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High-resolution local field potentials measured with deep brain stimulation arrays

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Abstract

Objective—Local field potential (LFP) recordings along a deep brain stimulation (DBS) lead can provide useful feedback for titrating DBS therapy. However, conventional DBS leads with four cylindrical macroelectrodes likely undersample the spatial distribution of sinks and sources in a given brain region. In this study, we investigated the spectral power and spatial feature sizes of LFP activity in non-human primate subthalamic nucleus and globus pallidus using chronically implanted 32-channel directional DBS arrays.

Approach—Subthalamic nucleus and globus pallidus LFP signals were recorded from directional DBS arrays in the resting state and during a reach-and-retrieval task in two non-human primates in naïve and parkinsonian conditions. LFP recordings were compared amongst bipolar pairs of electrodes using individual and grouped electrode configurations, with the latter mimicking the cylindrical macroelectrode configurations used in current clinical LFP recordings.

Main Results—Recordings from these DBS arrays showed that (1) beta oscillations have spatial ‘fingerprints’ in the subthalamic nucleus and globus pallidus, and (2) that these oscillations were muted when grouping electrode contacts together to create cylindrical macroelectrodes similar in relative dimension to those used clinically. Further, these maps depended on parkinsonian condition and whether the subject was resting or performing a motor task.

Significance—Development of future closed-loop DBS therapies that rely on LFP feedback will benefit from implanting DBS arrays with electrode sizes and spacings that are more consistent with the dimensions of oscillatory sinks and sources within the brain.

1. Introduction

Closed-loop approaches to deep brain stimulation (DBS) therapy, in which neurophysiological feedback is used to adapt the parameters of stimulation, hold promise for

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improving treatment consistency of neurological and neuropsychiatric disorders, minimizing induction of side effects, and potentially reducing the frequency of replacement surgeries for implantable pulse generators with primary cells. Recent applications of closed-loop approaches to DBS therapy for treating Parkinson's disease (PD) have relied on sampling local field potential (LFP) activity from a pair of millimeter-scale cylindrical macroelectrodes along the DBS lead and then using spectral features of those signals to determine when and how to stimulate [1,2]. While retrofitting DBS lead macroelectrodes for recording purposes has been convenient for moving closed-loop DBS concepts to clinical settings [3,4], the dimensions of and spacing between each macroelectrode in the bipolar recording pair likely under samples the spatial heterogeneity of oscillatory sinks and sources within the target nucleus [5,6].

Previous studies using monopolar or bipolar electrode configurations have noted that typical targets of DBS therapy for PD, including the subthalamic nucleus (STN) and the globus pallidus internus (GPi)/externus (GPe), can exhibit notable spontaneous and task-related oscillatory activity in the healthy [7–12] and parkinsonian conditions [6,8,13–20]. However, studies have also found significant inter-subject variability in the power and specific frequency bands of such oscillatory activity as shown in human [5,18,21–24] and non-human primates [8,21–23]. Such variability may certainly stem from physiological differences within the sampled target amongst subjects, but the differences could also reflect the degree to which recording electrode dimensions, locations, and configurations can faithfully limit electrical shunting of oscillatory dipole activity in the regions of interest [25] and at the same time selectively remove interference from far-field oscillatory sources [24].

This study investigated the hypothesis that DBS leads with smaller, segmented electrodes will uncover increased heterogeneity of LFP activity within basal ganglia targets of DBS therapy. Acute intraoperative human studies leveraging DBS arrays indeed suggests that oscillatory activities in the STN have a finer spatial resolution than what is detectable with commercially-available DBS leads with four cylindrical macroelectrode contacts [13]. What remains unclear is the degree to which this concept varies amongst the primary DBS targets for treating PD – that is, the STN and GPe/GPi. Additionally, little is known concerning the degree of spatial heterogeneity of oscillatory activity in these targets across behavioral states (resting versus active) and between naïve and parkinsonian conditions. To investigate these questions, DBS arrays with electrodes segmented both along and around the lead body [26] were chronically implanted within the STN and within the GPe/GPi in two non-human primates rendered parkinsonian with systemic administration of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine).

2 Materials and Methods

2.1 Animals

Two rhesus monkeys (*macaca mulatta*, female) were used in this study (Subject G, 17 years old, 9.0 kg; Subject N, 18 years old, 6.0 kg). All procedures were approved by the Institutional Animal Care and Use Committee of the University of Minnesota and complied with the United States Public Health Service policy on the humane care and use of laboratory animals. The animal subjects were provided with environmental enrichment,

water *ad libitum*, and a range of food options including fresh fruit and vegetables. All efforts were made to provide care and alleviate any discomfort for the animals during the study. Both animals underwent pre-operative 7T MRI at the Center for Magnetic Resonance Research at the University of Minnesota using a passively shielded 7T magnet (Magnex Scientific) using methodology described previously [27].

2.2 Cranial Chamber and DBS Implants

Under isoflurane anesthesia, each animal was implanted with a titanium headpost (Gray Matter Research) and two cranial chambers (Crist Instruments) over the right hemisphere. The orientation and position of each cranial chamber were guided by a preclinical neurosurgical navigation software called *Monkey Cicerone* [28] in Subject G and an updated version called *Preclinical Cicerone* [29] in Subject N. This program enabled 3D visualization of prospective DBS lead implant trajectories with the goal of targeting the GPe and GPi or the STN and further avoiding trajectories through large sulci, ventricles, and primary motor cortex. A post-implant CT scan was used to verify chamber placement and plan for the DBS lead implantation in the software packages.

2.3 Microelectrode Mapping

A Narishige microdrive was attached to each chamber and used to guide a microelectrode (250 μm diameter, 0.8–1.2 M Ω , FHC) through a dura-penetrating cannula into the brain. Five microelectrode tracks were performed for each target to locate and then map the sensorimotor territories of the GPe/GPi and the STN [30–32]. Firing rate and patterns of isolated neurons in each of the targets were used to localize the borders of each nucleus of interest. Sensorimotor territories within these nuclei were identified as those containing neurons whose firing rate was modulated by passive joint articulation or volitional movement. The location of the recording tracks relative to the corticospinal tract of internal capsule was determined using microstimulation (50–200 μA , 300 Hz, 0.5 sec) to evoke movement of the face, upper extremity, and lower extremity. For both subjects, the GPe/GPi target was mapped and implanted with a DBS array prior to the mapping and implantation of the ipsilateral STN-DBS array.

2.4 DBS Array Implant

The same Narishige microdrive used for the initial mapping experiments was also used for the DBS array implant. Two versions of a segmented DBS array were fabricated by NeuroNexus Technologies as described previously [26]. The DBS arrays consisted of 32 ellipsoidal electrodes arranged in eight rows and four columns around a 600 μm diameter shaft, with electrode diameters of 360 $\mu\text{m} \times 360 \mu\text{m}$ for the STN implant and 370 $\mu\text{m} \times 470 \mu\text{m}$ for the GPe/GPi implant. Center-to-center electrode pitch along the axis of the DBS lead was 572 μm and 750 μm for the STN- and GPe/GPi-DBS arrays, respectively. Following the implant of the two DBS arrays, a CT scan was performed in each subject to localize the array positions within the context of the pre-operative MRI. DBS array orientation was determined using two approaches. First, each DBS array assembly had a flexPCB cable extending from the lead body within the cranial chamber. This assembly served as a fiducial for the alignment of electrode columns located distally along the lead shank. Prior to implantation, the DBS arrays were inspected under the microscope to confirm this

alignment. Additionally, stimulus-induced muscle contractions resulting from putative activation of the corticospinal tract of internal capsule were measured. The threshold amplitudes around a row of electrodes was used to identify the electrode contact(s) that most closely faced the internal capsule and further confirmed results from the fiducial analysis. Lastly, for the STN-DBS array in Subject G, EMG surface electrodes were placed on the forearm and bicep, and capsule-evoked EMG potentials were measured directly in lieu of visual observation of muscle activation.

2.5 Impedance Spectroscopy Measurements

Prior to and following implantation of each DBS array, electrochemical impedance spectroscopy measurements were performed on each electrode site using an Autolab potentiostat (PGSTAT12, Metrohm). Electrode site impedances outside the range of 10–300 k Ω at 1 kHz and 200–700 Ω M at 20 Hz were deemed non-functional and were excluded from further analysis to avoid biasing LFP signal analyses. There were seven electrodes in Subject N's GPe/GPi implant and five electrodes in Subject G's GPe/GPi implant that were deemed non-functional.

2.6 Local Field Potential Recordings

Monopolar field potential recordings were sampled concurrently at 1.375 kHz from each of the 32 electrodes on the STN-DBS array and 32 electrodes on the GPe/GPi-DBS array through an Alpha Omega SnR system. The recordings were electrically referenced to a posterior titanium headpost, which was anchored to the cranium with 10–15 titanium bone screws. LFP recordings were performed during (1) resting state conditions with the animal seated in a primate chair with its eyes open and minimal movement, and (2) during a voluntary reaching task to retrieve pieces of fruit from a Klüber board. During the voluntary reaching task, joint position data was collected from reflective markers placed on the limbs using infrared motion capture cameras (Vicon, T-series) and webcams (Logitech). Limb positions were reconstructed in Vicon Nexus software and kinematic parameters were extracted in MATLAB (Mathworks). The motion capture cameras were synced to the recordings via a TTL pulse delivered at the beginning of the recording session, and the video cameras were synced to the LFP recordings by a large motion artifact induced by tapping on the wires at the end of the trials.

2.7 MPTP Injections

Following measurements in the drug naïve condition, systemic MPTP injections were administered to each animal, after which the LFP recordings were repeated. MPTP is a neurotoxin that, when delivered systemically, causes degeneration of dopamine neurons in the substantia nigra pars compacta [33] as well as neurons within the pedunculopontine nucleus [34] and centromedian nucleus [35], among other structures that are known to degenerate in Parkinson's disease. Subject G was given systemic injections over two consecutive days (0.7 mg/kg total). Subject N was given three rounds of systemic injections, first over three consecutive days (0.5 mg/kg total), next over two consecutive days (0.6 mg/kg total), and finally over another two consecutive days (0.6 mg/kg total). Through these systemic MPTP injections, both subjects were rendered into a stable, moderately severe

parkinsonian state as assessed by a modified Unified Parkinson's Disease Rating Scale (mUPDRS) [8].

2.8 LFP Signal Processing and Spectral Analysis

The recorded monopolar LFP data were analyzed offline using custom MATLAB scripts (v2016b, Mathworks) and the Chronux toolbox [36]. In post-processing, the LFP recordings were re-referenced into bipolar recordings by subtracting adjacent signals by columns or by rows. If an adjacent electrode was deemed non-functional (see Section 2.5), the next available channel down the row was used for the bipolar calculation, and this calculation was adopted for all recordings for that particular DBS array to maintain consistency. In the resting state, common average referenced LFPs were also calculated on each channel by subtracting the average of the monopolar LFP data from the other functional channels.

For resting state recordings, the first two seconds of the data were cropped to remove electronic settling offsets. A 1 Hz high pass filter and 100 Hz low pass filter were used to remove baseline drift and hardware noise. Power spectra of resting state LFPs (20–30 seconds in duration) were calculated using the multi-taper method using 5 tapers (Chronux) [36]. Multitaper spectrograms were also generated, using one taper and a one second moving window with 100 ms step size, resulting in a 2 Hz multi-tapered frequency resolution. Recording data were further visually inspected for large and transient broadband power increases indicative of movement artifacts. These epochs were removed from further analyses. The overall power spectrum for a given resting-state test condition was calculated by averaging over spectrogram windows. Bands of interest were defined as theta band (3–8 Hz), alpha band (8–12 Hz), beta band (12–30 Hz) and gamma band (30–90 Hz). Once a band of interest (e.g., beta-band activity) was identified, a bandpass filter (3rd order Butterworth) at the corresponding frequency range was applied to the bipolar LFP data, and the average band power was calculated by averaging the power spectrum of the frequency band of interest in the frequency spectrum, and converted to dB. A contour map of spectral power averaged across all recording trials was then generated across the array and spatially smoothed using a Gaussian filter. These contour maps were compared against electrode site impedances (see supplementary data) using Pearson's correlation ($p < 0.05$) under naïve and parkinsonian conditions.

LFPs during the reach and retrieval task were aligned to the time of movement initiation and spectrograms for each trial were calculated. Multitaper spectrograms were calculated using three tapers and a 200 ms moving window with 20 ms step size, resulting in a 5 Hz multi-tapered frequency resolution. The average triggered spectrograms were calculated by averaging the individual spectrograms across all reaches in the time-frequency domain, and normalized to a z-score against a pre-reach period 1.5 to 1 second before the reach onset [37]. Outliers of the normalized z-score spectrograms were identified as time windows when power in all frequencies exceed five standard deviations from the mean and were excluded. Once a z-score spectrogram was obtained, the standard deviation $\sigma_{z\text{-score}}$ of the z-score spectrogram maps across the entire DBS array was calculated:

$$\sigma_{z-score}(t, f) = \sqrt{\frac{\sum_{i=1}^N (Z_i(t, f) - \overline{Z(t, f)})^2}{N-1}} \quad (1)$$

where N is the total number of bipolar pairs of electrodes, $Z_i(t, f)$ is the individual z-score spectrogram, and $\overline{Z(t, f)}$ is the average of all z-score spectrograms across all pairs. The z-score spectrograms were also directly subtracted to produce a difference z-score spectrogram:

$$Z_{diff}(t, f) = Z_1(t, f) - Z_2(t, f) \quad (2)$$

and the standard deviation of the difference spectrogram was also calculated:

$$\sigma_{Z_{diff}}(t, f) = \sqrt{\frac{\sum_{i=1}^N (Z_{diff_i}(t, f) - \overline{Z_{diff}(t, f)})^2}{N-1}} \quad (3)$$

The individual bipolar z-score spectrograms were compared to grouped macroelectrode z-score spectrograms using Equation 2, and a standard deviation of the resulting z-score spectrogram values were calculated using Equation 3. This produced either three $\sigma_{Z_{diff}}$

corresponding to each grouped macroelectrode bipolar pair, or one overall plot reflecting the entire DBS array. Statistical significance was defined at ± 3 z-scores.

3. Results

3.1 DBS Array Implant Locations and Orientations

Implant trajectories for each DBS array was identified by co-registration of the pre-operative 7T MRI and post-operative CT imaging. The STN-DBS array in each subject was implanted along a parasagittal trajectory such that the DBS lead body passed through the STN with electrode rows 1–5 (Subject N) and rows 6–8 (Subject G) having at least one electrode within the subthalamic nucleus (Fig. 1). The GPe/GPi-DBS arrays were implanted along a pseudo-coronal trajectory with electrode rows 3–7 in GPe and rows 0–2 in GPi in Subject N and rows 5–7 in GPe and rows 0–4 in GPi in Subject G. Histological confirmation of the DBS array positions was performed for Subject G [26,38], but no histology was available for Subject N who remains active on other studies.

As verification of DBS array orientation, biphasic stimulus pulse trains (300 Hz, 100–400 μ A, 0.5 sec duration) were delivered through one or more electrodes along a single column of a DBS array to find stimulus amplitude thresholds to elicit muscle twitches. For all DBS arrays, the contralateral hand first observed a twitch, followed by forearm and leg twitches upon ramping up stimulation amplitude. The stimulus threshold for the hand were found to be lower for electrode contacts facing internal capsule than for electrode contacts facing

away from internal capsule for both STN- and GPe/GPi-DBS arrays (Fig. 1). For the STN-DBS array in Subject G, evoked EMG potentials were measured in lieu of calculating a threshold amplitude. These potentials were found to be highest when stimulating through the lateral column of electrodes that was closest to the internal capsule.

3.2 Resting State LFP Recordings through the DBS Arrays

Power spectra calculated from resting state LFP recordings exhibited greater relative variability amongst bipolar than monopolar recording montages (Fig. 2). In comparison to monopolar montages, bipolar recordings that used common average referenced and individual site (between rows) referenced configurations displayed greater relative variations in background spectral power as well as peak spectral power in the low beta band (12–20 Hz) for DBS arrays in the STN and DBS arrays in the GPe/GPi (Fig. 2A, C). Similar results were observed for bipolar recording montages amongst grouped macroelectrodes (Fig. 2B, D). In all four DBS array implants, common average referenced bipolar and individual site bipolar recording montages resulted in instances of higher peak beta band power than what was observed with bipolar recordings from grouped macroelectrode configurations (Fig. 2E). Additionally, the range of peak beta band power along each DBS array was larger when using individual site versus grouped macroelectrode bipolar recording montages. Because individual site bipolar LFP recordings exhibited comparable spectral power and range to common average referenced LFP recordings, further analyses were limited to individual site bipolar LFP recordings.

3.3 Spatial ‘fingerprints’ of beta band activity in the STN and GPe/GPi

Across all DBS arrays in both the naïve and parkinsonian condition, beta band spectral peaks were observed in the 12–20 Hz range for bipolar recording montages using row subtraction. The spatial distribution of this beta band activity was compiled into spatial contour ‘fingerprints’ for each DBS array and averaged over all resting state recording sessions in a given condition (Fig. 3). In both naïve and parkinsonian conditions, the STN-DBS arrays in both subjects exhibited pronounced beta band power distributed primarily along a single column. In Subject N, beta band power was highest in column 2 (facing lateral-anterior) with an additional beta band hotspot emerging more dorsally in columns 0 and 3 (facing lateral-posterior and lateral-anterior) in the parkinsonian condition. The column-based distribution was also observed in more distal contacts in Subject G, but shifted from column 1 (anterior facing) to column 2 (lateral facing) between naïve and parkinsonian conditions with a similar spread of beta band activity to more dorsolateral electrodes as observed in Subject N.

In the naïve condition in Subject N, the GPe/GPi-DBS array’s row subtraction bipolar recordings showed elevated beta power in the internal medullary lamina between GPe and GPi and in columns 0 and 3, which faced posterior and lateral. In the parkinsonian condition, the spatial peak beta power increased and shifted dorsally to within GPe centered between columns 2 and 3, which faced anterior and lateral. In the naïve condition in Subject G, the GPe/GPi-DBS array spatial peak beta power was primarily located in the upper rows in column 2 (GPe, medial-anterior direction) and in the lower rows in columns 0 and 2 (GPi, lateral-posterior and medial-anterior). In the parkinsonian condition in Subject G, the

contour map showed a similar pattern to the naïve condition except that the stronger beta band power observed in the upper rows of column 2 was muted.

3.4 Spatial Distribution and Resolution of Oscillatory Activity during Voluntary Reaching

Both subjects performed a reach and retrieval task in the naïve and parkinsonian states during which LFP recordings were collected on both DBS arrays. These recordings were processed in terms of individual electrodes (bipolar: adjacent row subtraction) or grouped macroelectrodes (bipolar: adjacent grouped row subtraction). Spectrograms with z-score coloring showed significant decreases in beta band power immediately before and after the onset of the reach movement on a portion of the bipolar recording pairs. Additionally, there was pronounced low gamma band (30–50 Hz) activity immediately following the onset of the reach movement. An example comparison between spectrograms for individual bipolar electrodes and bipolar macroelectrodes is shown in Fig. 4A–C for Subject G's GPe/GPi-DBS array in the parkinsonian state.

To investigate which time-frequency components of the spectrograms varied between individual and grouped bipolar pairs, the standard deviation of the differences between each of the grouped macroelectrode bipolar spectrograms (Fig. 4A) and the corresponding twelve (i.e. three bipolar rows) individual bipolar spectrograms (Fig. 4C) for all combinations across the entire DBS array were calculated, and a single standard deviation map of the z-score differences was computed (Fig. 4C). The results of this single measure for all DBS arrays are summarized in Fig. 4D. In both Subject N and G's GPe/GPi-DBS array in the naïve condition, most of the variation between individual and grouped bipolar spectrograms occurred between 1–12 Hz and overlapped with movement onset. In the parkinsonian state, an additional gamma band variation occurred immediately following reach onset in both subjects. For the STN-DBS arrays in the naïve condition in both subjects, variation between individual and grouped bipolar spectrograms was found in beta band (12–30 Hz), also overlapping with movement onset. In the parkinsonian condition in both subjects, individual and grouped bipolar spectrograms were more consistent in the beta band at movement onset, but also exhibited greater variation in 1–10 Hz band and gamma band (30–50 Hz).

3.5 Orientation of Bipolar LFP Signals in the STN and GPe/GPi

The DBS arrays also provided an opportunity to investigate how referencing of the bipolar LFPs affected recordings in the resting state and during the voluntary reach task. Power spectra with prominent beta band spectral peaks were found for bipolar LFPs calculated horizontally across columns as well as vertically across rows of the DBS arrays (Fig. 5). In the resting state, there were no significant differences in average peak beta band power for row versus column referencing (Fig. 5A–C, Wilcoxon ranksum test, $p > 0.05$). However, for any given recording and in a fraction of electrode pairs, low beta band activity could be detected more strongly in one referencing montage than in another suggesting variation in oscillatory dipole orientations from recording to recording.

Variation in spectral features of the LFP recordings between row and column referencing was more notable in the context of the voluntary reaching tasks. Examples from two DBS arrays are shown in Fig. 5D. In this case, for the GPe/GPi-DBS array, the top row bipolar

electrode configuration facing the medial direction exhibited significant low frequency desynchronization (1–10 Hz), which was not the case for the complementary column bipolar configurations between medial-anterior or medial-posterior facing electrodes. These differences are shown in a standard deviation map for a single row or column (Fig. 5E) indicating that most of the variation was in the low frequency band (1–10 Hz) immediately before and after the onset of movement. For the STN–DBS array electrodes shown in Fig. 5D–E, on the other hand, the strongest variation between row and column configurations was found in the beta band coincident with the onset of movement.

To investigate differences in spectrogram variation between row and column referencing, the standard deviation maps for adjacent rows and columns were subtracted from one another (Fig. 5E). A summary plot for all subjects across all DBS arrays and conditions is shown in Fig. 5F. In Subject N's GPe/GPi-DBS array in both naïve and parkinsonian conditions, the column bipolar referencing exhibited more variance in delta-beta bands (1–20 Hz) before the movement onset, while row bipolar referencing exhibited more variance in delta-theta bands (1–8 Hz) after the movement onset. In Subject N's STN-DBS array, row bipolar referencing exhibited more variance in delta-alpha bands (1–10 Hz) both before and after the movement onset, while column bipolar referencing exhibited more variance in the beta band in the naïve condition. In Subject G in both DBS arrays, row bipolar referencing contributed to beta-gamma band (20–40 Hz) variance in the parkinsonian condition, while column bipolar referencing contributed more variance in delta-beta bands (1–20 Hz) and gamma bands (40–50 Hz) in parkinsonian GPe/GPi and naïve STN.

4 Discussion

We demonstrated that LFP signals recorded with DBS arrays showed significant heterogeneity in the spatial distribution of oscillatory activity in the STN and GPe/GPi in naïve and parkinsonian non-human primates. The use of smaller segmented electrodes around and along the DBS array was shown to limit shunting of underlying oscillatory dipoles, particularly in the beta and gamma band, resulting in higher spectral power and more spatial heterogeneity compared with grouped macroelectrode configurations that are consistent with the larger cylindrical electrodes used in most commercially available DBS systems. The results suggest that future closed-loop DBS systems that utilize LFP feedback signals will strongly benefit from the use of DBS leads with smaller electrode sizes and interelectrode spacings.

4.1 Rationale for DBS Array Designs

In both human and non-human primate studies, DBS lead electrodes and interelectrode spacings typically allow for 2–3 cylindrical macroelectrodes to be located within the STN or GPi. Anatomical studies, however, have indicated that there is notable heterogeneity of afferent and efferent projection patterns within the STN and GPe/GPi at sub-millimeter scales. For instance, anatomical projections from primary motor, premotor, and supplementary motor cortex are known to terminate in topographically distributed subregions within the sensorimotor STN [39,40]. Each of these subregions has one or more dimensions less than 1 mm and a somatotopic arrangement along the long axis (dorsal-

lateral to ventral-medial) of the nucleus. Within the sensorimotor GPe and GPi, inputs from the sensorimotor striatum form a laminar structure parallel, and in some cases tangential, to the GPe/GPi border with striatal afferent inter-laminar spacing ranging less than 1 mm in non-human primates [41]. Similar and convergent laminar structures have been observed in the GPe and GPi from axonal processes extending from the STN [42]. The organization of such axonal projections into STN, GPe, and GPi suggests that synchronous input through these topographically arranged afferent processes should result in prominent oscillatory LFP activity [43].

Basal ganglia field potentials are indeed prominent and have been recorded through the use of wire microelectrodes [11,44,45], 250 μm diameter bipolar concentric electrodes [22], clinical DBS leads with four cylindrical electrodes [46–50], and most recently through 8-channel segmented DBS leads [51]. Electrode size and spacing between electrodes in the calculation of a local field potential is thought to impact detection of oscillatory activity within the brain. The larger surface area of cylindrical electrodes found in commercial DBS leads may short electric dipoles in the surrounding tissue and therefore under-detect salient oscillations that are observable with pairs of microelectrodes [26]. Conversely, if the electrode size and spacing is too small, common-mode potentials detected at each electrode may very well eliminate oscillations from large synchronous populations of neurons.

In this study, the DBS arrays were designed to provide a balance in function between microelectrodes and clinical macroelectrodes. Two versions of a 32-contact DBS array were designed with one for targeting the STN and the other for targeting the GPe/GPi at sub-millimeter scales. The STN-DBS array consisted of electrode rows that spanned approximately 4 mm to allow for at least several rows of electrodes to be located within the STN and for several rows of electrodes to be located slightly dorsal and ventral to the STN. The GPe/GPi-DBS array consisted of electrode rows that spanned approximately 6 mm to enable LFP recordings from both the GPe and GPi. For both DBS array designs, segmentation of the electrode rows into four columns further enabled sensing subregions within the same DBS target.

4.2 Improvement in Oscillatory Signal Detection with DBS Arrays

We demonstrated that spectral information collected by grouped macroelectrodes (obtained by averaging two rows of recorded monopolar field potential signals to match the surface area of the scaled-down non-human primate version of clinical DBS electrodes [26]) showed smaller ranges in peak beta band power (Fig. 3E, Subject N and to some extent Subject G) and smaller maximum peak beta power across all electrodes (Fig. 3E, both subjects). Closed-loop DBS systems rely on the ability to record LFP signals faithfully from deep brain targets, and improving input signal power using DBS leads with smaller electrodes will no doubt help in the design constraints for amplifiers for these systems. Additionally, these results indicate that grouped macroelectrode configurations not only short underlying dipole activity, but also that the strength of the dipole activity when measured using individual electrode bipolar configurations strongly depends on electrode positions relative to the DBS target. For resting-state recordings collected from all DBS arrays in both subjects, the grouped macroelectrode beta power range was narrower than for the individual

bipolar electrode configurations. Further, in the context of the reach and retrieval task recordings, the grouped macroelectrode configurations exhibited less variability in several frequency bands in comparison to bipolar electrode configurations with individual DBS array electrodes. This indicates that the conventional clinical DBS leads are not effectively capturing sub-regional activity within the STN and GPe/GPi that is engaged during task-based behaviors. This again has importance for future closed-loop DBS therapies that seek to adapt stimulation parameters during free-ranging behaviors in that DBS arrays with smaller electrode sites may be more capable of classifying behaviors in the context of pathophysiological disease processes.

4.3 LFP Recordings during Resting State and Voluntary Reaching Task Behaviors

Spontaneous LFPs within the sensorimotor basal ganglia are thought to represent information selective to naïve versus parkinsonian conditions. Similar to a report from Bour and colleagues [13], we observed that the spatial distribution of beta band activity varied between individual rows and columns across the DBS arrays. These ‘fingerprint’ maps showed stronger beta band activity along columns in the case of the STN-DBS arrays and within smaller isolated subregions for the GPe/GPi-DBS arrays. In the former case, the columns exhibiting the stronger beta band activity were directed towards the dorsolateral STN, which is consistent with higher beta activity reported in the dorsolateral sensorimotor territory of the STN [6,30,47,52]. Following the induction of a parkinsonian condition with MPTP treatment, the locations of the stronger beta band activity shifted slightly by one column in Subject G and extended more dorsally in both subjects, suggesting that while beta activity is present in both naïve and parkinsonian conditions, the precise location(s) of strong beta activity adapt within the STN between naïve and parkinsonian conditions.

Numerous studies in rats [11] and non-human primates have shown that LFP signals in the basal ganglia are modulated by voluntary movements [9,53,54]. There have also been studies in humans that have investigated these movement-related LFP oscillations in the context of Parkinson’s disease motor signs and therapy [46–50], albeit limited to the use of 4-channel DBS lead with cylindrical macroelectrodes. In our study, the non-human primate subjects performed a reach and retrieval task during which LFPs were recorded from both STN-DBS and GPe/GPi-DBS arrays. While in the resting state, both row and column bipolar contributed similar frequency information on average. However, during the voluntary reach task, row bipolar and column bipolar montages contributed different time-frequency information to the LFP measurements, reflecting the influence of the dipole locations and orientations in interpretation of LFP activity within the STN and GPe/GPi (Fig. 5).

4.4 Limitations and Interpretation of LFP Oscillatory Activity

Impedance of the electrode-tissue interface typically increases days after implantation [55–57] because of the nervous system’s foreign body reaction and development of an encapsulation layer around the implanted device [58–62]. After several weeks, impedances typically stabilize [55],[63], but this stability can be perturbed with electrical stimulation [56,64],[65]. In this study, all LFP recordings were recorded at least three weeks following implantation and before stimulation on each day to avoid potential confounding factors of impedance variability over time. However, even at this post-implant time point, signal

quality of LFP recordings in relation to electrode impedance is not well understood. Kappenman and Luck [66] performed a study on the effect of EEG electrode impedance on signal quality and concluded that high impedance led to a poorer signal-to-noise ratio and produced an increase in the noise level in the lower frequencies ($<4\text{Hz}$) under warm and humid conditions. They showed that such noise could be partially mitigated by high-pass filtering and artifact rejection. In our study, we only included electrodes with impedances less than $700\text{ k}\Omega$ at 20 Hz , because from visual inspection, electrodes with impedance higher than $700\text{ k}\Omega$ showed visible broad-band noise across all frequencies, biasing the bipolar calculation. We correlated the resting state beta frequency power to the impedance in both the monopolar and bipolar case, and the resulting correlation was low and not significant (Fig. S1), indicating that electrode impedance's effect on signal detection of beta-band oscillatory activity was minimal as long as the electrodes were within a reasonable range. This suggests that, at least in this study, beta band power recorded in the bipolar LFP signals were likely reflections of intrinsic biological processes in the targets, instead of a result of impedance artifacts. To verify that the LFP signals were not affected by averaging in post-processing, we also recorded signals with physically shorting the electrode connector wires instead of post-processing the individual monopolar recordings into grouped macroelectrode bipolar montages in software. The results between the hardware and software shorting did not show any significant differences in frequency content or signal quality.

For the STN-DBS array in both Subjects N and G, there was an average of 6 dB power drop among all electrodes in isolated beta oscillation power between the naïve and parkinsonian conditions. This was also observed for the GPe/GPi-DBS array in Subject G, but not in Subject N. There are several possibilities for this observation. For one, the tissue encapsulation layer could have adapted over time pushing neural tissue exhibiting oscillatory activity farther away from the DBS array contacts. It is unlikely that the DBS leads moved considerably as the fingerprint maps remained generally stable between pre-MPTP and post-MPTP measurements. Additionally, the DBS array electrode or substrate material could have changed, although impedances remained largely stable between pre-MPTP and post-MPTP conditions. The overall beta band power between normal and parkinsonian conditions could also be of a physiological origin. Such decrease was found in a fraction of subjects reported previously with LFP recordings in a progressive non-human primate model of Parkinson's disease [8], but further study is warranted to better understand these baseline power changes following MPTP treatment.

5. Conclusions

We demonstrated that segmented DBS arrays with higher density and smaller contacts were able to detect finer spatiotemporal changes in LFP activity in the basal ganglia for both resting state and active reaching task behaviors, as well as between naïve and parkinsonian conditions. These spectral changes exhibited a spatial heterogeneity within the target nuclei that for many features could not be sensed using larger grouped macroelectrode configurations. Future development of closed-loop DBS therapies that rely on sensing LFP activity will likely benefit from the use of smaller electrode sizes and interelectrode spacings that are more consistent with known anatomical subregions within target nuclei of DBS therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

DBS array implant locations and orientations in Subjects N and G. (**A**, **D**) The DBS arrays consisted of 8 rows and 4 columns of electrode sites with smaller electrode sizes and interelectrode spacings for the STN-DBS array (**B**, **C**) than the GPe/GPi DBS array (**E**, **F**). Polar plots indicate either stimulus amplitude thresholds to evoke muscle twitches (**B**, **E–F**) or stimulus-induced EMG peak voltages (**C**) when stimulating through electrodes along a single column. In the latter case (**C**), a higher level on the polar plot corresponds to a stronger EMG response. Dashed lines on the polar plot indicate that a maximum current threshold could not be found to elicit a movement.

Figure 2.

Comparison of peak low beta band (12–20 Hz) power amongst resting state LFP recording montages. Example monopolar and bipolar row subtraction recordings (**A**) and power spectra (**C**) from one column of DBS array electrodes in Subject N in the naïve condition. (**B**, **D**) Reanalysis of the same recordings using dual-row averaging to create grouped macroelectrodes. (**E**) Summary comparison of peak beta band (arrow, 18 Hz) power for bipolar recordings and common average referenced recordings using either individual electrode pairs or grouped macroelectrode pairs.

Figure 3.

Spatial ‘fingerprints’ of averaged resting state low beta band (12–20 Hz) power amongst DBS arrays. Average row-subtracted bipolar low beta band power contour maps for (A–B) STN-DBS arrays and (C–D) GPe/GPi-DBS arrays in Subjects N and G in the naïve and parkinsonian conditions. Cross-hatched locations on the contour map indicate locations where non-functional sites precluded calculation of bipolar recording montages. Contour line values are in dB.

Figure 4.

Spectrogram analysis of DBS array recordings in the context of a voluntary reach task. **(A)** An example of bipolar spectrograms derived from the grouped macroelectrode montage **(B)** on the GPe/GPi-DBS array in Subject G in the parkinsonian condition. **(C)** The corresponding bipolar spectrograms from individual electrodes calculated from row subtraction. **(D)** Summary standard deviation maps of the z-score difference between bipolar pairs of individual electrode spectrograms and the corresponding grouped macroelectrode spectrograms for all DBS arrays in both naïve and parkinsonian conditions.

Figure 5.

Effects of bipolar electrode referencing on resting state and reaching task LFP recordings.

(A) Montages including row and column subtraction. (B) Examples of resting state power spectra for row and column bipolar LFPs from both DBS arrays in Subject N in the naïve condition. (C) In the resting state across all DBS arrays, peak beta band power did not differ between naïve and parkinsonian conditions. (D) Example of z-scored spectrograms across subsets of electrodes on the GPe/GPi-DBS array and the STN-DBS array in Subject N while in the naïve condition. (E) Resulting difference of z-score standard deviation maps between row and column bipolar LFPs. (F) Summary of all differences in z-score standard deviation maps for both subjects, both DBS arrays, and naïve and parkinsonian conditions.