Localization of clinically effective stimulating electrodes in the human subthalamic nucleus on magnetic resonance imaging

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Object. The authors sought to determine the location of deep brain stimulation (DBS) electrodes that were most effective in treating Parkinson disease (PD).

Methods. Fifty-four DBS electrodes were localized in and adjacent to the subthalamic nucleus (STN) postoperatively by using magnetic resonance (MR) imaging in a series of 29 patients in whom electrodes were implanted for the treatment of medically refractory PD, and for whom quantitative clinical assessments were available both pre- and postoperatively. A novel MR imaging sequence was developed that optimized visualization of the STN. The coordinates of the tips of these electrodes were calculated three dimensionally and the results were normalized and corrected for individual differences by using intraoperative neurophysiological data (mean 5.13 mm caudal to the midcommissural point [MCP], 8.46 mm inferior to the anterior commissure–posterior commissure [AC–PC], and 10.2 mm lateral to the midline).

Despite reported concerns about distortion on the MR image, reconstructions provided consistent data for the localization of electrodes. The neurosurgical procedures used, which were guided by combined neuroimaging and neurophysiological methods, resulted in the consistent placement of DBS electrodes in the subthalamicus and mesencephalon such that the electrode contacts passed through the STN and dorsally adjacent fields of Forel (FF) and zona incerta (ZI). The mean location of the clinically effective contacts was in the anterodorsal STN (mean 1.62 mm posterior to the MCP, 2.47 mm inferior to the AC–PC, and 11.72 mm lateral to the midline). Clinically effective stimulation was most commonly directed at the anterodorsal STN, with the current spreading into the dorsally adjacent FF and ZI.

Conclusions. The anatomical localization of clinically effective electrode contacts provided in this study yields useful information for the postoperative programming of DBS electrodes.

KEY WORDS • deep brain stimulation • subthalamic nucleus • Parkinson disease • neurosurgery • magnetic resonance imaging

The neurosurgical treatment of selected patients with medically refractory PD has undergone a renaissance since the revival of Leksell’s pallidotomy procedure by Laitinen. Although many patients have been helped by pallidotomy, especially by the subsequent reduction in drug-induced dyskinesias, the implantation of DBS electrodes bilaterally, which was adapted from the experience of thalamic stimulation for relief of tremor, has gained considerable popularity.32,48,57,106 With advances in our understanding of the pathophysiology of PD, based on findings in animal models, the STN was reexplored as a potential target.2 It was observed that stereotactically guided lesions in the STN of the monkey MPTP model,9,18 as well as strokes involving the STN in patients with PD,90,103 resulted in a dramatic alleviation of symptoms. Although a number of patients have been reported who have been successfully treated with lesioning of the subthalamus (that is, of the STN and adjacent structures, particularly the FF and ZI),63 neurosurgeons remain concerned about the possibility of inducing ballismus or other adverse events.2,4,30,31 Thus, the placement of bilateral STN DBS electrodes has become the treatment of choice in many neurosurgery centers.14,32,52,53,57,92 Experience with pallidal and thalamic DBS revealed that high-frequency stimulation appeared to mimic the effects of lesions, but in a modifiable and potentially reversible manner.15,58 In appropriately selected patients, the clinical outcome to date has been excellent, often resulting in a mean reduction of their medication by 50% and a significant alleviation of disabling symptoms.48,50 In relatively young patients the clinical benefit from STN DBS has been...
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shown to last for 5 years or more, without significant cognitive compromise. Older patients and those with a marginal preoperative cognitive profile or psychiatric history may, however, suffer varying degrees of cognitive loss or they may decompensate behaviorally. There have even been cases of depression or inappropriate laughter and mirth attributed to STN stimulation.

In addition to the STN, however, stimulation of adjacent structures, for example the ZI, FF, and SNr, caused by spread of the current or imprecise targeting, could also account for the benefit seen in these patients. This might also account for differences in the described effects on such symptoms as dyskinesias, with some investigators reporting induction or worsening of dyskinesias in the absence of drug dosage reduction, and others claiming a direct anti-dyskinetic effect. The question arises as to the exact location of stimulation in or adjacent to the STN that most often yields the best clinical result. There are currently no data available to address this point; there is only anecdotal information about clinically useful electrodes being located within the STN. The systematic evaluation of the anatomical location of the electrodes is necessary groundwork for the analysis of many important issues, including the differential effects of stimulation on specific symptoms, on limbs affected, and on the evocation of adverse events. In addition, such an analysis is crucial for providing feedback to neurosurgeons about the accuracy of their methods and for correlating optimal electrode placement with intraoperative neurophysiological mapping. Finally, knowledge of the exact position of the DBS electrodes may be useful in programming stimulation parameters, especially in patients requiring days or weeks (in some cases months) for the optimization of symptom control.

Methodologically, there is a debate not only about the reliability and accuracy of MR imaging for stereotactic guidance, but also concerning the necessity of neurophysiological recording intraoperatively. In the final analysis, however, postoperative verification of the anatomical location of the stimulating electrodes is necessary for the analysis of many important issues, including the differential effects of stimulation on specific symptoms, or limbs affected, and on the evocation of adverse events. In addition, such an analysis is crucial for providing feedback to neurosurgeons about the accuracy of their methods and for correlating optimal electrode placement with intraoperative neurophysiological mapping. Finally, knowledge of the exact position of the DBS electrodes may be useful in programming stimulation parameters, especially in patients requiring days or weeks (in some cases months) for the optimization of symptom control.

Clinical Material and Methods

Patient Selection

Criteria for admission to the surgical program have been reviewed elsewhere. Briefly, all patients had received a clinical diagnosis of definite idiopathic PD, including a documented good response to levodopa. Patients were screened using detailed neurological and neuropsychological assessments, with additional review of their psychiatric history. Our series represents the first 29 patients for whom complete clinical and neuroimaging data were available, and in whom there were no surgical complications such as intracerebral hemorrhage. In four patients in whom unilateral pallidotomy had been performed previously, data are reported only for the side on which there was an STN electrode but no pallidotomy. Patient demographics and clinical characteristics are reported in Table 1.

Neuroimaging Methods

Before surgery, patients underwent high-resolution MR imaging (1.5-tesla unit, Signa model; General Electric Medical Systems, Milwaukee, WI) to identify the STN (Fig. 1) and its coordinates relative to the AC and PC. The importance of aligning the imaging plane parallel to the AC–PC plane for axial images, and orthogonally to it for coronal images (which often required oblique series), became apparent early in this study. The target coordinates can be expressed in a triplanar system relative to the MCP, the distance from the midline, and the depth below the AC–PC plane. Specific low-bandwidth MR pulse sequences were developed to maximize tissue contrast, thereby facilitating visualization of the STN, and to minimize image artifact and distortion caused by the presence of DBS electrodes postoperatively (Table 2). In some of our early cases, MR images either were not performed before stereotactic surgery planning or were not useful for the identification of the STN, because the optimal pulse sequences had not yet been developed.

Magnetic Resonance Parameters

On the morning of surgery, a stereotactic frame (Leksell series G; Elekta Instruments, Atlanta, GA) was pinned to the patient’s skull after a local anesthetic agent was applied to the pressure points. Using the standard reference system affixed to this frame, the AC and PC coordinates were calculated relative to its center. With the STN visualized, or by applying target coordinates obtained from the preoperative scan, or by applying coordinates assigned according to clinical experience, the surgical approach was planned.

<table>
<thead>
<tr>
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<th>Value</th>
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<tr>
<td>no. of patients</td>
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</tr>
<tr>
<td>M/F ratio</td>
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</tr>
<tr>
<td>mean age (yrs)*</td>
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</tr>
<tr>
<td>at diagnosis</td>
<td>60 ± 12</td>
</tr>
<tr>
<td>mean preop Hoehn &amp; Yahr stage</td>
<td>III</td>
</tr>
</tbody>
</table>

* Values are expressed as the means ± SD.

TABLE 1

Demographics and clinical profile in patients treated with DBS

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Surgical Methods

The surgical protocol, including neurophysiological methods, has been reported in detail elsewhere. For each side, qualitative (offline quantitative) single-unit recordings (which test single units for responses to active and passive movement) were made. As each microelectrode was withdrawn, microstimulation (maximum 100 μA) was delivered at approximately 1-mm intervals. All results were mapped intraoperatively, permitting the location of the STN and neighboring structures to be estimated from the completed physiological map. Subsequently, a trajectory and depth were selected, and the DBS quadripolar electrode (that is, one with four contacts through which current can be delivered) (Medtronic 3387; Medtronic, Inc., Minneapolis, MN) was implanted stereotactically. The choice of trajectory was determined by identifying the track in which the maximal dorsoventral extent of STN-like unit activity was found, with emphasis on the presence of unit responses to passive or active movements of the limbs. In addition, care was taken to avoid those trajectories in which microstimulation elicited low-threshold paresthesias or muscle contractions because of the likely proximity to the lemniscus or the internal capsule, respectively.

The DBS electrode target depth was determined from the microelectrode mapping and a point at the ventral border of the STN was chosen. Under fluoroscopic guidance, the DBS electrode was positioned so that the two lowest contacts (0 and 1) bridged the ventral border of the target. In this way, Contact 1 was positioned just above the ventral border of the STN. Contact 2 was expected to lie slightly dorsal to the center of the STN, and Contact 3 was expected to lie just above the dorsal border of the STN. Trial monopolar stimulation was applied to all contacts (numbered from 0 distally to 3 proximally at intensities of up to 5–6 V or roughly 5–10 mA) by using a dual-screen apparatus (model 3628; Medtronic) to determine thresholds for adverse effects such as strong and sustained paresthesias, muscle contractions, speech arrest, or any other adverse effect. If PD symptoms were present, the clinical effect of stimulation was also briefly assessed. The electrodes were affixed to the skull with the standard cap (Medtronic), with continuous fluoroscopic monitoring of electrode positions. The DBS leads were left externalized for several days (usually 3–5 days), followed by subcutaneous implantation of a neurostimulator (Medtronic Itrel II or Soletra) in the infracavicular region.

Postoperative Imaging

Postoperatively (typically after 1–5 days for most patients), the position of the electrodes was assessed using a high-resolution T2-weighted fast–spin echo sequence (Table 2) developed to reduce magnetic susceptibility artifacts and minimize noise. For patients in whom controllers were already implanted, the voltage was set to 0 as a precaution before the patient entered the magnet, although the safety of this procedure has been established. A conventional transmit/receive head coil was used to avoid electrode tip heating issues that are theoretically possible if the body coil is used to transmit radiofrequency power. The DBS electrodes were visualized in each of the three planes. An example of the postoperative scans is presented in Fig. 1.
Use of MR imaging to locate clinically effective DBS electrodes

Postoperative Patient Management

One to 6 weeks after implantation of leads and controllers, patients returned for electrode programming. With patients off medication since the previous evening (in a few cases for only 4 hours if necessary to assure adequate mobility to get to the clinic), standard screening of each electrode was undertaken. The effects of stimulation at each point were assessed using portions of the UPDRS Motor Examination subscale, depending on target symptoms (typically rigidity and tremor). Over the course of the next 3 to 4 weeks, the contact and stimulation parameters were optimized to obtain maximum clinical benefit and minimal adverse effects. Typically, this permitted the dosage of antiparkinsonian medications to be reduced. Three months and 6 months postoperatively, patients underwent a systematic UPDRS evaluation on and off medication and stimulation, as previously described. Although monopolar stimulation (that is, case positive with one of the contacts negative; for example, represented as C+, 1) was most commonly used, a few of these patients required bipolar (for example, 3+, 2) or even tripolar configurations (for example, C+, 2, 3; 3, 2, 1; or 3+, 2, 1). Care was taken to measure the AC–PC distance on the MR image from the ventricular edges of each commissure, as shown in the Schaltenbrand and Wahren atlas (often most clearly seen on sagittal T-weighted images). It must be noted that the midpoint of each commissure, as measured on axial images, is used for surgical planning. This could introduce a mean overestimate of 3 mm in the calculation of the AC–PC length, because the AC may vary in diameter from 3 to 8 mm, thus yielding a mean anterior bias of 1.5 mm for the location of the MCP (see Discussion). Those measurements and decisions were reviewed by two analysts (a neurosurgeon [L.C.M.P.] and a neuroanatomist [J.A.S.C.]). If the postoperative images were of poor quality (because of patient movement or availability of only a CT scan), patients were brought back for a high-resolution MR image and new measurements were made.

For these and all the other series of neuroimages, measurements were also made of the AC–PC length (verified in both sagittal and axial planes), of the MCP, and of the electrode tip location; this was done directly from the MR images without reformatting. When needed to correct for pitch, roll, or yaw, geometric corrections were made. All measurements were calculated independently by two trained analysts (T.H. and J.A.S.C.). Comparisons were made between the data reformatted on the workstation and sometimes an earlier image without reformatting. When needed to correct for pitch, roll, and yaw, geometric corrections were made. Discrepancies were most often encountered in the anteroposterior plane, by the superior–inferior (dorsoventral axis), and least commonly in the mediolateral axis. (Most significant departures from MR imaging–or coordinate-based targeting, as seen on physiological recordings obtained during surgery, were in the anteroposterior plane.) Similarly, in the case in which there was discordance between intraoperative mapping and postoperative MR imaging, this was in the anteroposterior plane and was usually on the order of 1 mm. With regard to the reformatting used in the Advantage Windows workstation, especially if the slice thickness was greater than 2 mm or when there was a gap between sections, larger discrepancies with the other data sets were found in two cases (5–8-mm discrepancies compared with physiological data and with other scans).

Visualization of the STN was difficult, especially on standard clinical T- and T-weighted sequences. We often found that the STN would appear to be fused with the adjacent SN, especially on axial views. The rostral and caudal limits of the STN were not always clearly defined. Using the low-bandwidth sequence (right–left phase direction) described in Table 2 proved to be the most reliable way to demarcate the STN.

In the T-weighted MR images, electrodes appeared to be larger than their actual size (the diameter of Medtronic 3387 electrodes is 1.27 mm and the length from the distal tip to the top of Contact 3 is 12 mm). Direct, calibrated measurements indicated an electrode image artifact width of 2.27 ± 1.7 mm (diameter, mean ± SD). The center of that image, however, was used to estimate the mediolateral and anteroposterior distances, and this did not introduce significant error. With regard to depth, it was assumed that the plastic tip below the most distal contact (that is, Contact 0) contributed to the image of the electrode tip, and calculations were made accordingly. If the image originated solely from the distal contact, then the calculated location of the electrode contacts would be too dorsal by a factor of approximately 1 mm. This would locate the average clinically active contact clearly above the STN and very often in the

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<tr>
<td>bandwidth (kHz)</td>
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*Fast–spin echo T- weighted sequences were performed for visualization of the STN.
ventral thalamus, contrary to the reconstructions made from postmortem pathological studies now underway at our institution. Therefore, for the measurements obtained as described earlier, given that the electrodes were implanted at an angle of approximately 60° from the horizontal axis (sagittal plane) and 10° from the vertical axis (coronal plane), the potential error is actually close to 1 mm, which is within the resolution of the MR images used in our study (2-mm sections and a voxel size of 2\texttimes 2\texttimes 1.2 mm). In an ongoing investigation at our institution of autopsy studies in which verification of electrode location is being performed, the concordance between intraoperative neurophysiological data, MR image localization, and histological reconstruction is within a 1-mm margin of error.

After we obtained the corrected coordinates for the electrode tips, the angles of implantation, both in the mediolateral (roll) as well as in the anterofrontal (pitch) planes, were directly measured on the images. The frame angles, as described in the operating room notes, did not correspond exactly to those shown on the postoperative images because the frame was not always placed in a position orthogonal to the patient’s brain (that is, the horizontal axis of the frame was not oriented exactly along the Reid plane [canthomeatal line]; therefore, deviations occurred in pitch and roll, whereas yaw could be controlled by the use of earbars, although this was not systematically done).

The final data were then entered into a computer program (Solve-It Solutions, Inc., Toronto, ON) into which the digitized outlines from the sagittal series of the Schaltenbrand and Wahren atlas had been entered. With the AC–PC distance and all measurements normalized to the atlas AC–PC length of 23 mm (actual mean AC–PC length 26.16 ± 1.41 mm [mean ± SD]), electrode trajectories were plotted in all three planes. Sagittal representations plotted in normalized coordinates with the computer program were resolved onto the digitized 9- and 12-mm sagittal Schaltenbrand and Wahren atlas plates relative to the midline, according to best fit from the neurophysiological data. Electrode contacts along the reconstructed trajectories were plotted according to the known dimensions of the electrode. Geometric corrections were applied to correct for angles of implantation. Because the size and position of the STN is known to be patient specific,23 the data were plotted relative to the MCP across patients and the mean alignment

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<th>Parameter</th>
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<th>Side Stimulated (mean ± SD)</th>
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<td>frequency (Hz)</td>
<td>163 ± 25 (130–185)</td>
<td>156 ± 25, 169 ± 24</td>
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<td>89 ± 38 (60–210)</td>
<td>89 ± 36, 91 ± 38</td>
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<tr>
<td>impedance (\Omega)</td>
<td>1179 ± 44 (494-2000)</td>
<td>1282 ± 484, 1077 ± 391</td>
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<tr>
<td>current (mA)</td>
<td>3 ± 1 (0.7–5.0)</td>
<td>2 ± 1, 3 ± 1</td>
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<td>levodopa equiv/day (mg)</td>
<td>pre-DBS 1115.1</td>
<td>post-DBS 743.09</td>
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* There was a 33.36% reduction in the levodopa equivalent dosage; p = 0.00003, according to the t-test. Abbreviation: equiv = equivalent.

**Fig. 2.** Boxplots showing motor scores before and after DBS in patients with PD. The median is indicated by the horizontal line inside the box, and the box and whiskers represent 1 SD and the 95% confidence interval (CI), respectively. The points outside the whiskers are the outliers. **Upper:** Combined clinical rating from the motor section of the UPDRS for symptom reduction contralateral to the right DBS electrode. **Center:** Combined clinical rating from the motor section of the UPDRS for symptom reduction contralateral to the left DBS electrode. **Lower:** Combined UPDRS motor ratings of symptom reduction after STN DBS on the right and left sides. **p < 0.01, **p < 0.0001.
of the atlas plate was superimposed. Each patient’s measurements, however, had been individually adjusted onto a “best STN” outline, taking into account the inconsistencies of the Schaltenbrand and Wahren atlas. The final reconstructions illustrated were considered to be a fair representation of these group data.

Results

Clinically, all patients benefited from the STN DBS. The reduction of symptoms due to STN DBS in this patient group is presented in Fig. 2 (data reflect the effect of the stimulation being on while patients had been off medication for 12 hours, compared with preoperative off-medication scores). Composite scores are given for contralateral limbs only; no axial measures were included (that is, neck rigidity, head or facial tremor, postural stability, gait, or whole-body bradykinesia). In general, tremor and rigidity responded best to DBS, whereas bradykinesia was more refractory.

The parameters used for effective stimulation are reported in Table 3, along with reductions in medication in levodopa-equivalent doses, as calculated previously. Using the combined methods of pre- and postoperative MR imaging, multiple analysts, and neurophysiological data, the best estimates of actual electrode position were determined. The results of these electrode reconstructions are shown in Figs. 3 through 5 and in Table 4. The surgery was planned so that the electrode tips were generally ventral to the STN and caudal to its midpoint. Given the angled implantation trajectories, this placed two to three electrode contacts in the STN for most patients.

Analysis of Electrode Configurations Relative to Location of Stimulation

The average current used was 3 mA, which is expected to spread in a 3-mm radius from the cathode (in a monopolar, C+ configuration). This mean current envelope was plotted on the reconstructions in all three planes, including the localization of stimulation with monopolar, bipolar, and tripolar configurations (Fig. 6). Forty-seven of 54 electrodes had a cathodal contact within a 3-mm radius of the geometric center of the spatial distribution of clinically effective contacts (1.62 mm posterior to the MCP, 2.47 mm inferior to the AC–PC line, and 11.72 mm lateral to the midline). This corresponds to the average current spread for all electrodes used clinically. Furthermore, within this radius all the monopolar sites (that is, C+ with a single cathode) were found, and these were all, on average, closest to the center. All the bipolar cathodal contacts except seven were also within that radius. Of those seven, in all but two cases the polarity of stimulation was such that the current flowed into that central zone. Of the remaining two, one was located dorsally in the ventral thalamus/thalamic fasciculus region, approximately 2.5 mm above the dorsal border of the STN, close to the FF and ZI. The other outlier was located at the caudal border of the STN, and was not optimally effective clinically. (All of the tripolar [double cathodal] electrodes had at least one cathode within the central 3-mm radius as well).

A multivariate analysis of covariance was used to determine if there was a relationship between the location of stimulation and current amplitude. Although there was a weak trend toward higher currents being delivered to contacts located caudally in the STN and lower currents being delivered to the rostrally located contacts after controlling for the effects of location in the other two planes, this was not statistically significant.

Based on intraoperative recording data, the STN region within which stimulation appeared to be most commonly delivered postoperatively also correlated quite well with the independently determined location of units responsive to
The data points reported in this communication correspond to findings obtained in a larger group of 38 patients treated at our center, of which the 29 patients in the current study are a subset. The unit data locations were superimposed onto our electrode maps to compare distributions (Fig. 7). The geometric center of the unit data was found to lie approximately 1 mm below the mean location of the clinically effective contacts. This is explained by the location of several clinically effective contacts above the STN in the ZI and FF, which shifts the geometric center of those points dorsally relative to the STN.

**Discussion**

The patients evaluated in our study all benefited from STN DBS in a manner and degree comparable to that reported previously. The clinical response was as expected for this treatment. Consequently, we have inferred that the sites of stimulation within and adjacent to the STN reported here are representative of the sites most likely to be related to a good clinical outcome. One caveat in the logic of this argument concerns the accuracy of the MR imaging–based measurements, because distortions have been reported, even without the presence of DBS electrodes. The question arises as to the possible distortion of the MR image when attempting to localize implanted electrodes in vivo. It is suspected, but not established, that the anatomical images are differentially distorted, not only by the imaging method itself (for example, inhomogeneity of the magnetic field and inadequate shimming), but also by the presence of the DBS electrodes. If both the brain structures and the electrode image are displaced congruently, then localization can still be ascertained. If displacement is differential, however, then some degree of error would be introduced. Our study was not designed to address these issues, but the consistency of the results, with MR imaging measurements within 1 to 2 mm of the neurophysiological mapping, lend credibility to the emerging picture. The correlation with results of neurophysiological, neuroanatomical, and hodological studies in animals provides additional support. The ultimate verification of accuracy is furnished by postmortem histological analysis. Data from several postmortem cases currently under analysis are revealing
that there is a very close correspondence (that is, within 1 mm) between the MR imaging–determined location and the actual electrode position reconstructed from histological sections (JA Saint-Cyr and W Halliday, unpublished observations).

Studies have shown that ventriculography, which has often been touted as the most accurate means of targeting for stereotactic surgery (because it is free of distortion and is only able to show accurately the AC and PC), can be replaced by CT scanning without compromising accuracy, although the infusion of air into the ventricles may provoke an anterior displacement of structural fiducial markers and enlarge the width of the third ventricle. Furthermore, a good correspondence has been shown between MR imaging and CT scanning in direct comparisons in which fusion techniques were used, as long as precautions are taken with respect to magnetic field homogeneity and alignment of the frame and the patient’s head in the neuroimaging apparatus. Holtzheimer, et al., concluded that the small differences between CT scanning and MR imaging were overshadowed by the better anatomical resolution of the MR images. In a study by Schuurman, et al., the mean 3D discrepancy of fiducial coordinates between MR imaging and ventriculography was significant only for the anteroposterior coordinate (that is, posterior to the MCP in the AC–PC axis), and even that was on the order of 1 mm (that is, 0.5 pixel) and therefore negligible. Overall, the mean 3D distance between the fiducial markers in the two data sets was approximating 1 mm. Bejjani, et al., have recently proposed that the rostral border of the red nucleus may be a more reliable internal fiducial marker in determining target coordinates for the STN, compared with the MCP.

In an analysis of targeting methods, in which microelectrode recording data were used as the ultimate determinant of effective coordinates, the use of MR imaging–compatible frames has resulted in the elimination of any significant distortions. Holtzheimer, et al., concluded that the small differences between CT scanning and MR imaging were overshadowed by the better anatomical resolution of the MR images. In a study by Schuurman, et al., the mean 3D discrepancy of fiducial coordinates between MR imaging and ventriculography was significant only for the anteroposterior coordinate (that is, posterior to the MCP in the AC–PC axis), and even that was on the order of 1 mm (that is, 0.5 pixel) and therefore negligible. Overall, the mean 3D distance between the fiducial markers in the two data sets was approximating 1 mm. Bejjani, et al., have recently proposed that the rostral border of the red nucleus may be a more reliable internal fiducial marker in determining target coordinates for the STN, compared with the MCP.

In an analysis of targeting methods, in which microelectrode recording data were used as the ultimate determin-

<table>
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<tr>
<th>Electrode Position</th>
<th>Mean</th>
<th>Side Stimulated</th>
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<tr>
<td>tip coordinate (mm)</td>
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<tr>
<td>AP relative to MCP</td>
<td>−5.13 ± 2.35</td>
<td>5.37 ± 2.21 posterior (−2 to −9.3)</td>
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<tr>
<td>DV relative to PC</td>
<td>−8.46 ± 1.81</td>
<td>−8.67 ± 1.73 (−5 to −13.5)</td>
</tr>
<tr>
<td>ML relative to midline</td>
<td>10.2 ± 1.48</td>
<td>9.87 ± 1.51 (7 to 12)</td>
</tr>
<tr>
<td>clinical contact</td>
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<tr>
<td>AP relative to MCP</td>
<td>−1.62 ± 1.98</td>
<td>−1.24 ± 1.81 (2 to 5)</td>
</tr>
<tr>
<td>DV relative to PC</td>
<td>−2.47 ± 1.76</td>
<td>−2.12 ± 1.51 (1 to 9)</td>
</tr>
<tr>
<td>ML relative to midline</td>
<td>11.72 ± 1.50</td>
<td>11.52 ± 1.65 (8.4 to 13.7)</td>
</tr>
</tbody>
</table>

* AP = anteroposterior; DV = dorsoventral; ML = mediolateral.
nant of coordinates for implantation, Zonenshayn and colleagues\textsuperscript{113} came to the conclusion that MR imaging provided the least accurate guide, compared with physiological recordings (all values expressed as the mean ± SD); the error for MR imaging was 2.6 ± 1.3 mm. The atlas-based (error 1.7 mm ± 1.1 mm) and midcommissural methods (error 1.5 ± 0.8 mm) proved to be the most accurate. This is surprising, considering the variation in location of the STN in individual patients compared with atlas plates.\textsuperscript{83} Moreover, no postoperative MR imaging or postmortem studies were

Fig. 6. Clinically effective contacts plotted in all three planes (sagittal in upper panel, coronal in center panel, and axial in lower panel) after monopolar, bipolar, or tripolar stimulation, with a 3-mm radius sphere of current spread from the geometric mean location indicated by the large circles.
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Conducted to validate the accuracy of the different methods. Nevertheless, it was finally recommended that all three methods be combined (that is, imaging, unit recording, and macrostimulation).

Because stereotactic coordinates are ultimately derived from measurements obtained relative to the AC and PC, precision in initial targeting comes down to the resolution and accuracy of the MR imager in aligning frame-based and anatomical coordinates. In addition, there is an inherent limitation of resolution because a 2-mm section thickness is used (2 × 2 × 1.2-mm voxels). Finally, it should be noted that the cross-sectional area of the AC may vary as much as sevenfold in individuals who are free of neurological disease (that is, roughly from 3–8 mm in diameter), and the PC may be difficult to resolve on T1-weighted images. Thus, a variety of factors may contribute to errors in measurement, supporting the routine use of neurophysiological recording intraoperatively to ensure optimal positioning of electrodes. It appears that current MR imaging methods yield acceptably accurate spatial coordinates and that distortion can be avoided.

These analyses reveal that the electrode contacts chosen for chronic stimulation (that is, those with the best efficacy and fewest adverse effects) are most commonly located in the anterodorsal STN and/or in the FF and ZI dorsally adjacent to it. That region corresponds to the portion of the STN wherein the majority of units responsive to active and passive displacement of the limbs is found during intraoperative recording. This should not be surprising because the location of such responsive areas was used to select the final position of the electrodes for implantation. Nevertheless, the two data sets are at least partially independent, because we could have found that either more caudoventral or anterodorsal contacts were best clinically. These data are concordant with the conclusions reached by Rodriguez-Oroz, et al., with regard to the region of the STN in which movement-related cells were located. In a recent study in which the MPTP primate model was used, Baron, et al., not only mapped out a homologous region in which neurons with sensorimotor proprioceptive fields were found, but they also demonstrated that the muscimol-induced inactivation of that portion of the STN resulted in reduced akinesia and bradykinesia.

Comparison of the selected target coordinates from different centers (Table 5) reveals relatively good agreement if one considers that different angles of implantation may result in variations in the laterality of tip location. Furthermore, the actual electrode contact that was used clinically was not specified in those studies, and therefore it is not possible to make a direct comparison between centers with regard to the ideal location of stimulation. The Grenoble group usually uses Contact 2 (that is, the one second from the top or proximal pole of the electrode) (AL Benabid and P Pollak, personal communication, 2002). This would bring their results into close agreement with those found in the present study, although to date there have been no published reports of the actual position of the electrodes in their series.

Our results reveal that, although there is some variability in the location of clinically effective stimulation sites, the observations falling within 1 SD of the mean cluster anatomically in the anterodorsal sector of the STN and the dorso-adjacent FF and ZI. The voltages being used clinically are being in the range of 2 to 3 V and the electrode impedance is typically between 750 and 1500 Ω; the best estimates of current spread thus translate into distances of 2 to 3 mm radially from a monopolar contact.

Quantitatively, if one superimposes the mean current values calculated (3 mA), and assumes a uniform spherical spread of current (3-mm radius), then the current envelope would encompass the STN from a point 1 mm anterior to 4.5 mm caudal to the MCP, from the dorsal border of the STN and adjacent FF and ZI to within 1.5 mm of its ventrostral border, covering the entire width of the nucleus, and slightly overflowing laterally but not medially. It is often inferred, but has not been established, that some adverse effects (for example, ocular deviation and muscle contractions; see later discussion) are caused by current spread into structures adjacent to the STN, such as the red nucleus and third cranial nerve. The results of muscimol injections in the MPTP primate model indicate, however, that it is specifically the lateral portion of the anterodorsal STN that is related to the control of rigidity.

![Fig. 7. Plot showing the distribution of responsive units (cells responsive to active or passive movement) with the geometric mean location (unit average) compared with the mean DBS clinically effective contact location (DBS average), with 95% CI indicated.](image-url)

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benabid, et al., 1996 &amp; 2000</td>
<td>10</td>
<td>0</td>
<td>2–4†</td>
</tr>
<tr>
<td>Hutchison, et al., 1998</td>
<td>10.5 to 12</td>
<td>-2 to -4</td>
<td>-4 to 6†</td>
</tr>
<tr>
<td>Yokoyama, et al., 1998</td>
<td>8 to 10</td>
<td>-3 to -4</td>
<td>-5 to 6†</td>
</tr>
<tr>
<td>Starr, et al., 1999</td>
<td>10 to 12</td>
<td>-1.1 to -4</td>
<td>-3.1 to 6†</td>
</tr>
<tr>
<td>Zonenshayn, et al., 2000</td>
<td>13</td>
<td>-4</td>
<td>-5§</td>
</tr>
<tr>
<td>Present study§</td>
<td>11.72 ± 1.5</td>
<td>1.62 ± 1.98</td>
<td>2.47 ± 1.76</td>
</tr>
<tr>
<td>10.2 ± 1.48</td>
<td>-5.13 ± 2.35</td>
<td>-8.46 ± 1.81</td>
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</tr>
</tbody>
</table>

* X = lateral to midline; Y = posterior to MCP; Z = depth to AC–PC.
† Inferior.
‡ Coordinates are for the center, rather than the tip of the electrode.
§ First row of coordinates refers to clinically effective contact locations, second row of coordinates refers to the coordinates of the tips of the electrodes.

**Table 5**

**Literature review comparing target coordinates for tips and stimulation sites within the STN**

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The lack of a significant relationship between the point stimulated and the current amplitude may not be too surprising. One reason for this lack of relationship may be that there were insufficient data points for adequate statistical power. One could argue that the current may have been limited at some distal points to avoid adverse effects. In addition, contacts that are within the STN but not ideally placed could have necessitated more current for adequate spread to the anterodorsal region. Finally, because the bulk of the stimulation points was within a sphere with a 3-mm radius, there was little opportunity for variability of stimulation parameters. Given our ignorance of the conductivity in tissue compartments in and adjacent to the STN, such an exacting analysis may not be possible or appropriate when using current measurements and estimates of current density distribution that are based on models in which tissue conductance homogeneity and low anisotropy are assumed. New diffusion-weighted MR imaging methods may help resolve these issues, however, and might be applied to assess electrical brain stimulation.45

It may not be coincidental that the anterodorsal sector of the STN (especially laterally) is the site of clinically effective stimulation. Parent and Hazrati72,73 and others42,65,66 have shown that this sector of the STN also corresponds to its sensorimotor region because it receives afferents from the supplementary motor cortex, the motor division of the external pallidum,72,73 and the centromedian nucleus of the thalamus42 (itself reciprocally connected to the motor cortex and in receipt of cerebellar inputs).42,44 Experiments conducted by our group46 have shown that the effects of STN DBS are mimicked by the direct application of lidocaine defocusing in the pallidum 25,26,41 caused by the dopamine denervation of PD. This indicates that the focus on the anterodorsal sector of the STN may be defined by the afferents derived from motor portions of the pallidum, thalamus, and cortex.42,65,66,72,73,82 Studies have also shown that there may be a lower threshold for the activation of myelinated fibers than for cell bodies.7,8 The widespread projections from the STN80 indicate that stimulation would affect the entire basal ganglia circuitry, as required by currently accepted criteria for this treatment.

With regard to the FF and ZI, fibers coursing immediately dorsal to the STN have at least two sources of origin, namely, the internal pallidum, which projects to the thalamus (portions of the ventralis anterior, ventralis intermedius, medialis dorsalis, and centromedianus/parafascicularis nuclei) and the SNc, which sends dopaminergic fibers to the striatum.10,71,72 Ashby and colleagues7,8 have suggested that the parameters typically used for clinically effective DBS should preferentially affect myelinated fibers, such as the pallidal efferents in this case, whereas the use of longer pulses should activate unmyelinated fibers, such as the dopamine-carrying SNc fibers that remain. Because, in contrast with DBS in the internal pallidum or posteroventral pallidotomy, STN DBS permits the reduction of levodopa dosage, activation of the SNc may induce an increased release of dopamine.

Long considered a vaguely defined rostral component of the reticular system, it has recently been shown that the ZI has a limited role in the reticular nucleus, as it has been shown that the ZI receives supplementary motor area (in the monkey65,66) and somatosensory cortical afferents (in the rat41), as well as inputs from the cerebellar nucleus interpositus,64 and from a wide range of visual areas.72 In addition, ZI projects to the thalamus bilaterally in a manner reminiscent of the thalamic reticular nucleus.72,76 Like the reticular nucleus, the ZI contains a leaflet of cells that stain positively for calbindin, calretinin, and parvalbumin,27 although, in sharp contrast to the reticular nucleus, there are limited reactions to markers for GABA.38,69 Thus, the ZI is histologically and neurochemically complex, with different sectors staining positively for GABA, glutamic acid decarboxylase, somatostatin, calbindin, calretinin, parvalbumin, and serotonin.46 Our data indicate that current spread or direct stimulation of the FF and ZI may have to be taken into account to explain part of the STN DBS effect, in confirmation of the observations of Zincone, et al.,100 and of Velasco, et al.102 The results of Baron, et al.,11 mentioned earlier, cannot address the issue of the effects of stimulation in the dorsally adjacent ZI and FF, except to point out that one injection of muscimol in that area had no behavioral effect. This could be interpreted as an indication that the inhibition of the ZI alone is ineffective.

One must also consider the possibility of antidromic activation of fibers with DBS. Considering the known anatomical connections in these circuits,64,72,73 STN stimulation could influence the external pallidum, which is known to project directly to the reticular shell of the thalamus and the internal pallidum. By the former route, stimulation would inhibit the reticular shell, which is itself inhibitory to specific thalamic relay nuclei, the final result being a facilitation of thalamocortical projections. Alternatively, external pallidal activation may directly inhibit the internal pallidum, which, being overly active in PD, would also yield a facilitation of thalamocortical projections.70,94 In addition, the antidromic effects on the centromedianus nucleus may be important because of its cerebellar and motor cortical links.5,72 Stimulation of the centromedianus/parafascicularis nuclei has been reported to reduce both tremor and levodopa-induced dyskinesias, supposedly because of its projections to the pallidum.22 Finally, antidromic activation of fibers from the SNr and SNc could liberate GABA in both nuclei, and dopamine in the remaining pars compacta neurons, the latter with uncertain behavioral results. The modest remaining dopamine innervation of the STN29,77 could also conceivably be influenced.

Neurophysiological studies in the rat have shown that high-frequency stimulation of the STN can induce a transient blockade of voltage-gated currents within the STN,19 and that it can either inhibit or excite adjacent SNr neurons.16,17 In addition, STN DBS has been shown to facilitate thalamocortical transmission in intact rats.16 Ashby7 has suggested that DBS with the typical parameters used clinically is most likely to depolarize myelinated axons at distances up to at least 3 mm from the point stimulat-
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ed, while having a more spatially confined (on the order of 1–2 mm) blocking action on proximal neurons, caused at least in part by the liberation of inhibitory neurotransmitters (GABA in this case), and also by blocking membrane currents. In applying these considerations to the currently emerging scenario, one would expect that fibers coursing through the FF would almost certainly be depolarized, whereas the anterdorsal sector of the STN would be inactivated. Remote effects on pallidal, thalamic, and even cortical afferent and efferent connections must remain speculative.

Efforts are now under way to seek correlations between the exact anatomical location of stimulation and observed changes in symptoms, as well as in the production of adverse effects. For example, in our own experience and as outlined by Volkman, et al., if stimulation is too rostral in the AP axis, the current spreads to the internal capsule, necessitating a reduction to avoid inducing muscle contractions. Alternately, one could encounter the induction of autonomic effects, such as diaphoresis or tachycardia, because of the proximity to the posterior hypothalamus. On the other hand, if the electrode is too caudal, an increase in the current may be needed for it to spread to the anterdorsal sector of the STN. Excessive current with very caudal placements, however, typically activates the lemniscal fibers, causing paresthesias. In the dorsoventrally axis, stimulation may be reduced if it is delivered more dorsally, because the threshold to activate fibers in the FF may be lower than that needed for the STN. This could duplicate the effects of direct stimulation of the internal pallidum. More ventrally, the current may again be beneficially increased to spread to the anterdorsal sector of the STN and into the underlying SNr.

In the mediolateral axis, there is very little variability in the amount of current delivered, probably because the anteroposterior and dorsoventral positions of the electrode determine how close the electrodes lie to the center of the nucleus, and this in turn determines the amount of current to be delivered. Extremely medial electrodes may require lower currents to avoid encroachment on the red nucleus (which produces proximal muscle contractions), whereas caudomedial placements have been shown to activate the third cranial nerve, with ipsilateral nasal intorsion of the eye and somet ime ptosis ensuing (linked to the third cranial nerve innervation of the medial rectus and levator palpebrae). The observation has also been made (especially during intraoperative DBS screening) that eyelid opening apraxia may be induced. This could be explained by spread of the current, which was destined for the third cranial nerve, to corticobulbar fibers.

One could therefore make an argument for the definition of a zone within the STN that should be the target for clinically optimal electrode placement. The limits of that zone can be defined conjointly by the statistically determined spatial distribution (that is, the most probable locations, 95% confidence limit) of clinically effective contacts with a 3-mm-radius sphere of current spread that originates from the coordinate center of the electrode location.

The limits of that region can be compared with the reported coordinates of targets chosen by a variety of groups in different countries (Table 5). If one assumes that the angles of implantation are roughly similar to the ones used by our group, and given that most centers report that Contact 2 is the one most frequently used (AL Benabid, P Pollak, and J Vitek, personal communications 2002), then it is likely that successful stimulation sites are within the zone defined in this current study.

Conclusions

In this study, high-resolution MR imaging with optimized scanning parameters yielded a very consistent determination of electrode location, which was confirmed by neurophysiological recordings. Because the presence of the electrode on the image often obscured the STN, a comparison had to be made with the preoperative visualization of the location of the STN. Even those images were at times ambiguous, in that the STN often appears fused with the ventrally adjacent SN. The ventral border and either the rostral or caudal limit of the nucleus were therefore determined by single-unit recordings, thus providing all the necessary information for a final determination of the best fit between electrode location and anatomy. The clinically effective anatomical region most commonly stimulated corresponded to the anterdorsal sector of the STN and dorsally adjacent ZI and FF. Both local, neurochemically induced neural inhibition and excitation (anti- and orthodromically conducted) of fiber systems, especially in the FF, may contribute to the clinical outcome of STN DBS.

Despite the optimal use of convergent neurosurgical targeting methods to guide implantation (that is, neuroimaging, neurophysiological, and trial macrostimulation), it is nevertheless expected that there will continue to be some variability in the final location of implanted electrodes. Because not all symptoms in all patients are equally alleviated by STN DBS, it is possible that a relationship exists between the exact site of stimulation and the clinical benefit derived. Data from a larger series of patients are currently being analyzed to explore such relationships. To that end, the use of more precise anatomical stereotactic atlases and data registration methods is expected to be of critical importance.96

References

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