Diurnal fluctuations of local field potentials follow sleep-wake behavior in Parkinson's disease

Alexander Baumgartner (alexander.baumgartner@cuanschutz.edu)
University of Colorado Anschutz Medical Campus https://orcid.org/0000-0002-0009-2756
Lisa Hirt
University of Colorado Anschutz Medical Campus
Drew Kern
University of Colorado Anschutz Medical Campus
John Thompson
University of Colorado Anschutz Medical Campus

Article

Keywords:

Posted Date: January 20th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2468375/v1

Abstract

Background: Sleep disturbances are among the most common non-motor symptoms of Parkinson's disease (PD). Deep brain stimulation (DBS) of the subthalamic nucleus (STN) reduces local field potential (LFP) activity in the STN, particularly in the beta frequency range (13 – 30 Hz). Although well-characterized in the short term, little is known about how beta frequency oscillations change chronically, across the sleep-wake cycle. Better understanding of these pathological signals in sleep may permit optimization of stimulation to improve sleep in PD.

Objectives: Here, we sought to characterize LFPs over several days and nights while patients remained in the home setting.

Methods: LFPs were recorded from the subthalamic nucleus in 13 PD subjects (18 hemispheres) over an average of 14.7 ± 4.2 days. Fluctuations in LFP activity were characterized by arousal state, as determined by actigraphy.

Results: Beta frequency LFPs showed a clear and consistent diurnal pattern. In all subjects, beta power was higher during wakefulness than during sleep, with little overlap in the magnitude of beta power between these two activity states. LFP snapshots obtained across a broad frequency range at subject-indicated going-to-bed and waking-up times showed significant differences in power across multiple canonical frequency bands, though these differences were not significant at the group level.

Conclusions: Beta frequency LFPs fluctuate in a clear and consistent manner that is closely linked to time of day and to activity state. These fluctuations can be detected in the home setting using commercially available devices, including in patients who have been treated with deep brain stimulation for several years.

Introduction

Sleep disturbances are among the most common non-motor PD symptoms, and have a significant impact on quality of life for patients as well as caregivers.[1–6] Though numerous symptomatic therapies exist, the treatment of sleep disorders in PD is limited by a lack of adequately powered, randomized studies providing high quality evidence.[7] DBS is an established, effective therapy for the motor symptoms of PD,[8–10] though studies have shown that DBS improves sleep as well,[11–13] and nascent research has begun to explore how DBS might be tailored specifically to treat sleep.

In recent years, recording of LFPs has identified unique patterns in oscillatory activity that provides novel insight into sleep architecture and basal ganglia physiology in PD. During non-rapid eye movement (NREM) sleep, power in the beta frequency range (typically 13–30 Hz) is reduced compared to wakefulness, while power in the delta (0–3 Hz), theta (4–8 Hz), and alpha (9–12 Hz) ranges is increased.[14–16] REM sleep is characterized by increased beta frequency power, though the magnitude of the beta power is variable and may be lower than or similar to that during wakefulness.[14–16] In parkinsonian primates, a similar increase in alpha and low beta activity during NREM sleep was associated with a decrease in the power of slow oscillatory firing of the basal ganglia, and higher beta power was associated with decreased propensity for sleep and an increased frequency of awakenings.[17] Furthermore, beta frequency LFP power gradually decreased across the basal ganglia at the time of sleep onset and became more prominent preceding awakening.[17] Thus, a potential mechanism for sleep disturbance in PD emerges, whereby synchronized beta oscillations from the basal ganglia are relayed to the cortex, disrupting cortical slow oscillations that are characteristic of NREM sleep.[17,18]

Several limitations hamper our current understanding of basal ganglia electrophysiology in sleep. Prior studies were conducted via externalized DBS leads for recording, thus restricting data collection to a single night and limiting

conclusions about the significance of between-night differences in individuals.[14–16] Recordings were also acquired in a hospital or sleep laboratory setting, creating an unfamiliar environment that likely affected naturalistic sleep behavior. Experiments were carried out between two days and one month following DBS implantation, making it difficult to know with certainty whether lesional effects, inflammation, or other peri-procedural factors influenced the results. Although devices capable of chronic sensing and recording are now commercially available, it is still unknown whether these devices can faithfully capture the diurnal fluctuations of LFPs in the home setting, and how these signals will vary across multiple nights of recording.[19,20]

In this study, we sought to determine whether LFP beta fluctuations within the subthalamic nucleus (STN) exhibited tight coupling with the circadian profile validated via actigraphy monitoring. We obtained long-term recordings of beta frequency STN LFPs from subjects implanted with the Medtronic Percept PC device, and correlated these with daily tracking of wakefulness and sleep. We show that beta frequency LFPs vary significantly in a manner that is closely linked with sleep-wake behavior. These findings provide key insight into the chronic behavior of LFPs across the circadian cycle.

Materials And Methods

Subjects

Thirteen subjects with idiopathic PD treated with STN DBS were recruited at the University of Colorado Hospital Movement Disorders Center from March 2021 to April 2022. The study was approved by the Colorado Multiple Institutional Review Board. All participants provided written, informed consent before any study procedures. Inclusion criteria included: (i) an established clinical diagnosis of idiopathic PD according to UK Brain Bank criteria, (ii) treatment with STN DBS and a Percept PC implanted pulse generator (Medtronic, Minneapolis, MN, USA), (iii) active stimulation parameters that would allow chronic sensing (a monopolar configuration using either of the middle two contacts of a quadripolar electrode, or both in a double monopolar configuration), (iv) ability and willingness to wear and use a wristband-style monitor and log events in the DBS patient programmer. Exclusion criteria included: (i) diagnosis of dementia, (ii) current or recent (within the last 30 days) use of a sedative-hypnotic agent for sleep, and (iii) fulfillment of criteria for circadian sleep-wake rhythm disorder, as defined by the International Classification of Sleep Disorders, Third Edition.[21] PD subtype was determined using Movement Disorders Society Unified PD Rating Scale, as previously described.[22] Levodopa equivalent dose (LED) was calculated according to a previously published systematic review.[23]

Subjective sleep quality was assessed with the Epworth Sleepiness Scale (ESS),[24,25] the Pittsburgh Sleep Quality Index (PSQI),[26] the Fatigue Severity Scale (FSS),[27] and the PD Sleep Scale, version 2 (PDSS-2),[28] which were completed prior to the in-home study. If participants had a bed partner, the partner was asked to complete the Mayo Sleep Questionnaire (MSQ).[29] Question 1 of the MSQ specifically screens for the present of dream-enactment behavior suggestive of RBD (“Have you ever seen the patient appear to ‘act out his/her dreams’ while sleeping?”).

Local field potentials

Peak frequency bands for chronic LFP recording via BrainSense TimeLine and BrainSense Events functions were selected in power spectra generated by the BrainSense signal test, which automatically computes a fast Fourier transform (FFT) of 20-second LFP recordings from the possible bipolar recording configurations in each hemisphere. During open loop stimulation, chronic sensing is only possible when the active electrode configuration is a monopolar setting using one or both of the middle two contacts (1 or 2) as the cathode(s). Stimulation settings were not changed as a part of this study. Therefore, the active contact was used as the recording contact, regardless of whether larger beta peaks were identified on adjacent contacts. Sensing was enabled only for hemispheres that met these parameter

restrictions. Using BrainSense TimeLine for the active contact, a 5 Hz window was extrapolated, based on hardware configuration, around the largest peak frequency for chronic sensing of LFP power in microvolts peak (μVp). We chose to record LFPs from the largest available peak in order to obtain the highest possible quality of recording, rather than limit recording to exclusively the beta range. Medications and stimulation amplitude were not adjusted as part of the study, but patients were permitted to adjust stimulation amplitude at home within predetermined ranges, as per standard of care.

The Percept PC system also allows for the annotation of LFP data with the 'Events' function. Events are pre-specified by a clinician and available to subjects in their DBS patient programmer device. When a subject uses their programmer to mark an event, a 30-second snapshot of LFPs is recorded. These time domain data are then converted to the frequency domain across a range of frequencies (approximately 0–82 Hz). Participants in this study were provided with two events, "going to bed" and "waking up" and instructed to mark events upon lying down in bed to sleep and upon waking in the morning, respectively.

TimeLine data pre-processing

Local field potential data were extracted from the Percept PC as JSON files using the 'Export Report' routine in the clinician programmer. The Percept formatted JSON files were imported into the Matlab (2021a-2022b; Mathworks, Natick, MA) programming environment. In the JSON file, raw BrainSense TimeLine data were accessed from the following data field tree: DiagnosticData → LFPTrendLogs → HemisphereLocationDef_Left ('_Right' was used for right hemisphere recordings). From these data, the following were obtained: 1) 144 samples per day representing each 10-minute average of the LFP power spectrum data for the 5 Hz frequency band of interest, 144 annotations per day for stimulation amplitude (corresponding to the averaged bins), 144 time stamps per day with a resolution of seconds. Sharp positive deflections that exceeded two standard deviations of the daily LFP average, reflecting artifactual fluctuations, were infrequent. To mitigate these fluctuations the following process was used: for any 10-minute sample that exceeded the threshold of two standard deviations, the value was replaced with the average of activity in the preceding one hour (six samples) and following one hour (six samples), in effect interpolating the time point of interest with respect to LFP power. In addition, a Savitzky-Golay filter[30] was applied to a moving window of six samples as a final pre-processing step to smooth the raw data. This was the final form of the data used in subsequent analyses and for comparison with actigraphy data.

Events data pre-processing

Similar to TimeLine data, Events data were exported from the clinician programmer as a JSON file. In the JSON file, raw BrainSense Events data were accessed from the following data field tree: DiagnosticData → LfpFrequencySnapshotEvents → HemisphereLocationDef_Left ('_Right' was used for right hemisphere recordings) → FFTBinData. FFTBinData were the raw power spectra data (frequency resolution 0.98 Hz; range 0–82 Hz). Each individual Event power spectra was smoothed with a Savitzky-Golay filter with a moving window of 5 samples (3.91 Hz).

Actigraphy

Subjects wore an actigraphy monitor (Actiwatch Spectrum Pro, Philips-Respironics, OR) on the wrist (side per patient preference) throughout the study. The device has a 30 second resolution. Subjects were instructed to use the monitor's event marker button to record going-to-bed and waking-up times, to mirror the LFP event capture.

Actigraphy data pre-processing

Raw CSV (comma delimited) files were exported from the Philips Respironics software. In addition to the 'activity' data, which is an integer representation of accelerometer-based changes in position, each epoch had a corresponding timestamp in seconds resolution. Timestamps from the raw actigraphy data were used to calculate aligned time bins with the TimeLine LFP data. A Python package 'pyactigraphy'[31] was used to apply standard sleep/awake extraction algorithms to the raw actigraphy data. Given the implied rhythmicity of the actigraphy data, we applied a single component cosinor. The cosinor is a least-squares regression model commonly applied to circadian rhythms and is a standard approach for modeling chronobiological data.[32–34] In addition, to classify epochs as awake and sleep we used the combination of two algorithms: 1) Roenneberg,[35] a threshold based algorithm that applies a series of cosine fits correlated with various bout lengths to determine the optimal consolidated periods of sleep and awake, and 2) Crespo,[36] a two-stage, threshold-based algorithm that uses a binary closing-opening filter, of a specific window size in minutes, to interpolate or remove extraneous short periods of activity or rest bracketed by long periods of rest or activity.

Data Analysis

TimeLine and Actigraphy analysis

The degree of lag between actigraphy and LFP activity was assessed by computing the cross correlation between the two signals, with actigraphy binned to the same resolution as the LFP and time synchronized. Further, blocked sleep and awake bins were isolated into epochs based on the combination of the Roenneberg and Crespo actigraphic algorithms. These epochs were then used to the conduct cross correlation between the actigraphy and LFP data separated by sleep and awake epochs.

Comparison of LFP between sleep and awake epochs based on actigraphic classification was conducted by normalizing all LFP data across subjects (range 0–1). Summary data were calculated from normalized LFP data including: 1) mean difference in LFP power (μVp) between sleep and wakefulness, probability density functions of normalized LFP for sleep and wakefulness, and the fraction of overlap between probability density histograms between sleep and wakefulness.

Finally, to assess the co-variance between sleep and wake epochs between LFP and actigraphy, dynamic time warping was used to estimate the distance between the two time series signals, across all individual epochs and as an average per individual subject.[37,38] Dynamic time warping matches data in two different time series, from which the minimum Euclidean distance between data points in each series can be calculated.

Events analysis

For Events data, the FFT output from the JSON file was used to quantify the difference between 'Going to bed' and 'Waking up'. FFT data were normalized within each subject for all recordings, and individual frequency bands of interest were isolated: theta (4–8 Hz), alpha (9–12 Hz), beta (13–30 Hz) and gamma (31–82 Hz).

Comparison of TimeLine data within a single subject for two stimulation periods

In one subject (11) whose stimulation parameters were changed, two separate stimulation configurations were acquired. For this within-subject analysis, we did not have access to actigraphy data for both stimulation conditions. Therefore, to assess the impact on TimeLine LFP data between stimulation conditions we applied an analysis employed by van Rheede *et al*.[39] which models LFP activity as a function of circadian cycling and estimates the degree of variance that is accounted for by time of day.

Statistical analysis

Individual frequency band analysis of 'Going to bed' and 'Waking up' events were compared with a one-way ANOVA (frequency band × event marker) and post-hoc comparisons for each frequency by event marker were made using Tukey's honestly significant difference (HSD) test. Individual 10-minute epochs determined by actigraphy to be associated with sleep or wakefulness were compared across all subjects using a paired *t*-test and within subject using a Kolmogorov-Smirnov test to assess whether epoch distributions were derived from separate populations. Pearson correlations were conducted to compare both the peak frequency by scaled LFP difference and mean stimulation by scaled LFP difference. Minimum distance between LFP and actigraphy blocks as measured by Euclidean distance following dynamic time warping was compared between sleep and awake using a paired *t*-test. Group differences between 'Going to bed' and 'Waking up' events were compared with a one-way ANOVA (frequency band × event marker) and post-hoc comparisons for each frequency by event marker were made using Tukey's HSD test. To account for the variability in LFP data recorded during event marker detection, for each subject a one-way ANOVA (frequency band × event marker) and post-hoc comparisons for each frequency by event marker were made using Tukey's HSD post-hoc test. To assess the difference between the first and second stimulation settings for subject 11, we estimated the average variance explained by time of day for all days separately in the first and second stimulation periods, using the "Circa Diem" toolbox.[39] Scaled LFP data collected from the 10 minute bins were compared between the first and second stimulation period using a Kolmogorov-Smirnov test.

A multivariate correlation analysis was used to evaluate correlations between subjective sleep quality (ESS, PSQI, FSS, and PDSS-2), temporal measures of disease (disease duration and DBS duration) and the scaled difference in LFP power between wakefulness and sleep.

Results

We successfully recorded LFP data from all 13 participants during the study period. In five participants, LFPs were recorded from both hemispheres, resulting in a total of 18 hemispheres of recording. Demographic and clinical information is summarized in Table 1. In most cases (15 out of 18), the largest LFP peak frequency occurred in the beta range (average peak frequency 17.8 ± 3.7 Hz), but for some subjects (three out of 18) the largest peak was found at lower frequencies in the alpha range (average peak frequency 9.4 ± 1.1 Hz). Stimulation parameters and sensing frequencies are provided in Table 1. Data were collected for an average of 14.7 ± 4.2 days.

Table 1
Participant demographics and historical characteristics

Participant ID	Age (years)	Gender	Disease Duration (years)	PD Subtype	LED (mg)	H&Y[a] Stage	Survey Results				
							PSQI	ESS	FSS	MSQ, q1	PDSS-2
1	67	M	14	PIGD[b]	625	3	9	22	6.67	Y	32
2	71	M	14	PIGD	900	2	5	15	2.89	-	6
3	71	M	7	TD[c]	450	2	10	2	2.78	-	17
4	65	F	21	PIGD	750	2	10	14	6.33	Y	28
5	60	F	14	TD	1100	2	7	5	2.89	Y	13
6	66	M	16	PIGD	300	3	18	4	5.89	Y	36
7	59	M	9	PIGD	520	2	10	13	2.44	-	14
8	71	M	18	PIGD	348	3	6	14	2.89	N	13
9	71	F	21	PIGD	150	3	6	4	2.44	Y	18
10	78	M	14	PIGD	500	2	8	4	3.67	Y	23
11	63	M	11	TD	1375	2	5	16	5	Y	12
12	65	M	10	PIGD	1200	2	7	7	1.33	Y	16
13	46	M	12	PIGD	1203	2	3	16	5.33	N	11

[a]H&Y: Hoehn and Yahr

[b]PIGD: postural instability and gait disturbance

[c]TD: tremor dominant

Data from a representative subject are shown in Fig. 1, including long-term beta power measurement overlaid with sleep and wake times derived from actigraphy, as well as activity counts, results of cross-correlation analyses, LFP power spectra obtained at the time of DBS event marking, and probability densities for different LFP frequencies during these events. Clear circadian fluctuation in beta frequency LFP power is seen and is strongly linked to activity state as defined by actigraphy as well as self-recorded going-to-bed and waking-up times. Beta power is consistently higher during wakefulness and reduced during sleep. LFP spectra obtained at bed and wake times show higher beta power at the time of waking than of going to bed. For the subject whose data is shown in Fig. 1, there is a statistically significant difference in scaled beta frequency LFP power between going-to-bed and waking-up, while this difference in other frequency bands was not significant. However, this does not hold true across all subjects.

Although there is significant variability both between subjects and between individual nights for each subject, all subjects had an observable difference in beta frequency LFP power between wakefulness and sleep. Figure 2A shows beta power for all subjects separated by arousal state, as well as results of the Kolmogorov-Smirnov test for each subject. We also calculated the degree of overlap in beta LFP power between wakefulness and sleep. A histogram from a representative subject showing the probability densities for LFP power separated by arousal state is shown in Fig. 2B. Overall, there was little overlap in LFP power between wakefulness and sleep, with all but one recorded hemisphere showing less than 25% overlap (Fig. 2C).

To examine whether the variability in LFP signals between subjects was associated with identifiable electrophysiological or subjective clinical attributes, we compared the scaled difference in beta LFP power between wakefulness and sleep against several parameters. There was a statistically significant positive correlation between the value of the beta frequency peak (Hz) recorded and the scaled LFP difference between sleep and wakefulness (Fig. 3A, r = 0.602, $p = 0.008$). That is, participants with an LFP peak in the higher range of beta displayed a larger difference in the LFP power at this frequency between wakefulness and sleep. We also found a statistically significant negative correlation between average stimulation amplitude (mA) used and the difference in LFP power between sleep and wakefulness (Fig. 3B, r = -0.513, $p = 0.029$). There was a statistically significant negative correlation between the sample lag between actigraphy and LFP data and the scaled LFP difference between sleep and wakefulness ($r = -0.605$, $p = 0.017$, not shown in figure). That is, the larger the difference in LFP power between sleep and wakefulness, the better the alignment between actigraphy and LFP data. We believe this to be a measure of the reliability of data collection, as those participants with a large difference in LFP power between wakefulness and sleep (i.e., those in whom the underlying physiology seems to be captured most faithfully) showed very little lag between actigraphy and LFP data.

Figure 4 shows scaled LFP power across canonical frequency bands, which was captured using the Percept PC's 'Events' function. Recordings which contained significant ECG artifact were not included in this analysis. In contrast to the data from a single participant shown in Fig. 1, where a statistically significant difference in LFP power between going-to-bed and waking-up was seen in the beta frequency range but not in any other frequency band, LFP power was not significantly different between going-to-bed and waking-up in any frequency band when averaged for all participants (Fig. 4A). We also compared LFP power across frequency bands for individual subjects, which is shown in Fig. 4B. In four of 12 hemispheres which did not have significant ECG artifact, beta LFP power was significantly higher at the time of going to bed than waking, while in three hemispheres beta power was significantly lower at the time of going to bed compared to waking. In five hemispheres, the difference was not statistically significant.

To assess the validity of our two time series data, we performed a dynamic time warping analysis. Figure 5 shows the minimum distances between LFP and actigraphy data, separated by activity state (wakefulness vs. sleep) for individual epochs across all subjects (Fig. 5A) and as an average for each participant over the recording period (Fig. 5B, $p = 5.8 \times 10^{-6}$). In both cases, the distances were larger and there was much more variability in the difference between LFP and actigraphy data during wakefulness than during sleep.

In subject 11, stimulation parameters were changed part way through the study period. This was done due to feelings of anxiety, irritability, and emotional lability that had newly developed after initial DBS programming and enrollment in the study. Decreasing stimulation amplitude did not alleviate these symptoms. He was asked to wean and then discontinue taking methylphenidate, which had been prescribed previously for fatigue.[40] Subsequently, BrainSense survey performed 10 days after initial programming revealed more prominent beta peaks in both hemispheres than had been seen previously, with the highest power in contact 2 in both the left and right STN. These changes improved his mood and personality changes within days. Initial and subsequent stimulation settings and sensing parameters are found in Table 2, and further details of this case have been described elsewhere.[40] In this subject, LFP recordings demonstrated consistent fluctuations both before and after the change in parameters. These data are shown in Fig. 6. Clear circadian fluctuations in beta frequency LFP power were seen both before and after the change in stimulation, though overall higher beta power was seen after the change, particularly during wakefulness (Fig. 6B, 6C). The proportion of variance in LFP power explained by the time of day in left STN was 0.53 before parameter change and 0.70 after parameter change, and in the right STN was 0.65 before parameter change and 0.70 after parameter change.

Table 2
DBS historical characteristics and LFP recording settings

Participant ID	Recorded hemisphere	DBS Duration (years)	Lead model	Stimulation settings	Sensing contacts	Sensing frequency (Hz)
1	Right	8	3389	C + 1-, 3.0mA/130μs/90Hz	0, 2	10.7
2	Left	5	3389	C + 1-, 3.2mA/60μs/130Hz	0, 2	21.5
3	Left	7	3389	C + 1-, 2.0mA/60μs/140Hz	0, 2	20.5
4	Right	8	3389	C + 2-, 2.6mA/100μs/60Hz	1, 3	24.4
5	Right	8	3389	C + 2-, 3.1mA/70μs/180Hz	1, 3	13.7
6	Right	12	3389	C + 1-, 2.0mA/270μs/90Hz	0, 2	12.7
7	Bilateral	R: 5 L: 5	3389	R: C + 1-, 3.8mA/60μs/130Hz L: C + 2-, 4.4mA/60μs/130Hz	R: 0, 2 L: 1, 3	R: 15.6 L: 8.8
8	Left	16	3389	C + 1-, 3.4mA/60μs/130Hz	0, 2	14.7
9	Bilateral	R: 12 L: 12	3389	R: C + 2-, 6.0mA/60μs/130Hz L: C + 2-, 4.6mA/90μs/130Hz	R: 1, 3 L: 1, 3	R: 14.7 L: 8.8
10	Right	7	3389	C + 2-, 2.6mA/60μs/135Hz	1, 3	19.5
11	Bilateral	R: <1 L: <1	B33005	R: C + 1-, 2.0mA/60μs/130Hz L: C + 1-, 2.5mA/60μs/130Hz	R: 0, 2 L: 0, 2	R: 20.5 L: 21.5
			B33005	R: C + 2ABC-, 2.0mA/60μs/125Hz L: C + 2ABC-, 1.5mA/60μs/125Hz	R: 1, 3 L: 1, 3	R: 19.5 L: 21.5
12	Bilateral	R: <1 L: <1	B33005	R: C + 2ABC-, 1.8mA/60μs/125Hz L: C + 1ABC-, 1.0mA/60μs/125Hz	R: 1, 3 L: 0, 2	R: 14.7 L: 13.7
13	Bilateral	R: <1 L: <1	B33005	R: C + 2ABC-, 1.5mA/60μs/130Hz L: C + 2ABC-, 1.8mA/60μs/130Hz	R: 1, 3 L: 1, 3	R: 20.5 L: 19.5

A multivariate correlation analysis between subjective sleep scale scores, disease duration, DBS duration, and the scaled difference in LFP power between wakefulness and sleep found no significant correlations between any of the sleep scales and the scaled LFP metric. Further, there was no significant correlations between the temporal measures of disease and the scaled LFP metric. The only significant correlations were the following: disease duration and stimulation duration ($r = 0.70$, $p < 0.05$), PSQI and PDSS-2 ($r = 0.80$, $p < 0.05$), and FSS and PDSS-2 ($r = 0.60$, $p < 0.05$).

Discussion

In this study, we used a commercially available DBS device to sense and record LFPs in the home setting during continuous therapeutic stimulation. We demonstrate that beta frequency oscillations follow a consistent diurnal pattern. Actigraphy demonstrated that these fluctuations were associated with activity state and not simply with time of day, as has been demonstrated previously.[39] These findings provide important insight into basal ganglia electrophysiology during sleep and highlight the importance of accounting for circadian variation in LFP signals in the development of closed loop DBS systems.

Beta frequency LFP power recorded from the STN was consistently elevated during wakefulness and decreased during sleep (Figs. 1, 2, 6). This is consistent with existing literature on the physiological basis of LFP activity in relation to sleep.[14,15,41] Nonetheless, there was significant variability in our data, with some recordings showing a large difference in LFP power between wakefulness and sleep, and others a smaller difference (Fig. 2). We sought to identify potential causes for this variability. One possible explanation is that poorer quality of the recording limited our ability to detect differences between wakefulness and sleep. This is supported by the fact that participants with little difference in scaled LFP power between wakefulness and sleep consistently had higher lag between actigraphy and LFP data, a marker of general recording quality and reliability. Another possible explanation for the variability in the magnitude of differences in LFP power between wakefulness and sleep is the effect that chronic stimulation has on basal ganglia oscillatory activity. We found a significant positive correlation between the value of the LFP peak recorded (in Hz) and the difference in LFP power between wakefulness and sleep (Fig. 3A). This may bolster the notion that DBS differentially modulates STN activity in the low beta (13–20 Hz) and high beta (21–30 Hz) ranges. Feldmann *et al*.[42] recently demonstrated a more pronounced reduction in low beta power compared to high beta power by STN DBS, which was associated with clinical improvement in a finger-tapping task. Furthermore, in a linear mixed effects model, low beta suppression was a superior predictor of improvement in bradykinesia over high beta suppression. It remains unknown whether differential suppression of high versus low beta activity has a meaningful impact on other motor or non-motor symptoms, including sleep. Our findings suggest this is a possibility that warrants further investigation. Specifically, we found participants with LFP peaks in the low beta range had a smaller magnitude of difference in LFP power between wakefulness and sleep. If indeed STN DBS produces a more dramatic improvement in parkinsonian symptoms when low beta LFPs are targeted, this would result in greater overall suppression of LFP power and thus a smaller difference in LFP power between wakefulness and sleep, which is consistent with our results.

STN DBS may also shift LFP peaks to lower frequencies.[42] Our finding that larger differences in beta LFP power between wakefulness and sleep are correlated with lower stimulation amplitudes and higher beta frequency peaks (Fig. 3B) would be concordant with this, particularly if higher stimulation amplitudes are shifting LFP peaks to lower frequencies and also suppressing the circadian variation in beta power. In this scenario, it is the higher stimulation amplitude that suppresses beta oscillatory activity and thus minimizes the observed difference in LFP power between wakefulness and sleep. Alternatively, it could be hypothesized that stimulation delivered in an optimal location, where more prominent beta oscillations are seen and thus the difference in LFP power between wakefulness and sleep is more pronounced, lower stimulation amplitudes may be used to adequately control motor symptoms. The exact nature of this relationship will need to be clarified by future studies.

Our data make several important contributions to understanding the role of LFP activity in sleep physiology. Whereas prior studies utilized an externalized DBS lead for LFP recording and were thus limited to a single night of monitoring in a hospital setting, we have demonstrated that LFP recording can be done in the home setting, without the need for externalization of the DBS, thus providing a more accurate picture of naturalistic sleep. We recorded LFP data in patients chronically treated with DBS, thus minimizing any chance of lesional or other peri-procedural effects of DBS implantation on the data. In doing so, we demonstrate that a clear difference can be seen in beta frequency LFP power between wakefulness and sleep, regardless of duration of disease or duration of treatment with DBS.

Further studies will need to establish how best to incorporate diurnal fluctuations in beta power into closed-loop DBS. Because beta activity is not eliminated during sleep, and because DBS likely delivers at least some improvement in sleep in PD patients,[11,12,43] it will likely be advantageous for closed-loop DBS to continue delivering some amount of stimulation during sleep. One conceivable way to do this is by incorporating some representation of a beta LFP chronotype into the adaptive controller, where the chronotype is defined as an individual's natural inclination to sleep at a particular phase of the day-night cycle.[39,44,45] The optimal timescale for measuring and responding to this chronotype remains to be determined, but our results suggest that a 10-minute interval provides sufficient signal to at least detect it. Similarly, recent studies suggest that longer feedback time scales for closed-loop DBS may improve signal-to-noise ratios and thus better differentiate pathological from physiological changes in oscillatory activity, at least for addressing motor symptoms, though no direct comparison has been made with dynamic, burst control algorithms.[46–48]

In conclusion, beta frequency LFP activity shows significant and consistent fluctuation across the sleep-wake cycle. Although variability exists between subjects and across individual nights, diurnal fluctuations in STN oscillatory activity can reliably be recorded using commercially available devices and does not seem to be negatively impacted by concurrent stimulation, duration of disease, or duration of DBS therapy. Incorporation of diurnal LFP fluctuations will be critical to optimize closed-loop DBS algorithms.

Data availability

Data will be made available upon acceptance for publication at the Open Science Framework: https://osf.io/t5wuk/

Declarations

Running title: Naturalistic sleep in PD

Relevant Financial Disclosures/Conflict of Interest: DSK has served as an advisor for the Colorado Clinical and Translational Sciences Institute (CCTSI) data safety monitoring board, and medical boards for Boston Scientific, Medtronic, and AbbVie; received honoraria from AbbVie, Abbott, and Boston Scientific; received grants from Boston Scientific and Medtronic. JAT has received research support and speaking honoraria from Medtronic, research support from Boston Scientific. AJB and LH have nothing to disclose.

Funding: This work was funded by a University of Colorado Movement Disorders Center pilot grant.

Data availability

Data will be made available upon acceptance for publication at the Open Science Framework: https://osf.io/t5wuk/

Acknowledgements

The authors would like to thank all the patients who participated in this study.

Authors' Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

AJB: 1A, 1B, 1C, 2C, 3A

LH: 1B, 1C, 3B

DSK: 1A, 1B, 2A, 2C, 3B

JAT: 1A, 1B, 1C, 2A, 2B, 3B

Financial Disclosures

DSK has served as an advisor for the Colorado Clinical and Translational Sciences Institute (CCTSI) data safety monitoring board, and medical boards for Boston Scientific, Medtronic, and AbbVie; received honoraria from AbbVie, Abbott, and Boston Scientific; received grants from Boston Scientific, Medtronic, and the Parkinson Foundation. JAT has received research support from Medtronic and Boston Scientific, and honoraria from Medtronic. AJB and LH have nothing to disclose.

References

1. Barone, P. *et al.* The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov. Disord. **24**, 1641–1649 (2009).
2. Avidan, A. *et al.* Associations of sleep disturbance symptoms with health-related quality of life in Parkinson's disease. J. Neuropsychiatry Clin. Neurosci. **25**, 319–326 (2013).
3. Gallagher, D. A., Lees, A. J. & Schrag, A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? Mov. Disord. **25**, 2493–2500 (2010).
4. Gómez-Esteban, J. C. *et al.* Impact of psychiatric symptoms and sleep disorders on the quality of life of patients with Parkinson's disease. J. Neurol. **258**, 494–499 (2011).
5. Bartolomei, L. *et al.* Relevance of sleep quality on caregiver burden in Parkinson's disease. Neurol. Sci. **39**, 835–839 (2018).
6. Happe, S. The association between caregiver burden and sleep disturbances in partners of patients with Parkinson's disease. Age Ageing **31**, 349–354 (2002).
7. Chahine, L. M., Amara, A. W. & Videnovic, A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. Sleep Med. Rev. **35**, 33–50 (2017).
8. Deuschl, G. *et al.* A randomized trial of deep-brain stimulation for Parkinson's disease. N. Engl. J. Med. **355**, 896–908 (2006).
9. Krack, P., Volkmann, J., Tinkhauser, G. & Deuschl, G. Deep brain stimulation in movement disorders: From experimental surgery to evidence-based therapy. Mov. Disord. **34**, 1795–1810 (2019).

10. Schuepbach, W. M. M. *et al.* Neurostimulation for Parkinson's disease with early motor complications. N. Engl. J. Med. **368**, 610–622 (2013).
11. Arnulf, I. *et al.* Improvement of sleep architecture in PD with subthalamic nucleus stimulation. Neurology **55**, 1732–1735 (2000).
12. Iranzo, A., Valldeoriola, F., Santamaria, J., Tolosa, E. & Rumia, J. Sleep symptoms and polysomnographic architecture in advanced Parkinson's disease after chronic bilateral subthalamic stimulation. J. Neurol. Neurosurg. Psychiatry **72**, 661–664 (2002).
13. Amara, A. W. *et al.* Effects of subthalamic nucleus deep brain stimulation on objective sleep outcomes in Parkinson's disease. Mov. Disord. Clin. Pract. **4**, 183–190 (2017).
14. Urrestarazu, E. *et al.* Beta activity in the subthalamic nucleus during sleep in patients with Parkinson's disease. Mov. Disord. **24**, 254–260 (2009).
15. Thompson, J. A. *et al.* Sleep patterns in Parkinson's disease: Direct recordings from the subthalamic nucleus. J. Neurol. Neurosurg. Psychiatry **89**, 95–104 (2018).
16. Chen, Y. *et al.* Automatic sleep stage classification based on subthalamic local field potentials. IEEE **27**, 118–128 (2019).
17. Mizrahi-Kliger, A. D., Kaplan, A., Israel, Z., Deffains, M. & Bergman, H. Basal ganglia beta oscillations during sleep underlie Parkinsonian insomnia. *Proc. Natl. Acad. Sci.* **117**, 17359–17368 (2020).
18. Mizrahi-Kliger, A. D., Kaplan, A., Israel, Z. & Bergman, H. Desynchronization of slow oscillations in the basal ganglia during natural sleep. *Proc. Natl. Acad. Sci. U. S. A.* **115**, E4274–E4283 (2018).
19. Jimenez-Shahed, J. Device profile of the percept PC deep brain stimulation system for the treatment of Parkinson's disease and related disorders. Expert Rev. Med. Devices **18**, 319–332 (2021).
20. Goyal, A. *et al.* The development of an implantable deep brain stimulation device with simultaneous chronic electrophysiological recording and stimulation in humans. Biosens. Bioelectron. **176**, 112888 (2021).
21. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. (American Academy of Sleep Medicine, 2014).
22. Stebbins, G. T. *et al.* How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: Comparison with the unified Parkinson's disease rating scale. Mov. Disord. **28**, 668–670 (2013).
23. Tomlinson, C. L. *et al.* Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov. Disord. **25**, 2649–2653 (2010).
24. Johns, M. W. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep **14**, 540–545 (1991).
25. Johns, M. W. Reliability and factor analysis of the Epworth sleepiness scale. Sleep **15**, 376–381 (1992).
26. Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R. & Kupfer, D. J. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Res. **28**, 193–213 (1989).
27. Krupp, L., LaRocca, N., Muir-Nash, J. & Steinberg, A. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch. Neurol. **46**, 1121–1123 (1989).
28. Trenkwalder, C. *et al.* Parkinson's disease sleep scale—validation of the revised version PDSS-2. Mov. Disord. **26**, 644–652 (2011).
29. Boeve, B. F. *et al.* Validation of the Mayo sleep questionnaire to screen for REM sleep behavior disorder in a community-based sample. J. Clin. Sleep Med. **09**, 475–480 (2013).

30. Savitzky, A. & Golay, M. J. E. Smoothing and differentiation of data by simplified least squares procedures. Anal. Chem. **36**, 1627–1639 (1964).
31. Hammad, G. *et al.* pyActigraphy: Open-source python package for actigraphy data visualization and analysis. PLOS Comput. Biol. **17**, e1009514 (2021).
32. Cornelissen, G. Cosinor-based rhythmometry. Theor. Biol. Med. Model. **11**, 16 (2014).
33. Halberg, F. Chronobiology. Annu. Rev. Physiol. **31**, 675–726 (1969).
34. Fossion, R., Rivera, A. L., Toledo-Roy, J. C., Ellis, J. & Angelova, M. Multiscale adaptive analysis of circadian rhythms and intradaily variability: Application to actigraphy time series in acute insomnia subjects. PLoS ONE **12**, e0181762 (2017).
35. Roenneberg, T. *et al.* Human activity and rest in situ. in *Methods in Enzymology* (ed. Sehgal, A.) vol. 552 257–283 (Academic Press, 2015).
36. Crespo, C., Aboy, M., Fernández, J. R. & Mojón, A. Automatic identification of activity–rest periods based on actigraphy. Med. Biol. Eng. Comput. **50**, 329–340 (2012).
37. Martin, D. Using dynamic time warping for quantifying effects of sinusoidal oscillation deviations during EEG time series prediction and for finding interesting EEG and fMRI changes. BMC Neurosci. **16**, P63 (2015).
38. Huang, H. C. & Jansen, B. H. EEG waveform analysis by means of dynamic time-warping. Int. J. Biomed. Comput. **17**, 135–144 (1985).
39. van Rheede, J. J. *et al.* Diurnal modulation of subthalamic beta oscillatory power in Parkinson's disease patients during deep brain stimulation. Npj Park. Dis. **8**, 1–12 (2022).
40. Kern, D. *et al.* Methylphenidate effects on a clinically informative oscillatory signal within the subthalamic nucleus in Parkinson's disease during deep brain stimulation programming. Brain Stimulat. **15**, 747–749.
41. Christensen, E., Abosch, A., Thompson, J. A. & Zylberberg, J. Inferring sleep stage from local field potentials recorded in the subthalamic nucleus of Parkinson's patients. J. Sleep Res. **28**, e12806 (2019).
42. Feldmann, L. K. *et al.* Toward therapeutic electrophysiology: Beta-band suppression as a biomarker in chronic local field potential recordings. Npj Park. Dis. **8**, 44 (2022).
43. Baumann-Vogel, H. *et al.* The impact of subthalamic deep brain stimulation on sleep–wake behavior: A prospective electrophysiological study in 50 Parkinson patients. Sleep **40**, (2017).
44. Roenneberg, T. What is chronotype? Sleep Biol. Rhythms **10**, 75–76 (2012).
45. Fleming, J. E. *et al.* Embedding digital chronotherapy into bioelectronic medicines. iScience **25**, (2022).
46. Gilron, R. *et al.* Long-term wireless streaming of neural recordings for circuit discovery and adaptive stimulation in individuals with Parkinson's disease. Nat. Biotechnol. **39**, 1078–1085 (2021).
47. Yin, Z. *et al.* Cortical phase-amplitude coupling is key to the occurrence and treatment of freezing of gait. Brain **145**, 2407–2421 (2022).
48. Little, S. & Brown, P. Debugging adaptive deep brain stimulation for Parkinson's disease. Mov. Disord. **35**, 555–561 (2020).