and 150 Hz (second-order Butterworth, quality factor = 5) to remove the electrical power interference. Data were analyzed using custom-developed scripts in MATLAB 2018b (MathWorks, Natick, MA).

Spectral Power Densities and Band Powers

The PSD of each 30-second segment of LFP data was estimated using Welch's method with a 1-second window length and 50% overlap. To estimate the total power in the alpha band, the integral of the power spectrum from 5 to ~13 Hz was estimated and normalized with respect to the total power between 1 and 400 Hz. When calculating the total power, the power in the range of the stimulation frequency and its first harmonic, 130 ± 5 and 260 ± 5 Hz, was subtracted from the total to exclude stimulation artifacts. The normalized beta band power was similarly estimated in the range from 13–30 Hz, with L-beta band from 13 to ~20 Hz and H-beta band from 20 to 30 Hz, and the normalized high gamma + HF band power from 100-400 Hz.

Calculation of PAC

Phase-amplitude coupling in the STN was estimated using the Kulback–Leibler model based on modulation index (MI)[37] for each of the four different combinations of medication and stimulation. The MI detects PAC between two frequency ranges of interest, representing the phase-modulating (beta) and amplitude-modulated (high gamma+HFO) frequency bands.[21,22,25,30]

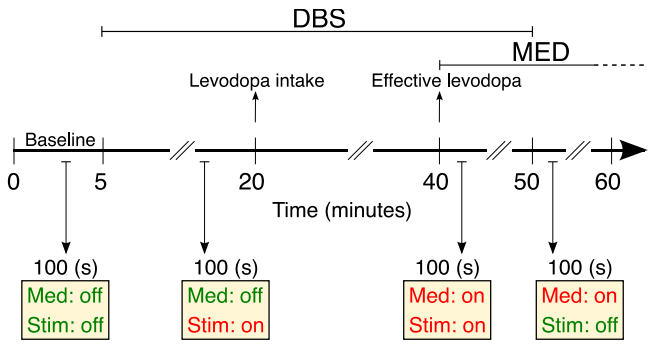

Figure 1. The experimental protocol similar to the one reported by Giannicola et al.[13] [Color figure can be viewed at www.neuromodulationjournal.org]

In brief, the MI-based method measures the entropy of the phase-amplitude distribution for each frequency bin of the phase frequency band and amplitude frequency band. LFPs were band-pass filtered once in the beta band and once in high gamma+HFO band, and the Hilbert transform was applied to extract the phase and amplitude. The entropy of the instantaneous amplitude envelope distribution was estimated for each 20-degree interval of the instantaneous phase distribution. The computed entropy was then normalized by its maximum value to obtain MI, where higher values of MI indicate a higher correlation between the frequencies of the phase and amplitude. Here, the filtering was performed for the phase frequency from 10–30 Hz in 2 Hz steps with a 4 Hz bandwidth. The amplitude frequency was extracted from 200–400 Hz in 4 Hz steps with a bandwidth of 10 Hz. The PAC between L-beta and HFO, and H-beta and HFO, were separately investigated and are referred to as L-PAC and H-PAC, respectively.

Statistical Analysis

To estimate the statistical significance threshold for the PAC, surrogate data were generated based on the original data by splitting the amplitude vector (the magnitude of the signal after performing Hilbert transform) in half and switching the position of the resulting vectors before recombining and recomputing the PAC (the surrogate PAC).[38,39] This was repeated 100 times. The mean of the resulting PAC was subtracted from the original uncorrected PAC values to obtain the corrected PAC, which is free of spurious peaks with reduced noise. The PAC values were normalized with respect to the maximum MI value in the first subject. Finally, we compared the PAC values for each subject (100 times from different 30-second time windows over a 100-second signal duration) by the shuffled PAC values (100 surrogates explained above), using a *t*-test ($p < 0.01$). Only significant PAC values, following Bonferroni correction, are reported. Mixed effects linear models (or linear mixed models [LMM]) were applied to statistically investigate the effects of medication and stimulation conditions on the features examined (relative power in each frequency band and PAC).

In addition to a different rhythmic band definition in this paper, the data were analyzed using LMM, which can accommodate missing data and account for correlation in the data without requiring subjects to be removed from the data set. In other words, LMM handles variability within and across subjects and also gaps in the data.

RESULTS

Power Changes in Different Band Rhythms due to Medication and Contralateral Stimulation Concomitant Effects

The total power in the STN LFP signal, recorded on the contralateral side to the applied stimulation, was estimated for the alpha, L-beta, H-beta, and high gamma+HFO frequency bands to examine changes across different medication-stimulation conditions. Figure 2a illustrates the power spectral densities estimated as an average across all subjects during the four different conditions, off/on medication and off/on stimulation. Figure 2b demonstrates one case representative with the same layout as Figure 2a.

Stimulation alone and stimulation and medication combined had a significant effect on the power in each frequency band when compared with the baseline values. Alpha power was reduced with stimulation alone and when stimulation was combined with medication, Figure 3. Turning stimulation off led to the return of the alpha power to the baseline.

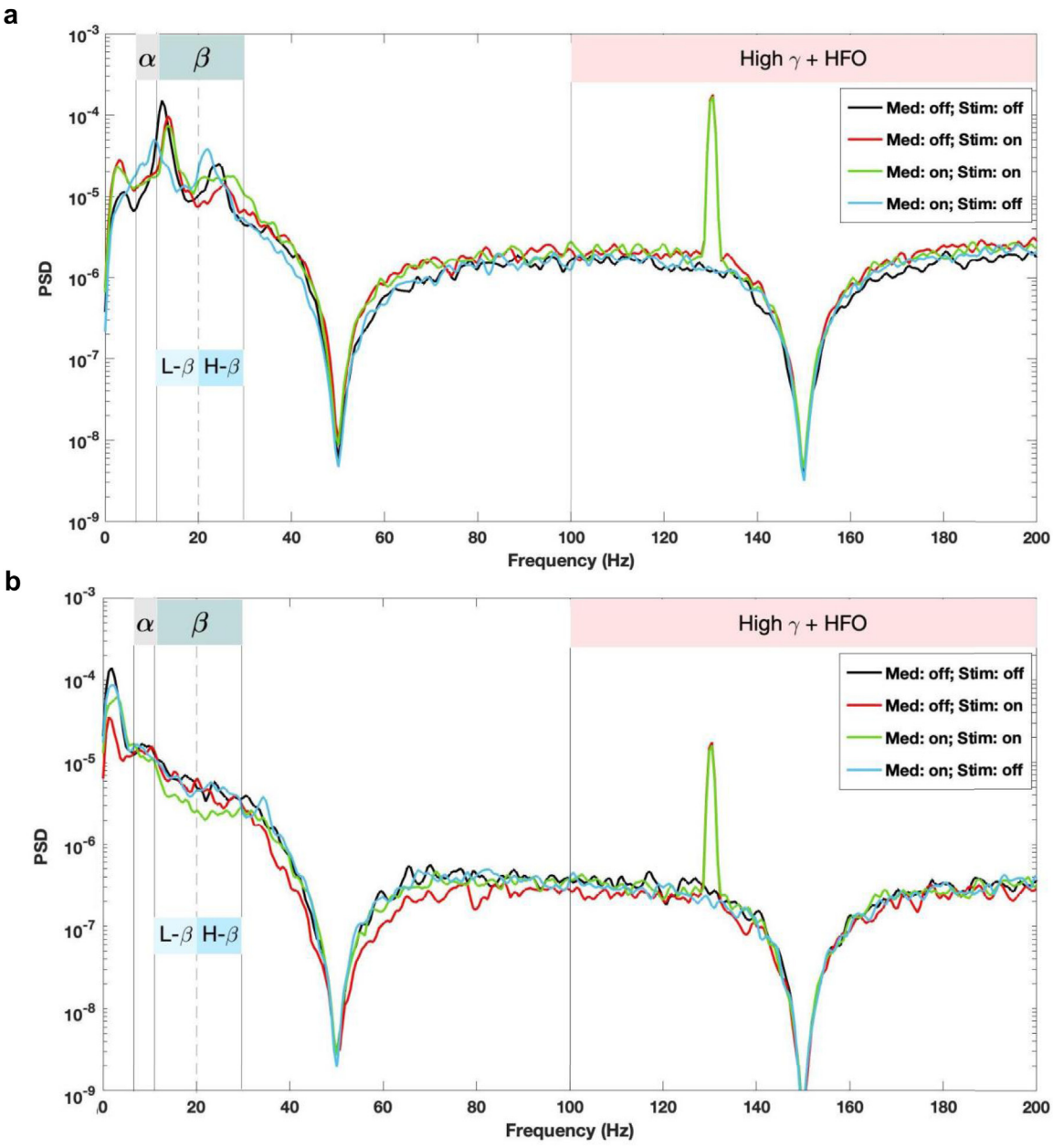

Figure 2. a. Power spectral densities estimates during the four different combinations of medication and stimulation states, averaged across the subjects. b. The same as panel a but for patient number 1 only (case representative). High γ + HFO, high gamma plus high-frequency oscillation. [Color figure can be viewed at www.neuromodulationjournal.org]

The total beta power was reduced when stimulation was on both with and without medication, Figure 4. With stimulation on, beta power decreased slightly when medication was on, compared with the "Med: off; Stim: on" condition. However, this difference was not statistically significant. Similar patterns of a reduction in oscillatory activity with stimulation were observed when beta activity was subdivided into the low and high beta frequency bands, though only L-beta activity remained significantly lower than baseline with medication on while stimulation was off, Figure 4c.

Regarding the high gamma+HFO, medication increased the baseline power but not significantly when DBS was off, Figure 5. However, excluding the DBS main drive at 130 Hz and its first harmonic at 260 Hz (explained in Materials and Methods section), DBS significantly increased the power in this band regardless of medication status. The effect of stimulation and medication on the power in the gamma band (Fig. 5) was in the opposite direction to their effect on the alpha and beta band power (Figs. 3 and 4).

PAC in STN and the Mixed Effects of Medication and Stimulation

Traditional spectral analyses of LFP signals, such as Fourier or wavelet transforms, provide insight into the distribution and modulation of neural activity across the different neurophysiological

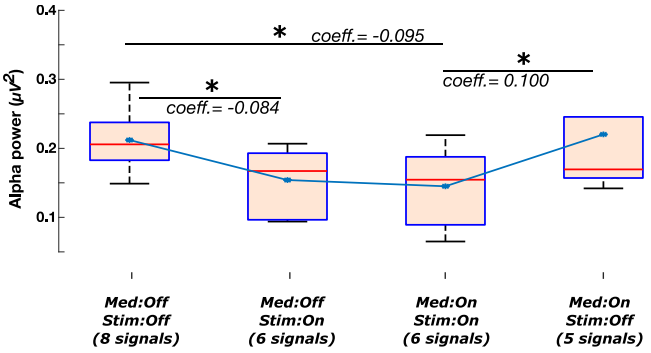

Figure 3. STN LFP alpha power for the four different medication and stimulation conditions (Med: off/on and Stim: off/on). The significant differences evaluated by LMM are shown by * ($p < 0.05$). [Color figure can be viewed at www.neuromodulationjournal.org]

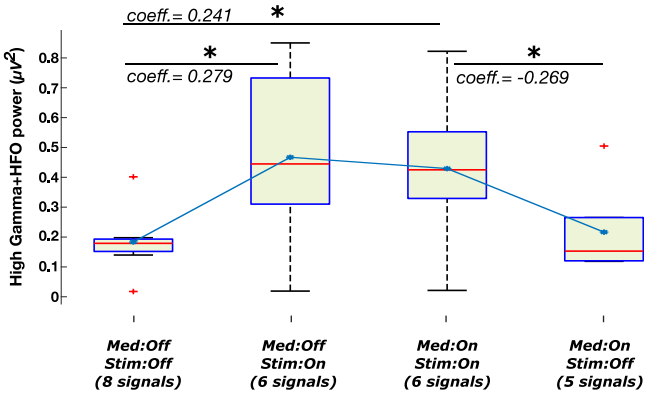

Figure 5. STN LFP high gamma+HFO broadband power for the four different medication and stimulation conditions (Med: off/on and Stim: off/on). The significant differences evaluated by LMM are shown by * ($p < 0.05$). [Color figure can be viewed at www.neuromodulationjournal.org]

frequency bands. The instantaneous phase can additionally be assessed using, for example, Hilbert transforms. Complementary to these tools, CFC measures such as PAC enable the correlation between different frequency components and bands in one or more biosignals to be examined.

The existence of PAC was characterized by a deviation of the amplitude distribution *P* from the uniform distribution in a phase-amplitude plot. Following this, MI quantifies the deviation of *P* from the uniform distribution.[37] We computed the corrected PAC with statistical significance as described for each signal in all four medication-stimulation conditions (Med: off/on, Stim: off/on). The grand average PAC in each condition was computed and is presented in Figure 6a–d. It is evident in Figure 6a that high levels of PAC are present in the baseline condition (Med: off, Stim: off). The PAC was almost completely suppressed once stimulation was turned on, Figure 6b,c. Turning off the stimulation, with medication on (Fig. 6d), resulted in a partial reemergence of the PAC at frequencies similar to those observed at baseline. A summary of the total PAC estimated for each subject under each condition is presented in Figure 6e.

Using LMM to examine the effect of condition, only stimulation was found to have a significant effect on the reduction in total PAC compared to baseline (Med: off, Stim: off), denoted by * in Figure 6e. The reduction of PAC due to stimulation (Fig. 6a,b) was attributable to the modulation of the high gamma+HFO by L-beta (L-PAC) (Fig. 6g). PAC reappeared when stimulation was turned off, Figure 6d, in parallel with an increase in H-beta modulation of the high gamma+HFO (H-PAC) (Fig. 6f). Medication had no effect on baseline PAC values, regardless of the DBS application.

PAC and the Correlation With Beta and High Gamma+HFO Powers; Other Correlations

Finally, the linear correlation between PAC and power in the alpha, L-beta, H-beta, and high gamma+HFO bands was examined using Pearson's rank correlation, Figure 7. L-beta power did not show a correlation with the total PAC values, as illustrated in Figure 7a ($r = 0.18$, $p = 0.19$), while H-beta power was positively correlated with PAC ($r = 0.56$ **, $p = 0.001$), Figure 7b. Alpha power was not correlated with PAC values ($r = 0.05$, $p = 0.4$), Figure 7c;

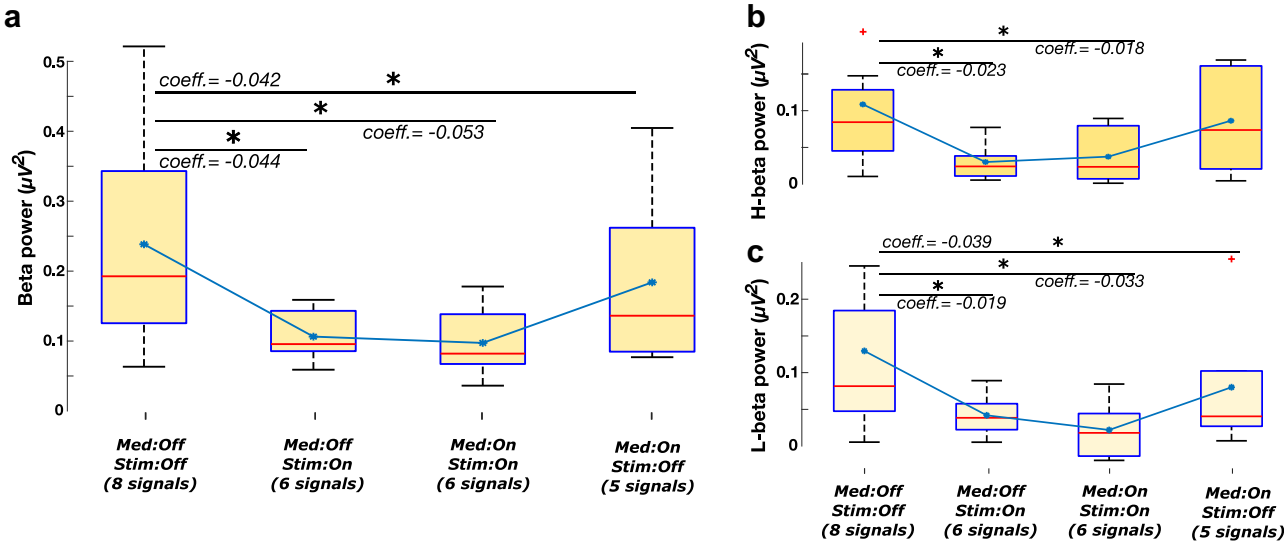

Figure 4. STN LFP (a) beta power (b) L-beta power and (c) H-beta power for the four different medication and stimulation conditions (Med: off/on and Stim: off/on). The significant differences evaluated by LMM are shown by * ($p < 0.05$). [Color figure can be viewed at www.neuromodulationjournal.org]

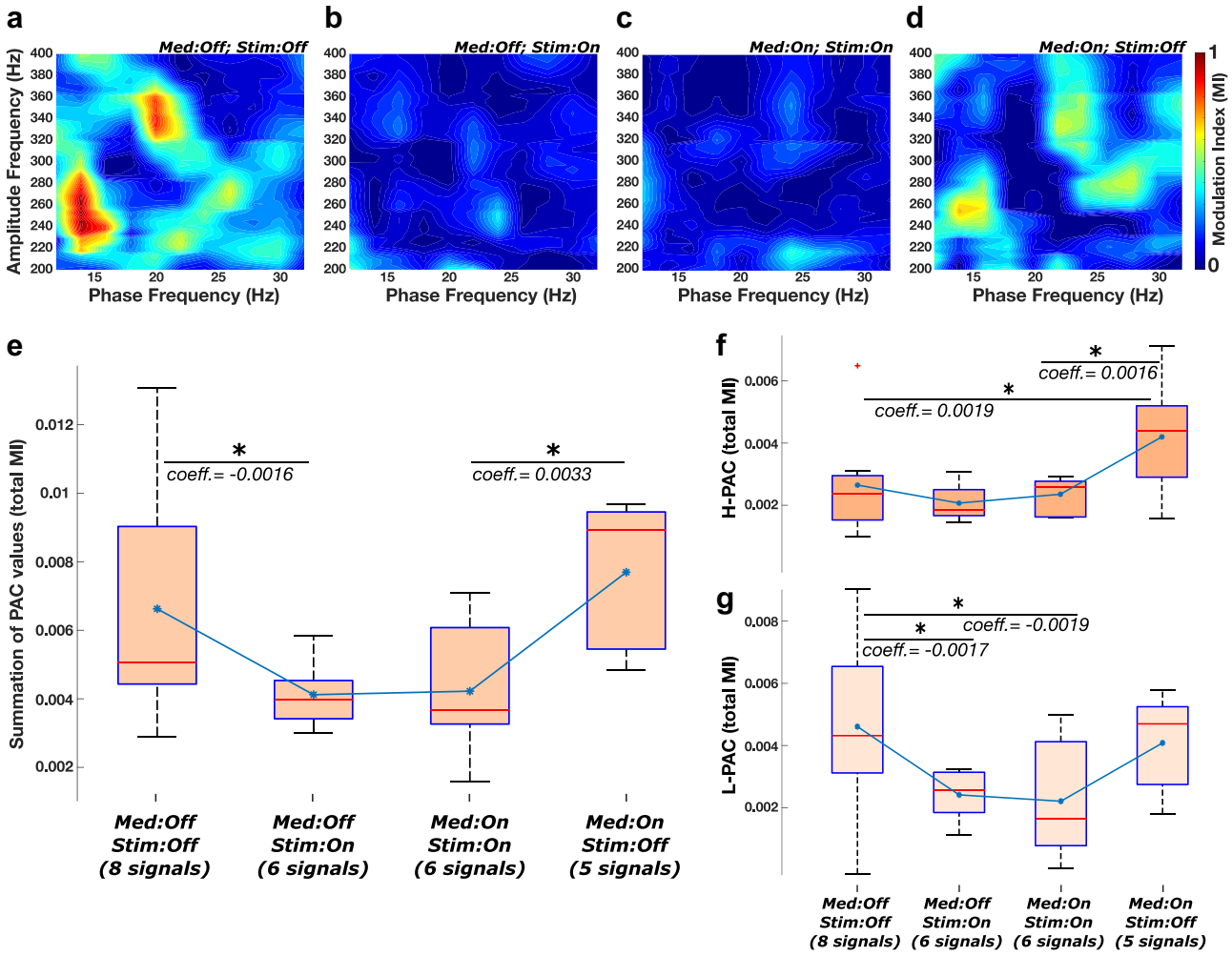

Figure 6. PAC within the STN LFP averaged over all subjects for (a) no medication, no stimulation (Med: off, Stim: off), (b) no medication, on stimulation (Med: off, Stim: on), (c) on medication, on stimulation (Med: on, Stim: on) and (d) on medication, no stimulation (Med: on, Stim: off). (e) The summation of the significant PAC for the four different medication and stimulation conditions (Med: off/on and Stim: off/on). (f) As panel e but showing the PAC between the high beta rhythm and high-gamma+HFO (H-PAC). (g) As panel e but showing the PAC between low beta rhythm and high-gamma+HFO (L-PAC). The boundaries of the box plots indicate the 25 and 75 percentiles of the distributions, and the red lines show their median. The means of the distributions were added as blue-filled circles. Significant differences evaluated by LMM are shown by * ($p < 0.05$) along the coefficient of variation in the intercept between the states. [Color figure can be viewed at www.neuromodulationjournal.org]

high gamma+HFO power was negatively correlated with PAC, though not at 0.05 significance level ($r = -0.3$, $p = 0.07$), Figure 7d.

Beta power was also positively correlated with the subjects' disease duration ($r = 0.82$, $p = 0.001$) at the baseline, where PAC did not show a significant correlation with the disease duration at the baseline. Disease duration was positively correlated with H-PAC values, though this was not significant after correcting for multiple correlations ($r = 0.4$, $p = 0.05$).

DISCUSSION

In this study, using the same experimental protocol and patients reported in Giannicola et al,[13] we considered STN LFP data recorded contralateral to the stimulation side and investigated boradband alpha (5 to ~13 Hz), low and high beta band (13–30 Hz), and high gamma band and high-frequency oscillations (high gamma+HFO; 100–400 Hz) during different combinations of DBS on/off and medication on/off. The main findings of the work are summarized and discussed in the following paragraphs.

Beta band power, with either DBS, medication, or combined application of DBS and medication, decreased with respect to the baseline where no medication or stimulation was present (Fig. 4a). In a previous study examining LFP activity on the same side as the applied stimulation in the same patients and under the same experimental protocol,[13] an additive effect of DBS over levodopa was not observed when medication and stimulation were concomitant. A significant effect of medication on the attenuation of total beta band power (Fig. 4a) was observed[13] in the stimulated STN nucleus. STN LFP beta power is known to be correlated with motor impairments in PD and has been proposed as a biomarker for control strategies in DBS[40–42] and to identify the optimum parameter values for DBS frequency and amplitude.[43,44]

We also subdivided the total beta band into L-beta and H-beta bands (Fig. 4 b,c). A significant effect of medication alone on the L-beta power was observed, confirming earlier findings that

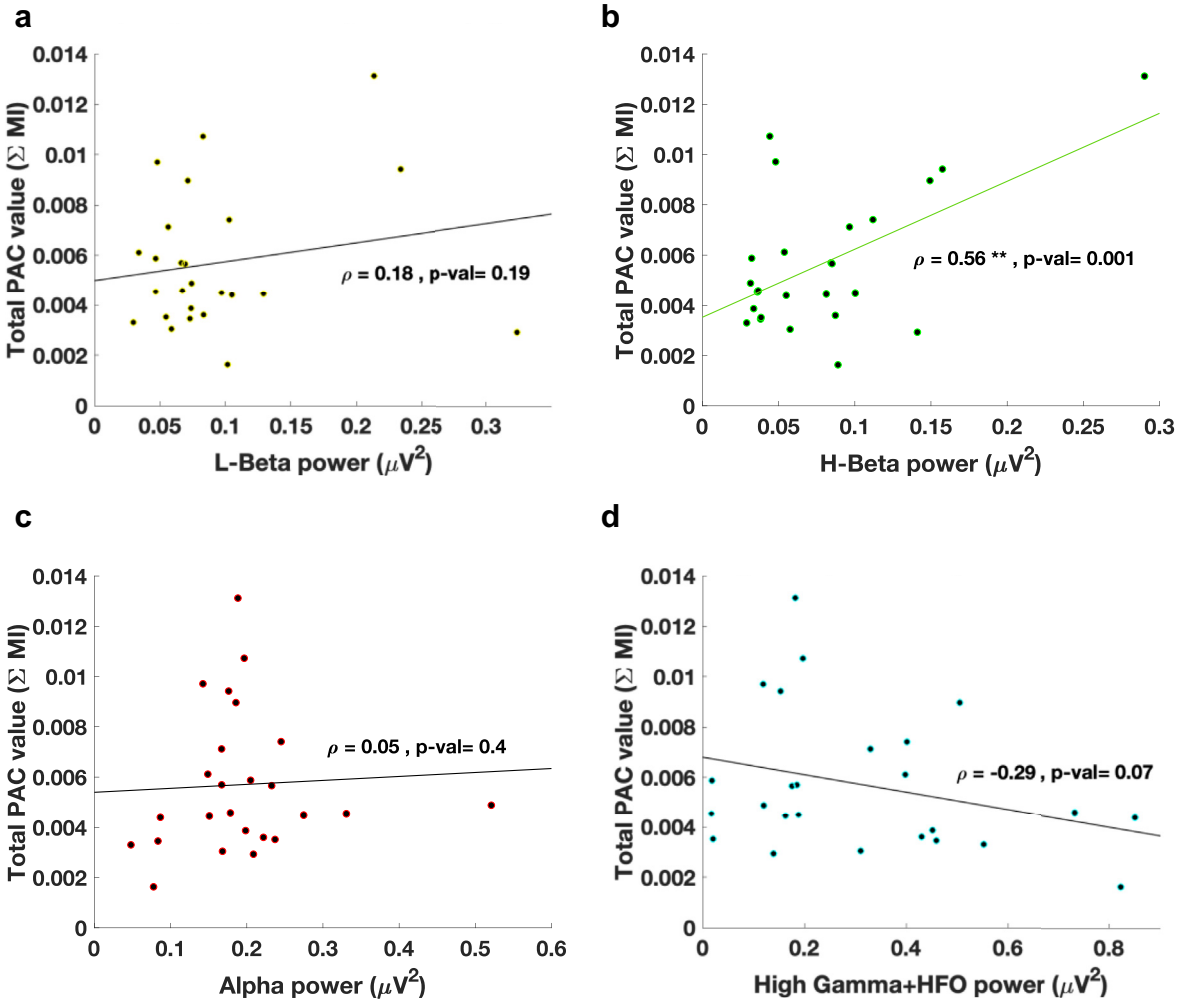

Figure 7. The correlation between the total PAC values in all four states with (a) L-beta power, (b) H-beta power, (c) alpha power, and (d) high gamma+HFO power. H-beta power and total PAC values show a significant positive correlation (Pearson's correlation, $r = 0.56$ and $p = 0.001$ with multiple correlation correction). [Color figure can be viewed at www.neuromodulationjournal.org]

effective levodopa dose suppresses the power in this band.[1,2,45] In previous studies, STN DBS at high frequencies were shown to attenuate the exaggerated beta power, analyzing both STN nuclei LFP recordings during stimulation,[46] in hyperacute and chronic states[11] and after intra-operative STN DBS.[6] Dividing the beta band in this study into low and high bands further revealed that contralateral DBS was more effective at suppressing power in H-beta band rather than L-beta, although the difference is relatively modest, Figure 4b,c.

In addition, we investigated the modulation of high gamma+HFO band activity by the beta band rhythm in the four different conditions utilizing PAC. The results demonstrate that PAC between the beta band and gamma+HFO rhythm effectively disappeared when DBS was on, with the reduction in total PAC attributable to changes in PAC between low-beta activity and high gamma+HFO (Fig. 6). PAC was not significantly influenced by levodopa (Fig. 6) and appeared to be shifted instead to higher phase frequencies (Fig. 6a,d) as was also observed in a previous work[18] where the existence of significant PAC was revealed in both on and off medication states along with modulation of the frequency at which PAC occurs.

In our results, we noted that while L-beta and H-beta power change similarly (Fig. 4b,c), L-PAC and H-PAC show slightly different behaviors (Fig. 6f,g). This could suggest that PAC is not simply a reflection of the total beta power. In support of this observation, a consistent reduction in cortical PAC across subjects during DBS on has been observed, regardless of whether beta power increased or decreased, although the magnitude of PAC was correlated with the beta power.[25] Our results indicate a significant positive correlation between H-beta power and PAC values across all conditions (Fig. 7b). The correlation between high gamma+HFO power with PAC values, though, revealed a slight negative correlation (Fig. 7d). The results also revealed a significant high correlation between the relative beta power and disease duration during the baseline condition (Med: off; Stim: off).

DBS alone decreased the STN LFP alpha power (Fig. 3), in line with a previous report[43] where attenuation of both resting state alpha and beta STN LFP power was observed. DBS, in combination with medication, decreased the STN LFP alpha power (Fig. 3). Medication alone had no effect on alpha activity. It has been previously reported that changes in STN LFP activity due to levodopa administration affects low-frequency rhythm (2–7 Hz) and beta band activity,[2] and here we confirmed the changes in L-beta on the

contralateral side to the stimulation. Note that the alpha band defined here (5–13 Hz) is distinct from the low-frequency oscillations (2–7 Hz) reported in previous studies[2,14] and is broadband.

High gamma+HFO power significantly increased during DBS, both with and without medication (Fig. 5). Medication alone, however, did not have a significant effect on gamma+HFO power. Previous studies have observed an increase in gamma and HFO activity increase with levodopa administration.[16–19] In the present study, we focused on a broader oscillation band that covers both high gamma and HFO together (100–400 Hz).

It is known that unilateral STN DBS modulates the contralateral subthalamic activity and reduces beta band oscillations,[36,47] as was also observed here. An increase in contralateral STN firing rate is also observed,[34,35] which may be due to increased excitatory input to the STN via orthodromic activation of the hyperdirect pathway from deep layers of the motor cortex or a decrease of the inhibitory inputs to the STN via both ipsilateral and contralateral GPe nuclei.[44,48–50] The phenomenon of modulation of the contralateral STN activity by unilateral STN DBS is likely associated with activation of both orthodromic and antidromic pathways in the basal ganglia-thalamocortical network, which could alter activity in the contralateral motor cortex and ipsilateral thalamus nuclei. While the possibility that volume conduction of the applied stimulation through the tissue to directly affect neurons on the contralateral side should also be considered, computational modeling studies indicate that this is unlikely, given the distance between the two.[51]

A number of limitations of the study and proposed approach should be considered. The experimental protocol dictated that LFP data were recorded three days after surgery while the stimulator wires were still accessible. This limitation is a potential confounder of the results, particularly the baseline activity, which may be affected by acute effects post-surgery. Contralateral LFP signals had the advantage of not being contaminated by the stimulation pulse or saturation, which enabled the analysis to be performed. Among the contralateral signals, however, there were a relatively large number of signals which were contaminated with noise from unknown sources that could not be readily removed using standard filtering and artifact removal methods and hence were removed from the analysis. The high level of contamination and noise in the removed signals was due to the experimental setup using externalized leads and is not necessarily a limiting factor for newer closed-loop DBS systems that use implanted sensing devices. Nevertheless, the problem of signal-to-noise ratio remains a challenge for modern adaptive DBS devices.[52,53] This limitation left us with a smaller sample population and uneven number of signals between different conditions. The use of LMM for the statistical analysis partially addressed this limitation enabling all the remaining data to be used. More recent developments with chronically implanted systems should assist researchers in reducing external noise and motion artifacts in practice. All the patients in this study had a unified Parkinson's disease rating scale–III smaller than 30, indicative of mild PD symptoms. It would be important to confirm the findings in a population of patients with moderate or severe PD symptoms. We propose performing the analysis on a larger population of patients with PD to further investigate the potential of the proposed method as a biomarker for closed-loop neuromodulation controllers. A limiting factor on this is DBS is typically applied bilaterally, and even if unilaterally, there would be only a single electrode implanted in one of the STN nuclei to reduce surgical risk, making it difficult to record LFPs from the contralateral side. Finally, it should be noted that the alpha band rhythm, as defined in this paper, is extended at its lower limit and partially covers theta band oscillations.

In conclusion, the results presented provide new insights into the effects of DBS and levodopa administration on oscillatory STN LFP activity in patients with PD observed on the side contralateral to the applied stimulation. A significant decrease in alpha and beta band power, and an increase in high gamma+HFO power, due to the combined effects of medication and stimulation was observed. Exaggerated PAC in the baseline PD condition was attenuated by DBS in the off-medication state, while levodopa administration had no effect on PAC. The findings of modulation of the different frequency bands and PAC by DBS on the contralateral side also indicates that these signals may provide biomarkers that are less sensitive to stimulation artifact, which could be used for closed-loop DBS. Reduction of primary motor cortex PAC has been proposed as a control variable for closed-loop DBS,[25] and it has been suggested that patient-specific biomarkers may be required.[54] The results presented here, however, suggest that PAC and oscillatory activity of STN LFP signals on the contralateral side to unilateral DBS could also provide reliable, consistent, and accessible features for the sensing strategy used in closed-loop DBS systems.

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Authorship Statements

AmirAli Farokhniaee and Madeleine M. Lowery designed and conducted the study. AmirAli Farokhniaee performed data analysis. AmirAli Farokhniaee prepared the manuscript draft with important intellectual input from Madeleine M. Lowery, Sara Marceglia, and Alberto Priori. The Science Foundation Ireland provided support in analyzing the data with input from AmirAli Farokhniaee and Madeleine M. Lowery. AmirAli Farokhniaee, Sara Marceglia, and Alberto Priori had complete access to the study data. All authors approved the final manuscript.

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COMMENT

In the past, when patients with PD were treated using ablative surgeries, like pallidotomy, it was not uncommon to observe not just contralateral, but also ipsilateral motor improvements (Fazzini E, Dogali M, Sterio D, Eidelberg D, Berić A. Stereotactic pallidotomy for Parkinson's disease: a long-term follow-up of unilateral pallidotomy. *Neurology*. 1997;48:1273–1277. https://doi.org/10.1212/wnl.48.5.1273). Exploring the effects of levodopa medication and DBS on changes in LFP oscillatory activity and PAC in individuals with PD is an interesting method to understand the mechanisms related to the motor modulation promoted on both contralateral and ipsilateral nuclei, affecting surgical decisions, as staged implants, multi-target or unilateral procedure.

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