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Long-Term Recording of Subthalamic Aperiodic Activities and Beta Bursts in Parkinson's Disease

Ghazaleh Darmani, PhD,[1*] Neil M. Drummond, PhD,[1] Hamidreza Ramezanpour, PhD,[2] Utpal Saha, BSc,[1] Tasnuva Hoque, BSc,[1] Kaviraja Udupa, MD, PhD,[3] Can Sarica, MD,[1] Ke Zeng, PhD,[1] Talyta Cortez Grippe, MD,[1] Jean-Francois Nankoo, PhD,[1] Til Ole Bergmann, PhD,[4,5] Mojgan Hodaie, MD, MSc, FRCSC,[1,6] Suneil K. Kalia, MD, PhD, FRCSC,[1,6] Andres M. Lozano, MD, PhD, FRCSC,[1,6] William D. Hutchison, PhD,[1,6] Alfonso Fasano, MD, PhD,[1,7,8] and Robert Chen, MBBChir, MSc, FRCPC[1,7,8*]

[1]*Krembil Research Institute, University Health Network, Toronto, Canada*
[2]*Centre for Vision Research, Department of Biology, York University, Toronto, Canada*
[3]*Department of Neurophysiology, National Institute of Mental Health & Neurosciences, Bengaluru, India*
[4]*Neuroimaging Center, Johannes Gutenberg University Medical Center, Mainz, Germany*
[5]*Leibniz Institute for Resilience Research, Mainz, Germany*
[6]*Division of Neurosurgery, Department of Surgery, University of Toronto, Toronto, Canada*
[7]*Division of Neurology, Department of Medicine, University of Toronto, Toronto, Canada*
[8]*Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, University Health Network, Toronto, Canada*

ABSTRACT: Background: Local field potentials (LFPs) represent the summation of periodic (oscillations) and aperiodic (fractal) signals. Although previous studies showed changes in beta band oscillations and burst characteristics of the subthalamic nucleus (STN) in Parkinson's disease (PD), how aperiodic activity in the STN is related to PD pathophysiology is unknown.

Objectives: The study aimed to characterize the long-term effects of STN–deep brain stimulation (DBS) and dopaminergic medications on aperiodic activities and beta bursts.

Methods: A total of 10 patients with PD participated in this longitudinal study. Simultaneous bilateral STN-LFP recordings were conducted in six separate visits during a period of 18 months using the Activa PC + S device in the *off* and *on* dopaminergic medication states. We used irregular-resampling auto-spectral analysis to separate oscillations and aperiodic components (exponent and offset) in the power spectrum of STN-LFP signals in beta band.

Results: Our results revealed a systematic increase in both the exponent and the offset of the aperiodic spectrum over 18 months following the DBS implantation, independent of the dopaminergic medication state of patients with PD. In contrast, beta burst durations and amplitudes were stable over time and were suppressed by dopaminergic medications.

Conclusions: These findings indicate that oscillations and aperiodic activities reflect at least partially distinct yet complementary neural mechanisms, which should be considered in the design of robust biomarkers to optimize adaptive DBS. Given the link between increased gamma-aminobutyric acidergic (GABAergic) transmission and higher aperiodic activity, our findings suggest that long-term STN-DBS may relate to increased inhibition in the basal ganglia. © 2022 International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; deep brain stimulation; local field potential; beta burst; aperiodic activity

***Correspondence to:** Dr. Ghazaleh Darmani, Krembil Research Institute, University Health Network, 399 Bathurst Street, Toronto, ON, M5T 2S8, Canada, E-mail: ghazaleh.darmani@uhnresearch.ca; Dr. Robert Chen, Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, University Health Network, Toronto, ON, M5T 2S8, Canada, E-mail: robert.chen@uhn.ca

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Exaggerated power of the beta band (13–35 Hz) in the local field potentials (LFPs) recorded from the subthalamic nucleus (STN) is a hallmark of Parkinson's disease (PD).[1–4] The beta oscillatory characteristics including beta burst, beta amplitude, and beta waveform shape may reflect different aspects of the pathophysiology of PD as longer duration and higher amplitude of beta bursts are associated with motor impairment, including bradykinesia, gait impairment, freezing of gait, and the sharpness of beta oscillations predict motor rigidity.[4–11]

Deep brain stimulation (DBS) of the STN is an established treatment for selected patients with PD. The effects of STN-DBS and dopaminergic medications on beta oscillations have been investigated extensively. STN-DBS or dopaminergic therapy attenuates beta power, shortens beta burst durations, and decreases the beta sharpness ratio in patients with PD.[4,10,11] These recordings were initially only possible in a short time window prior to internalization of the pulse generator, either during the electrode implantation surgery or in 1 to 5 days after insertion of DBS electrodes when the leads were externalized. With the development of implantable devices capable of local field potential (LFP) sensing, long-term recordings from DBS electrodes became possible.[12–15] This new technology provides us an opportunity to study the long-term effects of STN-DBS on STN-LFP signals and how it might be correlated with the disease progression long after the well-known microlesion effect that commonly occurs after electrode insertion has dissipated.[16,17] Using the Activa PC + S devices (Medtronic Inc., Minneapolis, MN) capable of chronic recordings, the first aim of this study was to investigate how beta oscillation characteristics, specifically beta burst duration and amplitude, changed during the course of 18 months as a function of disease progression, DBS, and levodopa treatment.

Although the characterization of oscillations in the power spectrum is important, neural activities also entail a dominant nonoscillatory background activity that follows the power-law function (P is proportional to 1/f), where power (P) decreases with increasing frequency (f).[18–20] Aperiodic activity has been linked to filtering properties of neuronal tissue[21–24] and the state of populational neuronal activity, which may reflect the excitation/inhibition balance of neural networks.[25–27] Human electroencephalography (EEG) and LFP studies have shown that aperiodic activity can reflect task performance,[28] arousal state,[29,30] age,[31–33] and disease.[34–37] For example, visual attention led to flattening of EEG power spectra over the visual cortex,[28] and movements decreased the slope of 1/f compared with rest.[34] Stronger decay of 1/f aperiodic background activity has been reported not only in propofol anesthesia but also during sleep.[29,30] Aging and brain development has been reported to reduce the slope of 1/f power spectral density.[31–33] Aperiodic activity can also reflect disease severity, progression, and response to interventions. For instance, a study showed that medication-naive children with attention deficit hyperactivity disorder had greater offsets and steeper slopes compared with typically developing children.[36] Another study reported that subcallosal cingulate cortex DBS for treatment-resistant depression can increase the 1/f slope in the setting of treatment response.[37] Aperiodic components have been shown to be greater in patients with schizophrenia compared with healthy control subjects, which can be normalized with medication.[35]

Although LFPs are a mixture of oscillations and aperiodic activities, the majority of studies on patients with PD have not analyzed nonoscillatory activities. Classical Fourier-based spectral analyses of beta oscillations might be confounded with broadband 1/f aperiodic background activity, that is, changes in the power of the aperiodic background signal at beta frequency band being mistaken for changes in the oscillatory power, obscuring the genuine relationship between the STN beta bursts, aperiodic activities, and PD pathophysiology. Thus, the second aim of this longitudinal study was to separate aperiodic and oscillatory components to analyze their characteristics that are likely generated through distinct neural mechanisms.

Several algorithms to parameterize neural power spectra as a combination of oscillatory peaks and aperiodic components have been introduced.[38,39] Here we used a method called irregular-resampling auto-spectral analysis (IRASA)[39] to separate aperiodic and oscillatory components in the STN-LFPs. The aperiodic part of the power spectrum, also known as fractal component, can be parametrized with two scalars: "exponent" and "offset." "Exponent" is a negative slope and "offset" is the power spectrum's intercept after separating the oscillatory part of the signal in log–log space (see Fig. 1C). We hypothesized that chronic STN-DBS and levodopa treatment in patients with PD will not only change the oscillatory part of the beta band but also modulate the aperiodic component of beta band LFP signals. The results of this study shed light on the pathophysiology of PD through the characterization of changes in STN-LFP signals during an 18-month period and provide useful information for the development of adaptive DBS systems.

Materials and Methods

Participants, Surgical Procedure, and Lead Localization

A total of 10 patients with idiopathic PD[60] participated in this study (see Table 1 for patient details). To be included in the study, patients had to be scheduled to undergo bilateral STN-DBS surgery

and had no previous brain surgery or other neurological disorders and no unstable medical conditions. All patients provided written informed consent prior to participating. The study was conducted in accordance with the ethical guidelines of the Research Ethics Board at the University Health Network (Toronto) and conformed to the latest version of the Declaration of Helsinki.

Patients underwent DBS surgery at the Toronto Western Hospital as per standard clinical care. In the first

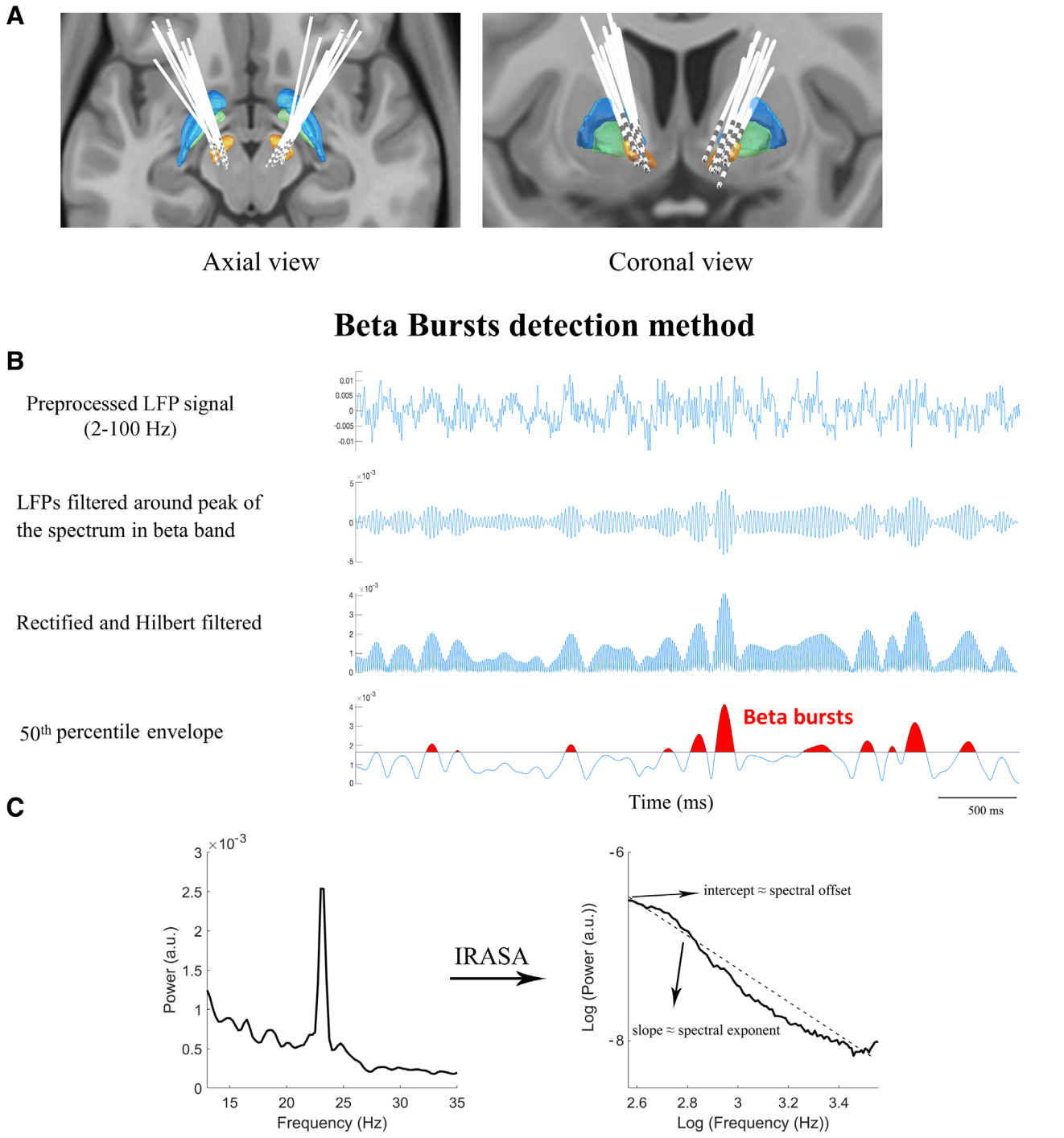

FIG. 1. (**A**) Bilateral deep brain stimulation lead locations for subthalamic nucleus (n = 20): orange, subthalamic nucleus (STN); green, globus pallidus internus (GPi); blue, globus pallidus externa (GPe). (**B**) Beta burst detection method. Bursts were detected by applying a threshold (50th percentile) to the signal envelope obtained by rectification and Hilbert filtering of the STN-LFPs around the peak of the spectrum in the beta band. (**C**) An example of power spectral density (left). Aperiodic spectrum (right) is extracted by applying IRASA to the power spectral density. Spectral offset (intercept) and exponent (negative slope) components of aperiodic spectrum are derived from the linear regression parameters of the aperiodic spectrum. IRASA, irregular-resampling auto-spectral analysis; LFP, local field potential. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 *Participant demographics*

Patient identification	Age, years	Sex	Disease duration at visit 1, years	Most affected side, body	Main symptoms, visit 1
S01	53	Female	18	Left	Rigidity, dyskinesia, bradykinesia, gait shuffling
S02	58	Male	10	Left	Rigidity left, bradykinesia, dystonia right foot
S03	47	Male	8	Right	Tremor, rigidity, dystonia right side
S04	64	Female	20	Left	Dyskinesia, tremor, freezing of gait
S05	55	Female	8	Left	Rigidity, slight tremor
S06	69	Male	9	Left	Dyskinesia, rigidity, restless legs syndrome
S07	61	Male	7	Symmetric	Dystonia, dyskinesia, "wearing off" periods, rigidity, freezing of gait, slight tremor
S08	53	Male	7	Right	Tremor rigidity, gait disturbance, slight dyskinesia
S09	55	Male	30	Left	Tremor, bradykinesia, dyskinesia
S10	67	Male	11	Right	Tremor, rigidity, gait, and balance disturbance

stage of the surgery, quadripolar macroelectrode leads (model 3387; Medtronic Inc.) were inserted bilaterally into the STN and connected to externalized leads to allow bilateral LFP recordings via external devices. Bilateral insertion of the leads into the STN was performed using a standard procedure with frame-based stereotaxic and microelectrode recording techniques. In the second stage (2–4 days after stage 1), the internal pulse generator (Activa PC + S, Medtronic Inc.) was implanted subcutaneously to provide both standard therapeutic stimulation and bilateral LFP recordings. To confirm DBS lead placement, localization was performed using Lead-DBS version 2.3.2 software (https://www.lead-dbs.org/),[40] in keeping with previously reported methodology.[41] After correction of inhomogeneity, we registered the immediate postoperative magnetic resonance imaging (MRI) scans to the preoperative MRI scans using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Afterward, the postoperative images were nonlinearly normalized to a Montreal Neurological Institute (MNI) template brain (International Consortium of Brain Mapping 2009b nonlinear asymmetric) using the "effective low variance" Advanced Normalization Tools and Symmetric image Normalization approach that incorporated an additional subcortical refinement step (http://stnava.github.io/ANTs/).[42,43] Another subcortical linear transform was applied as necessary to correct for postoperative brain shift due to pneumocephalus. DBS leads were manually localized following initial, semiautomated trajectory reconstruction. The resultant lead models were warped to MNI space using the aforementioned transforms. Fig. 1A shows that the bilateral STN-DBS lead locations for all subjects (n = 10).

Experimental Protocol

Simultaneous bilateral STN-LFP recordings were conducted in six separate visits; visit 1 was 1 to 3 days after lead insertion using externalized leads, and visits 2 to 6 were at 1, 2, 6, 12, and 18 months postoperatively using the Activa PC + S device. Here we present data from chronic recordings from visits 2 to 6, collected via the sensing-enabled implantable pulse generator (IPG). Each visit was composed of two sessions and was conducted over 2 days in random order: 1 day in the *off* dopaminergic medication (overnight withdrawal) state and 1 day in the *on* dopaminergic medication state (Supplementary Materials, Table S1). Four patients (of 10) failed to complete all study sessions and/or visits. Data from the sessions and visits they completed were included in the main analysis. The data from the six patients who completed all study visits are presented in the Supplementary Materials (Figs S1 and S2). Because LFPs were recorded from both hemispheres, we considered the data recorded from each hemisphere independently. LFP recordings were approximately 5 minutes in length while the patient was at rest, eyes closed, and seated comfortably in a chair with no stimulation. At each visit, motor symptoms in the *off* medication state were evaluated (see Supplementary Materials, Table S2) by a certified rater according to the Movement Disorder

Society–Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS-III). Visit 2 occurred prior to initial DBS activation and programming, whereas visits 3 to 6 occurred post-DBS activation, and thus stimulation was turned off 30 minutes prior to data collection to wash out the effect of DBS on STN-LFPs.[44] The experimental sessions were performed at a similar time in the morning to ensure consistency across visits.

Data Acquisition

Each DBS electrode has four contacts numbered 0 to 3, with 0 being the deepest. Bilateral STN-LFPs were recorded from the contact pairs on either side of the contact of interest, limited to either 0 to 2 or 1 to 3 on the DBS leads, via the sensing-enabled IPG. The contact of interest for visit 2 (1 month after surgery) was always contact 1 (recording from 0–2), corresponding to the motor region of the STN based on intraoperative recordings and lead depth placement. The contact of interest for visits 3 to 6 was either contact 1 or 2 (Supplementary Materials, Table S3), corresponding to (or closest to) the cathodic clinical contact providing therapeutic benefit that still enabled recording from contact pairs above and below (eg, clinical contact 3 = contact of interest 2 [recording from 1–3], clinical contact 0 = contact of interest 1 [recording from 0–2]). LFPs were high-pass filtered at 0.5 Hz, low-pass filtered at 100 Hz within the device, and amplified (gain 1000×) and sampled at 422 Hz. Uncompressed neural data were recorded in the Activa PC + S system and then extracted via telemetry using the Activa PC + S tablet programmer. The data were then transferred and stored in a laboratory computer for offline processing.

Data Analysis

Preprocessing

LFP data recorded in visits 2 to 6 were analyzed using MATLAB (MathWorks, Natick, MA) and the Fieldtrip open-source toolbox, developed at the Donders Institute for Brain, Cognition and Behaviour, Radboud University, the Netherlands (www.ru.nl/fcdonders/fieldtrip).[45] For the preprocessing, 5 minutes of resting-state LFP data were segmented into 4-second epochs, and 2 Hz fourth-order Butterworth high-pass filtered, followed by 100 Hz low-pass filtering and demeaning. Subsequently, trials were inspected visually using the summary function of Fieldtrip to remove artifact-contaminated trials. On average, 4 ± 2 (mean ± standard deviation [SD]) trials were removed from each block of 75 trials. We did not apply notch filter to the data as the frequency band of interest (13–35) was unaffected by the line noise (60 Hz). The changes in the spectrograms (*off* medication − *on* medication) at the five time points before separating aperiodic components can be found in the Supplementary Materials (Fig. S3).

Beta Bursts

Beta band signals were obtained by 13 Hz high-pass filtering and 35 Hz low-pass filtering of the preprocessed data. Power spectra were determined via a Hanning-tapered fast Fourier transform for frequency bins from 13 to 35 Hz in steps of 1 Hz, and the spectra were averaged across segments for *on* and *off* medication conditions separately. The frequency of the peak activity within the beta frequency range was determined manually. Then, trials were linearly detrended and demeaned to remove the signal drifts and correct the DC offsets. At this stage, the trials were concatenated to reconstruct the continuous resting-state LFP trace. A fourth-order Butterworth bandpass filter around this peak frequency (range, 3–9 Hz around the peak frequency, determined for each subject individually based on the width of the peak frequency) was applied to the reconstructed signal, and the resulting data were rectified and Hilbert filtered to extract its upper envelope (Fig. 1B). For each condition, a threshold was then set at the 50th percentile of the envelope. The duration of the beta bursts was determined from the time points at which the final signal exceeded the threshold amplitude and then fell below this threshold.[4,11] As the precise amplitudes of percentile-defined thresholds could vary between *on* and *off* conditions, the applied threshold was set as the average of the amplitudes corresponding to the selected percentile, and the same threshold applied to both *on* and *off* conditions for a given hemisphere. Burst amplitude was defined as the total sum of the amplitudes of the envelope at each time point of the detected burst.

Irregular-Resampling Auto-Spectral Analysis (IRASA)

The IRASA method, which separates the aperiodic and oscillatory components in the power spectrum of the LFPs, rests upon the self-affine property of aperiodic time series and the frequency-specific nature of oscillatory time series. In this method, the spectral component due to the aperiodic activity is first extracted from the spectrum of the mixed signal, and then the spectral component due to the oscillatory activity is approximated by taking the difference between the mixed spectrum and the extracted aperiodic spectrum. In brief, the power spectrum is calculated multiple times from resampled (upsampled and downsampled) time series using pairwise symmetric noninteger resampling factors. The consequence is that the power spectrum of the aperiodic activity will remain the same as the original data (due to the self-affine property), whereas the spectrum from the resampled activity of an oscillation will systematically shift the peak frequency at the scale

of resampling.[39] Afterward, the auto-power spectra of the resampled signals are statistically summarized by using the median to robustly separate the aperiodic component from the oscillatory component in the frequency domain according to their distinct temporal and spectral characteristics. In this study, the IRASA function was applied to the preprocessed data for the beta frequency band (13–35 Hz) in steps of 0.25 Hz. The rescaling factors (hset) were set from 1.5 to 1.9 in steps of 0.05. After the decomposition of oscillation and the aperiodic spectrum, we quantified the offset (intercept) and exponent (negative slope) from the linear regression parameters of the IRASA-decomposed aperiodic spectrum (Fig. 1C). To better visualize differences between signals with low and high aperiodic activities, we simulated two LFPs in the time domain that did not contain any oscillatory activity. The signal with the higher spectral exponent was generated by following a $1/f$ power law relationship (pure white noise) and the other that followed a $1/f^{0.5}$ relationship resulted in a smaller offset and exponent. This simulation is presented in Fig. S4.

Statistical Analysis

Separate two-way repeated-measure analyses of variance (ANOVAs) with the main factors medication (two levels: *off* and *on*) and time (five levels: visits 2–6) were used to investigate whether beta burst characteristics (amplitude and duration) or aperiodic components (spectral exponent and offset) changed over time. When a significant main effect or interaction was found ($P < 0.05$), post hoc *t* tests were applied.

Results

PD Motor Signs

A one-way ANOVA with a main factor of time (five levels: visits 2–6) did not show significant changes in MDS-UPDRS-III scores over time ($P = 0.51$).

Beta Bursts

We first compared beta burst durations and amplitudes over time across the five visits (n = 74 hemispheres; number of hemispheres in each visit = [18 16 14 14 12]). Levodopa significantly shortened burst durations by 53.81 ± 130.27 milliseconds (mean ± SD; $P = <0.001$, *t* test) and decreased burst amplitudes by 0.03 ± 0.05 a.u. (mean ± SD; $P = 0.01$, *t* test). These findings are shown in the scatter plots in Fig. 2A,B, which depict the distribution of beta burst durations and amplitudes for each individual hemisphere. As expected, most of the individual data points are located above the diagonal equivalency line, indicating longer durations and larger amplitudes after the withdrawal of medications. Furthermore, a two-way repeated-measure ANOVA revealed a significant main effect of medication ($P = 0.002$), but no significant effect of time ($P = 0.1$) or time × medication interaction ($P = 0.9$) for beta burst durations. Similarly, there was a significant main effect of medication ($P = 0.001$), but no significant effect of time ($P = 0.4$) or time × medication interaction ($P = 0.9$) for beta burst amplitudes. The findings that the effects of medications on beta burst durations and amplitudes were stable over time are shown in Fig. 2C,D. Post hoc *t* tests revealed a significant within-session reduction in both burst durations and amplitudes with medications at 1, 6, and 12 months following surgeries. Moreover, using the 75th percentile as the threshold for beta bursts yielded similar findings with reduced burst amplitudes and durations on the *on* medication state and no change overtime. A similar pattern was observed in the data from the six patients who completed all study sessions (see Supplementary Materials, Fig. S1).

Aperiodic Activity

Figure 3A,B demonstrates the overall pattern of individual exponent and offset values pooled across hemispheres (n = 74) and five visits (number of hemispheres in each visit = [18 16 14 14 12]). In contrast to the findings for beta burst amplitude and duration, medications had no significant effect on the exponent (*t* test, $P = 0.12$) or the offset ($P = 0.14$) values. Furthermore, a two-way ANOVA with the main factors of medication (two levels: *off* and *on*) and time (five levels: visits 2–6) revealed a main effect of time ($P < 0.001$), but no significant effect of medication ($P = 0.7$) or time × medication interaction ($P = 0.4$) for the exponent. Similarly, there was a main effect of time ($P < 0.001$), but no significant effect of medication ($P = 0.7$) or time × medication interaction ($P = 0.7$) for the offset. Figure 3C,D shows the exponent and the offset values calculated for each individual hemisphere in each session for the dopaminergic medication *on* or *off* states. Post hoc *t* tests revealed that although aperiodic spectrum parameters (exponent and offset) are not affected by medication, both exponent and offset were increased at 6 months following surgery compared with visit 2 as baseline (*t* test, all $P < 0.01$, except for the offset at visit 5: $P < 0.05$). Increased values of exponent and offset remained stable until 18 months, and there was no significant difference between visits at 6, 12, and18 months after surgery. A similar pattern was observed in the data from the six patients who completed all study sessions (see Supplementary Materials, Fig. S2).

The data derived from externalized recordings (visit 1, see Fig. S5A) showed the same within-session pattern as the data derived from PC + S (visits 2–6) despite differences in data collection parameters and the potential influence of the surgical stun effect. There was a significant reduction in burst durations and amplitudes with

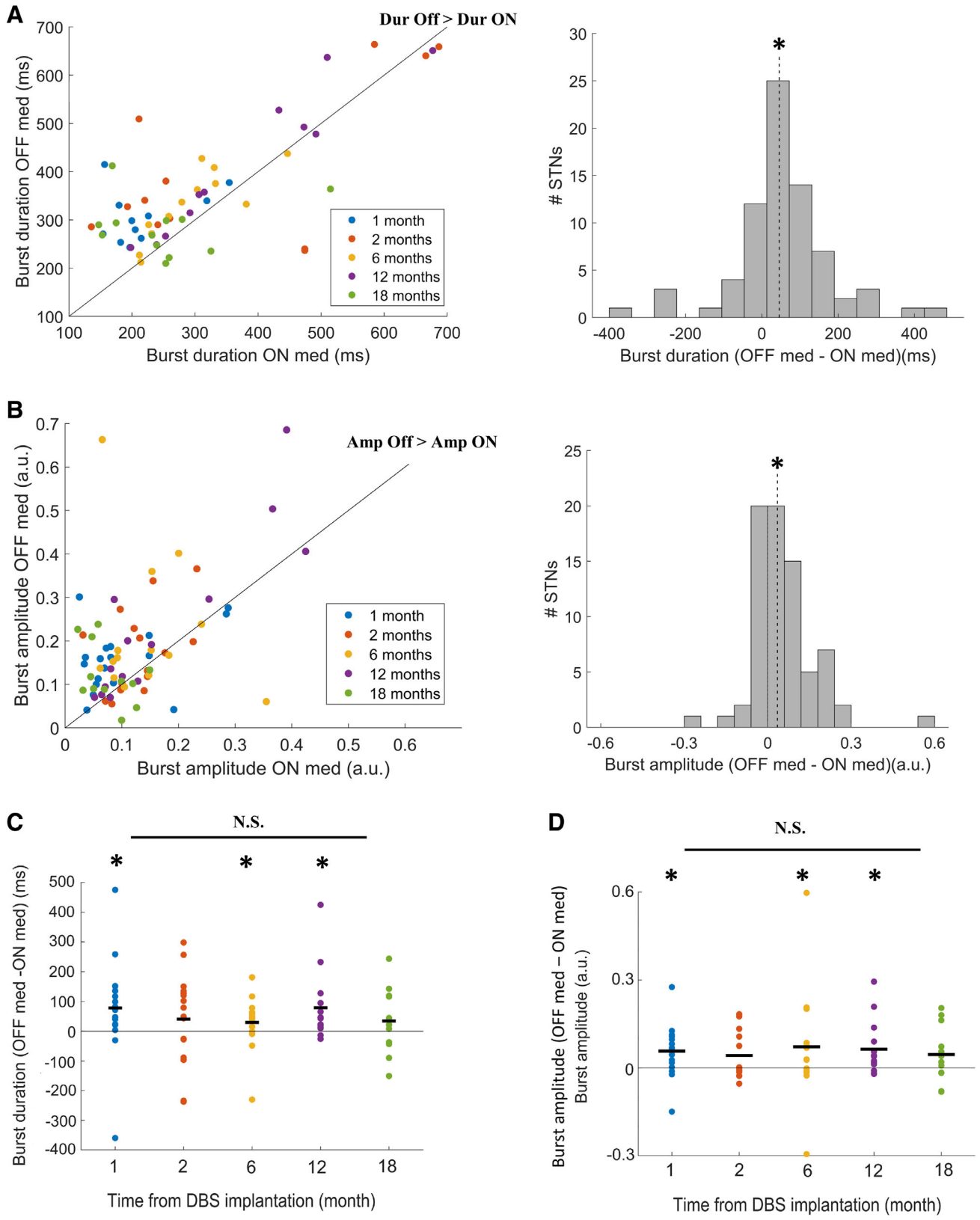

FIG. 2. Effects of dopaminergic medications on beta burst durations (**A**) and amplitudes (**B**). The scatter plots and histograms show that dopaminergic medications reduce beta burst durations and amplitudes pooled across the five visits. Each dot represents one STN, and dots above the equivalency line represent higher values in the *off* medication state compared with the *on* medication state. Dashed lines in the histograms represent medians of the distributions. Further analysis revealed a significant within-session reduction in both burst durations (**C**) and amplitudes (**D**) at 1, 6, and 12 months following surgeries with dopaminergic medication, but no significant changes over time. Amp, amplitude; DBS, deep brain stimulation; Dur, duration; N. S., statistically not significant; STN, subthalamic nucleus. *$P < 0.05$. [Color figure can be viewed at wileyonlinelibrary.com]

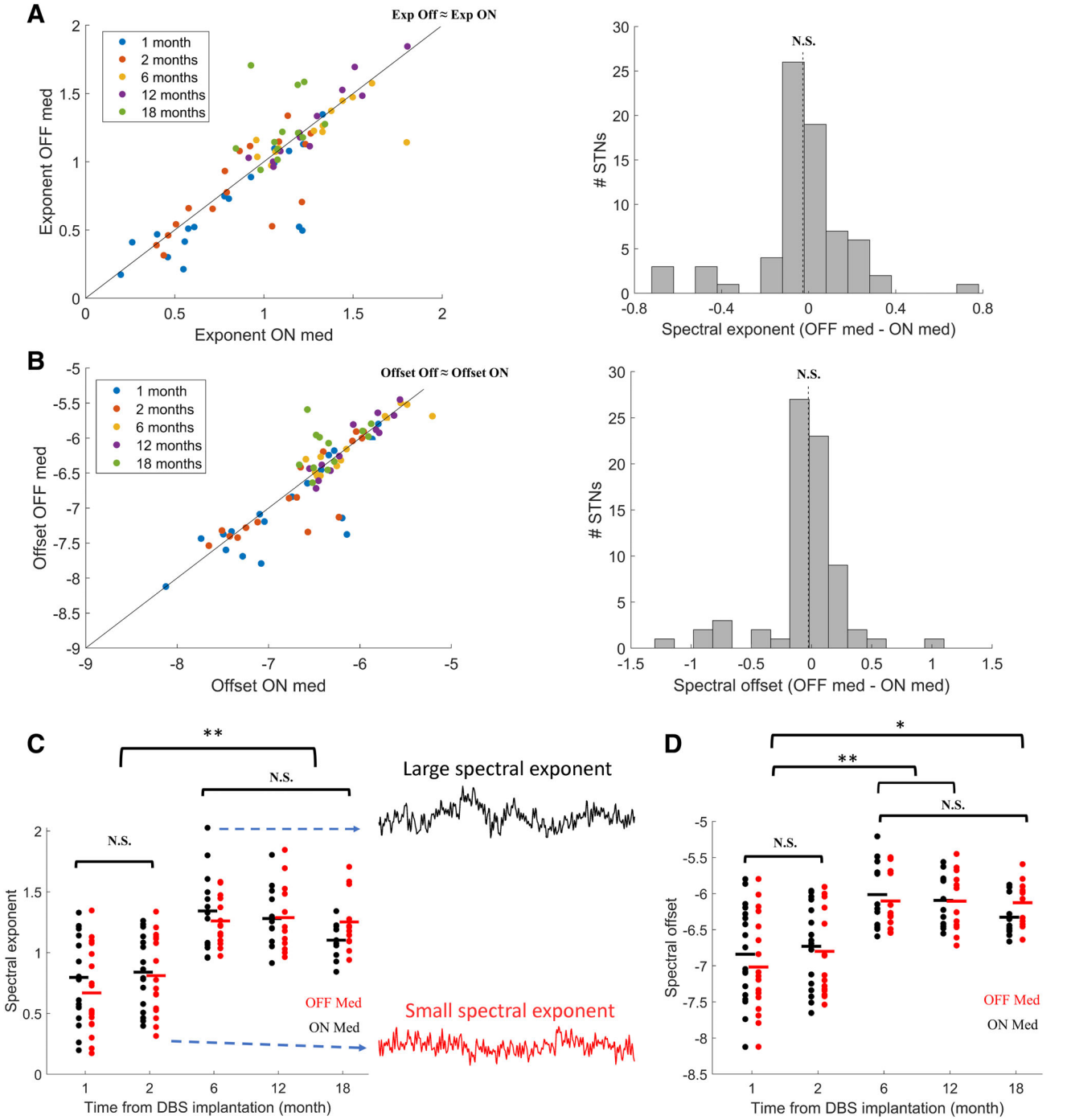

FIG. 3. Overall effects of dopaminergic medications on aperiodic spectrum parameters: exponent (**A**) and offset (**B**). The scatter plots and histograms showed that medications had no significant effect on the exponent or the offset with data pooled from all visits. Each dot represents one STN, and dots above the equivalency line represent higher values in the *off* medication state compared with the *on* medication state. Dashed lines in the histograms represent medians of the distributions. Further analysis revealed no significant within-session effect of medication, but a significant increase in both exponent (**C**) and offset (**D**) starting at 6 months after surgery when compared with visit 2 (1 month following DBS implantation) as baseline. Two examples of raw local field potentials corresponding to high (black) and low (red) spectral exponents are plotted in C. DBS, deep brain stimulation; Exp, exponent; N.S., statistically not significant; STN, subthalamic nucleus. *$P < 0.05$ and **$P < 0.01$. [Color figure can be viewed at wileyonlinelibrary.com]

medication ($P < 0.05$, t tests), but no effect of dopaminergic medication on the aperiodic spectrum parameters in visit 1 ($P > 0.05$, t tests, see Fig. S5B). Because the method of recording in visit 1 (externalized recording) was different than recordings derived from PC + S (visits 2–6) and given that DBS was turned on at 1 month postoperatively (visit 2), we did not compare the data from visit 1 with the data from subsequent visits.

Discussion

To provide a better understanding of the long-term effects of STN-DBS in conjunction with dopaminergic medications, we investigated changes in the oscillatory and aperiodic components of the beta frequency band in LFP signals in a longitudinal study. We demonstrated that beta burst durations and amplitudes recorded in the STN in patients with PD were relatively stable for 18 months. This is consistent with other studies that showed that pathologic beta oscillations in PD do not substantially progress during the initial 6 to 12 months following DBS implantation.[13,15,44] A recent study showed no significant progression of *off* medication pathologic beta oscillations for up to 3 years following STN-DBS.[12] Although these studies mainly focused on the power of beta band oscillations, our study provides evidence for stable measures of beta bursts for 18 months. When comparing beta bursts in the *off* and *on* medication states, we observed that levodopa reduced burst durations and amplitudes at each session. Previous studies examined the effects of levodopa on beta bursts up to only a few days after the surgery, when the stun effect of DBS placement may still be present.[4,11] We found no change in the effects of dopaminergic medications on beta bursts over time (up to 18 months), consistent with the finding that there was no change in MDS-UPDRS-III scores during the same period.

Although the selection of a given percentile amplitude threshold to determine beta bursts seems arbitrary, previous work has shown that relative differences in beta burst properties between *on* and *off* medications are preserved using different thresholds.[11] We also found that using the 50th or 75th percentile as the threshold yielded similar findings with reduced beta burst amplitudes and durations with dopaminergic medications, with no significant change for 18 months after DBS implantation. It should be noted that the method used here to extract beta bursts is sensitive to high-power bursts, even if the lower thresholds such as the 50th percentile was used. Lower power with prolonged bursts may also be pathological but would not be captured by this method.

Chronic STN recordings are prone to artifacts such as movement and electrocardiogram (ECG) artifacts, especially if IPGs are implanted on the left side. In all our patients, the IPGs were implanted on the right side, which generally leads to almost none or minimal ECG artifacts.[46] We observed minor ECG artifacts only in a few hemispheres. Although we did not employ an automatic ECG detection algorithm such as the one proposed by Neumann and colleagues,[46] the data were visually inspected in several analysis steps, and segments with artifacts were removed. In addition, we filtered the data around beta peak frequency, and this removes to a large extent noise from low-frequency fluctuations such as ECG or movement artifacts. Future studies may use more sophisticated ECG artifact rejection algorithms to further reduce the possibility of ECG artifact contaminating the LFP data.

The spatial heterogeneity of the leads and the changes in the contacts from which we could record during this study might be a limitation of this study. Although microelectrode recordings were performed before DBS electrode implantation, the lead contacts might have been placed in different subregions or occasionally even outside of the STN during the surgery in some patients. This seemed to be the case for one of the patients (see Fig. 1A); however, because the patient benefited from the DBS with improvement of motor symptoms, we included her data in the analysis. The change in aperiodic activities, which occurred between 2 (visit 3) and 6 months (visit 4) (Fig. 3C,D) after DBS electrode implantation, cannot be explained by differences in the contacts used for LFP recordings because the same contact was used in these two visits in 19 of 20 STN studied (Table S3).

There is evidence that long-term STN-DBS leads to brain plasticity and a reconfiguration of neural pathways in patients with PD.[13,47,48] If these plastic changes from STN-DBS are not reflected in beta oscillations, what could capture the long-term effects of STN-DBS? To our knowledge, this is the first report on the relationship between the aperiodic component of STN-LFP and the pathophysiology of PD. To investigate the possibility that non-oscillatory components of the STN-LFPs might better reflect the underlying plastic changes from STN-DBS, we separated beta oscillations from the rest of the LFP signal, that is, aperiodic activity using IRASA.[39] Our results revealed that aperiodic spectrum parameters (exponent and offset), in contrast to beta bursts, were not influenced by dopaminergic medication. However, both exponent and offset of the aperiodic spectrum increased over time.

It has been shown that an increased offset in the broadband LFP recordings correlated with the firing rate of local neurons or cortical activity, whereas narrowband oscillations (oscillatory peaks) were not a reliable predictor of neuronal spiking.[20,26] The spectral exponent has been suggested to be related to the balance of excitatory (E) and inhibitory (I) activity (E:I ratio) in populations of cortical neurons such that a decline in the spectral exponent (a flatter spectrum) is associated with an increase in the excitatory activities, whereas an increase in the spectral exponent (a steeper spectrum) suggests an increase in the inhibitory activities.[25] This notion is supported by pharmacological studies on the sensitivity of the spectral exponent to the E:I balance during different conscious states. In these studies, EEG spectral exponents were lower in awake participants compared with when under anesthesia induced by the administration of propofol and xenon, which are associated with inhibitory activities.[28,29] Also, patients with schizophrenia and attention-

deficit hyperactivity disorder (associated with cortical E:I balance deficits) have greater aperiodic spectrum parameters compared with healthy subjects.[35,36] Altogether, the aforementioned studies suggest that alterations in spectral exponent and offset may reflect changes in E:I balance. Therefore, the increase of the aperiodic spectrum parameters in our study starting at 6 months following surgery may suggest increased inhibitory activities in the STN.

How may a higher level of inhibition have been achieved in the STN? Our analysis of the aperiodic activity in this study was based on LFPs. Previous studies have shown that synaptic input currents are the major contributors to LFPs.[49,50] To better understand the mechanisms behind potential increased inhibition in the STN following long-term DBS, the role of areas projecting to the STN should be considered. The STN has direct glutamatergic (excitatory) projections from the centromedian-parafascicular nucleus of the thalamus and the cerebral cortex. It also receives reciprocal inhibitory inputs from the GPe, and modulatory inputs from the substantia nigra pars compacta. The STN also receives cholinergic and glutamatergic projections from the pedunculopontine nucleus.[51] Plastic changes in the strength of these inputs due to long-term STN-DBS might change the E:I ratio toward more inhibition and could potentially lead to increased aperiodic spectrum parameters. Our findings of potential increased inhibition at the level of the STN together with the finding that both beta bursts and MDS-UPDRS-III scores did not progress over time (which would have been excepted without DBS treatment), support the suggestion that DBS could induce brain plasticity and can alter the expected disease course in PD.

Could the observed effects on aperiodic spectrum parameters simply reflect disease progression and aging process independent of STN-DBS plastic effects? Aging is unlikely to be the main factor driving increases in the aperiodic spectrum parameters as previous studies found an inverse relationship between the aging and aperiodic spectrum parameters.[38] Notably, aperiodic spectrum parameters of EEG recordings are attenuated during infancy, childhood, and adult life with time.[31–33] The underlying mechanisms for this attenuation with aging in healthy subjects is not clear.[28,52] The change in aperiodic spectrum parameters from 2 to 6 months after DBS surgery is unlikely to be related to disease progression because PD also progressed between 6 and 18 months after surgery. Moreover, we found no change in *off* medication MDS-UPDRS-III scores over time. The finding is most likely due to the plastic effects of STN-DBS. STN-DBS was activated about 1 month after surgery, and therefore the data at 2 months represent the short-term effects of STN-DBS, whereas the data from 6 to 18 months represent the long-term effects. This is consistent with the observation that normalization of measures of sensorimotor integration known as short latency afferent inhibition (SAI) and long latency afferent inhibition (LAI) with STN-DBS were observed at 6 months but not at 1 month after surgery.[48] In contrast to the findings for beta burst durations and amplitudes, the aperiodic spectrum parameters in the STN were not altered by dopaminergic medications, which is similar to the findings for SAI and LAI.[53,54] Thus, aperiodic spectrum parameters in the STN could be related to the nondopaminergic features of PD.

In this study, stimulation was turned off 30 minutes prior to data collection to partially wash out the effect of DBS on STN-LFPs in visits 3 to 6 (visit 2 occurred prior to the initial DBS activation and programming). Further studies are required to investigate whether the aperiodic activities change immediately with DBS OFF or with DBS ON. Because it is not possible to obtain STN-LFP data from healthy controls, we are unable to determine whether the aperiodic activities in patients with PD differ from healthy subjects.

Recent studies have used aperiodic spectrum parameters of the LFPs in other deep brain structures such as the subcallosal cingulate (SCC) and habenula regions to monitor the severity of depression and the effects of DBS in treating depression.[37,55] For example, the exponent of the aperiodic spectrum in the right SCC increased following 6 months of SCC-DBS therapy in patients with treatment-resistance depression. Moreover, the exponent of the aperiodic spectrum in the left habenula, another target region for DBS therapy in patients with treatment-resistance depression, positively correlated with depression severity. Our findings are in line with these studies.

We used IRASA to separate oscillations from aperiodic activities of the STN over 18 months in 10 patients with PD. The aperiodic spectrum parameters were not affected by dopaminergic medications. However, the study has several limitations. First, there was a relatively small sample size of patients with PD at each recording session. Second, the IRASA algorithm might not be sensitive enough to capture subtle differences between the aperiodic component in the *off* versus *on* medication state. Other methods to estimate the aperiodic components such as Fitting Oscillations and One Over f (FOOOF)[38] can be applied to further validate our findings. Third, we only investigated long-term effects of DBS and dopaminergic medication on beta band oscillatory and aperiodic characteristics given the large body of literature on pathologic beta band activities in PD. Future studies can investigate whether DBS or dopaminergic medications induce long-term plasticity through non–beta band oscillatory or aperiodic activities. Fourth, there is evidence for changes in electrode impedance in chronic recordings.[56–58] Although we did not measure the impedance at each visit, the temporal pattern of impedance change reported in previous studies did not match the temporal changes in the aperiodic

spectrum parameters observed in our study, which was a stepwise increase starting at least 2 months after electrode implantation and remained stable for at least 18 months (Fig. 3C,D). Nevertheless, future longitudinal studies should assess the changes in electrode properties such as the impedance over time.

The aperiodic and oscillatory components of STN-LFP represent distinct neural mechanisms, and both should be considered in the development of biomarkers for adaptive DBS for PD. Because the changes in aperiodic activities occur over months, the aperiodic spectrum parameters could also be investigated as a potential biomarker for adaptive DBS in dystonia in which the clinical effects of DBS only occur after weeks to months and were associated with slow changes in LFP features.[59] As the technology of DBS hardware advances over time, adaptive DBS will likely be controlled or modulated based on multiple biomarkers over different time scales. Based on our findings, aperiodic activities of neural signals should be considered when developing future adaptive DBS algorithms for personalized DBS therapy.

Data Availability Statement

All data supporting the findings of this study are included in the article and its supplementary information files and are available from the corresponding authors upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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

G.D.: 1A, 2A, 2B, 2C, 3A, 3B
N.M.D.: 1B, 1C, 2C, 3A, 3B
H.R.: 2B, 2C, 3A, 3B
U.S.: 1B, 1C, 3B
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