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Identification of the subthalamic nucleus in deep brain stimulation surgery with a novel wavelet-derived measure of neural background activity

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Abstract

Object—A wavelet-based measure was developed to quantitatively assess neural background activity taken during surgical neurophysiological recordings to localize the boundaries of the subthalamic nucleus during target localization for deep brain stimulator implant surgery.

Methods—Neural electrophysiological data was recorded from 14 patients (20 tracks, $n = 275$ individual recording sites) with dopamine-sensitive idiopathic Parkinson's disease during the target localization portion of deep brain stimulator implant surgery. During intraoperative recording the STN was *identified* based upon audio and visual monitoring of neural firing patterns, kinesthetic tests, and comparisons between neural behavior and known characteristics of the target nucleus. The quantitative wavelet-based measure was applied off-line using MATLAB software to measure the magnitude of the neural background activity, and the results of this analysis were compared to the intraoperative conclusions. Wavelet-derived estimates were compared to power spectral density measures.

Results—The wavelet-derived background levels were significantly higher in regions encompassed by the *clinically* estimated boundaries of the STN than in surrounding regions (STN: $225 \pm 61 \mu V$ vs. ventral to STN: $112 \pm 32 \mu V$, and dorsal to STN: $136 \pm 66 \mu V$). In every track, the absolute maximum magnitude was found within the clinically identified STN. The wavelet-derived background levels provided a more consistent index with less variability than power spectral density.

Conclusions—The wavelet-derived background activity assessor can be calculated quickly, requires no spike *sorting*, and can be reliably used to identify the STN with very little subjective interpretation required. This method may facilitate rapid intraoperative identification of subthalamic nucleus borders.

Keywords

Subthalamic nucleus; deep brain stimulation; Parkinson's disease; neurosurgery

Introduction

Over the last decade, deep brain stimulation (DBS) of the subthalamic nucleus has become more prevalent and effective as a treatment for the symptoms of Parkinson's disease^{2, 6}. The most challenging aspect of DBS surgery for Parkinson's disease is localizing the correct target for stimulator placement within the subthalamic nucleus (STN), as the structure is very small and obscured by fiber tracts which makes it difficult to image²⁰. Millimeter-level precision in targeting is vital to the procedure, as incorrect stimulator placement leads both to lowered efficacy in symptom alleviation¹² and an increase in detrimental side effects²². Many different groups have concluded that examining the electrophysiological behavior of cells in the vicinity of the image-estimated target using microelectrode recording is vital to achieving the level of targeting accuracy necessary for effective localization due to imaging limitations as well as mechanical imprecision during electrode insertion^{1, 5, 7, 11}. As such, the current standard for target localization is a multi-modal approach that includes using stereotactic atlas coordinates, imaging the brain, estimating the location of the STN in the patient by overlaying the atlas onto the patient's brain image, identifying the boundaries of the pertinent basal ganglia structures using microelectrode recording, and confirming the final electrode placement with intraoperative electrical stimulation^{2, 8, 16, 21}.

This multi-step procedure is effective at localizing the STN, but is also time-consuming and requires that either the surgeon perform several non-surgical tasks (i.e. electrophysiology, operating the stereotactic guidance machine) or that the procedure be performed with a surgery team that includes an attending neurophysiologist. A typical bilateral STN DBS implantation procedure may last around eight hours start to finish, and most of that time is spent localizing the target. Also, though the electrophysiological properties that characterize the STN are well-researched^{3, 8, 17, 19}, interpreting these indicators in the surgical environment is generally a qualitative process based largely on auditory and visual observation. This qualitative nature allows room for interpretive differences in determining exact structural boundaries.

Audio monitoring of the background activity level is used universally to identify the subthalamic nucleus and its environment as the recording electrode moves through STN and neighboring tissues^{3, 8, 17, 19}. By "background activity" we mean the electrical activity between large and obvious action potential spikes, primarily from distant neurons, synaptic activity, and slow wave depolarization. The electrode signal is comprised of large action potential spikes from neurons close to the electrode tip along with a combination of spikes from other more distant neurons, electrical noise arising from synaptic activity and membrane channel opening and closing, and thermal noise in the electrode itself. This total envelope of electrical activity when monitored by an audio amplifier provides a characteristic signal that varies with the environment around the electrode tip. The combinations of features contributing to the characteristic signals are enormous. These

include the morphological features of cells and fibers, the packing density of neurons, dendrites, axons and glia, and the unique membrane characteristics of these elements. Although these morphological and electrical features are great in number such that each brain region might have its own unique signature of sound, they are relatively consistent between individuals because these features are guided genetically. The STN has a higher density of neuronal cell bodies than the structures and fibers that surround it along the recording tracks^{3, 8, 19}, and the neurons in the STN also display a robust increase in activity with multiple units discharging at relatively high frequencies¹⁷. As such, there are both more distant neurons present as well as more neurons firing in the STN, which combine to increase the background activity amplitudes.

Others have noted this phenomenon qualitatively during DBS implantation surgery. The increase in level on the audio monitor has been described along with the recognition that this change is due to an increase in background activity and not simply due to changes in single unit activity (large amplitude spikes of single neurons in the immediate proximity of the electrode)^{3, 8}. The increase in background has been illustrated off-line by capturing oscilloscope tracings and measuring its magnitude^{19, 21}. One group showed that the background neural noise level within the STN increased more than 2.0 fold compared the zona incerta or internal capsule⁹. This background increase also likely plays a large part in why calculating the power spectral density of data recordings along the track has shown some success in identifying the STN¹⁵. In this paper, we introduce a quantitative method to assess this background activity. The method is based on an index computed with a wavelet analysis of electrode signals. The index is robust and readily distinguishes STN and nearby structures. It has the advantage of being able to automatically separate background from large foreground spikes and it lends itself to eventual automation. Automating the micro-electrode recording portion of the targeting process would speed up the procedure, would lessen or remove the requirement of neurophysiological expertise during surgery, and would produce a quantifiable target to place the DBS electrode.

Methods

Data acquisition

Neural electrophysiological data was recorded from 14 patients with dopamine-sensitive idiopathic Parkinson's disease during the target localization portion of deep brain stimulator implant surgery at the University of Michigan. All recordings were taken from patients undergoing bilateral stimulator implantation on the same day. We analyzed neural data and surgery notes offline after surgery.

Intraoperative microelectrode recordings followed procedures described by others⁸. Briefly, conventional single-unit and multiunit extracellular recordings were made in parasagittal trajectories targeting the subthalamic nucleus, using a stereotaxic coordinate system⁸. The recordings were made in tracks based on MRI targeting. Penetration with tungsten microelectrodes (FHC Inc, Bowdoin, ME) proceeded from the ventral boundary of the thalamus through the zona incerta (ZI), the STN, and into the substantia nigra (SNr). The electrical activity detected by the probe was amplified, band-pass filtered (corner

frequencies: 400 Hz, 5 kHz) with an adjustable filter, and displayed during intraoperative recording with a Guideline 3000 (FHC Inc, Bowdoin, ME).

Clinical targeting (Surgery, neurophysiologist identified target)

During intraoperative recording, the STN was identified based on a combination of observations. The primary indicators were the neural firing patterns, displayed visually on a monitor and heard audibly through an audio amplifier and speaker system. Cells in the STN generally produced action potential spikes with higher firing frequencies, more tendency to burst, and characteristic firing rhythms when compared to the structures encountered in the track prior to the STN^{2, 3, 8, 19}. Based on these criteria, the neurosurgeon and attending neurophysiologist made the first approximation of the STN location.

The substantia nigra pars reticulata (SNr) is found immediately ventral to the STN at some locations, and is characterized by single-cell firing patterns (frequency, rhythmicity, sound) that differ from cells in the STN^{3, 8, 17} as well as a distinctive inhibitory pauses in cell firing in response to very low stimulation currents (2 – 5 μ A)⁸. Identifying the SNr when encountered was a useful indicator that the electrode has passed through the lower boundary of the STN.

Offline assessment of background activity measure

The quantitative measures of wavelet-derived background activity (described below) were compared to an offline assessment of notes describing neural activity taken during the surgery and visual records of the firing patterns using Axoscope software (Axon).

Quantifying *background* activity

We adapted specific noise removal techniques (specifically, wavelet transform denoising^{4, 10, 13}) and neural detection methods to quantify the amount of ‘background activity’. The signal energy concentration properties of the wavelet transform allow us to identify and separate large amplitude neural spikes from background noise, then measure the root-mean-squared amplitude of that background and output that as a single identification index. We used data recordings that were 5.0 seconds in duration (sampled at 20 kHz) for this analysis.

Non-parametric methods were used to correlate the background index values with the five demarcations identified along the track. Minima, maxima, mean, and quartile values were calculated for the dataset using SPSS.

For comparison sake, the power spectral density of each record was calculated using MATLAB. Because of the corner frequencies used by the bandpass filtering during data acquisition, the frequency range analyzed was between 300 Hz and 5000 Hz. A power index was calculated as the average power spectral density value between 400 Hz and 2 kHz for each data recording.

Results

Wavelet-derived background activity level vs. depth and clinical STN evaluation

In all, 20 tracks recorded from 14 different patients with clinically identified STN were analyzed ($n = 275$ individual recording sites). With each track, the wavelet-derived background activity amplitudes followed the same pattern. Recordings taken in regions ventral to the thalamus (i.e. ZI) at the beginning of the electrode track had low background activity values. As the electrode moved ventrally toward STN, background levels increased (Figure 1). The quantified wavelet-derived background levels were highest in regions encompassed by the clinically estimated boundaries of STN. The wavelet-derived background activity amplitude values recorded in the clinical STN were significantly higher than those points recorded from regions dorsal (Pre-STN) or ventral (Post-STN) to the clinically-demarcated STN (paired t-test, $p < .0005$). The mean wavelet-derived background magnitude within the STN across all recording passes is $225 \pm 61 \mu\text{V}$ ($N = 134$ STN samples), the mean Pre-STN background is $112 \pm 32 \mu\text{V}$ ($N = 54$), and the mean Post-STN is $136 \pm 66 \mu\text{V}$ ($N = 33$) (Table 1).

In every electrode penetration in which STN was identified clinically, the absolute maximum wavelet-derived background level value was located in that central region of increased background activity. On a per-penetration basis, the vast majority of the highest background values were measured within the clinically identified STN (highest quartile: 92% from STN, 7% from ventral to the STN ("Post-STN"), 1% from dorsal to STN ("Pre-STN")). Similarly, on a per-penetration basis the majority of the smaller background values were measured outside of the STN (bottom quartile: 65% in "Pre-STN", 20% in "Post-STN", 15% in STN). In penetrations where the STN was not encountered, the wavelet-derived background level remained flat (Figure 2). The absolute magnitude of the background in different areas varied from patient-to-patient, but on a case-by-case basis the peak was always in the STN as opposed to the regions surrounding it (Figure 3).

The average normalized difference between the minimum wavelet-derived background value measured within the STN and the maximum measured both dorsal

($\frac{Min_{STN} - Max_{Pre}}{Mean_{recordingtrack}}$) and ventral to the STN across recording tracks are positive values (24.8 and 7.3, respectively). This indicates that on average, a threshold could be set using the wavelet-derived background measure to identify STN boundaries separating it from surrounding structures. On a per-track basis, only 3.6% of the background values measured within the STN were lower than the maximum background value measured dorsal to the STN while 27.7% were lower than the maximum value measured ventral to the STN.

Wavelet-derived background level vs. power spectral density

The use of a power spectral density measure as a means to distinguish the STN from surrounding brain regions in DBS surgery has been recently described¹⁴. There are some similarities between this measure and the wavelet-based background index, as reflected by similarities in some statistics: The maximum power spectral coefficient in each penetration was also localized in the STN, 92% of the upper quartile power coefficient values were

again measured in the STN, and again 15% of the lower quartile values were measured in the STN.

On the other hand, there were two key differences in the measures: variation and overlap. The power spectral density measure displayed more variation than the wavelets-based background measure, perhaps in part because the power spectral density measure is highly influenced by “foreground” spikes, which varies with electrode proximity to the neuron. Our wavelet-derived measure suggests that background activity on its own is less variable. The standard deviation of the power spectral coefficients within the STN was 70% of the mean of all recordings taken along the track, whereas the standard deviation of the wavelets-based background measure was only 21% of the mean ($n = 134$ STN samples, 275 total samples). There was also more overlap between the power spectral coefficients measured within the STN and those measured outside of it than there was with the wavelets-based background measure. The average normalized difference between the minimum power spectral coefficient measured within the STN and the maximum measured ventral to the STN (Post-STN) was -15.6 , with the negative value indicating that on average the highest power spectral coefficient measured ventral to the STN was larger than the smallest measured within the STN. Also, the maximum power coefficient measured in the pre-STN was larger than the minimum measured within the STN of a recording track in 8.3% of the cases, more than twice as often as occurs with the wavelet-derived background measure (3.6%).

Taken together, these statistics indicate that setting a threshold to isolate the STN would be more feasible and produce fewer errors on average using the de-spiked wavelet-derived background level coefficient than the power spectral density measure. This can be illustrated with a direct comparison of the amplitudes of each measure within the same person with each normalized to Z-scores based on their respective Pre STN values (depth values 0–6 cm) (figure 4). While both measures yield a similar shaped Z-score vs. depth curve for this person, it is clear that the STN portion of the curve is vertically higher with a tighter cluster of values in the STN and less boundary overlap for the wavelet-based background measure than for the power spectral measure. Thus, for this patient an “STN threshold” line in the wavelet-background measure separates all wavelet-based background STN values from all non-STN values (figure 4). Conversely, a similar line could not be drawn to isolate all power spectral STN values from all non-STN values, as a line below the lowest STN value falsely includes five non-STN data points above that threshold (figure 4). Likewise, if a line were drawn above the highest non-STN value on the power spectral curve that line would exclude five of the data points that actually were measured within the STN. Interestingly, the STN data point with the lowest power spectral coefficient value (below five non-STN points) was recorded within the nucleus but not near any one isolated cell.

Discussion

In this study, we demonstrated that a wavelet transformation method to separate background activity from foreground spikes can be a useful way to demarcate nuclear boundaries. In penetrations through the subthalamic nucleus, it had the largest background in comparison to neighboring regions of thalamus, zona incerta, substantia nigra, and fiber regions. The wavelet-derived background activity level can be calculated quickly, and requires only short

recordings (~5 seconds, here) to be effective. The background level calculation is robust, requires no spike sorting, and requires no additional interpretation. In the 21 recording tracks that we examined, 92% of the upper quartile data points for each pass matched with the clinically-identified STN, and the peak wavelet-derived background level value always corresponded with the clinically identified STN. For tracks where the STN was missed the background level remained flat, lending credence to the argument that the amplitude corresponds to the presence of a nucleus.

Comparison with other measures

While visual monitoring of neural recording waveforms on an oscilloscope and auditory monitoring of the same signals can be used to qualitatively judge firing patterns and background activity, it remains a subjective conclusion that relies upon user expertise and judgment. Several values have been published for the general firing frequency or burst characteristics of neurons in the STN^{2, 8, 21}, but these values vary widely from study-to-study and from patient-to-patient. These measures also require accurate spike detection/sorting, good signal-to-noise recording environments, and longer recording times in order to produce reliable numbers which limits the use of single-cell firing pattern as a quantitative measure. In contrast, the wavelet-derived background activity level measure described here is quick to compute and requires no operator judgment.

The power spectral density index has been used in a similar manner and has similar advantages for identifying the STN¹⁵. However, the wavelet-derived background level has less variability in measurements within the STN (tighter clustering) and provides a greater differentiation between structures (less overlap) than does the power coefficient. One likely reason for this is that the power spectral density also computes the magnitude by including “foreground” spikes as well, which therefore will be affected by the proximity of the electrode to individual neurons, their firing rates, amplitudes, etc. Since the wavelet-derived background level method described here effectively removes spikes to analyze primarily the background between spikes, no such electrode/distance bias affects its accuracy.

Another implication of the fact that the wavelets-derived background measure effectively removes foreground spikes is that it may provide useful information even when the electrode has not been moved to optimize recordings from a single neuron. We note that in figure 4, two of the five STN data points measured with the power spectral coefficient that were smaller than non-STN measurements (including the smallest STN value) were recorded at sites where no prominent isolated spikes were observed.

Considerations

The substantia nigra pars reticulata, when encountered, also had elevated wavelet-derived background levels that were on the order of, though slightly smaller than, those found in the subthalamic nucleus. Even in those situations the measure was able to accurately demarcate the STN, though, because of the region of decreased background values between the STN and the SNr.

The red nucleus is located near the STN, and it has been mistaken for the STN in some instances using the standard target localization techniques of imaging, followed by

microelectrode recording¹⁸. The characteristics of the foreground spikes (i.e. firing rate, inter-spike interval) is similar between the two structures, which may contribute to mislabeling. On the other hand, the baseline noise (i.e. background level) is lower in the red nucleus than in the STN¹⁸ so we would expect a different pattern of background levels in trajectories that encountered red nucleus instead of STN. Thus, in principle, our method should discriminate the STN from the red nucleus.

There is no absolute wavelet-derived background amplitude that identifies the STN across all patients, but instead the relative peaks must be identified on a per-penetration/per-patient basis in order to demonstrate the characteristic pattern.

Implementation

The wavelet analysis used in this method is, for practical purposes, almost instantaneous on 5-second data recordings even on a laptop computer. It was implemented here using MATLAB software, but any computational software that performs wavelets analysis could be used. The analysis could be initiated by the user at specific times, or the program could be modified to perform at regular intervals. Thus, one potential use for this analysis is to identify STN boundaries with less required user supervision, and to eventually automate the microelectrode recording portion of the localization process. Data could be recorded at set locations (e.g., 200 μm intervals), the wavelets-derived background measure could be computed, and a graphical output could be used to identify likely borders of STN. An implementation of this sort could expedite electrophysiological mapping of STN location. Surgery and mapping could be accomplished more quickly and more conveniently with a quantifiable target for the placement of the DBS electrode.

Limitations

Simplification of analysis of neural activity such as was done in this study does not obviate the need for intraoperative physiological testing. It is known, for example, that the caudal (motor) portion of STN is the optimal target for deep brain stimulation. The wavelet-derived measure developed herein may not be able to differentiate between the various sub-regions of STN, and therefore does not substitute for kinesthetic testing. With greater experience, however, it may be possible to compare wavelet-derived measures in various locations within STN with an eye towards simplifying this aspect of the target localization as well.

Conclusions

The wavelet-derived background measure is a straightforward and robust method of characterizing the profile of activity in neural populations. The method is quick, objective and reliable. Similar in concept to a power spectral density measure, the wavelet method appears to improve the ability to “separate” the STN from surrounding structures based on the differential properties of neighboring regions. The computational requirements, which are modest and can be accomplished quickly, make it feasible to implement an automated system to assist the detection of subcortical nuclear structure boundaries in an objective manner and thus could provide valuable assistance to neurosurgical mapping procedures

with the eventual goal of automating the micro-electrode recording portion for added speed, convenience, and accuracy.

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Figure 1. Background level amplitude vs. depth for patient STN27. The background amplitude has a relative increase at the dorsal border (enter STN) and decrease at the ventral border (exit STN). A schematic depiction of one possible trajectory is juxtaposed.

Figure 2.

Plot of background magnitude vs. depth from the bottom of the cannula (mm) for patient STN30. When the STN was encountered in this patient the background increased significantly (Pass A, filled circles indicate STN sites). In another trajectory (Pass B), STN was not detected (background remained flat). Bottom: cartoon schematically illustrates two trajectories, A and B, one encountering cells in a nucleus and a second (B) skirting the outside of the nucleus.

Figure 3.

(A) Box plot of background amplitude vs. structure for all patients. On average across all subjects, the amplitude in the STN is significantly higher ($p < .0005$) than in recording sites above or below STN. (B) Individual comparisons for all recording tracks shows that mean background amplitudes in STN are always greater than sites above or below STN.

Figure 4.

Amplitude vs. depth for both the wavelet-derived background (solid line and 'x' marks) and power spectral density (dashed line and 'o' marks) measures for patient STN28. For comparison, the amplitudes of each measure have been normalized to Z-scores based on their respective Pre STN values (depth values 0–6). The clinically defined STN region is marked by the box (depths 6–9). The upper dotted grid-line indicates the “STN threshold” for the wavelet-based background method that separates all STN values from all non-STN values. A similar “STN” threshold grid-line for the power spectral method includes five non-STN points.

Table 1

Summary of background activity amplitude results across all 14 patients. Average measures in microvolts (μV).

Statistic	Pre (μV)	STN (μV)	Post (μV)
Mean	112	225	136
Standard Deviation	32	61	66
Number of samples (N)	54	134	33
Minimum	66	73	71
5th percentile	67	133	72
25th percentile	88	184	89
Median	105	222	113
75th percentile	139	270	160
95th percentile	170	317	236
Maximum	210	390	373