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Intraoperative *Macroelectrode* Local Field Potential Recordings in Essential Tremor

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Abstract— **Essential Tremor (ET) is a common movement disorder involving the presence of action tremor. While there are pharmacological treatment options, Deep Brain stimulation (DBS) of the ventral intermediate nucleus (VIM) of the thalamus is an effective and widely used surgical therapy for those patients who are intolerant of, or whose tremor is unresponsive to, medications. In this study, we recorded local field potentials (LFPs) at various depths along the trajectory to Vim in three ET patients. LFP recordings at various depths were processed by a PCA based de-noising method to remove ECG artifacts. The spectral characteristics of LFPs were investigated via frequency-vs-depth maps using a modified Welch periodogram using robust statistics, and further analyzed within different sub-bands to determine whether LFP activity encodes characteristic patterns for the identification of disease-specific subcortical areas. Our results demonstrated that a median-based spectrum estimation approach eliminates outliers better than the traditional averaging technique by preserving band-specific LFP activity. Results indicate that there was clear oscillatory beta activity around 20 Hz in two subjects. One patient displayed relatively high gamma (40 Hz) activity in the sub-thalamic region. In conclusion, despite the small number of subjects, the present study adds to existing knowledge about LFP-based pathophysiology of ET and its target-based spectral activities.**

I. Introduction

Essential Tremor (ET) is a common movement disorder involving the presence of action tremor. The pathophysiology of essential tremor, however, remains poorly understood. Preliminary studies suggest the presence of abnormally synchronized neural oscillations in the inferior olivary nucleus, usually at 4-12 Hz, which are transmitted via Purkinje cells to the dentate and interpositus nuclei, and subsequently to the Ventral intermediate nucleus of the thalamus (Vim) and cortex via ascending fibers [1]. These abnormally synchronized neurons are believed to influence cortical output to the spinal cord, resulting in tremor. While there are pharmacological treatment options, Deep Brain stimulation (DBS) targeting Vim has proven an effective treatment, and is in widespread use for patients who are intolerant of anti-tremor medications or whose tremor is refractory to these agents [2].

DBS involves the surgical implantation of a macroelectrode into a specific brain target, and the subsequent chronic stimulation of the target to influence neural activity and thereby ameliorate symptoms. For essential tremor, Vim is the target of choice based on its importance anatomically in the aforementioned tremor circuit. Other targets are under investigation including the posterior subthalamic area (PSA), which contains significant cerebellothalamic connections [1]. Vim is localized intraoperatively via a combination of indirect targeting using consensus coordinates on stereotactic imaging and physiological corroboration using micro-electrode recording and/or macrostimulation through the implanted DBS electrode to look for stimulation-induced benefits and side-effects. This combination of preoperative stereotactic MRI scan and intraoperative recording of single neuron activity via a microelectrode have allowed neurosurgeons to identify the location of the target.

More recently, however, research has suggested that alterations in patterns of neural oscillatory activity in local field potentials (LFP; summed activity of populations of neurons) may play a role in the pathophysiology of various neurologic disorders, including essential tremor [3]. Specifically, oscillatory activity from 8 to 27 Hz has been found in Vim of ET patients, and this band has been found to be coherent with activity in both the ipsilateral sensorimotor cortex and the contralateral muscles [4]. Moreover, low frequency theta (4-7 Hz) and alpha (8-12 Hz) band oscillatory activity has also been recorded in Vim in ET patients [3]. Taken together, these studies suggest the pathophysiology of ET may be more complicated than the simple historical model of the anatomic propagation of abnormal oscillation generated in the inferior olivary nucleus. Additionally, characteristic LFP patterns in Vim may provide neurosurgeons with a novel and possibly more reliable method of localizing Vim than imaging and microelectrode-based targeting.

In this study, we aimed to further our understanding of target localization and the ET pathophysiology by analyzing LFPs at multiple frequency bands, recorded by a macroelectrode at various depths along the trajectory of a DBS electrode during surgery for electrode implantation in Vim.

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II. METHODS

A. Patients and surgery

Three patients provided informed consent and, with approval of the University of Minnesota Institutional Review Board, were enrolled in this study. All study subjects carried a diagnosis of ET, and discontinued tremor medications 12 hours prior to surgery, per routine clinical protocol. As a standard clinical routine for target localization, microelectrode recordings (MER) from three different tracks were simultaneously recorded. A stereotactic MRI was fused to a stereotactic CT on a neuronavigational platform (StealthStation, Medtronic Corp, CO) were used, along with consensus target coordinates, for initial target localization and trajectory planning. Following implantation of micro electrodes and recording of single-unit activity by using a Neurodrive and Microguide system (AlphaOmega Inc., USA), DBS macroelectrodes (model # 3387: Medtronic Corp, Fridley, MN) were bilaterally implanted into the Vim in each patient. Each DBS electrode has four platinum–iridium rings with 1.5 mm length and 1.5 mm inter-contact separation that makes the entire electrode 12 mm in length (Fig.1A).

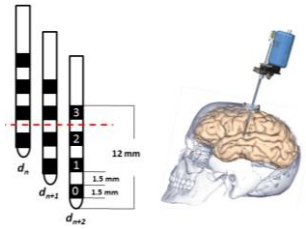

Fig.1. (A) DBS electrode (model #3387: Medtronic Corp, Fridley, MN) representation at three consecutive depths. The red dash line shows the different bipolar contacts at the same depth. (B) Implantation of macro LFP electrode by neurodrive.

B. Recordings

LFPs were recorded with an XLTEK-EMU128FS system (Natus, San Carlos, California), starting 21 mm above the MER-determined target, and culminating 3 mm below this target. A distance increment of 1-mm was used until reaching the estimated target, as determined by the aforementioned MER recordings. Monopolar LFPs were recorded from each of the four contacts of the macro electrode, along with EKG signal for 30 seconds, at each depth. Signals were sampled at 2 kHz with 16 bit A/D resolution. All raw data channels were high-pass filtered at 0.1 Hz. Signals were transferred into a PC for off-line spectral analysis.

C. Analysis

Before any processing, LFP data were visualized and annotated to distinguish artifact and determine epochs of resting, active, and passive movements in the XLTEK system. Annotated data were then extracted into MATLAB (Mathworks, Natick, Massachusetts) for analysis. The monopolar LFP data were low-pass filtered using an FIR filter with a 450-Hz cutoff frequency and then down-sampled to 1 kHz to be able to scan a broad band of activity. Down-sampled monopolar signals were converted into three bipolar derivations (Contacts 0-1, 1-2, and 2-3). Visualization of data demonstrated a high EKG influence on the neural data despite the elimination of other sources of artifact. Before eliminating EKG artifact, bipolar signals were filtered with a 2.5 Hz high-pass filter, whereas EKG signals were filtered with 2.5 Hz-to-40Hz band pass filter. For elimination of power line artifacts, 60 Hz and 120Hz notch filters were used. To remove the EKG's influence on neural data, a temporal principal component analysis (PCA) approach was used. The corrupted LFP time series were segmented with tapered cosine windows centered in the peak of the QRS complex obtained from the simultaneously recorded EKG signal. Then, temporal PCA was applied in order to obtain an EKG artifact template through the use of the first Principal Component, which was subsequently subtracted from each window to reconstruct artifact-free LFP recordings. Following artifact removal, LFP data derived from the same depths at each bipolar configuration were combined and processed together.

In order to explore the frequency content of the LFP data at each depth, depth-frequency analysis was generated similar to the well-published time-frequency analysis approach [5]. Despite the prior artifact removal steps, LFP signal corruption was still observable, and attributable by factors such as tremor and/or environmental factors in the operating room. Therefore, the LFP spectrum was computed with a modified Welch periodogram method, including robust statistics. In order to compare the results of two statistical approaches to frequency analysis, a mean operator over different segments and a median operator were individually used. For spectrum analysis, the fast Fourier transform (FFT) was computed with a 1024-sample-length Hanning window, and the window was shifted with 50% overlap. After computing the squared magnitude in each sliding window, mean and median operators were used for the LFP spectrum estimation. For further signal analysis, the median operator was preferred, in order to eliminate outliers. The same procedure was applied to each depth and a single depth-frequency spectrum was generated to dynamically visualize the frequency activity in a depth-based approach in ET.

To better visualize the activity in the frequency regions above the beta band (13-30 Hz) that are usually not well represented in depth-frequency or time-frequency maps due to the 1/f spectral characteristic of many electrophysiological signals, a normalization that tries to compensate for this effect was used. Spectra representing the activity in all depths were averaged to obtain a mean spectrum, which was trend-fitted with an exponential curve. The inverse of this

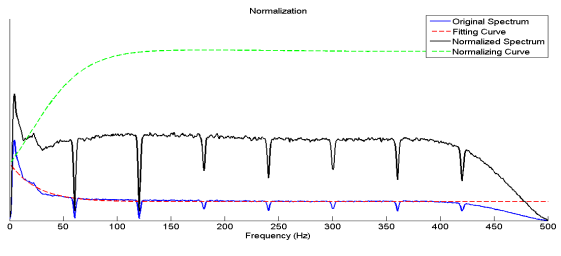

Fig.2. The 1/f Normalization. In blue: The original spectrum, obtained as the average of the spectra at all the depths. In red: the fitting curve (linear combination of two exponentials). In green: the normalization curve, which is the inverse of the fitting curve. In black: the normalized spectrum.

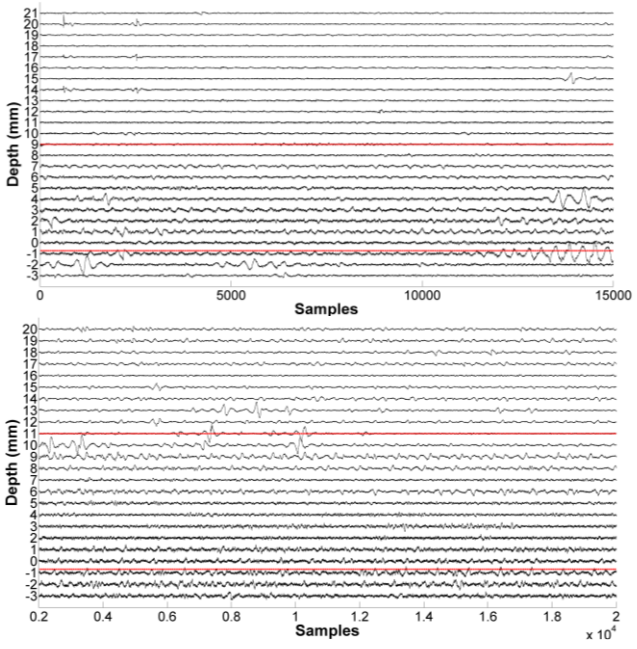

Fig.3. (A) Raw LFP data of the first subject while the electrode moved from 21 mm above the target down to -3 mm below it. (B) Raw LFP data of the second subject while the electrode moved from 20 mm above the target down to -3 mm below it. Red dashed lines show the upper and bottom borders of Vim, respectively.

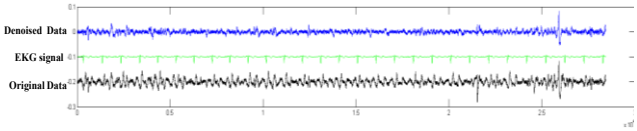

Fig.4. Raw LFP signals of the second patient at certain depth before and after EKG artifact removal.

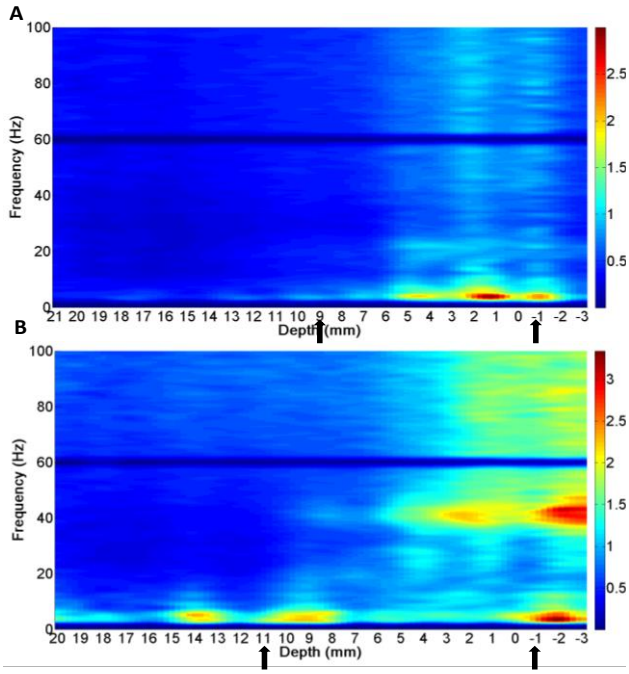

Fig.5. Spectral analysis for two subjects at various depths. Data were high pass filtered at 2.5 Hz. Black arrows show the superior and inferior Vim borders, respectively, from left to right.

fitting curve was then multiplied, point by point, to the single-depth spectra. The result of this procedure was to flatten the spectra with the purpose of making more visible the rising activity of mid- and high frequency regions compared to the surrounding background (Fig.2). Finally, the depth-frequency maps were smoothed using filter with Gaussian kernel.

III. RESULTS

The raw LFP data of two subjects from left Vim prior to artifact removal or application of normalization methods are shown in Fig. 3A-B. Red dashed lines indicate the MER-derived upper and lower borders of Vim, and correspond to the published rostro-caudal extent of the human Vim [Schaltenbrand and Warhen Atlas, 1977]. Typical artifacts which resulted from abrupt movements of the patient and other environmental factors can be seen at higher depths, while EKG-related artifacts are seen at various depths of the LFP signal. Because of the high peak nature of QRS complexes on EKG signals, it was crucial to eliminate these artifacts from the LFP data in order to obtain more informative signals about disease pathophysiology. As the electrode reached a certain depth, high amplitude LFP activity was observed, as well. This amplitude change occurred consistently in all subjects between the MER-identified superior and inferior border of Vim. It should be noted that higher LFP amplitudes were concentrated close to the lower border of the target.

Figure 4 demonstrates raw LFP data recorded in the second subject from left side, at a single depth, prior to and following EKG artifact removal. The temporal PCA-based approach effectively corrected for EKG-related artifacts, however, there remained some non-periodic artifact on the post-EKG period that the algorithm was unable to correct. It is likely that the randomly generated shape and location of these artifacts could not be detected by the algorithm and hence were not removed.

The depth-frequency maps of the two subjects are shown in Fig. 5 A-B. In the first depth-frequency map, high activity at a low frequency band is seen around 1 mm above the estimated target and spread ±3mm of it. There was clear and localized beta activity around 20 Hz, identified in between the MER estimated Vim borders. In the second depth-frequency map, there was localized low-band activity at 14 mm and 9 mm even after artifact removal, and most significantly around -2 mm. Beta activity was similarly seen after 6mm and possibly extended beyond -3 mm. The most novel finding in this analysis was the presence of pronounced 40 Hz gamma (>30 Hz) activity localized to a depth of -2 mm. This activity appeared to continue to increase at depths beyond -3 mm. Interestingly, the onset of the pronounced 40-Hz activity coincided with the optimal depth estimated by MER for DBS implantation in the subject, corresponding to a depth of approximately -0.7mm past the consensus target-derived bottom of VIM.

Finally, Fig.6 shows the comparison of median vs. mean operator in frequency analysis in original and normalized depth-frequency maps for the second subject. The top left graph (A) shows the effect of the median operator which was used to eliminate outliers. There is no obvious activity above 10 Hz at higher depths. The energies are more pronounced in the normalized map, as shown in Fig.6 (B). On the other hand, the mean-operator-based map in Fig.6 (C) shows widespread activity at higher depths with less localized activity at lower frequencies. Because this map averages all frequency values at each depth, it is contaminated by outlier values, such as sharp artifacts. The distribution of activity is clearly seen in the right bottom graph (Fig. 6D).

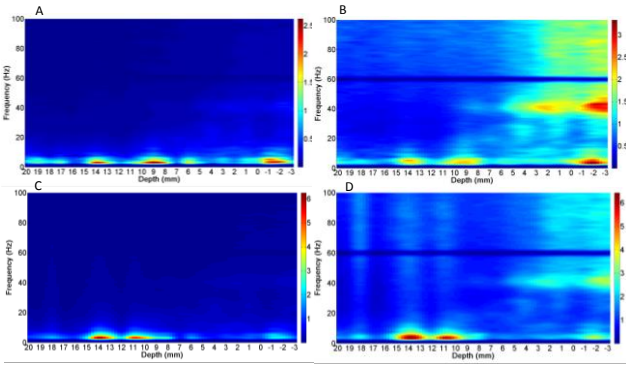

Fig.6. (A) Median operator based depth-frequency analysis for the second subject. (B) Median operator based depth-frequency analysis with 1/f normalization for the second subject. (C) Mean operator based depth-frequency analysis for the second subject. (D) Mean operator based depth-frequency analysis with 1/f normalization for the second subject.

IV. Discussion

The motor thalamus, or Vim, has historically been used as the main target for ablative surgical treatment of tremor, based on the hypothesis that tremor cells are most commonly found in this area [3], and more recently has become the target of choice for DBS in medication-resistant tremor [6]. In the present study, we recorded LFPs at consecutive depths during the implantation of a DBS *macroelectrode* into the Vim, via the DBS *macroelectrode* itself, rather than the typically-used recording microelectrode. We primarily investigated the spectral characteristics of ET. In contrast to prior studies of LFP activity in Vim which focused on demonstrating coherence between [3] oscillatory activity of thalamus and kinetic tremor, we focused on LFPs recorded during the resting state. The main reason of the selection of the resting state was to capture any basal ganglia oscillation in the beta range (13-30Hz), as beta oscillations are known to be suppressed by voluntary movements [7]. In this regard, two of three subjects with ET demonstrated 20-Hz beta activity at similar depth intervals (6 mm to -3 mm) while all patients demonstrated 5-Hz theta-band activity.

Interestingly, similar oscillatory activity in the beta range and tremor frequencies (3-8Hz) are seen in Parkinson's disease, as well [8]. The source of these beta oscillations in patients with movement disorders is still unknown. Whether a common pathophysiological mechanism exists for LFP beta oscillations recorded from the subthalamic nucleus in tremor-dominant Parkinson's disease and beta oscillations in the Vim in Essential tremor remains unknown. Moreover, it is unclear how this abnormal activity relates to tremor generation. These questions need to be studied in detail with larger subject populations.

In addition to the activity at these frequency bands, we also found increased low-gamma (40 Hz) activity in two subjects at lower depths. It has been postulated that different frequency activities may represent different electro-physiological signatures for different movement disorders [7]. It is possible that the 40-Hz activity which we observed is part of the electrophysiological signature of ET. Moreover, as this activity occurred below the MER-defined borders of the Vim, other nuclei—such as the subjacent subthalamic nucleus (STN)—may be involved.

Our results support the possibility that there is a depth-related difference between subjects in spectral scenery. Such differences might account for the observed variability in long-term tremor suppression in patients with ET treated with DBS [9]. Recent studies are investigating the similarities of network pathophysiology between ET and Parkinson's disease [10]. The findings presented here might contribute to this purpose from a spectral perspective.

ACKNOWLEDGMENT

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