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Cortical magnetoencephalography of deep brain stimulation for the treatment of postural tremor

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Abstract

The effects of deep brain stimulation (DBS) on motor cortex circuitry in Essential tremor (ET) and Parkinson's disease (PD) patients are not well understood, in part, because most imaging modalities have difficulty capturing and localizing motor cortex dynamics on the same temporal scale as motor symptom expression. Here, we report on the use of magnetoencephalography (MEG) to characterize sources of postural tremor activity within the brain of an ET/PD patient and the effects of bilateral subthalamic nucleus DBS on these sources. Recordings were performed during unilateral and bilateral DBS at stimulation amplitudes of 0 V, 1 V, and 3 V corresponding to no therapy, subtherapeutic, and therapeutic configurations, respectively. Dipole source localization in reference to the postural tremor frequency recorded with electromyography (EMG) showed prominent sources in both right and left motor cortices when no therapy was provided. These sources dissipated as the amplitude of stimulation increased to a therapeutic level ($p=0.0062$). Coherence peaks between the EMG and MEG recordings were seen at both 4 Hz, postural tremor frequency, and at 8 Hz, twice the tremor frequency, with no therapy. Both peaks were reduced with therapeutic DBS. These results demonstrate the capabilities of MEG to record cortical dynamics of tremor during deep brain stimulation and suggest that MEG could be used to examine DBS in the context of motor symptoms of PD and of ET.

Keywords

Parkinson's disease; Essential tremor; magnetoencephalography; deep brain stimulation

Introduction

Postural tremor is a prominent clinical motor sign, which is present in patients with Essential tremor (ET) and Parkinson's disease (PD). It is characterized by oscillations of the body, usually the limbs, while voluntarily maintaining a position against gravity, but not while making a dynamic movement (1). Postural tremor is thought to stem from abnormal oscillations in the cerebello-olivary circuits that propagate through the thalamocortical

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circuit and on through the spinal cord (2). Deep brain stimulation (DBS) in the vicinity of the subthalamic nucleus (STN) has been proven to be highly effective at relieving postural tremor in PD patients (3), in ET patients (4), and in patients with a combination ET/PD (5). STN-DBS is known to decrease the amplitude of postural tremor in PD patients (6), presumably through modulation of the cerebello-thalamic tract and ensuing changes in motor cortex activity (4). However, the involvement of motor cortex as a source or relay of postural tremor oscillations is still a matter of debate. Coherence between epicortical recordings and electromyography (EMG) of tremor have been observed in non-human primates (7) and humans (8), but other studies have not corroborated these results (9).

Magnetoencephalography (MEG) is a non-invasive imaging modality well-suited for studying oscillatory activity in the brain and its coherence with postural tremor due to the technique's excellent temporal resolution (ms) and spatial resolution (on the scale of fMRI) (10). Because no power is transmitted from the coils to the brain, MEG also has the potential for studying oscillatory activity in the brain during the delivery of DBS therapy. Only a few studies to date have used whole-brain MEG while delivering DBS therapy to a patient. Kringelbach, et al. reported a case study of a patient with unilateral low frequency DBS for pain and found significant changes in the areas known to be associated with pain (11). Ray, et al. reported another case study with high frequency DBS for cluster headache and found a correlation between pain scores and MEG imaging (12). Airaksinen et al. studied the effects of high frequency DBS in PD patients with MEG and used spatiotemporal signal space separation to remove external noise and internal cortical sources, but they did not specifically investigate the effects of DBS on tremor or other parkinsonian motor signs (13).

To further define the role of motor cortex in postural tremor, we performed simultaneous whole-head magnetoencephalographic and upper limb electromyographic recordings in a patient with ET/PD and bilateral STN-DBS implants. Recordings were performed in the off, unilateral, and bilateral on-stimulation conditions, which provided a means to investigate oscillatory processes associated with postural tremor at different levels of tremor severity and stimulation parameters in the same patient.

Methods

Magnetoencephalography

All MEG recordings were performed in an electro-magnetically shielded room using a 148 dense-array channel whole head Magnes 2500 WH system (4D Neuroimaging, San Diego, CA). Recordings were sampled at 2.0345 kHz and band-pass filtered between 0.1 and 400 Hz. A calibration recording was taken with a phantom head model and no electromagnetic source inside the MEG scanner. To characterize the electro-magnetic artifact of a stimulated DBS lead in the MEG head unit, a control experiment was performed from a standalone 4 channel DBS lead immersed in a beaker of saline (0.9% NaCl) and positioned within the MEG head unit. The lead extension cable was connected to an implantable pulse generator (IPG, Medtronic Itrel II) positioned outside of the head unit and on the patient table in a location consistent with the relative IPG location had a patient been present in the scanner. Each trial lasted 120 s with the following DBS parameters: contact 2 cathode, contact 1 anode, frequency 136 Hz, pulse width 90 μ s, amplitude 0–3 V.

These data provided an analytical basis by which to understand simultaneous whole-head MEG from an Essential tremor (ET) / Parkinson's disease (PD) patient with bilateral DBS leads in the left and right subthalamic nuclei for the management of refractory postural and resting tremor (IPG, Medtronic Soletra). The patient's motor symptoms were evaluated off stimulation and with bilateral therapeutic stimulation using selective motor scores from the Unified Parkinson's Disease Rating Scale (UPDRS, Table 1). The patient had a 50-year

history of action-postural bilateral upper limb tremor diagnosed as Essential tremor. However, the patient had developed parkinsonian motor signs including bradykinesia, muscle rigidity, and severe rest tremor over the last 10 years. His complex tremor became functionally disabling over the last five years and required treatment. Anti-tremor and dopaminergic medications were only mildly effective at treating the rest and postural tremor, which prompted the bilateral implantation of STN-DBS leads in order to better control both postural and resting tremors as well as other parkinsonian motor signs. At the time of the study, the patient had not been on any anti-tremor or dopaminergic medication for at least 24 hours.

An initial baseline MEG recording was performed on the subject with both stimulators turned off and with surface EMG electrodes placed on the patient's forearms to measure upper limb tremor. Subsequent trials were recorded with unilateral and bilateral stimulation at subtherapeutic and therapeutic levels, corresponding to 1 V and 3 V respectively, with the following DBS parameters: contact 2 cathode, contact 1 anode, frequency 136 Hz, pulse width 90 μ s. After reprogramming the IPG, trials were separated by at least 10 minutes. During each trial, the patient rested his arms at his side for 120 s and then postured his arms above his chest for 60 s. The study was approved by the local ethics committee, and the subject provided written informed consent for the research and publication of the study.

Imaging Co-Registration

Prior to the MEG recording session, volume acquisition MRI of the subject's brain was acquired at 3T using a spoiled gradient recovery series scan format. In preparation for the MEG recordings, the patient's 3D head shape was digitized, and indicator coils were placed on the left and right preauricular points and on the nasion point. Head position relative to the MEG sensor arrays was measured prior to each recording trial. Offline, data was imported into Neuroscan Curry 6 where the MR images and MEG array were aligned to the head coordinate system. A boundary element model (BEM) was automatically created from the MRI, segmenting the skin, outer skull, and inner skull into three surfaces with 5027 nodes and 10,042 triangles. Conductivity values were set to 0.33, 0.0042, and 0.33 S/m, respectively. The outer surface of the cortex was segmented and modeled with conductivity 0.33 S/m.

Data Pre-processing

Signal artifacts from line noise, the DBS device, and movement by the patient were removed from the data. The benchtop experiment was performed to 1) isolate the electromagnetic artifacts generated from the DBS pulse generator and detected through the extension cable and DBS lead and 2) investigate pre-processing techniques that could remove the stimulation-based artifacts. In Matlab, a fourth order butterworth notch filter was applied at 60 ± 2 Hz to remove line noise. Each channel of data was visually inspected and those channels that failed were removed from subsequent analysis. The remaining channels were high-pass filtered with a fifth order butterworth filter (cutoff 0.5 Hz) to remove baseline drift. A spectrogram of the data was then calculated and epochs containing transient frequency peaks were identified as those having amplitude greater than three standard deviations above the recording session mean at that frequency. Those epochs were removed before further processing. The same pre-processing was applied to the patient data. In addition, the patient data was common average referenced to remove global activity that could be caused by external noise sources. Previous authors have used other pre-processing techniques such as independent component analysis to remove eye blink, heartbeat, and head movement artifacts, but these were minimal in our MEG data set after removal of the contaminated epochs (14, 15). Heartbeat artifacts in EMG recordings were removed using a template-based subtraction algorithm.

Time-frequency analysis: Power spectra and Coherency

The time-frequency analysis was performed in Matlab using Chronux (<http://chronux.org/>) and FieldTrip (14) toolboxes. The overall data of length M samples was windowed into segments with length $K=M/5$ and 10% overlap (length $R=K/10$) yielding $L=41$ windows. Power spectra were calculated for each window using the continuous multi-taper method, with padding to the next highest power of 2, 5 tapers, and time-bandwidth product one half the length of the segment. The results were averaged across the windows. In addition, Jackknife error bars were calculated with a p-value of 0.05. Frequency-wise student's t-tests were performed on the power spectra to identify frequency bands that were statistically different between cases. Spectrograms were calculated based on the entire length of data using the continuous multi-taper method, a moving window of length 10 s with a 1 s overlap, and parameters similar to those used for the power spectra. Coherence was calculated based on the method outlined by Halliday et al. with frequency resolution 0.25 Hz, obtained by windowing the data into $L=12$ windows and padding to the next highest power of 2 (16). The results were smoothed with a 4-sample moving average window. To determine the statistical significance of coherence, we assumed the two signals were independent and calculated the 95% confidence limit $1-\alpha^{1/(L-1)} = 0.2384$.

Dipole fitting

Source localization was performed in Neuroscan CURRY 6 software. A band pass filter was applied between 3 Hz and 6 Hz to both MEG and EMG signals to isolate the tremor-related activity. A single oscillation of postured tremor EMG from peak-to-peak was used as a template waveform. The data was triggered into epochs with amplitude and correlation 90% similar to the template. Each epoch corresponded to a single tremor oscillation. Fixed dipoles were applied to the entire oscillation using the multiple signal classification (MUSIC) method and a patient-specific BEM volume conductor (17, 18). The dipole locations were fixed, as individual parts of the cortex are assumed to be activated at different times. The MUSIC algorithm has the ability to fit multiple dipole sources from a set of signals recorded from an array of sensors, and assumes the sources are independent. In general, the first dipole represented the location of the dominant source of activity for that oscillation, and any subsequent dipoles were not well localized. Events were categorized based on the location of the first dipole (left or right hemisphere), and epochs were averaged within the category. Fixed MUSIC dipoles were applied to the left-average and right-average epochs, resulting in the locations of dipoles triggered to the EMG activity. 95% confidence intervals were calculated in three dimensions around the dipole source location, yielding confidence ellipsoids. These ellipsoids represent the localization accuracy, as a low signal-to-noise ratio would result in a large confidence interval. An analysis of variance (ANOVA) regression model was used to analyze the statistical significance of therapy level, lateralization of therapy, and the interaction between level and lateralization on ellipsoid volume. The Tukey HSD post hoc test was applied to analyze the individual effects of different therapy levels.

Results

Characterization of DBS Artifacts

Magnetic fields generated within the brain are known to be on the order of femto-Tesla, which requires very low magnetic and electrical noise environments during MEG acquisition (10, 19). A phantom head model with a bipolar stimulation-configured DBS lead was imaged inside a MEG head unit such that the electromagnetic artifacts from the stimulation could be visualized independent of any patient-related brain activity and biological artifacts including movement, heartbeat, and eye blinking. With the phantom head model, the 136 Hz bipolar DBS signal dominated the MEG sensor recordings and could be

directly visualized (Figure 1A). As the amplitude of the stimulation increased, the amplitude of the recorded MEG signal also increased at the stimulation frequency (136 Hz, Figure 1B).

Time varying artifacts from the DBS device were also apparent in the MEG data. An initial DC offset and baseline drift was present from the MEG scanner itself and was removed with a high pass filter at 0.5 Hz. The data also contained transient artifacts, which were visualized as bursts with amplitude greater than three standard deviations from the mean. The data was epoched around the artifacts, and these epochs were removed from subsequent analysis. Stimulation artifacts at low frequencies were minimal during high frequency stimulation across a range of stimulation amplitudes (Figure 1C). However, a spectral peak was present throughout the entire recordings at 25 Hz across all stimulation amplitudes for both 1365 Hz and 185 Hz stimulation pulse trains, was visible when the IPG was set to 0 V (dark blue trace), but was not detectable when the DBS lead was removed from the phantom head model (green trace). It should be noted that these low frequency artifacts were six orders of magnitude smaller than the MEG recordings from the patient (Figure 1D,E). Thus, these results suggested that recording oscillatory brain activity in the low frequency band (<25 Hz) with MEG should be possible in patients with DBS implants stimulated at 136 Hz.

Therapeutic Effects of DBS

During the patient MEG scans, tremor activity was simultaneously recorded using electrodes placed on both forearms. The therapeutic effects of particular DBS settings could be correlated to the amplitude of tremor oscillations recorded by these electrodes. Traces of upper limb tremor activity showed increased 3–5 Hz spectral power when the patient postured his arms compared to at rest and an increase in peak tremor frequency from 3.9 Hz at rest to 4.4 Hz while posturing (Figure 2A). There also was a significant decrease in 3–5 Hz spectral power as DBS therapy level increased from off-stimulation and subtherapeutic-stimulation to therapeutic stimulation settings.

Spectrograms of the EMG recordings showed that while the spectral tremor frequency varied little over each recording session for rest or postured states (Figure 2B–C), spectral power at these frequencies fluctuated considerably during each recording session (Figure 2C). The non-stationarity visible in the spectrogram correlated with observations of fluctuating tremor severity noted during post-hoc video analysis of the patient in the MEG scanner room. Video analysis was also used to define epochs in which the patient exhibited voluntary movement during the recordings. These epochs were removed from the data set, and represented less than 50% of the recordings. Taking the power spectra of the EMG recordings revealed that the patient's resting and postural tremor were centered at 3–5 Hz, with harmonics visible at 7–9 Hz and 11–13 Hz (Figure 2D–E). As the amplitude of stimulation increased from 0 V to 1 V to 3 V, the EMG signal power in the 3–5 Hz tremor band decreased. At rest, therapeutic DBS settings (3 V) resulted in a significant reduction in EMG power between 3–5 Hz as compared to the case of subtherapeutic DBS (1 V) (Student's t-test, $p=0.0062$) and off-DBS (0 V) ($p=0.0098$). The off and subtherapeutic cases did not show a significant difference in 3–5 Hz EMG power ($p=0.2128$). With postural tremor, there was statistical difference between the off and subtherapeutic cases ($p=0.0212$) and between the off and therapeutic cases ($p=0.0076$) in the postural tremor band 3.5–5.5 Hz. There was also a significant difference between subtherapeutic and therapeutic stimulation in a narrower postural band (3.5–4.5 Hz, $p=0.0318$). EMG recordings were consistent with previous findings that posturing can exacerbate upper limb tremor (1, 20), as shown by the increased power in the postured spectra compared to the rest spectra. The power spectra confirm that 1 V stimulation produced subtherapeutic effects and 3 V stimulation produced therapeutic effects on both rest and postural tremor. In the remainder of the study, we focused our analysis on postural tremor given its larger EMG amplitudes.

Cortical-Tremor Related Activity

After confirming that the EMG recordings showed therapeutic changes in tremor symptoms with DBS, we investigated if these changes were associated with modulation of oscillations within cortex. MEG data were band-pass filtered for all channels between 3–6 Hz and triggered to each EMG oscillation from peak-to-peak. The triggered events were averaged, and fixed MUSIC dipoles were fitted using a BEM head model (Figure 3). For the trial with no stimulation, dipoles fitted to the triggered data localized to both left and right hand motor cortices. The 95% confidence ellipsoids for these dipoles were small (left volume 0.1 mm³, right volume 1.7 mm³), indicating that there was a strong source at these locations. The same technique was used for all other trials. When stimulation was unilateral, the off side continued to show a dipole over the motor cortex with small confidence ellipsoids. With unilateral subtherapeutic stimulation, the ipsilateral dipole was located near the hand representation of motor cortex, but the confidence ellipsoids were expanded to other areas of cortex (left volume 4.4 mm³, right volume 4 mm³). With unilateral therapeutic stimulation, the ipsilateral dipole was difficult to localize. When present, it was not centered over motor cortex and the confidence ellipsoids were diffuse (left volume 14.3 mm³, right volume 23.5 mm³). Similar effects were seen in the bilateral case to the unilateral case, but the expansion in confidence ellipsoids seemed to be amplified in the bilateral case (subtherapeutic: left volume 12.2 mm³, right volume 8.4 mm³; therapeutic: left volume 81.5 mm³, right volume 44.3 mm³). A large confidence ellipsoid indicates poor localization of a dipole. This was not a result of poor detection of EMG tremor oscillations because even at the most therapeutic settings, EMG peaks could still be identified (Figure 3A) and because the fixed MUSIC dipole algorithm is based only on MEG data. The decrease in tremor amplitude in the EMG caused by DBS therapy was thus associated with diffusing the source within the motor cortex. Postural tremor was significantly reduced at therapeutic levels of DBS, resulting in ellipsoids that covered nearly a quarter of the cortical area and a failure to localize a dipole.

ANOVA showed significant differences in ellipsoid volume with increasing therapy level ($F(2,11)=8.3556$, $p=0.0062$, Figure 4A). The Tukey HSD post hoc test showed significant differences in ellipsoid volume for therapeutic stimulation versus no therapy ($p=0.0058$) and for therapeutic versus subtherapeutic stimulation ($p=0.0286$), but not for subtherapeutic stimulation versus no therapy ($p=0.8013$). ANOVA did not show a significant difference in ellipsoid volume with stimulation side ($F(1,12)=0.1353$, $p=0.7194$, Figure 4B). A two-way ANOVA was used to investigate the interaction effects between therapy level and side on ellipsoid volume. This regression revealed no significant interaction between therapy level and side ($F(2,8)=0.1971$, $p=0.8250$). Therefore, the only variable that accounted for the increase in ellipsoid volume from trial to trial was the increase in therapy level.

Coherence Between Cortical Activity and Tremor in Ipsilateral Cortex

In order to further investigate the relationship between postural tremor and cortical activity, we analyzed the coherence between the two signals. The six sensors closest to the dipoles localized previously in the bilateral off case were chosen to represent motor cortex activity, and coherence was averaged across these sensors (Figure 5A). When both stimulators were turned off, there were significant peaks in the coherence in the 3–5 Hz tremor band and at twice the tremor frequency in the 7–9 Hz band. The effect of unilateral stimulation was analyzed by examining the sensors around the left dipole during stimulation from the left IPG (Figure 5B). The peaks in both bands were present with subtherapeutic stimulation, but the amplitudes dropped below significance with therapeutic stimulation. The effect of bilateral stimulation in the left and right motor cortices was also investigated (Figure 5C–D). As was seen in the unilateral case, subtherapeutic stimulation did not change the coherence between EMG and MEG in the motor cortex, but therapeutic stimulation abolished this

coherence. This decrease in coherence could account for the inability to localize a dipole in the motor cortex ipsilateral to stimulation.

Discussion

In this study, we have investigated the cortical pathophysiology of postural tremor in a patient with ET/PD and with bilateral STN-DBS implants. We first determined the feasibility of imaging a DBS device in a whole-head MEG scanner using a head phantom. Then we examined the role of motor cortex in postural tremor in a patient with ET/PD who was treated with bilateral STN-DBS. Tremor activity was characterized using time-frequency analysis and a dipole source was localized to the motor cortex. Coherence between MEG and EMG showed peaks at the tremor frequency and twice the tremor frequency, and therapeutic stimulation eliminated this coherence.

Cortico-muscular coherence has been used as a measure of connectivity between an oscillatory source in the brain and tremor (21). Previous studies have used MEG to demonstrate an overall increase in the correlation of power spectra between different frequencies in PD patients compared to healthy controls (22). Another study used MEG to show coherence between motor cortex activity and EMG recordings of rest tremor in PD patients (23). Rhythmical firing in motor cortex corresponding to tremor frequencies is still present after deafferentation of the limb, suggesting that oscillatory activity in the motor cortex is not epiphenomenal (24). However, not all studies have demonstrated coherence between motor cortex activity and tremor-frequency oscillations (9).

In our study, fixed MUSIC dipoles triggered to postural tremor were localized to both left and right motor cortices. The tremor signals were extracted from the MEG sensors closest to these dipoles, and coherence analysis showed that the dipoles were correlated with increases in coherence between cortical and muscular activity during tremor. With therapeutic DBS settings, this coherence was reduced, which was reflected in an inability to localize a dipole within the brain. This evidence supports the hypothesis that pathological postural tremor in ET/PD is coherent with oscillatory activity in the motor cortex. Further, deep brain stimulation therapy in the STN was shown to reduce tremor symptoms, which corresponded to a reduction in coherence between the motor cortex and upper limb tremor. This does not prove that the motor cortex is a source of tremor generation, but suggests that it is a part of the tremor pathway that is modulated by DBS.

The results also show cortico-muscular coherence in postural tremor, which disagree with the findings in (9). Both cases examined postural tremor, here in an ET/PD patient and previously in an ET patient. The pathophysiology of the two diseases is not the same, which could account for discrepancies in the results, as other studies have shown coherence in patients with PD (27). The previous study also used a single channel gradiometer over the hand area of motor cortex, while our study used whole-head MEG. The whole-head system gives a wider view of the activity in the brain, allowing for imaging of other motor and sensory areas in the cortex. It is possible that tremor cortico-muscular coherence was located in a cortical area around but not in hand motor cortex, which was not recorded in their study.

Previous studies have found that coherence between rest tremor and motor cortex activity was most significant at double the tremor frequency (~8 Hz) in PD patients off dopaminergic medication (28). These results align with the coherence data in our study in which changes in DBS therapy level modulated the power in the 7–9 Hz band in addition to the 3–5 Hz band. Coherence at the tremor frequency and the first harmonic have been shown previously from EEG recordings over the hemisphere contralateral to tremor (29). These results may stem from low-pass filter properties present between the motor cortex and

muscles as shown in parkinsonian vervet monkeys with prominent tremor (30). Similar effects are present in coherence between local field potentials and EMG in tremor-dominant PD patients, but further analysis is necessary to determine if coherence at double the tremor frequency is due to a separate source or simply a harmonic (31).

Our study was subject to several limitations. Since we report on a single patient, we cannot infer that localization of a tremor source to motor cortex will apply to all cases of postural tremor. This is especially true because the patient had combination ET/PD, which could result from a separate pathophysiology from others with only ET or PD. Tremor of the head may also lead to deviations in the MEG recordings. In this study, the head location was measured prior to each trial but not continuously throughout the trial. Review of video taken during the MEG scans did not show significant head tremor. However, if head tremor was present, it would be more significant in the trials without DBS, resulting in movement artifacts and decreased signal-to-noise ratio. However, the best dipole localization was found in the cases where significant tremor was present, supporting the assumption that the patient's head did not move during the recordings.

The EMG recording technique used here resulted in a bilateral measure of overall tremor activity, meaning the left versus right tremor could not be compared. Therefore, coherence was only evaluated in the cortex ipsilateral to DBS therapy, as the effect of DBS in the contralateral cortex is not well established. The resulting EMG recorded overall limb movement similar to an accelerometer signal. Previous studies have shown that kinematic limb recordings are a functional substitute for electromyographic recordings, and both are similarly correlated with motor cortex activity during movement (32).

Concurrently recording cortical activity during DBS is difficult given the incompatibility of most functional imaging modalities with stimulating hardware (33, 34), the susceptibility artifact arising from the stimulation lead (35), and the prominence of stimulation artifacts within the acquired signals (36). In some cases, these problems can be avoided by investigating the residual effects of DBS immediately after stimulation is turned off, or by selecting patients with minimal artifacts due to ideal lead wire placement (37). Here, MEG imaging of a DBS lead in a phantom head model showed DBS created artifacts in the beta frequencies (25 Hz) and at the stimulation frequency (136 Hz). The most salient artifact at 25 Hz was independent of stimulation amplitude and continuous throughout the entire recording, suggesting that it was due to a clocking mechanism within the IPG itself. Importantly, however, the power of the low-frequency signal artifact recorded during DBS in the phantom head model was six orders of magnitude smaller than those signals recorded from the patient. In theory, there should be little to no 25 Hz artifact visible in the human data, which was consistent with the patient recordings. However, one should be aware that different models of stimulators might have different characteristic artifacts.

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Figure 1.

Characterization of MEG recording artifacts detected during DBS. *A*: Examples of 50 ms duration raw traces of single-channel MEG scans recorded at increasing amplitudes of DBS from 0 V to 2 V. The traces shown are from gradiometers A65 and A56, corresponding to sensor locations nearest to the right and left motor cortices. *B*: Power spectra of gradiometer A56 with phantom alone (green) and with DBS at various amplitudes at the stimulation frequency (136 Hz). Inset of *B* shows power at ~136 Hz increases with stimulation amplitude. *C*: Power at low frequencies at different amplitude and frequency settings. *D*: Power spectra of gradiometer A75 in the patient around the stimulation frequency (136 Hz). As in *B*, inset shows power at 136 Hz increases with stimulation amplitude. *E*: Power of low

frequencies in the patient at different amplitude settings. Note the power in the low frequencies of DBS alone is substantially less than that observed during the patient MEG recording.

Figure 2. Characterization of the effects of DBS therapy on rest and postural tremor. *A*: Traces of filtered EMG activity during rest and postural tremor recording sessions at varying therapy levels. *B–C*: Spectrograms of rest and postural tremor, respectively, over the entire length of the MEG recording sessions at varying therapy levels. *D–E*: Power spectra of rest and postural tremor, respectively, with both DBS turned off (blue), at subtherapeutic (red), and at therapeutic (black) levels. The shaded areas indicate 95% confidence intervals.

Figure 3.

Source localization of EMG activity in the MEG recordings. *A*: MEG and EMG data for a single tremor oscillation. *B*: The BEM model used for dipole localization used three layers: skin (pink wireframe), outer skull (grey wireframe), and inner skull (black wireframe). The model was co-localized with the MEG sensors (blue circles). Tremor-related dipoles are displayed on the MRI-based 3D reconstruction of the patient's cortex (grey). The centers of the dipoles (left red and right blue poles) are located near motor cortex, and the ellipsoids show 95% confidence intervals around the dipoles. *C*: Both left and right IPGs off. Subtherapeutic stimulation settings on the *D*: left lead, *E*: right lead, and *F*: both leads. Therapeutic stimulation settings on the *G*: left lead, *H*: right lead, and *I*: both leads.

Figure 4.

Statistical analysis of variations in ellipsoid volume. *A*: The boxplot of ellipsoid volume versus therapy level showed that the mean and standard deviation of ellipsoid volume increased as therapy level increased, with statistically significant differences between off and therapeutic stimulation ($p=0.0058$) and between subtherapeutic and therapeutic stimulation ($p=0.0286$). *B*: The boxplot of the ellipsoid volume versus therapy side showed no statistical difference between left and right sides ($p=0.7194$).

Figure 5.

Coherence between MEG and EMG activity in the cortex ipsilateral to stimulation. *A*: Gradiometers are overlaid on the reconstructed cortex. Coils shown in red are closest to dipoles localized in the bilateral off state and are representative of coherence in the motor cortex. *B*: Average coherence across the six sensors closest to the dipole localized in the left hemisphere (*A top*). There were significant peaks in coherence in the off case (blue) in the 3–5 Hz band and the 7–9 Hz band, which remained in the unilateral left subtherapeutic case (red), but decreased below significance in the left therapeutic case (black). *C*: Average coherence across the sensors in *A top* for the bilateral stimulation cases. With bilateral subtherapeutic stimulation, there was a significant coherence in the 7–9 Hz band but not in the 3–5 Hz band (red), and there was no significant coherence with therapeutic stimulation (black). *D*: Average coherence across the six sensors closest to the dipole in the right hemisphere (*A bottom*). With bilateral subtherapeutic stimulation (red), there were significant coherence peaks in the 3–5 Hz and 7–9 Hz bands, but there was no significant coherence with therapeutic stimulation (black). Dotted lines show the 95% confidence level.

Table 1

Selective UPDRS Scores On/Off STN-DBS

	Bilateral OFF		Bilateral ON	
	Left Score	Right Score	Left Score	Right Score
Tremor at rest	4	4	3	2
Action or postural tremor of hands	4	4	1	1.5
Rigidity	1	2	0	0
Finger tapping	2	3	1	0.5