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Microelectrode recording-determined subthalamic nucleus length not predictive of stimulation-induced side effects

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Object. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become a popular treatment for patients with medically refractory Parkinson disease. Many surgeons believe that microelectrode recording (MER) during DBS electrode implantation is needed to optimize placement, whereas stimulation-induced side effects such as paresthesias, dystonic contractions, dyskinesias, and ocular motor signs that become apparent postoperatively may be an indicator of the proximity of the electrode to various boundaries of the STN. This study was performed to evaluate the relationship between mapping of the STN by using MER and postoperative stimulation-induced side effects.

Methods. Eighty-two electrodes implanted in 75 patients between March 1999 and March 2003 were retrospectively examined to evaluate the length of the STN defined by MER, and the number of and threshold for postoperative stimulation-induced side effects. Electrodes were typically tested with increasing stimulation amplitudes (maximum 6 V) by using a monopolar array.

The 82 electrodes were associated with 97 stimulation-induced side effects. The mean time between surgery and testing stimulation-induced side effects was 3.9 months. Statistical analysis (two-tailed t-test) revealed no significant difference in the number of stimulation-induced side effects (or the mean threshold for paresthesias, the most common side effect) for electrodes associated with an STN length less than 4.5 mm (13 electrodes) compared with those associated with an STN greater than or equal to 4.5 mm (69 electrodes, $p = 0.616$). For every electrode, the target adjustment based on MER results was within 2 mm of the image-planned target (usually 1 mm anterior). In the x axis (medial–lateral orientation), there was no systematic difference in adjustments made for the electrodes associated with the shorter compared with the longer STN lengths. In the y axis (anterior–posterior orientation), there was a very small statistically significant difference in the mean adjustment (0.4 mm) between the two groups.

Conclusions. Analysis of these results suggests that a shorter MER-determined STN length alone does not reliably predict the incidence of stimulation-induced side effects.

Key Words • Parkinson disease • subthalamic nucleus • deep brain stimulation • microelectrode recording • stimulation-induced side effect

Deep brain stimulation of the STN has become the most popular surgical modality for treating medically intractable PD and has largely replaced ablative stereotactic neurosurgical procedures.[2,3,14,17] Deep brain stimulation of the STN provides consistent clinical benefit[10,14] and can reduce dopamine replacement therapy requirements by 50 to 60%.[15,26]

The DBS electrode tip is 1.27 mm in diameter and is thought to typically produce a current spread of less than 4 mm[16,20] (the STN is approximately 5 mm in diameter).[9] Consequently, electrode tip position relative to the center of the STN is presumed to determine the clinical efficacy of stimulation therapy. Because this efficacy is thought to be in part due to precise targeting, many surgeons believe that MER during DBS electrode implantation is needed to map the boundaries of the STN and optimize electrode placement.[1,9,22–24,27]

Following electrode placement, stimulation-induced adverse side effects such as paresthesias, dystonic contractions, dyskinesias, and ocular motor signs may be an indicator of the electrode's proximity to various boundaries of the STN.[13,14] We performed this study to evaluate the relationship between MER mapping of the STN (that is, the length of the STN) and postoperative stimulation-induced adverse side effects.

Abbreviations used in this paper: DBS = deep brain stimulation; ICM = intercommissural midpoint; MER = microelectrode recording; MR = magnetic resonance; PD = Parkinson disease; STN = subthalamic nucleus.

CLINICAL MATERIAL AND METHODS

Patient Population

Patient selection criteria and preoperative evaluations were performed as described previously.[6] Between March 1999 and March 2003, 90 patients underwent STN DBS at our institution. On retrospective analysis, 75 of these pa-

tients had documentation of systematic evaluation of stimulation responses.

Stereotactic Planning

A functional Cosman-Roberts-Wells (Radionics, Inc., Burlington, MA) stereotactic frame was used during all implantation procedures, and stereotactic planning was performed as previously described.[6] The surgeon defined the anterior commissure–posterior commissure plane with the aid of either the StereoPlan platform (Radionics, Inc., Raynham, MA) or the Stealth FrameLink software (Medtronic, Inc., Minneapolis, MN), as previously described.[6] The Stealth software calculated the STN coordinates relative to the ICM (4 mm posterior, 4 mm inferior, and 12 mm lateral).

Neurophysiological Localization

High-impedance tungsten microelectrodes 24 mm in length with a tip size of 20 to 25 μm (FHC, Inc., Bowdoinham, ME) were advanced to 30 mm above the calculated anatomical target. Impedance at 1000 Hz was measured at 3 and 20 mm after the microelectrode was removed from the cannula. Subsequently, the recording microelectrode was advanced to the target by an electronic stepper microdrive, and the electrical signals from single neuronal units and background activity were filtered at 100 to 3000 Hz, preamplified and amplified to a total of 10,000 to 50,000 times, digitized, and sent to an oscilloscope and audio system for real-time monitoring as well as a digital recording device for offline analysis. The coordinate positions for MER; Fourier transforms of discharge frequencies; and action potential morphology of single units, fiber activity, and background changes were quantified and recorded. Typically, bursting cells of the anterior thalamus were encountered, followed by electrically quieter regions corresponding to the fields of Forel and zona incerta. Proceeding anteriorly, an area of increased background noise and irregularly firing neurons (often responsive to movement) was detected, corresponding to the STN. Farther anterior, below the STN, a region of more rapidly and regularly firing neurons corresponding to the substantia nigra pars reticulata was detected.

Subsequently, additional parallel microelectrode tracks were often made to obtain similar data. These data were used in conjunction with the Schaltenbrand stereotactic atlas[21] to determine a DBS electrode placement that was believed to be in the central region of the STN (~ 2 to 3 mm posterior to the anterior border and medial to the lateral border), with the distal electrode contact placed at the physiologically defined inferior boundary of the STN. Placement of the DBS electrode (model 3387 or model 3389; Medtronic, Inc.) was achieved without physiological guidance after removal of the MER and positioning of a longer guide cannula in the desired trajectory (as determined by previous MERs). The guide cannula was advanced to the appropriate depth (~ 15 mm above the target), and the DBS electrode was then advanced to the desired depth (generally with the distal electrode within 1 mm of the inferior STN boundary). Excessive proximity to the medial lemniscus and internal capsule was evaluated by macrostimulation by using DBS. Macrostimulation (3 V, pulse width 60 μsec, 185 Hz, bipolar configuration between the deepest and most superficial electrodes) at the final implant site did not produce sustained sensory symptoms or dystonic muscle contractions.

Stimulator Settings for the STN and Postoperative Evaluation

Typically, patients had their pulse generators initially programmed 1 to 2 weeks after the DBS electrode implant. Subsequent extended programming sessions were typically conducted at the 1- and 3-month follow-up visits, with the patient in a state of medication withdrawal. The final settings were those that produced the greatest improvement in tremor (if present), bradykinesia, and rigidity, without bothersome side effects. Stimulator setting data were obtained from chart review. Postoperative evaluation consisted of neurological examination using the Core Assessment Program for Intracerebral Transplantations protocol, postoperative MR imaging, and assessment of PD symptoms and medications as previously described.[12,17]

Electrode and STN Length Analysis

Electrodes studied in this investigation were the first (or only) implanted during a particular operative session. In general, when a contralateral electrode was implanted on a single operative day, less extensive MER was used (placed at a mirror image to the first side). Of the 75 patients, five underwent staged bilateral implantation, and an additional two had electrodes replaced using similar MER guidance, yielding a total of 82 electrodes with sufficient clinical data.

Electrodes were retrospectively examined to determine the length of the STN on the initial MER track and the number of and threshold for postoperative stimulation-induced side effects. Electrodes were typically tested with increasing stimulation amplitude (maximum 6 V, unless stimulation produced bothersome side effects) with a monopolar array. Because a particular electrode could yield multiple side effects and multiple electrodes could belong to the same patient, the number of side effects could be correlated only with the number of electrodes and not with the number of patients. The length of STN correlating with these 82 electrodes was determined based on postoperative reports. All STN lengths were based on the length recorded following the initial MER pass.

Statistical Analysis

Statistical analysis was performed using SPSS 10.0 software (SPSS, Inc., Chicago, IL). Because the data were approximately normally distributed, each series of comparisons between outcome measures was conducted using paired two-sample t-tests. Comparisons between proportions were conducted using chi-square analyses.

RESULTS

The mean time between surgery and testing stimulation-induced side effects was 3.9 ± 5 months (standard deviation; range 0–43 months). Twenty-one (25.6%) of the 82 electrodes were associated with no stimulation-induced side effects, whereas the remaining 61 electrodes were associated with 97 side effects, ranging from paresthesias to mutism (Table 1). Each electrode was associated with a mean of 1.2 side effects.

TABLE 1
Stimulation-induced side effect profile of 82 STN electrodes

Adverse Side Effect	No. of Electrodes (%)
paresthesia	49 (59.8)
dystonic contraction	13 (15.9)
eyelid-opening apraxia/ocular motor effects	8 (9.8)
dysarthria	6 (7.3)
dyskinesia	5 (6.1)
dizziness/ataxia	5 (6.1)
numbness	4 (4.9)
diplopia/blurred vision	2 (2.4)
lightheadedness	2 (2.4)
blepharospasm	1 (1.2)
confusion	1 (1.2)
mutism	1 (1.2)
none	21 (25.6)

For every electrode, the target adjustment based on MER results was within 2 mm (in the x and y axes) of the image-planned target. In the x axis, there was no systematic difference in adjustments made for the electrodes associated with the shorter (mean 0.15 mm) compared with the longer (mean 0.11 mm) STN lengths ($p = 0.683$). The adjustment differences (whether medial or lateral), however, were statistically significant in the y axis ($p = 0.012$) between the shorter (mean 1.27 mm) and longer (mean 0.88 mm, range 0–2 mm) STN lengths. The y-axis adjustment was 1 mm anterior for the majority of electrodes in both groups (seven of 13 in the shorter STN group, and 42 of 69 in the longer STN group), with no significant differences between groups. A subset of the seven electrodes associated with the shortest STN length revealed no difference in targeting adjustment compared with the remaining 62 electrodes. Eleven of 13 shorter STN electrodes were associated with more than one MER pass, compared with 46 of 69 in the longer STN group, a difference that was not statistically significant ($p > 0.05$).

The mean length of the STN was 4.9 ± 0.7 (standard deviation; range 2.5–6.9 mm). Statistical analysis (two-tailed t-test) revealed no significant difference ($p = 0.616$) in the number of stimulation-induced side effects for electrodes associated with STN length less than 4.5 mm (13 electrodes) compared with a length greater than or equal to 4.5 mm (69 electrodes). Among the 49 electrodes yielding paresthesias (the most common side effect), the mean threshold for paresthesias was similarly not different ($p = 0.208$) between electrodes associated with STN length less than 4.5 mm (mean 1.9 V, range 1–3.6 V) and a length greater than or equal to 4.5 mm (mean 2.3 V, range 1.1–4.4 V). Similarly, among the 17 electrodes yielding either dystonic contractions or dyskinesias, the mean threshold was not different between the two STN groups ($p = 0.602$). For the short STN group, the mean was 3.2 V (range 2.8–4 V), and for the long STN group, the mean was 2.8 V (range 0.9–4.6 V).

DISCUSSION

The role of MER in guiding DBS electrode implantation in the STN, performed since the prototype protocol by Benabid, et al.,[2] is based on the hypothesis that MER significantly improves the accuracy of electrode placement (in the central STN) over that provided by image and macrostimulation guidance alone.[1,9,19,22,25,27] It is widely believed that this electrode position optimizes clinical outcomes. In a previous study, however, our findings suggested that a DBS electrode placed anywhere within a 6-mm-diameter cylinder centered on the STN center provides indistinguishable clinical efficacy as measured by blinded videotape review of Unified PD Rating Scale motor scores and patient questionnaire data.[4,17]

To further elucidate the impact of MER on electrode placement, in this study we specifically examined the relationship between MER mapping of the STN and stimulation-induced side effects, because previous work has indicated a correlation between increasing side effects and proximity to the boundaries of the STN.[13,14] A number of centers have used multiple MER passes prior to DBS electrode implantation with the goal of identifying the boundaries of the STN to guide placement in the central part of the STN.[2,11,22,27] In this series, the adjustment of the DBS target based on MER results was relatively small and nearly uniform throughout. Therefore, the relationship between the initial anatomical target and the final DBS target location was relatively consistent. Thus, one might expect that an initial pass revealing a shorter STN would result in the placement of an electrode closer to an STN boundary than an electrode placed following a pass revealing a longer STN. Our goal was to test this hypothesis, specifically, that the length of the STN (as mapped by the initial MER pass) could be reliably correlated with the frequency and consistency of stimulation-induced side effects. Given that the reported length of the STN has ranged from 4 to 5 mm,[8,9,13] we chose 4.5 mm as a cutoff delineating two groups of STN length: "short" (< 4.5 mm) and "normal/long" (≥ 4.5 mm). Noteworthy limitations of this study include its retrospective nature, that we did not prospectively divide our patients between two different methods of implantation, and that we did not prospectively evaluate the stimulation parameters consistently in every patient.

As in our previous reports, the method of DBS implantation in this study was based on indirect MR imaging targeting (calculated from the ICM) supplemented by MER, which is very similar to the method described in several centers.[2,11,17,22,27] Based on our previously described technique and electrode tip locations,[17] we believe that our DBS tip locations (relative to the ICM and intended target) are similar to those obtained by other surgeons who perform DBS implantation.[2,3,5,14,17]

Retrospective chart review allowed us to assess the correlation between STN length and stimulation-induced side effects. The most common side effect was paresthesias. More than one fourth of the electrodes were not associated with any side effect. The most intriguing finding was that there was no correlation between STN length and incidence of stimulation-induced side effects. Even when we examined only electrodes that produced paresthesias, dystonic contractions, or dyskinesias, there was no difference in stimulation threshold between electrodes with an STN length less than 4.5 and those 4.5 mm or greater.

It is important to evaluate the possibility that MER led to a significant difference in target adjustment between the two groups. As in our previous reports, however, the target adjustment based on MER was usually 1 mm anterior, an adjustment that was small and similar in both groups. Ideal-

ly, this study would rely on the MER-determined length along the path of the final DBS trajectory. Many of the patients in this study did not have an MER along the final DBS path because the final path was within 2 mm of a track that was investigated using MER. The small difference in the y-axis adjustment (0.4 mm) between the two groups in this study (short compared with long STN length) was statistically significant, but probably too small to be clinically significant. The lack of significant differences between these two groups for both side effect incidence and threshold suggests that in our hands, a shorter STN length did not indicate closer proximity to the boundary of the STN than longer STN length. It could be that all of our initial targets were essentially in the same area of the STN, and that the difference in height is due to patient variation. Alternatively, this shorter distance may indicate that in patients with shorter STN length, we were in a different part of the STN than in patients with longer STN length, but that the difference is small enough that it does not produce obvious differences in clinical side effects. It is important to note that, as previously reported, the anatomical calculation invariably yielded a path through at least some part of the STN in all 82 electrodes.[17]

CONCLUSIONS

Our findings indicate that a shorter MER-determined STN length does not reliably predict the proximity of the DBS electrode to the boundaries of the STN. This should not be surprising, given that these findings are consistent with previous reports indicating that initial targeting of the STN using MR imaging is sufficiently precise to place the initial MER penetration within the STN.[13,18,24] The findings of another study from our center[17] that electrode variability within a 6-mm-diameter cylinder around the STN center does not significantly alter clinical outcome, and the similarity between our implantation method and that of other experienced centers raises a question about the optimal use of MER to guide DBS electrode implantation. It is not clear that varying the placement of the DBS electrode within the STN significantly alters efficacy or side effects. More extensive use of MER with the goal of placing the DBS electrode at the center of the STN may not improve upon this outcome, and thus may not be justified in light of the associated increased risk of hemorrhage and frontal lobe trauma, and increased operative time and cost.[3,7] The results of this study suggest that prospective trials may be justified for definitive determination of whether maximal compared with minimal (or no) use of MER improves clinical efficacy while reducing side effects.

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