Microelectrode Recording Duration and Spatial Density Constraints for Automatic Targeting of the Subthalamic Nucleus

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Key Words

Microelectrode recording • Deep brain stimulation • Parkinson's disease • Subthalamic nucleus • Neurosurgery

Abstract

Background: Accurate detection of the boundaries of the subthalamic nucleus (STN) in deep brain stimulation (DBS) surgery using microelectrode recording (MER) is considered to refine localization and may therefore improve clinical outcome. However, MER tends to extend operation time and its cost-utility balance has been debated. **Objectives:** To quantify the tradeoff between accuracy of STN localization and the spatial and temporal parameters of MER that effect the operation time using an automated detection method. **Methods:** We retrospectively estimated the accuracy of STN detection on data from 100 microelectrode trajectories. Our dense (average step = 0.12 mm) and long (average duration = 22.5 s) MER data was downsampled in the spatial and temporal domains. Then, the STN borders were detected automatically on both the downsampled and original data and compared to each other. **Results:** With a recording duration of 16 s, average accuracy for detecting STN entry ranged from 0.06 mm for a 0.1-mm step to 0.51 mm for a 1.0-mm

step. Smaller effects were found along the temporal axis. For example, a 0.1-mm recording step yielded an STN entry average accuracy ranging from 0.06 mm for a 16-second recording duration to 0.16 mm for 0.1 s. **Conclusions:** STN entry detection error was about half of the step size. Sampling duration of STN activity can be minimized to 1 s/record without compromising accuracy. We conclude that bilateral DBS surgery time utilizing MER may be significantly shortened without compromising targeting accuracy.

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Introduction

Deep brain stimulation (DBS) surgery of the subthalamic nucleus (STN) is an effective therapy in the management of the motor symptoms of advanced Parkinson's disease (PD). Accurate localization of the STN is essential for optimal outcome of DBS treatment [1–9]. Today, many centers use direct targeting of the STN based on MRI imaging with or without fusion technology. However, targeting the STN based on preoperative images alone may be suboptimal for at least two key reasons. Firstly, the STN target cannot always be well identified on the pre-

operative image [10–12]. Secondly, the clinical application accuracy of the various stereotactic systems is 0.1–5.0 mm [13–18], an error which approaches the dimension of the STN itself. Image fusion inaccuracies, MRI distortion and intraoperative brain shift may add to this error [19, 20]. Thus intraoperative validation of the target STN location is needed.

Microelectrode recording (MER) is often utilized for target validation and refinement. MER has been shown to facilitate the accurate detection of the anatomical and functional boundaries of the STN [3–5, 7, 9, 21–24]. Typically, MER signals are observed both visually and with audio by the physiologist and/or neurosurgeon during surgery to identify the functional targets. Recently, several studies have shown that MER data can be utilized for automatic localization of the STN with reduced variation and better accuracy [25–30]. Commonly used signal features include the background noise level, spike count and power spectral density (PSD) in the beta and theta (tremor) frequency bands.

In contrast, however, MER may extend the surgery time and, in some healthcare environments, may increase the cost of surgery [10, 31]. Increased operation time has many ramifications including reduced patient comfort and cooperation if surgery is performed awake.

The extra time associated with MER is likely related to the number of recorded points along the trajectory and to the duration of recording at each of these points. However, reducing the number of recording locations and/or recording duration may result in a lower STN detection accuracy. In this study we aim to quantify this tradeoff by measuring the accuracy and robustness of STN detection with various recording durations and spatial densities. Our results may therefore be used to optimize the tradeoff between the extra time associated with MER, and the STN detection accuracy required for effective DBS treatment.

Materials and Methods

We retrospectively reviewed 100 MER trajectories from 35 PD patients implanted with bi-lateral DBS electrodes in the STN between April 2008 and May 2011 at the Hadassah University Hospital at Ein-Karem, Jerusalem, Israel. All patients met the accepted selection criteria for STN DBS and signed an informed consent for surgery with microelectrode recording. This study was authorized and approved by the Institutional Review Board of Hadassah University Hospital in accordance with the Declaration of Helsinki (IRB 0545-08-HMO). The MER trajectories included in this study were selected such that the STN entry and exit points, and the STN dorsolateral beta oscillatory region (DLOR) could be

manually identified based on MER data, and represent 65% of the trajectories recorded in the above time frame. In a previous study our group found that the DLOR is a pathophysiological hallmark of the dopamine-deprived motor STN and the optimal location for the STN active contact [1].

In our surgical protocol, for each hemisphere, two simultaneous parallel MER trajectories are recorded. MER data is acquired using the MicroGuide Pro™ recording suite (Alpha Omega Engineering, Nazareth, Israel). The entire MER dataset is analyzed for the exact detection of the STN and DLOR entry and exit points using a Hidden Markov Model (HMM) analysis method [26] (fig. 1). Our MER trajectories contained recordings at every 0.12 ± 0.08 mm on average ($\pm$ STD), in the range of 0.001–0.4 mm, and with an average recording duration of 22.5 ± 20.8 s, in the range of 1.9–171.3 s. Typically, MER is begun 10 mm above the expected target center. Initially, large spatial steps (400 μ m) are used with short recording duration; the spatial resolution and recording duration are increased when approaching the STN region. The MER data is automatically recorded 1 s after the completion of the spatial step. The data are saved in separated files, one for each location such that the file time tags represent the actual time between successive recordings. The difference between time tags incorporates the recording duration plus the time needed for the electrode to move to the next location.

The 100 MER trajectories in this study were downsampled in the temporal and spatial domains to create gaps of at least 0.1, 0.2, 0.5 and 1.0 mm between successive recording depths and recording durations of at most 16, 8, 4, 2, 1, 0.5, 0.2 and 0.1 s starting at the beginning of the recording at each depth along the entire MER trajectory. The STN and DLOR entry and exit points were then detected automatically with the HMM detection algorithm [26] for each of the temporal and spatial sampling parameters. These were then compared with the STN and DLOR entry and exit points that had been detected from the entire dataset.

The following statistical values were computed to evaluate the effect of the sampling on accuracy: (1) average error – that is the average of the absolute (nonnegative) distances between STN points detected with the entire and with the sampled data; (2) standard deviation (STD) of the error; (3) median error; (4) 95th percentile of the error, and (5) maximum error value. The effect of sampling on robustness of the automated detection method was measured by counting the detection failures. For a robust computation of the STD suspected outliers above/below the 95th percentile were removed. The accuracy measures were calculated only for cases where detection was successful. All computations were performed using MATLAB (version 7.0, The MathWorks Inc., Mass., USA).

The intraoperative STN target exploration time was estimated for each trajectory by subtracting the earliest MER file time tag from the final one. To estimate the time reduction using larger gaps between successive MERs, MER files incorporated using the suggested recording gap are first marked. The MER duration time of unmarked files is then computed and subtracted from the total time. As a result, the time required for microdrive moving time was not neglected. This is a conservative estimate since the microdrive slows before stopping, and therefore the movement time for several small steps is larger than the movement time of a single large step. Nevertheless, since it is difficult to estimate this time saving, we report below only on the saving of MER recording time.

Fig. 1. Automatic detection example. The x-axis is the estimated distance from target (EDT) with respect to the target as per the preoperative MRI image. The y-axis of **a** is the normalized root mean square (NRMS), that is, the electrode signal RMS at a specific EDT divided by the RMS of the electrode signal in the white matter. The y-axis of **b** is the frequency (Hz) of the signal. Red colors in **b** are associated with relatively high PSD values and reflect strong oscillatory activity at that frequency, while blue colors are associated with low PSD values and weak oscillations. Our automatic method detects three transitions along the trajectory as in-

dicated by the green line and red box (**a**): (1) STN entry point at the increase of the green line from 0.5 to 1; (2) dorsolateral oscillatory region (DLOR) entry point at the left edge of the red box; (3) DLOR exit point at the right edge of the red box, and (4) STN exit point at the rightmost green line transition. Note the overlap between the red box (**a**) and the region with beta oscillations (**b**). The STN and DLOR entry points were similar in our results whenever beta oscillations were observed in the STN. In this example, the computed STN entry, exit, and DLOR region exit points are 4.3, -1.4 and 1.5 mm, respectively. Colors refer to the online version only

To estimate the time reduction using shorter MER durations, we first estimated the time reduction for each single MER location and then compute the collective result along the entire trajectory. For each MER location, the associated file time tag was subtracted by the previous time tag to reflect the time for MER and microdrive step time at this location. Then, the time of MER was computed from the associated MER file and subtracted from the total time computed at the previous step to reflect the net microdrive moving time. To estimate the duration time for sampled MER with microdrive moving time, the sampling duration time was added. To estimate the time reduction of a combination of the methods, we first estimated the time reduction using larger gaps between successive MERs, and then applied the method for shorter recording durations on the marked files only.

The HMM detection algorithm [26] detects four points along the MER trajectory (fig. 1a): (1) the STN entry point; (2) the DLOR entry point; (3) the DLOR exit point- that is the transition from the DLOR of the STN to its ventral non-oscillatory region, and (4) the STN exit point. The algorithm makes use of changes in the background noise level to detect the STN (fig. 1a) and combines the background noise level with power spectral density (PSD) measures to detect subterritories within the STN (fig. 1b). The background noise level is estimated by computing the normalized root mean square (NRMS) of the MER. Generally speaking, for a given MER signal, the PSD estimates the contribution of various oscillation frequencies to the input signal. That is, if a signal incorporates beta frequency oscillations, the PSD computation will facilitate its detection. For more information regarding our methods for background noise level estimation and computation of PSD, the reader is referenced to our previous work [1, 26].

Results

The MER trajectories contained records at every 0.12 ± 0.08 mm on average ($\pm$ STD), in the range of 0.001–0.397 mm, with an average record duration of 22.5 ± 20.8 s, in the range of 1.9–171.3 s. Figures 2–5 summarize detection accuracy and robustness of the STN and DLOR entry and exit points on the down-sampled data. The computed results are presented with respect to recording duration and to the gap between successive recordings. A surface mesh was generated based on the measured values to interpolate intermediate duration and gap values. The surface is color coded such that hot color (red) is associated with larger errors and cold colors (blue) with lower ones. The average error (in mm) and number of detection failures are also shown in tables 1–4 and tables 5–7, respectively. In our method, a failure to detect the STN oscillatory region results in a failure in detecting both the DLOR entry and exit points. Therefore, the number of failures in detecting these points is the same.

These results show that increasing the gap between successive recording points markedly influences the accuracy of detecting STN boundaries and subterritories (tables 1–4). Recording duration, however, seems to have low impact on the accuracy of detecting STN entry and

Fig. 2. STN entry point detection accuracy and robustness with respect to sampling parameters. The number of detection failures in **a** indicates the robustness of the method to the sampling parameters. The following parameters are computed for the cases where detection was success: **b** Average error. **c** Standard deviation of error. **d** Median error. **e** 95th percentile of error. **f** Maximum error. The surface was color coded such that red is associated with large errors and blue with low ones. Colors refer to the online version only.

exit points and DLOR entry point (tables 1–3), but a greater effect on STN DLOR exit point (table 4). The mean error for the DLOR exit point increases from 0.69 to 1.63 mm between recording durations of 1 and 0.5 s, respectively, with a gap of 0.1 mm (table 4). Averaging over all recording times and gap values, the STN entry and the DLOR entry point are localized most accurately (average error = 0.32 and 0.27 mm, respectively), the STN exit point is detected less accurately (average error = 0.45

mm), and the largest error was recorded at the DLOR exit point (average error = 1.23 mm).

The percentage of failures in detecting STN entry and exit points appears to be affected mainly by the gap between successive records (fig. 2a, 3a). The percentage of failures in detecting DLOR entry and exit points appears to be affected mostly by the record duration (fig. 4a, 5a). Detection of STN entry point was associated with lower detection failures percentage than the

Fig. 3. STN exit point detection accuracy and robustness with respect to sampling parameters. Same conventions as in figure 2.

Table 1. Average detection error (in mm) of STN entry point

Gap	Duration							
	16 s	8 s	4 s	2 s	1 s	0.5 s	0.2 s	0.1 s
0.1 mm	0.06	0.09	0.14	0.14	0.14	0.15	0.14	0.16
0.2 mm	0.13	0.20	0.19	0.20	0.21	0.31	0.18	0.19
0.5 mm	0.36	0.41	0.42	0.43	0.44	0.44	0.32	0.32
1.0 mm	0.51	0.55	0.58	0.59	0.63	0.59	0.57	0.57

Table 2. Average detection error (in mm) of STN exit point

Gap	Duration							
	16 s	8 s	4 s	2 s	1 s	0.5 s	0.2 s	0.1 s
0.1 mm	0.22	0.23	0.25	0.29	0.19	0.24	0.27	0.24
0.2 mm	0.30	0.35	0.36	0.41	0.27	0.44	0.32	0.36
0.5 mm	0.53	0.53	0.55	0.57	0.48	0.57	0.39	0.46
1.0 mm	0.71	0.82	0.75	0.73	0.78	0.74	0.67	0.51

Fig. 4. STN dorsolateral oscillatory region entry point detection accuracy and robustness with respect to sampling parameters. Same conventions as in figure 2.

Table 3. Average detection error (in mm) of STN DLOR entry point

Gap	Duration							
	16 s	8 s	4 s	2 s	1 s	0.5 s	0.2 s	0.1 s
0.1 mm	0.06	0.08	0.12	0.13	0.13	0.12	0.12	0.12
0.2 mm	0.12	0.16	0.19	0.18	0.17	0.16	0.18	0.19
0.5 mm	0.25	0.28	0.29	0.26	0.31	0.39	0.30	0.30
1.0 mm	0.47	0.45	0.52	0.50	0.60	0.46	0.47	0.52

Table 4. Average detection error (in mm) of STN DLOR exit point

Gap	Duration							
	16 s	8 s	4 s	2 s	1 s	0.5 s	0.2 s	0.1 s
0.1 mm	0.23	0.31	0.41	0.52	0.69	1.63	1.46	1.66
0.2 mm	0.33	0.39	0.43	0.58	0.69	1.33	1.28	1.62
0.5 mm	0.47	0.42	0.62	0.72	0.84	2.04	1.96	2.15
1.0 mm	1.53	1.66	1.52	1.85	2.06	2.43	2.49	3.03

Fig. 5. STN dorsolateral oscillatory region exit point detection accuracy and robustness with respect to sampling parameters. Same conventions as in figure 2.

other points. Note that for a 1.0-mm gap, the detection of STN entry failed only in $\sim 3\%$ of the cases in comparison to $\sim 30\%$ detection failures for STN exit and DLOR entry and exit points. Down-sampling to a 1-second record duration has little effect on the detection failures percentage (tables 5–7). However, using even shorter sampling duration increased the error rates. Thus, a 0.5-second record duration dramatically increased the DLOR entry and exit points detection failures percentage by more than 50%. Using a 0.1-second record duration dramatically increased the STN exit

point detection failures percentage to more than 50% for a gap of 1.0 mm (table 6).

Exploration of the STN along one trajectory using microelectrode recording lasted on average 45 min (STD = 11 min). Table 8 summarizes the expected time for exploration of one STN trajectory using various recording durations and different gap sizes between successive recordings. The exploration time can be decreased to a few minutes while maintaining good accuracy and robustness. For example, using gaps of 0.1 mm and a recording duration of 1 s is expected to reduce the average exploration

Table 5. Percentage of detection failures of STN entry point

Gap	Duration							
	16 s	8 s	4 s	2 s	1 s	0.5 s	0.2 s	0.1 s
0.1 mm, %	1	1	0	2	1	0	0	0
0.2 mm, %	1	1	1	2	2	0	0	2
0.5 mm, %	1	1	1	1	2	0	1	1
1.0 mm, %	3	3	3	4	2	1	2	3

Table 6. Detection failures percentage of STN exit point

Gap	Duration							
	16 s	8 s	4 s	2 s	1 s	0.5 s	0.2 s	0.1 s
0.1 mm, %	1	1	0	2	1	1	4	9
0.2 mm, %	1	1	1	2	3	0	3	12
0.5 mm, %	3	3	6	6	8	13	16	31
1.0 mm, %	28	28	31	38	37	22	27	51

Table 7. STN DLOR entry and exit points detection failures percentage

Gap	Duration							
	16 s	8 s	4 s	2 s	1 s	0.5 s	0.2 s	0.1 s
0.1 mm, %	7	5	4	9	8	51	36	22
0.2 mm, %	9	10	7	12	14	67	47	29
0.5 mm, %	22	21	18	21	22	74	54	33
1.0 mm, %	31	35	36	30	38	69	63	36

time of the STN along one trajectory to 13 min (table 8). Therefore, it may save more than half an hour on average for unilateral surgery and more than an hour for bilateral surgery.

Discussion

Our results show that increasing the spatial gap between successive microelectrode recording points directly reduces the accuracy and robustness of STN detection. This may be explained by the gradual increase of the background noise level (fig. 1). Thus, an interpolation method to estimate intermediate NRMS values may im-

prove the detection method and thus increase the STN detection accuracy.

Our results also demonstrate that using a short microelectrode recording duration of about 0.1 s does not significantly change the accuracy of detecting STN entry and exit points. The reason for this may be that the intra-STN NRMS value exceeds the threshold criteria within a very short time. In contrast, the STN DLOR exit detection accuracy is reduced for record durations that are shorter than 1 s. The STN DLOR exit point is detected based on the PSD in the beta range of 13–30 Hz. A reliable PSD computation requires several repetitions of the oscillatory signal within the dataset, and a 0.5-second record duration may be insufficient. Similarly, short record durations of less than 1 s resulted in considerable detection failures for the DLOR entry and exit for which the PSD in the beta range was used for detection. Therefore, we conclude that when the PSD in the beta range is used for detection of STN points, the record duration should be 1 s or longer.

An interesting observation is that a 0.5-second recording duration was associated with larger failures number than a 0.1-second recording duration (fig. 4f, 5f). One possible explanation is that a recording duration of 0.5 s may facilitate the accurate PSD computation for beta frequency oscillations at the high range of 20–30 Hz, but not at the low beta frequency range (13–20 Hz). Thus, there may be some inconsistency between computing the PSD for high and for low beta oscillation frequencies when using a 0.5-second recording duration. A recording duration of 0.1 s is probably insufficient for the accurate PSD computation in the entire beta range (13–30 Hz), but the error is consistent for high and low beta oscillations. Our detection method parameters were adjusted based on data with a duration of at least 2 s for which the PSD computation is consistent. Therefore, inconsistent PSD values such as resulted with 0.5 s are not expected in our HMM model. Finally, DLOR detection entry point maximum error value was increased when computed for a 0.5-mm gap and a 0.5-second recording duration (fig. 4e). We believe that this is an outlier in our measurements.

One limit of this study is that it utilizes a specific STN detection method. It is most likely that the effect of sampling on the detection accuracy and robustness might be different for other manual or automatic detection methods. The method used here has been our method of choice to confirm STN boundaries and it has been remarkably consistent for landmarks identified by our expert neurophysiologist. Furthermore, the technique is automatic and therefore the accuracy and robustness measures on the sampled data are objective and are not user-biased.

Table 8. Expected MER exploration time (min) for one trajectory at the STN (average $\pm$ SD)

Gap	Duration							
	16 s	8 s	4 s	2 s	1 s	0.5 s	0.2 s	0.1 s
0.1 mm	33 $\pm$ 13	22 $\pm$ 12	17 $\pm$ 12	15 $\pm$ 12	13 $\pm$ 11	13 $\pm$ 11	12 $\pm$ 11	12 $\pm$ 11
0.2 mm	21 $\pm$ 11	14 $\pm$ 10	11 $\pm$ 10	9 $\pm$ 10	9 $\pm$ 10	8 $\pm$ 10	8 $\pm$ 10	8 $\pm$ 10
0.5 mm	10 $\pm$ 8	7 $\pm$ 8	6 $\pm$ 7	5 $\pm$ 7	5 $\pm$ 7	5 $\pm$ 7	4 $\pm$ 7	4 $\pm$ 7
1.0 mm	7 $\pm$ 8	6 $\pm$ 8	5 $\pm$ 8	4 $\pm$ 8	4 $\pm$ 8	4 $\pm$ 8	4 $\pm$ 8	4 $\pm$ 8

This latter feature is essential for a comparative study such as this. Automatic detection methods are not integrated in current commercial systems. Most MER-based methods require the passive movement of patient's limbs or other manual time-consuming operations to verify that the electrode is located within the motor area of the STN. Recent studies have shown that oscillations in the beta band frequency within the STN are highly associated with motor activities [1, 32, 33]. A spectral analysis of the MER data may reveal not only the dorsal and ventral borders of the STN, but also its internal subdivision into motor and nonmotor areas. Therefore, the intra-operative passive movements of the limbs or other manual operations may become unnecessary, and the automatic methods with one second recording may save a significant amount of surgery time.

Conclusions

Intraoperative MER along surgical trajectories accurately confirms STN boundaries, but increases the operation time and may increase cost. We quantified the effect of sampling on a dense (average gap = 0.12 mm) and long duration (average duration = 22.5 s) MER dataset on STN detection accuracy, robustness and its effect on surgery time. The accuracy and robustness for the various sampling parameters of 100 MER trajectories from STN DBS surgeries of PD patients were measured. Our results show that increasing the size of the gap between successive recording depths significantly reduces detection accuracy and robustness. In contrast, record durations of 1–16 s resulted in similar accuracy and robustness values. Record durations of 0.5 s or less are associated with increased failures and/or increased error in STN DLOR exit/entry point detection. Therefore, when spectral analysis of the beta band is needed, as is the case in the detection of the DLOR, ultrashort recording durations (<1 s)

are not long enough for robust analysis. The DLOR entry, STN entry and exit points were localized more accurately than the DLOR exit point. Our results suggest that the average time for bilateral DBS surgery in the STN can be reduced by 1 h. These results may assist to optimize the tradeoff between the duration of DBS surgery and the required STN detection accuracy, and to refine and improve the STN detection method. Investigating the sampling effect with other detection methods may further improve our understanding on this topic. These data are also important for the development of a fully automatic microrecording system that might obviate the need for human control of microelectrode movement. Such a fully automated system utilizing the recording time and gap between successive recording points for optimal accuracy will complete even a long STN 'pass' in less than 15 min. Finally, it would be interesting to compare automatic and manual methods and examine the sampling effects for additional DBS targets.

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