Implantation of deep brain stimulators into the subthalamic nucleus: technical approach and magnetic resonance imaging–verified lead locations

PHILIP A. STARR, M.D., PH.D., CHADWICK W. CHRISTINE, M.D., PHILIP V. THEODOSOPOULOS, M.D., NADJA LINDSEY, R.N., DEBORAH BYRD, R.N., ANTHONY MOSLEY, M.D., AND WILLIAM J. MARKS, JR., M.D.

Departments of Neurological Surgery, Neurology, and Nursing, University of California, San Francisco; and Division of Neurosurgery and Departments of Neurology and Nursing, San Francisco Veterans Affairs Medical Center, San Francisco, California

Object. Chronic deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a procedure that is rapidly gaining acceptance for the treatment of symptoms in patients with Parkinson disease (PD), but there are few detailed descriptions of the surgical procedure itself. The authors present the technical approach used to implant 76 stimulators into the STNs of patients with PD and the lead locations, which were verified on postoperative magnetic resonance (MR) images.

Methods. Implantation procedures were performed with the aid of stereotactic MR imaging, microelectrode recording (MER) in the region of the stereotactic target to define the motor area of the STN, and intraoperative test stimulation to assess the thresholds for stimulation-induced adverse effects. All patients underwent postoperative MR imaging, which was performed using volumetric gradient-echo and T2-weighted fast–spin echo techniques, computational reformatting of the MR image into standard anatomical planes, and quantitative measurements of lead location with respect to the midcommissural point and the red nucleus. Lead locations were statistically correlated with physiological data obtained during MER and intraoperative test stimulation.

Conclusions. The authors’ approach to implantation of DBS leads into the STN was associated with consistent lead placement in the dorsolateral STN, a low rate of morbidity, efficient use of operating room time, and robust improvement in motor function. The mean coordinates of the middle of the electrode array, measured on postoperative MR images, were 11.6 mm lateral, 2.9 mm posterior, and 4.7 mm inferior to the midcommissural point, and 6.5 mm lateral and 3.5 mm anterior to the center of the red nucleus. Voltage thresholds for several types of stimulation-induced adverse effects were predictive of lead location. Technical nuances of the surgery are described in detail.

KEY WORDS • subthalamic nucleus • deep brain stimulation • Parkinson disease • microelectrode recording • magnetic resonance imaging • surgical approach


Abbreviations used in this paper: A = anterior; AC = anterior commissure; AP = anteroposterior; DBS = deep brain stimulation; FSE = fast–spin echo; IC = internal capsule; IPG = implanted pulse generator; L = lateral; M = medial; MER = microelectrode recording; ML = medial lemniscus; MR = magnetic resonance; P = posterior; PC = posterior commissure; PD = Parkinson disease; RN = red nucleus; SN = substantia nigra; SNr = SN pars reticulata; STN = subthalamic nucleus; UPDRS = Unified PD Rating Scale; 3D = three-dimensional.
Deep brain stimulation of the subthalamic nucleus predict the anatomical location of a lead based on intraoperative physiological findings.

Clinical Material and Methods

Patient Population

We reviewed and analyzed our initial 76 consecutive cases of MR imaging–guided implantation of stimulators into the STN for the treatment of idiopathic PD. Approval was obtained from our Institutional Review Board. All patients had experienced a definite improvement in motor symptoms in response to administration of levodopa. The patients’ mean scores on Part III (motor subscale) of the UPDRS were 48 during the off-medication period (all antiparkinsonian medications withheld overnight) and 22 during the on-medication period. The mean age of the patients at the time of surgery was 60.5 years (range 46–79 years). There were 77 attempted and 76 completed stimulator implantations in 44 patients. In one case the lead was not implanted because an intraoperative hemorrhage occurred. In six patients tremor was the predominant symptom, whereas in 38 patients, the symptoms were predominantly akinesia, rigidity, gait disorder, “on–off” fluctuations, and levodopa-induced dyskinesias or dystonias. Sixty-two stimulator implantations were performed as unilateral procedures or to the burr hole with a titanium miniplate. In the last two portions of staged bilateral procedures. In seven patients, 14 implantations in 44 patients. In one case the lead was externalized for 2 days so that we could perform functional MR imaging postoperatively. In five cases the pulse generators were put in place 2 to 14 days after lead placement; in other cases they were placed the same day. Postoperative MR imaging was performed in all patients within 24 hours after lead implantation.

Overview of the Surgical Procedure

Antiparkinsonian medications were withheld from patients for 12 hours before surgery to avoid medication-induced dyskinesias during the surgical procedure. The patient was given a local anesthetic agent, after which a stereotactic frame was applied, taking care to align the frame with the mid sagittal plane of the brain and with the AC–PC line. Stereotactic MR imaging was performed to define the anatomical target. After we drilled a 15-mm burr hole, we entered the dura mater sharply. Microelectrode mapping was then performed sequentially along multiple parallel trajectories to define the motor territory of the STN. The DBS lead (intercontact distance 3 mm from center to center) was cemented in place with the aid of methylmethacrylate and fixed posteriorly to the burr hole with a titanium miniplate. 15 In the last two cases that we treated, a lead-anchoring device was used. After the scalp wound had been closed, the headframe was removed, general anesthesia was induced, and the pulse generator was placed.

In one case the lead was externalized for 2 days so that we could perform functional MR imaging postoperatively. In five cases the pulse generators were put in place 2 to 14 days after lead placement; in other cases they were placed the same day. Postoperative MR imaging was performed in all patients within 24 hours after lead implantation.

TABLE 1
Parameters used for preoperative and postoperative imaging on two MR systems*

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* NEX = number of excitations; MPRAGE = magnetization-prepared rapid acquisition gradient echo; SPGR = spoiled gradient recalled acquisition; TEeff = effective echo time.

Magnetic Resonance Imaging and Target Point Determination

Before we began to use MR imaging as the sole modality for anatomical localization, we performed a study with a phantom head inside the stereotactic frame. 15 We found that the center coordinates of the phantom, as determined using our MR imagers with the fiducial markers, were identical (within a single pixel size) to the known coordinates of the center, based on the actual geometry of the phantom.

The MR imaging sequences that we used for preoperative targeting are provided in Table 1. Two different MR imaging units were used in this series and the sequence parameters differed slightly between the two magnets (Table 1). We obtained a 3D volumetric gradient-echo image set covering the entire brain in 1.5-mm-thick slices with a zero interslice distance, followed by a coronal T2-weighted FSE pulse sequence, with a 2-mm slice thickness, acquiring only 18 slices through the targeted region. The FSE images were acquired as two interleaved sets, each with a 2-mm gap between slices. The two sets were combined to provide a single FSE image set with a zero interslice distance. This interleaving technique doubled the time required for imaging, but avoided the signal degradation that would otherwise occur in FSE imaging when there is a zero slice separation and images are acquired as a single set. 20

To define the initial anatomical target on the basis of MR imaging, we used a hybrid of two methods: indirect targeting in which we used fixed distances from the midsagittal point and direct targeting by visualization of the STN itself. The gradient-echo images were used primarily for indirect targeting and for trajectory planning. The FSE images were used for direct visualization of the targeted structures because of the nuclear detail they revealed.

Indirect Targeting. The gradient-echo sequence was reformatted parallel to the AC–PC line and to the midsagittal
sured its AC–PC coordinates. A volumetrically acquired gradient-echo sequence is depicted (parameters are shown in Table 1), computationally reformatted to align with the intercommissural line and the midsagittal plane. The cross indicates the target with respect to the midcommissural point (lateral 12 mm, AP −3 mm, and vertical −3 mm). A: Axial plane. B: Coronal plane. The SNr is seen slightly inferior and medial to the target. C: Sagittal plane. D: Navigational view in the plane of the actual trajectory, showing the approach, which was planned to avoid traversing sulci or the lateral ventricle.

Entry Point Determination

In our first 40 implantation procedures, we determined the entry point by setting the stereotactic arc and rings for a standardized approach angle of 60° from the AC–PC line in the sagittal projection and to 5 to 10° lateral from the vertical line in the coronal projection. In the subsequent 37 cases, we used surgical planning software to examine the trajectory and make slight adjustments so that we could avoid traversing sulci or the lateral ventricle. A typical trajectory is shown in Fig. 1D.

Microelectrode Mapping

Single-unit extracellular action potentials were recorded using one of two types of microelectrodes: custom-made tungsten microelectrodes plated with gold and platinum or platinum–iridium microelectrodes, which were obtained commercially. Both types were coated with Parylene C, had impedances of 0.1 MΩ to 1 MΩ at 1000 Hz, and had 15- to 25-μm tip diameters. Action potentials were amplified, filtered (0.3–10 kHz), displayed on an oscilloscope, and played on an audio monitor. Microelectrodes and the subsequent DBS lead were advanced into the brain with the aid of a micropositioner (a motorized microdrive) or by using a custom-built micropositioner with hydraulic microdrive.

The goal of MER was to identify the characteristic spontaneous discharge patterns of the STN and surrounding nuclei and the locations of movement-related cells within the STN. While recording in STN, we paused every 0.3 to 0.5 mm to assess movement-related activity. Cells were considered to be movement-related if they exhibited modulation of cell firing during passive movement of the contralateral shoulder, elbow, or wrist (arm-related cells) or hip, knee, or ankle (leg-related cells). Examination of the face was not performed systematically. “Modulation” consisted of audible alteration in the discharge frequency that was reproducible and synchronous with passive movement. Single units located in the STN and SNr with good signal/noise ratios were digitized at 20 kHz for at least 30 seconds. Spikes were discriminated off line by using a waveform-matching algorithm and the spontaneous discharge rate was determined using subroutines written in commercially available software. During each microelectrode penetration, physiological data were recorded on graph paper in a scaled reconstruction of the microelectrode track.

Microstimulation up to 40 μA peak-to-peak (300 Hz, 200 μsec pulse width, 1–2 second train duration, biphasic pulses) was performed on microelectrode penetrations in which the STN was missed entirely or in which the STN was detected but the SNr was not recorded within 2 mm of the base of the STN. During microstimulation, we examined the patient for tonic contraction of the tongue, lips, face, or contralateral arm or for tonic eye deviation. Although microstimulation-induced effects were helpful when present, their absence did not necessarily imply a
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safe distance from clinically important microexcitable fiber pathways, we used low-current stimulation to avoid damaging the microelectrode tip.

The initial penetration was always directed at the stereotactic target. Additional tracks were made sequentially rather than simultaneously because the location of each subsequent penetration was individualized based on the information already obtained in the initial tracks. Tracks were separated by 2 mm or 3 mm. Typically, the second penetration was performed in the same parasagittal plane as the initial one, and a third was performed 2 to 3 mm lateral or medial to the initial plane of penetration. In cases in which earlier penetrations identified motor-responsive cells within the STN, relatively fewer tracks were performed; if early tracks did not identify motor responsive cells or missed the STN entirely (which was rare), relatively more microelectrode penetrations were performed.

Deep Brain Stimulation Lead Placement

Using the microelectrode map to determine DBS lead placement, the goal was to place the lead into the motor territory of the STN, but to avoid a location closer than 2 mm from the lateral, anterior, or posterior borders. If the initial penetration showed a segment of STN cellular activity greater than 4 mm in length and revealed movement-related activity, the lead was typically placed in or very near to the initial microelectrode penetration. Factors dictating significant deviation (> 1 mm) from the initial penetration including the following: 1) greater concentration of movement-related cells or a longer trajectory through the STN during penetrations other than the initial one; and 2) proximity to a border of the STN. For example, if additional tracks located 2 mm anterior and 2 mm lateral to the initial one showed no STN activity, the lead was placed more posteriorly and more medially than the initial penetration, even if the initial penetration represented a long segment with clear movement-related cells.

Test Stimulation

After a baseline neurological examination had been conducted by the surgeon or a neurologist, the lead was placed so that the middle two contacts (in the first 60 implantations) or the bottom two contacts (in the last 16 implantations) spanned the STN. Intraoperative test stimulation was performed between the two contacts spanning the STN by using a 60-µsec pulse width, 185 Hz, and 2 to 10 V. The following were monitored as the voltage was increased and decreased: the development of dysarthria; tonic contraction of face, arm, or leg; dyskinesia; diplopia or blurred vision; paresthesia; or any other subjective, but reproducible sensation that the patient could report. If resting tremor was present, we monitored the patient for tremor suppression, but we did not systematically monitor for improvements in other parkinsonian signs. The lead was moved to a new trajectory only if the threshold for dysarthria, muscle contraction, visual blurring, or diplopia was 2 V or less.

Measurement of Lead Location

The pulse sequences selected for postoperative MR imaging were the same as those for preoperative MR imaging (Table 1), except that the FSE sequence was acquired in the axial rather than coronal plane. Postoperative MR images were transferred to a computer for analysis, which was performed using appropriate software (Framelink). All image sets were reformatted to be parallel to the AC–PC line and orthogonal to the midsagittal plane. This ensured that lead location measurements in different patients were made in standardized anatomical planes. Lead locations were measured in two ways: 1) as a continuous variable in three dimensions with respect to the midpoint of the intercommissural line; and 2) as a continuous variable in two dimensions with respect to the center of the red nucleus, as measured on the axial plane 4 mm inferior to the intercommissural line.

Lead Coordinates With Respect to the Midcommissural Point. On the gradient-echo images, the AC and PC were identified by and registered on the Framelink software. Next, the distal tip of the stimulator was identified. It appeared as a relatively discrete round signal void, approxi-
Fig. 3. Representative MERs in various nuclei along a trajectory (dotted line) through the STN. The drawing is a parasagittal section adapted from the Schaltenbrand and Wahren human brain atlas. Each trace is 1 second long. **Upper Left:** Dorsal thalamic bursting cell. **Right:** Three recordings made in the STN. **Lower Left:** Recording made in the SNr.

ultimately 3 mm in diameter, that was larger than the actual diameter of the lead. The center of the round signal void was considered to represent the true lead position. Precise identification of the lead tip was facilitated by viewing the lead in three orthogonal planes on the Framelink software. The AC/PC–based coordinates of the distal tip were computed. The entry point of the lead into the brain was also identified (this was also a relatively discrete signal void) and its coordinates with respect to the AC–PC line were calculated.

The AC/PC–based coordinates of the tip and entry point were entered into a database. The coordinates of the active contact, with respect to the midpoint of the AC–PC line, were calculated from the choice of contact(s) made at the most recent programming session, from the known contact geometry (1.5 mm length, spaced 3 mm center–center) and from the coordinates of the tip and entry point. The angle of the electrode array with respect to the vertical line to the AC–PC line, in both sagittal and coronal projections, was calculated from the coordinates of the tip and entry point. The formulas for these calculations are provided in the Appendix.

**Lead Coordinates by Reference to Surrounding Nuclei.** To account for anatomical variability in spatial positions of targeted nuclei with respect to the AC and PC, we also measured lead location with reference to the red nucleus, the structure nearest to the STN that can be reliably located on MR imaging in the axial plane 4 mm inferior to the AC–PC line.

**Programming of Stimulation Parameters and Clinical Outcomes**

Programming of stimulation parameters was usually performed within 1 to 2 days after surgery, but it was post-

poned up to 1 month in patients in whom there was extreme early sensitivity to stimulation-induced dyskinesias or in whom there was transient postoperative disorientation. Programming was usually performed while the patient was in the on-medication state. In most patients programming was conducted in a monopolar configuration by using a single contact that had been placed in the dorsal STN, as confirmed by intraoperative observations. In cases in which mild stimulation induced dysarthria or facial contraction occurred in the therapeutic voltage ranges, bipolar stimulation was used, with the two contiguous contacts spanning the STN. The more dorsal contact of the pair was programmed to be the negative electrode. The frequency and pulse width were initially set at 185 Hz and 60 μsec. Voltage was titrated for clinical benefit over the initial months, usually to 2 to 3 V. We did not systematically assess the effects of stimulation through contacts outside the STN. However, in cases in which little or no benefit was reported by the patient after a few weeks in one configuration, more ventral or more dorsal contacts were used in an attempt to optimize clinical benefit.

Neurological assessment was performed preoperatively by using the UPDRS and timed motor tests. The UPDRS motor subscale (Part III) was performed on separate occasions when the patient was in the off- and on-medication states. The off-medication state was produced by withholding antiparkinsonian medication for 12 hours. In a subset of patients postoperative UPDRS testing was performed during periods of off- and on-medication and off- and on-stimulation.

**Data Analysis and Statistical Methods**

All data related to the surgical procedure, intraoperative physiological findings, lead locations, and programming were entered into a customized database. The hypothesis was that lead or microelectrode track locations that were associated with a particular physiological observation would be located at different coordinates than leads or microelectrode tracks that were not associated with that physiological observation. Hypothesis testing was performed using multivariate logistic, with the aid of commercially available software.

**Sources of Supplies and Equipment**

The Leksell series G stereotactic frame and the phantom head were purchased from Elekta (Norcross, GA). Medtronic (Minneapolis, MN) manufactured the model 3397 DBS lead and the Itrell II and Soleta pulse generators. Image Guided Neurologics (Melbourne, FL) manufactured the Navigus lead-anchoring device. Access software (Microsoft Corp., Redmond, WA) served as the database for the AC/PC–based coordinates. Two 1.5-tesla MR imaging units were used in this study: Symphony, provided by Siemens (Erlangen, Germany), and Horizon, provided by General Electric Medical Systems (Milwaukee, WI). The Stealth workstation and Framelink surgical planning software were obtained from Medtronic–Sofamor Danek. Two types of microelectrodes were used for recordings of extracellular action potentials: gold and platinum–plated tungsten microelectrodes, which were custom-made for us at Toronto Western Hospital, and platinum–iridium microelectrodes, which were obtained from Microprobe, Inc.
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(Gaithersburg, MD). The action potentials were visualized and given sound by using equipment obtained from Axon Instruments (model GS 3000; Foster City, CA). Axon Instruments also produced the Clinical Micropositioner and David Kopf Instruments (Tujunga, CA) manufactured the hydraulic microdrive.

The Multi-Spike Detector, produced by Alpha Omega Engineering (Nazareth, Israel) was used to discriminate spikes during MER, and Labview was used to make subroutines. Multivariate logistic regression analysis was performed using statistical software from SPSS (Chicago, IL).

**Results**

**Targeting Based on MR Imaging**

The STN was directly visualized on T1-weighted coronal FSE images for 70 (92%) of 76 procedures. In those cases in which the STN was not clearly visualized, the indirect target method (12 mm lateral, 3 mm posterior, and 4 mm inferior to the midcommissural point) was used as the sole method of anatomical targeting.

For the 70 procedures in which the STN was visualized, the mean and range of the AC/PC–based coordinates of the center of the STN were as follows: lateral 12.9 mm (range 11–15 mm), AP –3.5 mm (range –1 to –7 mm), and vertical –5.3 mm (range –2 to –8.5 mm).

In 24 (34%) of 70 procedures, the STN was visualized at a position that was greater than 1 mm more lateral than the AC/PC–based coordinate of 12 mm from the midline, resulting in a slight increase in the lateral coordinate. In 31 (40%) of 70 procedures the STN was seen greater than 1 mm more inferior than the AC/PC–based coordinate of –4 mm from the midcommissural point, resulting in a slight inferior adjustment in the vertical coordinate. After adjustments were made on the basis of direct visualization of the STN, the means and ranges of the initial anatomical target coordinates were the following: lateral 12.3 mm (range 11.5–14 mm), AP –3.3 mm (range –5.5 to –2 mm), and vertical –4.9 mm (range –2.5 to –7 mm).

**Spontaneous Neuronal Activity**

Recordings encountered during a typical microelectrode penetration are shown in Fig. 3. We usually recorded cells in the caudate nucleus and the anterior thalamus before moving into the STN. There was little difficulty in recognizing the STN, based on its characteristic irregular discharge at 20 to 50 Hz and dense cellularity, resulting in a noisy baseline and many multunit recordings. After exiting the STN, we explored another 2 mm in an attempt to identify the SNr by its characteristic rapid, regular discharge at 20 to 50 Hz and dense cellularity, resulting in a noisy baseline and many multunit recordings. After exiting the STN, we explored another 2 mm in an attempt to identify the SNr by its characteristic rapid, regular discharge.

The total number of MER tracks made during the 76 procedures was 245, for a mean of 3.2 per side (range 1–6). The STN was identified physiologically during the first penetration in 73 (96%) of 76 procedures, and in 58 procedures (76%) the first penetration traversed 3 or more mm of the STN. On average, a 3.8-mm segment of STN was recorded on the initial trajectory (range 0–5.9 mm). The SNr was recorded below the STN on 129 of MER tracks (53%).

The mean (± standard deviation) spontaneous firing rates were 34 ± 14 Hz for 102 STN cells and 86 ± 16 Hz for six SNr cells. In five patients in whom visible tremor was present during MER, cells with discharges grouped at tremor frequency were recorded.

**Movement-Related Neuronal Activity**

Movement-related activity was found on 131 of the MER tracks (53%). Movement-related activity was concentrated in the dorsal 3 mm of the nucleus, 10 to 14 mm from the midline. A total of 348 movement-related cells (mean 4.6 per procedure) were encountered. Of these cells, 35% were leg related, 59% were arm related, and 6% were mixed. Responses to proximal joint motions were more frequent than those to wrist, finger, or ankle motion. In eight procedures no movement-related cells were recorded. This was usually due to a pulsation artifact that interfered with the identification of movement-related activity. In two procedures, however, the lack of movement-related activity was probably due to the fact that all microelectrode penetrations (interpreted retrospectively after viewing the postoperative MR image) were located too anteromedial in nonmotor regions of the STN.

Using the lead location from postoperative axial FSE MR images as a marker, we retrospectively extrapolated the AP and lateral coordinates of all 62 microelectrode tracks along which at least three movement-related cells were encountered. For example, if a particular MER track was made 1 mm medial and 1 mm posterior to the location of the DBS lead and if the DBS lead was found to have a lateral coordinate of 12.5 mm with respect to midline and an AP coordinate of 3 mm with respect to the center of the red nucleus (defined at a vertical position of –4 mm), the MER track was assigned a lateral coordinate of 11.5 mm and an AP coordinate of 2 mm anterior to the red nucleus. Tracks associated only with leg-related cells had a mean lateral coordinate of 11.27 mm, whereas those associated only with arm-related activity had a mean lateral coordinate of 12.09 mm. Leg-related activity on an MER track was more often seen in medial tracks, whereas tracks with cells exclusively responding to arm movements were seen more laterally. This, however, did not reach statistical significance (p < 0.07). There was no apparent difference between mean AP locations for arm- and leg-related activities. We noted a tendency for leg-related activity to occur in a more concentrated area than arm-related activity. The leg-related area was not only relatively medial, but along the medial parasagittal planes, it was concentrated centrally, away from the anterior and posterior poles, compared with arm-related activity.

**Microstimulation Study**

Microstimulation was typically performed only on trajectories along which the SNr had not been encountered within 2 mm below the base of the STN, or where the STN and SNr were both missed. Stimulation-induced effects at less than 40 μA peak-to-peak were observed in six (16%) of the 37 procedures in which microstimulation was performed (biphasic square wave, pulse width 200 μsec, frequency 300 Hz). The following responses were noted: tongue contraction (four procedures), ipsilateral eye abduction (one procedure), and tremor arrest (one procedure).

**Use of MER and Microstimulation Data to Modify the Anatomical Target**

Figure 4 illustrates the most important ways in which
MER was used to modify the initial anatomical target. Four illustrative cases are shown, including the MER map in the region of the STN and immediate vicinity. The microelectrode tracks (dotted lines) are superimposed on a drawing of the STN derived from the closest available parasagittal plane of the Schaltenbrand and Wahren atlas. Tracks are labeled T1 through T4 according to the order in which they were made; the numbers in parentheses represent the AP and lateral positions in millimeters, respectively, with regard to the initial anatomical target (positive direction defined as anterior and lateral). Segments are shaded according to the corresponding cellular activity that was recorded: gray represents the STN, black the SNr, and unshaded the red nucleus. Movement-related cells are shown as triangles (leg related) or circles (arm related). Microstimulation thresholds (stim) are indicated where a positive result was obtained and labeled according to the current threshold in microamperes for the observed effect as well as the body part whose motion was observed. The column containing grids shows a schematic in the axial plane of the locations of each microelectrode track (labeled T1 through T4) and of the final lead placement (L). The grid lines are drawn every 2 mm. Ant, Post, Med, and Lat indicate the anterior, posterior, medial, and lateral directions. The last column contains postoperative axial FSE MR images (parameters shown in Table 1) obtained 4 mm inferior to the commissures. The lead corresponding to the case described is indicated by an arrow. Note that in some cases, there is a contralateral lead that had been placed during a previous operation.

In Case 1, the initial MER track missed the target completely, passing posteromedial to the STN to enter the red nucleus. The red nucleus can potentially be confused with the STN based on their similar firing rates and the presence of movement-related activity, but it may be distinguished from the STN by its lower cell density, more regular discharge pattern, and occurrence in a more ventral location along the MER track than would be expected for STN.

In Case 2, only a short segment (1–2 mm) of STN was encountered on the first MER track, indicating a peripheral localization in the nucleus. The clues that indicated that the first MER track was too lateral were provided by microstimulation-induced corticobulbar activation just below the STN, and by the absence of the SNr below the STN (because the SNr does not extend as laterally as the STN).

Cases 3 shows an “outlier” lead location from early in our series. Both the initial MER penetration and the final lead location were anteromedial to the desired target, passing through nonmotor regions of the STN. In retrospect this was evident from the MER map, based on the absence of
Deep brain stimulation of the subthalamic nucleus has been recorded. Movement-related activity in tracks nearest the final lead location. Subsequent to this case, we refined our mapping strategy. If the first penetration demonstrated STN spontaneous activity but no movement-related activity, we continued mapping in an area 2 to 3 mm more lateral and 2 to 3 mm more posterior to the initial target. Additional evidence of an excessively anteromedial location is sometimes afforded by microstimulation of the mesencephalic tract of the third cranial nerve (inducing eyelid opening and adduction of the ipsilateral eye), deep to the anteromedial STN.

Case 4 illustrates implantation of the DBS lead after a single MER track has been performed. We considered lead implantation after only one MER track had been obtained when the initial track was long (> 4-mm segment of the STN) and showed robust movement-related activity with at least some leg-related activity. The finding of leg-related activity is suggestive of a localization that is both relatively medial in the motor territory and away from the rostral and caudal poles. Thus, the identification of the leg territory is of high localizing value. We usually place the lead 1 mm lateral to a track where extensive leg-related activity has been recorded.

Intraoperative Stimulation-Induced Adverse Effects

Adverse effects elicited by intraoperative test stimulation are shown in Table 2 (bipolar mode using the two contacts spanning the STN with the settings at 185 Hz, 60-μsec pulse width, ≤ 10 V). In six procedures, complete evaluation of stimulation-induced effects was not possible because there was a lack of cooperation on the part of the patients; thus, the data in Table 2 represent 70 rather than 76 implantation procedures. Stimulation-induced adverse effects were always rapidly reversible with cessation of stimulation. Stimulation-induced dysarthria or contralateral facial contraction occurred at less than 10 V in 46 cases (66%) and contralateral paresthesias in 29 cases (41%). When present, the body part in which paresthesias were perceived at the lowest voltage threshold was variable: upper extremity (10 procedures), lower extremity (nine procedures), hemibody (six procedures), face or head (three procedures), and torso alone (one procedure). All other effects, at the parameters described earlier, were infrequent (Table 2). Diplopia occurred in patients during nine procedures (12%) and was usually subjective, without an obvious monocular deviation. Two patients (3% of procedures) reported stimulation-induced visual blurring that was not associated with diplopia. Only eight patients (11% of procedures) experienced acute stimulation-induced dyskinesias during intraoperative testing. Eight patients (11% of procedures) reported a vague, but unpleasant sensation in the head, typically described as head pressure or a sense of the head expanding. In five patients no objective or subjective stimulation-induced adverse effects were noted at the standard testing parameters given earlier; however, in all of these cases, dysarthria, paresthesias, or diplopia was inducible by higher pulse widths (up to 250 μsec) and voltages of 5 to 10 V.

During three procedures, intraoperative test stimulation thresholds for adverse effects were considered unacceptable (< 2 V), resulting in withdrawal and replacement of the DBS lead. The lead was moved to a more medial location in two procedures in which bulbar activation occurred at less than 2 V and to a more posterolateral location in one case in which diplopia was induced at less than 2 V.

While testing only contacts in the STN, no patient exhibited stimulation-induced mood changes. Although we did not systematically test deep contacts, we did observe stimulation-induced mood depression intraoperatively in one patient, with Contacts 0 (negative pole) and Contact 3 (positive pole), 60 μsec, 185 Hz, 4 V. In this case, Contact 0 was in the dorsal SNr, based both on intraoperative physiological findings and on postoperative MR images.

Intraoperative Stimulation-Induced Therapeutic Effects

During the 14 procedures in which there was resting tremor during test stimulation, there was a stimulation-induced reduction in tremor in 10 (71%) at 0 to 5 V and in 13 (93%) at 0 to 10 V (pulse width 60 μsec, frequency 185 Hz). In contrast to what is observed during thalamic stimulation, however, tremor was rarely totally eliminated with acute stimulation and, frequently, the reduction was modest. The degree of intraoperative tremor control did not seem to predict long-term control, because even those who displayed only modest or absent relief from tremor intraoperatively experienced more substantial tremor relief with chronic stimulation. We did not systematically search for improvements in parkinsonian symptoms other than tremor, although we noted that contralateral rigidity usually improved in response to microelectrode mapping or DBS lead insertion.

Time in the Operating Room

The mean operating room time per lead implantation (from incision to closure of the scalp, not including pulse generator insertion) shortened from 4.5 hours/lead in the first ten procedures to 2.5 hours in the last 10 procedures.

Magnetic Resonance Imaging–Verified Lead Locations

Examples of gradient-echo MR images demonstrating the lead tip and entry are shown in Fig. 5. The mean location of the contact arrays with respect to the midcommissural point are provided in Table 3, and their distribution

<table>
<thead>
<tr>
<th>Effect</th>
<th>Threshold</th>
<th>Lowest Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>dyssarthria or facial contraction</td>
<td>10 (14)</td>
<td>46 (66)</td>
</tr>
<tr>
<td>arm, leg, or truncal muscle contraction</td>
<td>2 (3)</td>
<td>10 (14)</td>
</tr>
<tr>
<td>paresthesia</td>
<td>15 (21)</td>
<td>29 (41)</td>
</tr>
<tr>
<td>diplopia</td>
<td>2 (3)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>blurred vision</td>
<td>1 (1.4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>conjugate eye deviation</td>
<td>0</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>vague sense of head discomfort</td>
<td>3 (4)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>dyskinesia</td>
<td>5 (7)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>vertigo</td>
<td>10 (14)</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

* Tests were performed in bipolar mode between the two contacts spanning the STN at a pulse width of 60 μsec, a frequency of 185 Hz, and a voltage of 0 to 10.
The mean AC/PC–based coordinates of the midpoint of the quadripolar array were the following: lateral 11.6 mm, AP –2.9 mm, and vertical –4.7 mm. Following programming of the devices, at a mean follow-up duration of 9 months, the mean coordinates of the active contacts were the following: lateral 11.8 mm, AP –2.4 mm, vertical –3.8 mm. The mean angulation of the leads in the sagittal projection, from the vertical line to the AC–PC line, was 29.2˚ (range 14.1˚–41.2˚). The mean angulation of the leads in the coronal projection, from the midsagittal plane, was 10.2˚ (range 0˚–24.3˚).

Fast–spin echo imaging in the axial plane demonstrated the position of the lead with respect to surrounding nuclei (several sample FSE MR images are shown in Fig. 4). The mean distance of the contact array with respect to the center of the red nucleus, measured on FSE images at an axial level of 4 mm below the intercommissural line were 3.5 mm anterior (range –1.2 to 8.1) and 6.5 mm lateral (range 3.5–9.3). On axial imaging, the “average” lead was lateral to the anterior border of the red nucleus.

### Differences Among the Anatomical Target, the Physiological Target, and the MR Imaging–Verified Lead Location

Table 4 summarizes the degree of modification of the initial anatomical target that occurred as a result of intraoperative physiological mapping. The data were analyzed both for bias (middle column) and for accuracy (right column). The middle column of the table provides the mean vector change in each coordinate subsequent to physiological mapping. This provides a measure of the degree of bias in the initial MR imaging–based targeting. The fact that the means were near zero indicates that, on average, there was no systematic tendency to move the lead in a particular direction based on physiological mapping. Of note, in the first 20 procedures, the AP coordinate used in the indirect targeting formula was –4 mm. In those procedures, the mean change in the AP direction was in fact +0.5 mm, indicating a systematic tendency to target too posteriorly with respect to the physiologically mapped STN. When the AP coordinate was adjusted to –3 mm after the first 20 procedures, the remaining 56 procedures had a mean AP adjustment of –0.03 mm, thus validating the choice of –3 mm over –4 mm as a starting coordinate.

The mean absolute change in coordinates (Table 4, right column) provides a measure of accuracy, that is, the difference between the positions of the initial and final intraoperative targets, without consideration of the direction of the difference. The mean absolute change was near 1 mm for the vertical and AP directions, but only 0.5 mm for the lateral direction. In 19 procedures (25%), however, a change of 2 mm or greater was made in the lateral or AP direction. Those cases did not appear to be associated with any particular age group, brain size, or degree of brain atrophy; thus, microelectrode mapping substantially altered the position of the DBS lead in a significant minority of cases.

The modification of the initial anatomical target according to intraoperative physiological findings provides one method of assessing the accuracy of anatomical targeting. An additional, less subjective method is to compare the predicted AC/PC–based coordinates of the lead center in stereotactic space—after adjustment for intraoperative physiological findings—with the actual coordinates of the lead center as measured on the postoperative MR image. This comparison is provided in Table 5. As in Table 4, the middle column represents bias (vector difference), whereas the right column represents accuracy (absolute difference). The discrepancy between the predicted coordinates of the lead and the actual coordinates is somewhat greater than the discrepancy between anatomical and physiological targets detailed in Table 4.

### Lead Locations Related to Intraoperative Test Stimulation

Figure 7 displays aggregate lead locations for all procedures in the axial plane, indicating the lowest-threshold adverse effect observed for each lead during intraopera-
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Clinical Outcomes and Complications

Clinical outcomes for a subset of patients are shown in Table 6. The follow-up period for unilateral DBS of the STN was 3 months and that for bilateral DBS of the STN was 12 months. In the off-medication state, the mean improvement in the score on the motor subscale (Part III) of the UPDRS was 23.3% for unilateral DBS and 45% for bilateral DBS.

We do not yet have sufficient outcomes data for a statistical correlation of lead location with clinical benefit. There were, however, two outlier leads in this series that were ineffective or unusable, and they are suggestive of the boundaries of clinically effective lead location. The first was the most anteromedially placed lead in this study, shown in Fig. 4, Case 3 (right lead) and in Fig. 6 (most anteromedial symbol). On the postoperative MR image, at an axial level of 4 mm below the midcommissural plane, this right-sided lead appeared to be 9.3 mm off the midline, 4.3 mm lateral to the center of the red nucleus, and 9.3 mm anterior to the center of the red nucleus, whereas the contralateral (left) implant was 13.4 mm from the midline, 6.8 mm lateral to the red

nucleus, and 4.8 mm anterior to the center of the red nucleus. The left lead alone resulted in an improvement in the off-medication UPDRS Part III score of 39% for unilateral (left) DBS. The inclusion of the right-sided, suboptimally located lead essentially added no incremental benefit, with an improvement in the off-medication UPDRS Part III score of 40% for bilateral DBS.

The second outlier lead location was excessively lateral: 14 mm from the midline and 9 mm lateral to the center of the red nucleus according to structures on the postoperative MR image. Although not the most lateral lead in this series, it was placed in a patient whose STN was more medial than normal, centered 11 mm from the midline. Its AP location was deemed “average,” at 3.3 mm anterior to the center of the red nucleus. The contact within the dorsal STN could not be programmed over 1 V without producing facial contraction. The lead was replaced with a new one, during a second stereotactic surgery (under fluoroscopic guidance without MER). Although the final lateral coordinate of 12.5 mm from midline (and 7.5 mm lateral to the center of the red nucleus) was only 1.5 mm more medial than the first, it allowed programming of the contact within the dorsal STN at more typical parameters (2.5 V monopolar, 60 μsec, 185 Hz) without adverse effects.

Complications are listed in Table 7. There were two hematomas visible on MR images in this series: one asymptomatic 0.7-ml hematoma in the caudate nucleus next to the DBS lead and one symptomatic 0.6-ml hemorrhage in the STN, genu, and posterior limb of the internal capsule. The latter occurred during withdrawal of the microelectrode after the initial penetration, producing facial and arm weakness. Lead implantation was not performed, and motor strength returned to normal at 1 month. No hemiballism or increased dyskinesias were observed. There was one wound infection that required intravenously administered antibiotic medication but no infections that required hardware removal.

<table>
<thead>
<tr>
<th>Coordinate</th>
<th>Middle of Contact Array (mm)</th>
<th>Active Contact (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP</td>
<td>−2.9 ± 0.16 (−7.63 to −0.74)</td>
<td>−2.4 ± 0.17 (−7.6 to +0.74)</td>
</tr>
<tr>
<td>lat</td>
<td>11.6 ± 0.16 (8.39–14.44)</td>
<td>11.8 ± 0.17 (8.4–14.7)</td>
</tr>
<tr>
<td>vertical</td>
<td>−4.7 ± 0.16 (−8.76 to −1.92)</td>
<td>−3.8 ± 0.19 (−7.5 to +0.1)</td>
</tr>
</tbody>
</table>

* Values are expressed as the means ± standard errors of the mean, with ranges in parentheses.
There were 10 procedures (13.1%) following which hardware-related problems required a return to the operating room (mean follow-up time 9 months). Problems included stereotactic repositioning of a poorly positioned lead (one procedure, discussed previously), stereotactic replacement of a broken lead associated with a connector in the cervical position (one procedure), elective repositioning of cervical connectors to the cranial position (two procedures), repair of component disconnection (two procedures), erosion of the lead extension over the clavicle (one procedure), suspected IPG malfunction (one procedure), lead extension malfunction (one procedure), and hematoma around the IPG (one procedure).

Behavioral changes lasting longer than 24 hours were initially common in patients undergoing simultaneous bilateral lead placement (the first five of our seven simultaneous bilateral procedures). These changes consisted of disinhibition, confusion, or flattened affect, and resolved by 1 to 2 weeks. Once our surgical protocol was modified so that we would place the lowest contact in the ventral STN rather than into the SNr, the subsequent patients who underwent simultaneous bilateral implantation procedures displayed no postoperative behavioral changes. Transient postoperative behavioral changes were infrequent following unilateral placement (four of 62 implantation procedures). One patient attempted suicide 1 month following unilateral placement of DBS leads into the STN. He had a history of depression prior to surgery, but no record of a previous suicide attempt. This patient did not believe that his mood was altered by activation or inactivation of the stimulator.

Discussion

Following the pioneering clinical work of Benabid and colleagues,25 stimulation of the STN is a procedure that is rapidly gaining acceptance for the symptomatic treatment of PD. Despite its growing popularity there are relatively few detailed descriptions of the technical aspects of this surgery.5,6,23,37,45,57 The goal of this report was to present and to evaluate critically our technical approach to stimulator placement into the STN in a way that is useful to other groups performing this procedure. Central to this goal is the MR imaging–based analysis of DBS lead locations and their correlation with intraoperative physiological findings. These correlations should assist other practitioners in interpreting the significance of intraoperative findings for the prediction of lead locations.

Magnetic Resonance Imaging–Based Anatomical Localization

Several groups have reported their anatomical targeting methods for the STN. Our targeting method, like that reported by others,6,51,57 was a hybrid of direct and indirect stereotactic targeting techniques. We used visualization of the STN on T2-weighted FSE images to measure directly the spatial position of the STN with respect to the AC and PC, using this to make small adjustments in the indirect coordinates (AP = 3 mm, lateral 12 mm, vertical − 4 mm). The relatively high degree of accuracy of our targeting method was demonstrated by microelectrode mapping, documenting that the anatomical target was within the boundaries of the physiologically defined STN in almost all cases.

Others have reported that the STN and its neighboring nuclei (the SNr and the red nucleus) can be visualized on T2-weighted FSE images.5,6,45,57 This is probably due to the high iron content of these nuclei, which decreases their T2 signal.14 Bejjani, et al.,5 reported on a series of 24 implantation procedures in which visualization of the STN was optimized, allowing anatomical targeting that was based exclusively on direct visualization of the nucleus, independent of the classic AC/PC–based indirect methods. To achieve optimal visualization of the STN, they reduced the field of view to the basal ganglia. This excluded visualization of the stereotactic fiducial markers and required computational fusion of images with another MR imaging data set with a larger field of view. Our imaging protocol, in contrast, maintains a large field of view for the FSE images, which includes the fiducial markers. This sacrifices some tissue contrast, but avoids the need to fuse image sets computationally.

Applying the protocols described here to a 1.5-tesla MR imaging system, it is rare that all borders of the STN are visualized with perfect precision, whereas the commissures are always clearly identified. We have therefore been hesitant to rely solely on direct targeting of the STN, with no reference to AC–PC coordinates. Slice thickness of the images with optimal nuclear visualization (the FSE images) is greater than that for the volumetric set used for AC/PC–based targeting, thus introducing greater error related to volume-averaging effects. Use of a hybrid of direct and indirect methods allows the surgeon to substitute indirect methods in cases or in certain dimensions of a case (for example, the AP dimension in our protocol), in which the coordinate of the target depicted on MR images is difficult to establish by direct visualization. Zonenshayn and associates,56 in an analysis of targeting accuracy in 30 implantation procedures, showed that better anatomical target accuracy is achieved using a hybrid of indirect and direct techniques rather than direct techniques alone. Although we did not systematically analyze the predicted accuracy that
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would have resulted from the use of different targeting methods, we found a hybrid method to be the most practical.

For groups that perform targeting solely with indirect (AC/PC–based) methods, as is necessary when ventriculography or computerized tomography scanning are the only imaging modalities, it appears that the formula used in our last 56 cases (lateral 12 mm, AP 3 mm, and vertical 4 mm) is reasonable in that it provides a low degree of systematic bias. Several lines of evidence support this. The mean coordinates of the MR imaging–visualized STN on the preoperative images were lateral 12.9 mm, AP 3.5 mm, and vertical 5.3 mm, which are close to the indirect formula we used. Second, the mean AC–PC coordinates of active contact(s) from postoperative MR imaging (which takes into account adjustments made for intraoperative physiological findings and programming for optimal clinical effect) were lateral 11.8 mm, AP 2.4 mm, and vertical 3.8 mm, values that also are close to the indirect target formula. Other groups have reported indirect target formulas for STN that are similar to ours, whereas some published formulas appear to place the initial anatomical target slightly too anterior (AP coordinate 0 mm) or slightly too medial (8–10 mm from midline) for the STN of the average brain.

In considering the coordinates of the center of the STN as seen on T2-weighted coronal imaging, individual variability in the AC–PC coordinates of STN was definitely observed. This variability, however, was somewhat less marked than is true for the globus pallidus, for which the importance of direct targeting in adjusting or supplanting indirect coordinates may be relatively greater than for STN.

Role of Physiological Confirmation

Despite the relative accuracy of anatomical targeting, our study contained a significant minority of cases in which the initial anatomical target was either outside the STN, near a border of the STN, or within nonmotor regions of the nucleus. After refining the final DBS lead position with the aid of microelectrode mapping, there were 19 procedures (25%) in which the final lead position was 2 mm or more away from the anatomical target in the AP or lateral direction. In such cases it is clear that intraoperative physiological findings resulted in a final lead location that was significantly closer to the motor area of the STN. Our data are consistent with those of several other groups that have quantitated target refinement by using intraoperative MER as the

### TABLE 6

<table>
<thead>
<tr>
<th>Condition</th>
<th>Motor Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unilat DBS</td>
</tr>
<tr>
<td>preop</td>
<td>(20 procedures)</td>
</tr>
<tr>
<td>off-medication state</td>
<td>48.1</td>
</tr>
<tr>
<td>on-medication state</td>
<td>22.1</td>
</tr>
<tr>
<td>postop w/ DBS turned off*</td>
<td>44.3</td>
</tr>
<tr>
<td>off-medication state</td>
<td>25.1</td>
</tr>
<tr>
<td>postop w/ DBS turned on*</td>
<td>33.4</td>
</tr>
<tr>
<td>off-medication state</td>
<td>20.1</td>
</tr>
<tr>
<td>% improvement†</td>
<td>23.3</td>
</tr>
<tr>
<td>off-medication state</td>
<td>14.6</td>
</tr>
</tbody>
</table>

* Test was administered at a single time point at 3 months (patients with unilateral DBS) or 1 year (patients with bilateral DBS) postoperatively.
† Between DBS on and DBS off periods.

### TABLE 7

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. of Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hemorrhagic stroke</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>asymptomatic hemorrhage</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>&gt;0.5 cm² seen on postop MR image</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>lead fracture</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>lead repositioning for poor initial position</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>return to op room for exploration/repair of lead extender or IPG</td>
<td>8 (10.4)</td>
</tr>
<tr>
<td>wound infection requiring intravenous antibiotics w/o hardware removal</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>intraop focal seizure</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>postop generalized seizure</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>postop behavioral change lasting &gt;24 hrs</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>suicide attempt</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>
gold standard. Bejjani, et al. demonstrated that five (21%) of 24 final stimulator locations differed by greater than 2 mm from the anatomical target. Rodriguez and colleagues found that in 53% of cases, the initial anatomical target was not within the motor territory of the STN according to MER and, thus, presumably was significantly modified. Zonnenberg and associates did not give a percentage of cases in which MER refinement was considered significant, but they reported a mean absolute adjustment of 1.27 mm in the initial coordinates as a result of MER, which is similar to ours. The role of “microelectrode refinement” in movement disorders surgery is frequently debated. Some groups reporting excellent outcomes for DBS of the STN do not use MER. Without more studies that correlate DBS lead or lesion location with outcome, it is not known how close is close enough. Our work and several other reports indicate that extremely meticulous anatomical targeting with historical (preoperative) MR imaging can place a lead within 1 mm of the physiologically confirmed target in many, but not all cases.

Factors that limit the accuracy of image-guided stereotaxis include the following: 1) the application accuracy of frame-based stereotactic systems; 2) image distortion effects (for MR imaging methods); 3) brain shifts that occur after preoperative imaging is complete; 4) imperfect visualization of the target structure that precludes the ability to compensate completely for anatomical variability; and 5) the fact that a specific physiological function may not always occur in the same anatomical location. The effect of microelectrode refinement on intraoperative target coordinates provides a summary measure of all these factors, but probably underestimates targeting errors because it rarely provides perfect correction of such errors. In this study, in addition to quantifying intraoperative target adjustments resulting from physiological mapping, we compared the final intraoperative target coordinates (after adjustment for physiological mapping) with MR imaging–verified lead coordinates. This provided an objective measure of errors in stereotaxis that related specifically to application accuracy, image distortion, and brain shift. We found the mean difference between predicted and actual lead coordinates to be 1.4 to 2 mm in all dimensions, with much higher deviations in individual cases. This discrepancy was greater than the degree of correction achieved by physiological mapping, suggesting that physiological mapping somewhat undercorrects the actual errors inherent in image-guided stereotaxis. Some of these errors could be overcome by the use of real-time rather than preoperative MR imaging, as has recently been described for brain biopsy.

Single-Cell Physiology and Somatotopy

The mean cell discharge rate in the STN in patients with PD has been reported to be 41 Hz, 37 Hz, 39 Hz, 33 Hz, 46 Hz, 47 Hz. In the present study, it was 34 Hz. These determinations are fairly consistent and support the view that the mean STN discharge rate in humans with parkinsonian symptoms is greater than that measured in healthy nonprimates, as is predicted in the current model of basal ganglia circuitry in PD.

We found that microelectrode penetrations during which leg-related activity was recorded were more medial than tracks for which arm-related activity was recorded. This is consistent with other physiological studies of the somatotopical organization of the STN in humans and nonhuman primates. In these studies, the leg territory is located more medially than the arm territory. In the AP domain, leg area is central, away from the rostral and caudal poles. Thus, if primarily leg-related cells are encountered on an MER track, it can be inferred that the microelectrode is relatively medial within the motor territory of the STN.

Failure to record motor-responsive cells on MER, despite recording a long segment of the STN, can occur with relatively anteromedial microelectrode penetrations. If no motor-responsive cells are found during the initial microelectrode exploration, our current practice is to continue exploration 2 to 3 mm posterolaterally.

Intraoperative Stimulation-Induced Effects

The major stimulation-induced adverse effects we observed were similar to those reported by other researchers in the context of intraoperative stimulation or postoperative programming and include paresthesias, dysarthria, facial contraction, oculomotor effects, and visual blurring. We observed stimulation-induced dyskinesias intraoperatively in only a minority of cases, whereas some authors have reported that dyskinesias are a frequent observation. This discrepancy may relate to the duration of intraoperative test stimulation. With long-term stimulation (following postoperative programming of the IPG), increased dyskinesias often develop after a lag time of a few minutes or hours. The relative infrequency of intraoperative stimulation-induced dyskinesias in our series may relate to the fact that our period of intraoperative test stimulation is brief, focusing on those effects that occur immediately at a given parameter choice.

In one case, in which we used bipolar stimulation where the negative contact was located in the SNr, we did observe acute stimulation-induced mood depression. This was phenomenologically identical to the case described by Bejjani, et al., in which the negative contact was also in the SNr. When testing contacts within the STN itself, we did not observe acute stimulation-induced mood changes, although this has been reported to occur while using the same contacts that are clinically effective for PD. Given the small size of the STN, the part of the nucleus participating in the limbic (rather than motor) basal ganglia–thalamocortical circuit should be close to the motor circuit; thus, it is perhaps surprising that mood-related effects are not observed more frequently.

The exact role of intraoperative test stimulation in guiding STN lead placement has not been established. We focus on determining voltage thresholds for adverse effects. We also assess stimulation-induced reduction in tremor if present. Our primary criterion for correct lead placement is microelectrode verification of the motor territory of the STN and not intraoperative stimulation-induced relief symptoms. Other groups may systematically test for intraoperative stimulation-induced improvements in rigidity or bradykinesia. We do not systematically assess these benefits intraoperatively for several reasons. Frequently, there is an improvement in rigidity and bradykinesia associated with microelectrode mapping or lead insertion, which can confound the ability to assess any additional stimulation-induced improvements. In addition, the expected time course of stimulation-induced improvements in rigidity and
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bradykinesia is not well described and may take more than a few minutes. Therefore, the absence of immediate stim-
ulation-induced improvements in rigidity or bradykinesia is not necessarily predictive of a poor long-term result.
Even with respect to tremor control, the acute improve-
ment in tremor with intraoperative test stimulation may be less robust and require higher voltages than is the case for acute thalamic stimulation,7 even though tremor control
with long-term STN stimulation is excellent.29,39

Correlation of Test Stimulation Findings With
Lead Location

Several types of stimulation-induced adverse effects cor-
related with the lead location measured on postoperative MR images. We performed intraoperative test stimulation
in a standardized way at a pulse width of 60 μsec and a fre-
quency of 185 Hz. When paresthesias were the lowest-
threshold adverse effect, the corresponding lead locations
proved to be slightly more medial, posterior, and superior
than leads not associated with paresthesias as the lowest
threshold effect. Paresthesias are likely to be due to an ef-
fector on the medial lemniscus, because this pathway courses
posteromedial to the STN. As it ascends dorsally, it curves
laterally and approaches closer to the medial border of the
STN, which probably accounts for the somewhat sur-
prising observation that contact locations associated with
paresthesias were slightly more dorsal than those not asso-
ciated with paresthesias. Lateral leads were more likely to
produce dysarthria or muscular contraction as the lowest-
threshold adverse effect. This is reasonable because the cor-
ticobulbar and corticospinal tracts travel immediately later-
al to the STN.

The occurrence of visual blurring as the lowest thresh-
old-adverse effect was predictive of medial lead locations.
Medial and ventral to the STN lies the Edinger–Westphal
nucleus and its exiting fibers in the superficial layers of the
tract of the third cranial nerve. Stimulation-induced visual
blurring could be due to the spread to these structures or to
the supranuclear pathways innervating them. Stimulation-
induced diplopia was also observed in some cases but was not as predictive of lead location as visual blurring because
leads associated with diplopia at the standard test stimula-
tion range were variably located. There are, however, many
ways in which stimulation in the STN region could induce
oculomotor effects, in addition to the most obvious mecha-
nism of medial spread of current to the nucleus or tract of
the oculomotor nerve. Both the STN and the SNr partici-
pate in circuits subserving oculomotor control,21,54 and mod-
ulation of these oculomotor subcircuit could affect eye
movements. Alternatively, activation of corticobulbar fibers
could cause unilateral contraction of periorbital muscles,
which would produce diplopia.

In one other study of STN stimulation the authors ana-
alyzed physiological–radiographic correlations. Ashby and
coworkers2 studied the effect of STN stimulation on volun-
tary electromyographic recordings of intrinsic hand mus-
cles. Production of a short-latency electromyographic effect
was associated with more lateral leads and was thought to
be related to corticospinal tract activation. Production of a
longer-latency electromyographic effect, which correlated
closely with tremor suppression, was associated with more
medially placed leads. This effect was postulated to relate
to activation of fibers of the cerebellothalamic pathways,
which are intimately associated with the lateral border of
the red nucleus, close to the medial border of STN. Testing
for these effects required electromyographic recording and
signal averaging, whereas our study demonstrates that ad-
verse effects that are directly observable or reported by pa-
ients may also be correlated with DBS lead location.

Use of MR Imaging to Document Lead Locations

Several other reports, one about DBS in the STN2 and
two about DBS in the globus pallidus internus,5,39 also pro-
vide descriptions of the use of postoperative MR imaging to
document lead locations systematically in a series of pa-
ients. A number of pitfalls encountered using this tech-
nique must be acknowledged. First, the manufacturer of
the Medtronic DBS system cautions against MR imaging of
their device outside a limited range of imaging parameters
and field strengths. No group that uses MR imaging to mea-
sure lead locations has reported adverse effects during the
imaging procedure.3,55 Two studies that formally addressed
the safety of performing MR imaging in patients who re-
cieve DBS found no indication of harmful effects (such as
significant heating or torque on the lead) when a 1.5-tesla
magnet and a headcoil were used.38,48 Nevertheless, it is not
known whether the use of higher field strength magnets,
other types of radiofrequency receiving coils, or other pulse
sequences would result in clinically dangerous effects.

As noted by Yelnik et al.,55 the DBS lead produces an ar-
tifact that is larger than the actual lead. In our work, as in
theirs, we assumed that the actual contact location is at the
center of the observed artifact. This has not been proven.
When measured near the lead tip, gradient-echo and FSE
images contain a relatively small, round, and discrete lead
artifact. If, however, the actual lead location is not in the
center of the observed artifact, this would decrease the ac-
curacy of MR imaging–based lead location measurements.

Finally, any method of documenting lead locations across
multiple patients is hampered by interindividual variability
in the shape and size of the target nucleus, as well as in its
exact position with respect to surrounding structures. Mag-
netic resonance images do not perfectly depict the borders
of the target (particularly with a superimposed lead artifact),
thus forcing us to infer lead location by reference to other
more reliable landmarks. We have attempted to deal with
this issue by reporting lead locations with respect to the
closest nuclear structure that is reliably visible on MR im-
ages (the red nucleus), in addition to reporting AC/PC–
based lead coordinates. Yelnik et al.55 deformed a brain
atlas linearly in three dimensions so that it could be super-
imposed on the MR image by using as landmarks those
deep structures that were reliably visualized on both the MR
image and the atlas. They acknowledge that linear transfor-
mation of a brain atlas is not necessarily accurate, because
it makes the questionable assumption that in any given di-
menion, all structures can be stretched or shrunk by the
same factor to compensate for individual variability. Com-
putational mapping of different individual brains onto a sin-
gle standardized brain map is a complex and important
problem that has not yet been solved.

Location of the Active Contact in the Dorsal STN

In the nonhuman primate that displays parkinsonian

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symptoms, the antiparkinsonian benefits of STN ablation appear to be due to an effect on cells within the dorsolateral STN. Given the likelihood that ablation and high-frequency stimulation are mechanistically dissimilar, we cannot assume a priori that the therapeutic effect of DBS is also due to an effect on the dorsolateral STN. Voges and coworkers suggest that the contact providing the best antiparkinsonian effect at the lowest stimulation parameters is located dorsal to the STN. Ashby and colleagues suggest that the antitremor effect of STN stimulation may be due to stimulation of surrounding fiber pathways and not due to an effect on STN cell bodies.

In this study, the mean location of the active contacts of the DBS leads, after programming for optimal clinical benefit, did correspond to the dorsolateral STN. This was true with respect to standard anatomical atlases and to intraoperative single-cell physiological findings. Because we did not systematically evaluate all contacts for clinical efficacy, we cannot prove that a contact outside the STN would not have similar efficacy. Nevertheless, it is clear that beneficial effects on parkinsonian symptoms that are obtained at moderate stimulation parameters, which are only expected to affect tissue in a radius of several millimeters, can occur with the active contact within the dorsal STN.

Our active contact locations (Figs. 6 and 7) do reflect some variability. This may relate to an imperfect measurement of leads by MR imaging or to the inherent difficulty in plotting contacts with respect to a single brain atlas (as in Fig. 7), which cannot reflect the variability among patients’ brains. It is likely, however, that some of this variability reflects the learning curve in performing the procedure. Some of the leads that we implanted are not located in the center of the motor territory of the STN (Fig. 4, Case 3). As we gained experience by correlating intraoperative physiological findings with postoperative images, we became more adept in the use of intraoperative physiological findings to direct appropriate intraoperative adjustments in lead location, resulting in more consistent lead locations.

Some of our more medially placed leads were located very close to the anterolateral edge of the red nucleus, probably close enough for part of the red nucleus to be affected during long-term stimulation. In humans, lesions in the region of the red nucleus may cause coarse tremor or gait ataxia. We have not, however, observed stimulation-induced tremor or ataxia, even in those patients with more medially placed leads.

**Approach Angle**

Stimulation-induced effects in neural tissue are sensitive to the orientation of the lead with respect to fiber pathways. Approach angles used to implant DBS leads in the STN vary significantly between surgeons. Bejjani, et al., report an approach to the STN that involves the use of a relatively lateral-to-medial trajectory, 20 to 30° from the vertical axis in the coronal projection compared with our mean lateral-to-medial angle of 10.2° from the vertical axis. With respect to the sagittal projection, Rodriguez, et al., report a relatively horizontal approach of 45° from the vertical axis compared with the 29.2° from the vertical axis used in our study. Voges and associates also report a relatively horizontal approach, with the entry point 2 to 3 cm anterior to the coronal suture. Such differences could influence which fiber pathways are most readily activated during intraoperative test stimulation. The approach angle of leads within the series, however, did not vary sufficiently to test this hypothesis.

We prefer the relatively vertical trajectory because it usually grasps the anterior thalamus. The length of the thalamic segment encountered becomes a useful landmark during microelectrode mapping. For example, if the STN is missed on the initial microelectrode penetration, the extent of thalamic activity superior to the target area may be used to determine whether the second MER track should be performed anterior or posterior to the first one.

**Clinical Outcomes**

In this series, unilateral DBS of the STN produced a 23% improvement in UPDRS Part III motor scores in the off-medication state at 3 months postimplantation. Bilateral DBS of the STN produced a 45% improvement at 1 year following the second implantation procedure. This is consistent with outcomes reported by others for unilateral and bilateral DBS of the STN. In nearly all published series of patients treated with bilateral DBS of the STN a 40 to 65% improvement in UPDRS motor scores have been reported, despite major differences in the technical approaches to the surgery. Thus, currently available outcomes data do not mandate the adoption of one particular set of implantation techniques.

**Lead Locations in the STN: Comparison With Other Groups**

Several groups have published STN locations of DBS leads, as verified by intraoperative ventriculography or postoperative MR imaging. Benabid, et al., reported locations of 95 STN active contacts in a graphic format (display of contacts on a Guiot diagram) but did not provide numerical mean contact locations. Their active contacts appear to have been located 10 to 14 mm from the midline, 0 to 5 mm posterior to the midcommissural point, and 3 to 5 mm below the intercommissural line. Our active contact locations are clustered in a region very similar to theirs. This is noteworthy in light of the fact that their primary endpoint for determining final lead position was intraoperative observation of a clinical benefit, whereas ours was placement within the microelectrode-defined motor territory of STN.

Lead locations reported by Voges, et al., and by Ashby and coworkers differ somewhat from those reported here. Voges and associates report the mean coordinates of the distal contact in 29 DBS implants in the STN as lateral 9.7 mm, AP −2.3 mm, and vertical −3.9 mm for right-sided leads, and as lateral 10.6 mm, AP −2.1 mm, and vertical −3.9 mm for left-sided leads. Their electrode arrays were located slightly more medial than those in our study. In addition, many of their active contacts were located more proximal along the quadripolar array than the distal contact and were located anterodorsally with respect to the STN. Therefore, their mean active contact locations were probably also more anterior and superior than those in our study. Ashby and coworkers described locations for 19 STN leads based on postoperative MR images. They quantified only the lateral coordinate of their leads, which on average was 9.7 mm from midline and, thus, 2 mm more medial than our average location.
Deep brain stimulation of the subthalamic nucleus

**Lead Location and Clinical Outcome**

Groups that have reported imaging-verified electrode locations\(^{2.6,51}\) have all reported stimulation-induced improvements in parkinsonian motor signs that are robust and similar to those reported here.\(^{38,27,53,52}\) Despite apparent differences in average lead location, analysis of our own outlier lead locations suggests that leads in the anteromedial STN may be clinically ineffective, whereas leads near the lateral margin of the STN may be unprogrammable due to low-threshold corticobulbar activation. We have not yet accumulated sufficient outcomes data, however, to allow formal statistical analysis of the relationship of lead location to clinical outcome. More detailed correlations of lead location with outcome will be needed to establish more clearly the range of active contact locations that are associated with optimal improvement in motor function.

**Complication Avoidance**

Our rate of serious complications was low, with two hemorrhages visible on neuroimaging, both of which were smaller than 1 ml and one of which was symptomatic. Postoperative changes in mental status were initially common following simultaneous bilateral implantation. During this series, we altered our protocol to place the distal contact in the ventral STN rather than in the SNr, thus reducing the degree to which we overshot the target. This decreased the incidence of postoperative changes in mental status, suggesting that such changes may be related in part to midbrain edema associated with deep lead placement.

The essential steps that we adopted to minimize complications while optimizing accuracy were as follows: 1) meticulous MR imaging–based anatomical targeting, with an attempt to use direct visualization of the STN to make fine adjustments in the AC/PC–based targeting formula; 2) use of surgical planning software for 3D trajectory planning to avoid traversing deep sulci and, where possible, avoid the ventricles; 3) judicious use of sequential single-channel MER in which the maximum degree of localizing information was inferred from the minimum number of penetrations; 4) maintenance of intraoperative systolic blood pressure at a level lower than 140 mm Hg; 5) placement of the DBS lead tip no deeper than the ventral border of the STN; and 6) postoperative high-resolution MR imaging in every case, which provided immediate feedback regarding the correlation of intraoperative physiological findings with anatomical lead location. The last step facilitated rapid ascension of the learning curve for performing DBS of the STN.

**Conclusions**

Our technical approach to stimulator implantation into the STN involved the use of MR imaging–based targeting, identification of the motor territory and confirmation of nuclear boundaries by using MER, placement of the lead within the motor territory of the STN, and brief intraoperative test stimulation to confirm the absence of low-voltage stimulation-induced adverse effects. This approach is relatively safe and time efficient and resulted in lead locations similar to those reported by groups that determine optimal lead placement by extensive intraoperative neurological testing. Microelectrode mapping resulted in a major change in the final location of the DBS lead in 25% of cases. Use of postoperative MR imaging to measure lead location quantitatively is technically feasible and provides valuable correlations with intraoperative physiological mapping.

**Appendix**

Formulas for Calculating AC–PC Coordinates of Active Contact(s) From Entry Point and Tip Coordinates

1. Let \( x \) = (lateral entry − lateral tip);
2. Let \( y \) = (AP entry − AP tip); and
3. Let \( z \) = (vertical entry − vertical tip)

where lateral entry, AP entry, and vertical entry refer to the lateral, AP, and vertical distances, respectively, between the DBS entry point and the midcommissural point; and where lateral tip, AP tip, and vertical tip refer to the lateral, AP, and vertical distances, respectively, between the DBS tip point and the midcommissural point.

4. Let \( L \) = length of lead in brain = square root \( (x^2 + y^2 + z^2) \);
5. Let \( D \) = distance between midpoints of adjacent contacts (3 mm for the Medtronic model 3387 lead);
6. Let \( Q \) = distance from tip to midpoint of active contact array;
7. then \( Q = 0.75 + D \) (mean of active contact numbers)

Examples: If the system is programmed as monopolar Contact 2 only, then the mean active contact number = 2; if the system is programmed as bipolar or monopolar with Contacts 2 and 3, then the mean active contact number = 2.5.

Then the lateral, AP, and vertical coordinates of the center of the active contact array are the following:

8. Lateral center = \( (Q/L)x \) + lateral tip;
9. AP center = \( (Q/L)y \) + AP tip, and
10. vertical center = \( (Q/L)z \) + vertical tip;

and the angles of approach in the coronal and sagittal projections are the following:

11. approach angle in sagittal projection = arc tan \( (y/z) \) and
12. approach angle in coronal projection = arc tan \( (x/z) \).

**Acknowledgments**

We thank Drs. Thomas Wichmann, William Dillon, Nicholas Barbaro, Paul Larson, and Robert Turner for their critical reading of the manuscript. We thank Kathleen Lamborn for assistance with statistical analysis, and Tammy Damalcherevu for administrative assistance. We thank Heidi Clay, R.N., and Susan Heath, R.N. for their work in DBS programming.

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Manuscript received July 19, 2001. Accepted in final form April 29, 2002.

This work was supported in part by a grant from Medtronic Neurological (Minneapolis, MN) to Philip A. Starr and by the Parkinson’s Disease Research, Education, and Care Center (PDRECC) at the San Francisco Veteran’s Affairs Hospital.

Address reprint requests to: Philip A. Starr, M.D., Ph.D., Department of Neurological Surgery, University of California at San Francisco, 779 Moffitt Hospital, 505 Parnassus Avenue, San Francisco, California 94143. email: starrp@itsa.ucsf.edu.