DUAL MICROELECTRODE TECHNIQUE FOR DEEP BRAIN STEREOTACTIC SURGERY IN HUMANS

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Received, December 8, 2005.

Accepted, December 3, 2006.

OBJECTIVE: To improve functional stereotactic microelectrode localization of small deep brain structures by developing and evaluating a recording system with two closely separated independently controlled microelectrodes.

METHODS: Data were obtained from 52 patients using this dual microelectrode technique and 38 patients using the standard single microelectrode technique for subthalamic nucleus localization in patients with Parkinson's disease.

RESULTS: There was a decrease in the incidence of noncontributory trajectories, defined as a single penetration made by the pair of closely spaced parallel microelectrodes, owing to microelectrode failure (from 7.2% to <1%), an improved localization and verification of nuclear borders, and a significant decrease in the number of trajectories used to localize the subthalamic nucleus from a median of three to two per initial operative side ($P < 0.001$). The technique also provides the novel opportunity to examine population activity by correlating the discharge between two closely spaced simultaneously recorded neurons and can be used to monitor the electrophysiological effects of local electrical stimulation or microinjections of pharmacological agents.

CONCLUSION: Our experience indicates that the use of two closely spaced microelectrodes improves the utility of microelectrode localization in minimally invasive functional neurosurgery.

KEY WORDS: Deep brain stimulation, Microelectrode recordings, Parkinson's disease, Stereotactic functional neurosurgery, Subthalamic nucleus

Neurosurgery 60[ONS Suppl 2]:ONS-0-ONS-0, 2007

DOI: 10.1227/01.NEU.0000255389.85161.03

Microelectrode techniques are commonly used in functional stereotactic neurosurgery to provide physiological localization in conjunction with initial targeting by magnetic resonance imaging (MRI) (2, 17, 18, 39, 42, 49). Together, microelectrode recording and electrical stimulation provide precise delineation of subcortical structures, such as the subthalamic nucleus (STN), globus pallidus internus (GPi), and thalamic nuclei, for the treatment of a variety of neurological disorders (5, 23, 33, 35, 47, 48). Neuronal recordings from these structures have added considerably to our understanding of basal ganglia pathophysiology in patients with Parkinson's disease (PD) (22, 24, 27, 31, 45).

However, the disadvantages of microelectrode recordings include an increased intraoperative time, the necessity of a high degree

of technical support, the fragility of the microelectrodes, and the requirement for multiple trajectories that may further damage cortical and subcortical tissue. In addition, the data obtained represents only information collected from single neurons, not correlated population activity. Therefore, motivated by a need to improve the efficiency of microelectrode localization, to keep the surgery minimally invasive, and gather as much information as possible to determine a meaningful functional localization, we discuss our experience with dual microelectrode recordings for STN localization in patients with PD. We present a versatile head stage design that allows us to record from two closely spaced, independently controlled microelectrodes and demonstrate an improved utility over single microelectrode techniques.

METHODS

Head Stage Assembly, Microelectrodes, and Cannulas

F1 A photograph of the dual microdrive head stage assembly is shown in *Figure 1*. This assembly was designed to fit the standard Leksell G stereotactic frame (Elekta Instruments, Stockholm, Sweden) and consists of a platform that holds two hydraulic microdrive slave-cylinder units and a detachable guide tubes assembly. Each microdrive has a range of motion of 21 mm, with the platform allowing for 25 mm of clearance. The two inner guide tubes were constructed by soldering two 23-gauge, thin walled stainless steel tubes (HTX-23TW; Small Parts Inc., Miami Lakes, FL) side by side. These were then set in the guide tubes assembly in a position mediolateral to each other relative to the patient. The dual inner guide tubes fit easily into the standard stereotactic frame outer guide tube, which, in our setup, was constructed from 17 gauge stainless steel tubing (HTX-17; Small Parts Inc.). The distal ends of the inner guide tubes were flush with the outer guide tube. As seen in *Figure 1*, a gradual 30-degree curve in one of the guide tubes allowed for adequate separation of the microdrive units. This feature did not cause any noise owing to friction as the microelectrode was driven down. The configuration of the inner guide tubes set the center of each 23-gauge guide tube at approximately 300 μ m off the central axis of the stereotactic frame outer guide tube (see *Figure 1*). The microelectrodes were parallel and were separated by a mediolateral distance of 600 μ m and by 0 to 20 mm in the superior-inferior direction. The dual microdrive assembly is quite light as it is made from aluminum and did not cause any problems (e.g., distortion of the frame).

For all patients in this study, identical microelectrode tips were used in either single or dual recording methods. For dual record-

ings, parylene-C coated tungsten microelectrodes with tip dimensions of 25 μ m (we300325A, Microprobe) were proximally **AQ:1** stripped of 2 cm of insulation and elongated by backing the microelectrodes into a 30-cm length of 30-gauge stainless steel tubing (HTX-30, Small Parts Inc.), leaving 10 mm exposed distally. Polymide tubing was used to insulate the stainless steel tubing (#28, Micro ML) and was joined to the microelectrode **AQ:2** using epoxy resin. Microelectrodes used in the single microelectrode setup were similarly constructed with 25-gauge stainless steel tubing (HTX-25, Small Parts Inc.) and appropriately sized polymide tubing (#23, Micro ML). All microelectrodes were plated with gold and platinum to a final impedance of approximately 100 Kohms at 1000 Hz. At the proximal end of the microelectrode, the polymide tubing was stripped by 1 cm to create a site for connection to the amplifier head stage.

Lastly, we sometimes used the dual guide tube setup to perform macrostimulation, record local field potential (LFP) activity, or to locally inject drugs simultaneously with single microelectrode recordings. These could all be accomplished by using a cannula constructed from 30-gauge stainless steel tubing (HTX-30, Small Parts Inc.) and insulated by polymide tubing (#28, Micro ML) instead of one of the microelectrodes. For LFP recordings and macrostimulation, 1 mm of polymide tubing was removed at the distal end of the cannula. This length of exposure was chosen as the best trade off between the dimensions of the deep brain stimulator (DBS) leads used for chronic stimulation (diameter, 1.27mm; length, 1.52mm) and small enough to record discrete LFPs in a relatively small nucleus (maximum, approximately 10 $\times$ 6 mm in the parasagittal plane). An external stimulus generator connected to an isolated current source was used to perform macrostimulation using the cannula (stimulus isolator A360; World Precision Instruments, Sarasota, FL). For injection of drugs, a 2-cm length of 23-gauge tubing (HTX-23, Small Parts Inc.) was soldered at the proximal end to provide for a tight fit with polyethylene tubing that was connected to a 25 μ l Hamilton syringe (Hamilton Co., Reno, NV). Electrophysiological and clinical data for LFP recordings and drug injections in the STN have been described previously (28, 32).

Intraoperative Recording Methods

Detailed descriptions of operative procedures have been described elsewhere (26, 34). Briefly, a Leksell stereotactic frame was installed under local anesthesia. MRI or computed tomographic scanning was used to locate the frame coordinates for the anterior and posterior commissures. A digitized stereotactic atlas plate of a sagittal map (46) at the appropriate laterality for the target that was adjusted to match each patient's intercommissural distance was calculated and displayed on a computer screen and used to determine the frame coordinates of the target. The target for the first track was a site approximately 1mm dorsal to the ventral border of the STN at the 12mm lateral plane. A small hole was then made in the cranium under local anesthesia, and physiological mapping of neuronal activity was performed.

Single unit neuronal activity recorded from each microelectrode was amplified, high-pass filtered (200–300 Hz), and monitored on a loudspeaker and displayed using two dedicated

FIGURE 1. A, head stage and detachable guide tubes assembly. B, microelectrodes extending from the distal end of dual guide tubes. Note that the microelectrodes were oriented mediolaterally with respect to the patient and were centered approximately 300 μ m off the center axis of the stereotactic frame guide tube.

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GS3000 systems (Axon Instruments, Foster City, CA.). Both microelectrodes shared a common ground with the amplifiers (black wire in *Figure 1*) and the entire head stage was further grounded (green wire in *Figure 1*) to the Axon instrument chassis. Identification of nuclear boundaries was made by finding well-isolated single neurons and background multiunit activity with characteristic firing properties typical of either the STN or the substantia nigra pars reticulata (SNr), as described previously (23). Patients included in this study were those undergoing bilateral or unilateral microelectrode mapping of the STN for the insertion of DBS electrodes. This was performed using either a standard single microelectrode microdrive or the dual microelectrode microdrive described above. For the latter technique, only patients in whom both microelectrodes were used throughout the entire surgery were included. In this report, a "trajectory" is defined as a single penetration made by the pair of closely spaced parallel microelectrodes, i.e., the continuation of the axis of the 17 gauge outer guide tube through which the inner guide tube is located and through which the microelectrodes pass. A "track" is defined as the path of an individual microelectrode. Electrophysiological features were documented intraoperatively by noting and plotting the firing and receptive field characteristics of the neurons recorded in the pair of microelectrode tracks in the one trajectory. Dual recordings were used in 52 patients, whereas single microelectrode-based localization was used in 38 patients.

RESULTS

The typical use of the dual recordings involved moving each microelectrode past the other stationary microelectrode, allowing us to record from single neuron pairs that were in a staggered position. Recordings were quite stable when one microelectrode was moved past the other; neurons were rarely "lost" at the stationary microelectrode. The use of two microelectrodes allowed us to independently sample twice as many neurons in each trajectory. However, our effort was concentrated on recording from the most well-isolated and stable neurons in each track, thereby bypassing those neurons with low signal-to-noise ratio. Qualitatively, there was a minor increase in the time required to explore each trajectory.

A distinct advantage of the dual electrode technique is that if a microelectrode failed (i.e., did not satisfactorily record single unit activity), the second microelectrode could be used as a backup for what would otherwise be a noncontributory track. Microelectrode tips are fragile and liable to be damaged and may, therefore, result in unreliable information collection from a track. This occurrence can sometimes be detected immediately by a very high or low impedance, and the electrode can be replaced. In other cases, it may not be clear whether the lack of recordings are the result of a defective electrode (despite normal impedance) or passage through white matter or damaged brain. Also, in some cases, the presence of injury discharge of neurons before the spikes are well-isolated or a poor signal-to-noise ratio suggests a defective electrode. In these cases, repeating the track with a new electrode would be time consuming and may not yield good data owing to

its passage down the previous electrode penetration and, thus, is not advisable. In such cases, we would usually proceed with the other microelectrode. Under these circumstances, this technique was more time efficient than the standard setup because we were able to quickly verify our findings using the second microelectrode, thereby avoiding possible additional electrode penetrations owing to possible false-negative data or having to remove the head stage apparatus to replace the microelectrode in cases where the electrode was suspected to be malfunctioning. The total number of trajectories performed in the dual microelectrode setup was 118; hence, the total number of microelectrode tracks was 236. Seven tracks in one guide tube and 10 tracks in the other were deemed unreliable, resulting in an overall microelectrode "failure" rate of 7.2%. There were no instances of both microelectrodes being unreliable in the same trajectory. The expected theoretical failure rate using the dual technique is less than 1%.

The distances of borders identified with individual microelectrodes to the initial dorsal-ventral target locations are shown in *Figure 2A*. There were a total of 444 borders identified with individual microelectrodes. The dorsal and ventral borders of the STN were located a median of 3.0 and -0.2 mm from the initial target, respectively. The dorsal border of the SNr was located a median of -2.5 mm from the initial dorsal-ventral STN target. The use of a second microelectrode allowed the confirmation of electrophysiological landmarks such as nuclear borders. The instances of individual trajectories in which borders were identified on both or neither microelectrodes (i.e., similar findings) were compared with the instances in which a border was found on one microelectrode but not the other. *Table 1* shows that there were similar findings on both microelectrodes in approximately 95% of the trajectories for the dorsal and ventral border of the STN. In the case of the dorsal and ventral STN borders, there was a low incidence of cases in which a border was identified on one microelectrode but not the other (approximately 5%). There was no difference regarding which microelectrode was in disagreement. *Figure 2B* shows the dorsal-ventral distances between identified borders when dual microelectrodes were used. There were 77, 74, and 56 pairs of borders identified with both microelectrodes for the dorsal STN, ventral STN, and dorsal SNr borders, respectively. The mean separation in identified borders was approximately 0.6 mm, and there was no difference in separation between the three identified borders ($P = 0.856$, one-way analysis of variance on ranks).

Figure 2C compares the number of trajectories used to localize the STN with the dual and single techniques. In the case of bilateral recordings, only data from unilateral exploration and the initial side of the brain (typically the right side) was used. There was a significant difference of a median of two versus three trajectories (mean, 2.3 versus 3.6 trajectories) for dual and single recordings, respectively ($P < 0.001$, Mann-Whitney Rank Sum Test). *Figure 2D* displays this information as a function of patient chronological order. It can be seen that there was a decrease in the number of trajectories required to accurately localize the STN. We did not obtain postoperative CT scans on patients but the incidence of symptomatic postoperative hemorrhage using either technique was similar (1 to 2%).

FIGURE 2. A, line graph showing the distances from the initial dorsal-ventral target locations as derived from MRI to the nuclei borders as identified with individual microelectrodes. B, bar graph showing the distances between the borders identified on each microelectrode (mean and standard error of the mean) when dual recordings were used ($P = 0.856$, one-way analysis of variance on ranks). C, bar graph showing that there was a significant decrease in the number of trajectories used to localize the STN when dual recordings were used. This bar graph shows the mean and standard error of the mean (asterisk, $P < 0.001$, Mann-Whitney rank sum test). D, line graph showing the number of trajectories needed to localize the STN using dual versus single microelectrode recordings as a function of patient chronological order. The solid line represents the average number of trajectories using the single technique (excluding Patients 23–27 and 35, who had dual recordings) for the current and four previous patients. The dashed line represents the average number of trajectories using the dual technique (excluding Patients 45, 72, 73, and 77, who had single recordings) for the current and four previous patients. dSTN, dorsal STN border, vSTN, ventral STN border, dSNr, dorsal SNr border.

Lastly, the use of two independently controlled microelectrodes allowed for the experimental characterization of population activity and the analysis of neuronal responses to local electrical stimulation. *Figure 3A* displays a schematic of a trajectory through the STN of a single patient. Autocorrelograms of some individual STN neurons displayed oscillations at approximately 20 Hz (not shown) and were designated as STN β cells (i.e., neurons displaying β band 13–30 Hz oscillations). Cross-correlograms of oscillatory neuron pairs demonstrate that an approximate 20 Hz in-phase synchronization is present in a group of dorsally located STN neurons. Neuron pairs displaying 13 to 30 Hz oscillatory in-phase synchronization were similarly clustered in the dorsal aspect of the STN in other patients examined. Oscillatory synchronization was not encountered in pairs of SNr neurons. *Figure 3B* shows the response of STN and SNr neurons to local electrical stimulation in four patients. After the stimulation artifact, a period of inhibited activity can be seen in the STN and SNr for both high (300 Hz) and low frequency stimulation (20 and 10 Hz, respectively). It was observed that approximately half of the STN neurons examined displayed a period of inhibition lasting up to several hundred milliseconds after high frequency stimulation. Detailed results of the responses of STN neurons to local stimulation have been reported previously (15).

DISCUSSION

This study compared the use of two closely spaced, independently controlled microelectrodes with the standard single microelectrode technique for the localization of the STN in PD patients. A practical advantage of this setup is that the second microelectrode can be used as a backup when there are concerns regarding microelectrode reliability (approximately 7% of microelectrode tracks in our group of 52 dual technique patients). This result suggests that standard single microelectrode mapping can run the risk of providing false-negative results as marked by a low signal-to-noise ratio or acellularity in as many as 7% of the trajectories explored (i.e., guide tube penetrations). It should be noted that the surgeon was not committed to using both microelectrodes and could, therefore, explore trajectories using just one microelectrode if desired. However, in

TABLE 1. Comparison of similar findings to dissimilar findings between the two microelectrodes with the dual microelectrode technique^a

	Dorsal border of STN	Ventral border of STN	Dorsal border of SNr
Total no. of trajectories	101	98	98
Borders identified by both microelectrodes	77	74	56
Borders not identified by either microelectrode	19	20	21
Total percentage of similar findings	95%	96%	79%
Border only identified with S1	3	2	11
Border only identified with S2	2	2	10
Total percentage of dissimilar findings ^b	5%	4%	21%

^a STN, subthalamic nucleus; SNr, substantia nigra pars reticulata; S1, right-sided guide tube; S2, left-sided guide tube.

^b Total percentage of instances in which there was disagreement between the two microelectrodes in a single trajectory (i.e., a border was found on one microelectrode but not the other).

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many instances, the availability of a second microelectrode in the same trajectory was certainly very helpful. The second microelectrode also serves to confirm and better delineate electrophysiological landmarks such as the dorsal and ventral borders of the STN. The use of dual recordings helped to confirm the presence or absence of STN borders in 95% of the trajectories performed. The median values for the distance of the final dorsal and ventral borders of the STN from the initial dorsal-ventral target location are consistent with a report by Hamani et al. (18) and with the prediction based on the location of the predicted target for the electrode track within the STN. However, as shown in Figure 2A, there is a considerable spread in the distances of borders from the initial targets. Values markedly different from the median indicate a considerable discrepancy between the MRI and atlas map prediction, and the microelectrode exploration findings and may be related to imaging distortions and brain structure variability. In a series of 12 patients, Zonenshayn et al. (49) demonstrated an average distance error of approximately 4 mm between the final physiological targets and the MRI-derived targets, which is considerably larger than that found in our study. In our study, when borders were found on both microelectrodes, they were separated in the dorsal-ventral direction by usually less than 0.7 mm regardless of the distance from the initial MRI target. A second closely spaced microelectrode reassures the surgeon of the quality of the information obtained, improves the efficiency of the procedure, and may reduce the need for more trajectories.

There was a significant decrease in the number of trajectories needed to localize the STN from a median of three to two when dual microelectrode recordings were used. The decrease in the number of trajectories may be attributable to an increased confidence in the quality of the sampled single neurons in each trajectory, the decrease in the effects of unreliable recordings, and the improved delineation of nuclear borders. However, a possible drawback of this technique is that an extra microelectrode track is made through the STN for each explored trajectory so that the number of electrode tracks is actually higher (median, four versus three). A reduction in the number of electrode tracks is important because microelectrode recording techniques are not without the risk of severe complications (6, 13, 20, 21); thus, there is an impetus to reduce the number of these invasive trajectories (10, 16). However, the incidence of symptomatic post-operative hemorrhage using the dual microelectrode technique was 1 to 2%, which is in the same range reported in a recent review of the literature (19). An approach we have demonstrated in this article is to maximize the neuronal data obtained from each trajectory. A caveat is that the reduction in the number of trajectories needed to localize the STN may be confounded by the learning curve, in which the general trend is to perform fewer trajectories with increasing experience (see solid and dashed lines in Figure 2D). However, as shown in Figure 2D, the learning curves for either technique reached a plateau after approximately 25 patients, suggesting that the use of dual recordings can further reduce the number of trajectories. Lastly, commercially available systems incorporating multiple simultaneous recording schemes (Alpha Omega MicroGuide Pro sys-

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tem [Alpha Omega Co., Alpharetta, GA], Medtronic Leadpoint system [Medtronic, Inc., Minneapolis, MN], FHC microTargeting Drive System with maTriX Mount [FHC, Inc., Bowdoinham, ME], Inomed ISIS MER system [Teningen, Germany]) incorporate a multichannel array comprising five separate fixed guide tubes that are spaced 2 mm apart and arranged in a cruciate pattern. This configuration commits the surgeon to perform five trajectories. It has been noted that only two or three of the five microelectrodes usually provide for STN localization (5).

The analysis of neuronal firing rates and patterns in the STN of patients with PD provides us with an opportunity to characterize pathophysiological activity such as tremor-related activity (23, 31, 36, 37, 44) and somatosensory responses (1, 14, 30, 45). The use of dual microelectrode recordings allows for the correlation of spiking activity of neurons separated by 600 μ m to 20 mm, thereby permitting analysis of local and widespread population activity. The characterization of population activity involves the correlation of neuronal discharge and can be used to extract information regarding neuronal physiological states that is not available from single neuron data. The importance of correlated population activity has been highlighted in the basal ganglia of patients with PD (7–9, 22, 29, 31, 41). Individual STN neurons may display oscillatory discharge activity in the β band frequency range of 13 to 30 Hz. When crosscorrelated, closely spaced pairs of these neurons show an in-phase oscillatory population activity that is more synchronized in the dopamine depleted state (see Figure 3A). This synchronized activity has also been shown to decrease with movement (4, 28). These changes in neuronal activity can be detected (25, 28) in a reduction of the β frequency spectral power of LFPs recorded from the DBS electrodes (8, 12, 28, 43). The clinical relevance of these findings is that DBS at sites displaying these pathological β frequency range LFP oscillations produces the most effective motor benefit in patients with PD (38). Therefore, the ability to identify areas in the STN through the correlation of pairs of neurons or indirectly through LFP recordings may lead to the optimization of DBS parameters in both intra- and postoperative scenarios.

The dual microdrive head stage assembly can also be used to characterize neuronal responses to microstimulation and, similarly, macrostimulation by replacing one of the electrodes with a cannula. We have previously shown that there are characteristic patterns of neuronal inhibition in subgroups of STN and GPi neurons (11, 15). The information provided can be used as an aid for identification of these structures in conjunction with neuronal recording and the clinical effects of stimulation. Lastly, the thin cannula allows for the local injection of pharmacological agents. A local reversible anesthetic block using 5 to 10 μ l of 2% lidocaine can mimic the effects of DBS and lesions in the STN of patients with PD; the spread of drugs can be monitored by simultaneously recording neural activity at a short distance from the injection cannula (32). This method can, therefore, facilitate the subsequent placement of permanent lesions in the STN (3, 40) to predict lesion outcome in a reversible manner.

In summary, we have demonstrated the utility of closely-spaced dual microelectrode recordings to improve STN localization by increasing the amount of relevant functional data per trajectory, decreasing the effects of unreliable recordings and improving the delineation of nuclear borders. These features may be reflected as a decrease in the number of trajectories required to adequately localize the STN. The ability to examine synchronized population activity by correlating the discharge of closely spaced individual neurons has also substantially increased our knowledge of basal ganglia pathophysiology and may be used as an additional tool to localize the STN in conjunction with LFP recordings, simultaneous recording with micro- or macrostimulation, and local drug injection. A future research focus will be to correlate the use of dual electrode techniques to patient outcome such as the efficacy of DBS or lesions targeted at specific pathological activity.

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Acknowledgments

Funding was provided by the Canadian Institutes of Health Research FRN: 42505 and the United States National Institutes of Health RO1 nanosecond 40872. Andres M. Lozano, M.D., Ph.D., is a Canadian Institutes of Health Research clinician scientist.