Imaging alone versus microelectrode recording–guided targeting of the STN in patients with Parkinson's disease

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OBJECTIVE The clinical results of deep brain stimulation (DBS) of the subthalamic nucleus (STN) are highly dependent on accurate targeting and target implantation. Several targeting tactics are in current use, including image-only and/or electrophysiologically guided approaches using microelectrode recordings (MERs). The purpose of the present study was to make an appraisal of imaging only–based versus imaging with the addition of intraoperative MER-guided STN electrode targeting.

METHODS The authors evaluated 100 consecutive patients undergoing STN DBS. The position of the STN target was estimated from preoperative MR images (direct target) or in relation to the position of the anterior and posterior commissures (indirect target). MERs were obtained for each trajectory. The authors tracked which targets were adjusted intraoperatively as a consequence of MER data. The final placement of 182 total STN electrodes was validated by intraoperative macrostimulation through the implanted DBS electrodes. The authors compared the image-based direct, indirect, MER-guided target adjustments and the final coordinates of the electrodes as seen on postoperative MRI.

RESULTS In approximately 80% of the trajectories, there was a good correspondence between the imaging-based and the MER-guided localization of the STN target. In approximately 20% of image-based targeting trajectories, however, the electrophysiological data revealed that the trajectory was suboptimal, missing the important anatomical structures to a significant extent. The greatest mismatch was in the superior-inferior axis, but this had little impact because it could be corrected without changing trajectories. Of more concern were mismatches of 2 mm or more in the mediolateral (x) or anteroposterior (y) planes, discrepancies that necessitated a new targeting trajectory to correct for the mis-targeting. The incidence of mis-targeting requiring a second MER trajectory on the first and second sides was similar (18% and 22%).

CONCLUSIONS According to the present analysis, approximately 80% of electrodes were appropriately targeted using imaging alone. In the other 20%, imaging alone led to suboptimal targeting that could be corrected by a trajectory course correction guided by the acquired MER data. The authors' results suggest that preoperative imaging is insufficient to obtain optimal results in all patients undergoing STN DBS.

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KEYWORDS deep brain stimulation; subthalamic nucleus; targeting; MRI; microelectrode recording; Parkinson's disease; functional neurosurgery

SUBTHALAMIC nucleus (STN) deep brain stimulation (DBS) surgery is commonly used to treat Parkinson's disease (PD) throughout the world. With the passage of time, there have been a number of innovations in surgical technique. These include a shift away from electrophysiological confirmation of the STN target with

microelectrode recordings (MERs) and a trend toward surgery with the patient awake or asleep, relying solely on MRI of the target for electrode placement in some centers.^{2,3,6,8} The relative merits and limitations of the imaging-only methods are, however, largely unknown.

There are two main imaging-based approaches for tar-

ABBREVIATIONS AC = anterior commissure; DBS = deep brain stimulation; MCP = midcommissural point; MER = microelectrode recording; PC = posterior commissure; PD = Parkinson's disease; STN = subthalamic nucleus.

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FIG. 1. Axial T1-weighted MR image showing the approximate location of the STN outlined in white.

getting the STN. In the “direct” targeting method the location of the STN is identified directly on the preoperative MRI. The other approach is the “indirect” method, a formulaic estimation of the STN position based on the coordinates of the midcommissural point (MCP). While imaging-only approaches may offer advantages related to surgical time, patient comfort, and tolerability, their ability to guide the placement of electrodes accurately in a robust and consistent manner and their comparative clinical efficacy have not been thoroughly evaluated in a controlled manner.

With the increasing use of imaging-only targeting, a critical appraisal is needed. How often is the imaging-only approach on target versus missing the mark? To gain an estimate of the potential reliability of an imaging-only approach and to assess whether and how often this approach may lead to mis-targeting, we reviewed our data comparing STN targets as chosen by preoperative imaging versus those chosen with the benefit of intraoperative MER-guided data. We report that imaging alone provides adequate placement of electrodes in the majority of the patients, but importantly, there are a significant number of patients for whom the imaging-only approach leads to suboptimal electrode placement.

Methods

Patients and Measurements

We retrospectively reviewed 100 consecutive PD patients who underwent STN DBS at the Toronto Western Hospital between April 2006 and June 2016 by a single staff surgeon (A.M.L.). In 7 patients, the imaging data were incomplete and they were excluded. Of the remaining 93 patients, 4 had unilateral implantations and 89 had bilateral implantations for a total analysis of 182 STN electrodes. There were 91 STN targets on the right side and 91 were on the left side. We determined 3 targets for each of the 182 electrodes in 93 patients. These targets were designated as: 1) the preoperative imaging-based direct target, 2) the MCP coordinate-derived indirect target, and 3) the

postoperative final electrode position as determined by MRI.

DBS Targeting and Surgery

STN target planning occurred on the day of surgery using the preoperative T1-weighted SPGR (TR 11.2–12.7 msec; TE 5.0–5.4 msec; FA 30°; isotropic voxel 1–1.4 mm) and FSE-IR T2-weighted (TR 4000–6000 msec; TE 40–45 msec) using a GE 1.5-T Signa MR unit. Patients had a Leksell frame applied under local anesthesia. Images were imported into a workstation (Stealth, Medtronic), where they were registered to stereotaxic space. The coordinates of the anterior commissure (AC), posterior commissure (PC), and MCP were identified. The x, y, and z coordinates were defined as the lateromedial, anteroposterior, and superoinferior distances in millimeters, respectively. Indirect targeting was derived formulaically based on the coordinates identified for the AC, PC, and MCP. The formula used was:

$$x_{STN} = x_{MCP} \pm 12 \text{ mm}$$

$$y_{STN} = y_{MCP} \pm 4 \text{ mm}$$

$$z_{STN} = z_{MCP} \pm 4 \text{ mm}$$

The surgical team planned the direct target STN electrode coordinates based on the best available visualization of the STN and the red nucleus (Fig. 1) on either the T1- or T2-weighted images (direct targeting) as previously described.¹

Microelectrode Adjustment of Electrode Position

Procedures were performed under local anesthesia with the use of propofol, fentanyl, and dexmedetomidine as required for patient comfort. Burr holes were placed 2 cm from the midline and 1 cm anterior to the coronal suture. MER and DBS electrodes were inserted in the right hemisphere followed by the left in all patients with bilateral electrodes. MERs corresponding to the imaging-derived direct target trajectories were obtained as detailed elsewhere.⁷ Dual microelectrodes were inserted via guide tube along the planned trajectory until it reached about 10 mm above the planned target. At this point, single-unit electrophysiological recordings were started and continued along the depth of the trajectory as described previously.⁴ The recordings were used to identify the location of major landmarks, including the ventral border of the thalamus, the superior and inferior borders of the STN with the nucleus spanning a minimum of 4 mm in vertical dimension, the sensorimotor territory of the STN as confirmed by the presence of neurons with kinesthetic receptive fields, and the dorsal border of the substantia nigra pars reticulata as previously detailed.⁴ If these expected structures were not encountered, a new trajectory was chosen based on the estimated offset as determined from the physiological data, and the recordings were repeated. The MER trajectories were made within a cannula that was coaxial with the DBS electrode insertion tracks to allow accurate placement and minimize the risk of electrode misplacement. The final positioning of the DBS electrode was validated by testing for an acceptable threshold for adverse effects with macrostimulation (> 3.5 V) through the implanted electrode.

TABLE 1. Demographics of patients undergoing STN DBS

Characteristics	Value ($\pm$ SD)
No. of patients	93
Male/female	73/20
Mean age, yrs	58.7 (7.2)
Mean duration of illness, yrs	11.4 (4.5)
Mean L-dopa equivalents	1224.9 (570.0)
Mean UPDRS III—off*	35.0 (11.1)
Mean UPDRS III—on*	13.3 (7.2)

UPDRS III = Unified Parkinson's Disease Rating Scale part III (on or off medication).

* Mean L-dopa equivalents calculated as previously described.⁵

Postinsertion Analysis of Electrode Localization

Medtronic model 3387 DBS electrodes were used in every case. We obtained postoperative MR images (Signa 1.5-T unit, General Electric) to visualize the position of the DBS electrodes to analyze the relationship between the planned and final electrode positions. These postoperative T1-weighted SPGR images (TR 11.2–12.7 msec; TE 5.0–5.4 msec; FA 30°; isotropic voxel 1–1.4 mm) along with their corresponding preoperative images were imported into a workstation (Stealth, Medtronic) for analysis. Briefly, the postoperative images were aligned and fused to the preoperative images using a 6-parameter affine registration. Subsequently, the AC, PC, and MCP were marked in reference to the frame that allowed conversion to stereotaxic space. We recalculated the indirect targets of the STN using the formulas outlined previously. We then found the coordinates corresponding to the final electrode position by identifying the center of the artifact of the bottom-most contact on the postoperative scan. The differences in coordinates between the three methods (direct targeting, indirect targeting, and postoperative target as seen on imaging) were taken as absolute values. The mean position of the direct, indirect, and postoperative image-derived target was compared using t-tests.

Results

Patient demographics are shown in Table 1. We determined the preoperative imaging-based direct target, the MCP coordinate-derived indirect target, and the postoperative final electrode position by MRI. The coordinates of AC, PC, and MCP as well as the position of the deepest electrode contact based on the three targets are shown in Table 2. Direct and indirect targeting yielded similar results with a difference in the indirect target y coordinate ($p < 0.0001$) but not the mean x and z coordinates ($p > 0.1$).

We obtained postoperative MR images in all patients to examine the relation between the expected and the final position of the implanted DBS electrodes. The coordinates of the deepest electrode contacts are shown in Table 2. There was a significant discrepancy in the direct or indirect targeting methods versus the final target on both the right and left sides (Table 2). When comparing the direct target versus the postoperative MRI-derived final coordinates, there was a difference of up to 2.2 mm in the

TABLE 2. Mean values for coordinates of AC, PC, MCP, and STN target in stereotaxic space

Coordinate	X $\pm$ SEM	Y $\pm$ SEM	Z $\pm$ SEM
AC	100.1 $\pm$ 0.19	112.1 $\pm$ 0.68	108.2 $\pm$ 1.18
PC	99.9 $\pm$ 0.19	86.1 $\pm$ 0.68	109.1 $\pm$ 1.29
MCP	99.6 $\pm$ 0.27	99.0 $\pm$ 0.66	108.7 $\pm$ 1.24
Right STN			
Indirect	88.1 $\pm$ 0.20	95.4 $\pm$ 0.65*	112.6 $\pm$ 1.24
Direct	88.1 $\pm$ 0.23†	97.2 $\pm$ 0.66	112.7 $\pm$ 1.31†
Final	89.7 $\pm$ 0.22‡	95.2 $\pm$ 0.65‡	115.9 $\pm$ 1.28‡
Left STN			
Indirect	112.0 $\pm$ 0.18	95.2 $\pm$ 0.64*	112.6 $\pm$ 1.24
Direct	111.6 $\pm$ 0.20†	97.3 $\pm$ 0.65	112.4 $\pm$ 1.33†
Final	109.8 $\pm$ 0.22‡	95.6 $\pm$ 0.66‡	115.4 $\pm$ 1.28‡

The final STN target was obtained using postoperative MRI. All values are presented as millimeters in stereotaxic space with the SEM.

* Indicates a significant difference ($p < 0.0001$) in the direct right versus indirect right STN groups or the direct left versus indirect left STN groups.

† Indicates a significant difference ($p < 0.0001$) between the final right versus indirect right STN groups or the final left versus indirect left STN groups.

‡ Indicates a significant difference ($p < 0.0001$) between the final right versus direct right STN groups or the final left versus direct left STN groups.

average x and up to 2.0 mm in y coordinates and approximately 3 mm difference in the average z coordinates. The position of the DBS electrodes as assessed on postoperative MRI tended to be more medial and deeper on both right and left sides and these differences were significant ($p < 0.0001$).

Moving to the intraoperatively acquired data, in 82% of right-sided trajectories and in 78% of left-sided trajectories, the MERs identified the expected pattern, location, and extent of neuroanatomical structures along the trajectory, and confirmed a vertical stretch of STN measuring at least 4 mm in length. In 18% of right trajectories and 22% of left trajectories, however, there was a mismatch between the expected neuroanatomical structures and the MER findings. In these cases, the most common occurrence was finding little, insufficient (< 4 mm), or no identifiable STN nucleus—which was interpreted as a mis-targeting. When this occurred, a corrective new trajectory 1–3 mm away in the x or y plane was examined. If this again failed to reveal the expected findings, a third trajectory was carried out. The maximum number of trajectories per hemisphere was 3. In total, there were 36 of 182 electrodes that were implanted along a trajectory other than that chosen by direct imaging (Table 3). The distribution of coordinate differences between direct MRI-planned and final coordinates of moved electrodes on the right side ($n = 16$) and moved electrodes on the left side ($n = 20$) is summarized in Figs. 2 and 3, respectively. Of the 16 patients who had their right-side electrode adjusted after MER, 5 of them (31%) also had their left-side electrode adjusted, even taking into account a target possible recalibration after acquiring the MER data on the right side.

The mean differences in the planned versus final location of these electrodes as revealed by postoperative imaging are shown in Tables 4 and 5. The majority of trajectory

TABLE 3. Final positions of implanted DBS electrodes

Electrode	Right Side	Left Side	Total
No. of implanted electrodes	91	91	182
No. of electrodes inserted in proposed imaging-based trajectory	75	71	146
No. of electrodes not implanted in the imaging-based trajectory but required additional trajectories more than 1 mm away in the x or y plane	16 (17.6%)	20 (22.0%)	36 (19.8%)

Electrode implantations in the proposed preoperative imaging-based direct target trajectory versus a different trajectory based on intraoperative MER localization findings.

movements were 1 or 2 mm, but in a certain number of patients, greater adjustments were made. In some cases, adjustments were made in both x and y planes simultaneously. The desired z coordinate was achieved by adjusting the depth of the insertion of the DBS electrode.

Discussion

We found that in approximately 80% of cases, the preoperative imaging trajectory was on target and passed through an appropriate volume and location of the STN nucleus. In contrast, in 20% of cases, the MER data suggested that the trajectory was mis-targeted. Placing electrodes in such trajectories would be predicted to lead to suboptimal clinical results. The addition of MER data allowed a correction in electrode placement, possibly contributing to a better outcome in those patients than relying on the imaging only–based approach.

We determined the location of the deepest of the 4 DBS contacts (contact 0) on postoperative MRI. In reality, however, the contacts most often used are contacts 2 or 3 located in the dorsal portion of the STN. These more dorsal contacts used clinically lie lateral and more anterior to the deepest contact.⁷ The location of the deepest contact thus is more medial and posterior than the optimal therapeutic target. Depending on the angle of the trajectory and because the distance between the 4 DBS contacts spans 10.5 mm, the deepest of the 4 contacts could very well lie over 2 mm more medial and posterior to the most proximal contact. This may account for some of the discrepancy between the planned (upper or mid contacts) and final (here, the deepest contact) electrode positions. We did not have as much concern for mis-targeting in the z plane as this can be readily corrected by adjusting the depth of the DBS electrode insertion without the need of additional trajectories. Likewise, postoperatively programming a different contact along the vertical axis of the lead can correct slight misplacement in the z plane.

Indirect and direct targeting resulted in overall similar targets. Interestingly, the y coordinates of the indirect target were on average closer to the final target compared to direct targeting in the moved electrodes. This suggests that in the future, perhaps the indirect targeting should be moved slightly posterior by 1–2 mm.

A head-to-head comparison of imaging alone versus imaging supplemented by electrophysiological recordings for STN DBS surgery is not available, nor is it likely to be conducted in the near future. Our study aimed to start addressing this issue but has a number of important limitations. First, we believe that several factors could have contributed to the mis-targeting we observed. These include inadequate visualization of the STN on imaging, MR image distortion, stereotactic trajectory errors or inaccuracy,

FIG. 2. Frequency distribution of coordinate differences between direct MRI-planned and final MRI coordinates of 16 moved right-side electrodes. The figure shows the shift distances in millimeters among the 16 right-side electrodes that were adjusted according to MER data. Preoperative direct imaging targeted the upper to midportion of the STN, while postoperative MRI localized the deepest contact of the DBS electrode. Figure is available in color online only.

FIG. 3. Frequency distribution of coordinate differences between direct MRI-planned and final MRI-determined coordinates of 20 moved left-side DBS electrodes. The figure shows the shift distances in millimeters among the 20 left-side electrodes that were adjusted according to MER data. Preoperative direct imaging targeted the upper to midportion of the STN, while postoperative MRI localized the deepest contact of the DBS electrode. Figure is available in color online only.

and brain shift, particularly on the second operated side. Perhaps our preoperative imaging could be improved to better visualize the STN by adjusting the MRI sequences, scanning the patients at higher field strength or under general anesthesia. In addition, because image registration and targeting had a subjective component when it came to choosing the position of the AC and PC, this may have introduced error. We found that the AC and PC could be identified on about 3 adjacent slices of the postoperative MR images, so one of these slices had to be chosen. The voxel size limitation of the MRI also introduced an element of error. Because of these limitations, the location of the commissures chosen for post hoc analysis could have been slightly different than those chosen on the day of surgery. Another source of error was the selection of the final electrode position. The artifacts produced by the electrode contacts on the postoperative image were not always clear cut, making it challenging to decipher where the actual contact was. The artifact bloom was also much larger (up to 6 mm, Fig. 4) than the actual electrode (1.27 mm in di-

ameter), which added another element of imprecision (Fig. 4). This most likely contributed to the difference between the direct target coordinates and the final electrode position we measured, when, in theory, 80% of the electrodes were unchanged from the intended direct coordinates. Of the electrodes that were implanted at targets other than the preoperatively planned target based on the MER data, most of the electrode trajectory adjustments were 1 to 3 mm. One may argue that a movement of 1 mm may not be so clinically relevant since the stimulation parameters can be adjusted in an attempt to provide optimal clinical benefit and avoid adverse effects. Nevertheless, subclinical direct pyramidal tract activation has been recently found to occur at stimulation thresholds that are within the range used in clinical routine, thus contributing to some stimulation-related side effects (e.g., dysarthria).⁵ In the future the tolerance for mis-targeting may increase with the advent of directional leads, which may allow for better shaping of currents and increase of the therapeutic window. In addition, intraoperative MRI may help improve the accuracy

TABLE 4. Mean distance separating direct targeting-planned and final postoperative imaging-based electrode locations for 36 electrodes that were implanted in a location other than the initially planned image-based trajectory

Distance	Right Side			Left Side		
	X	Y	Z	X	Y	Z
Mean	1.83	2.01	3.29	1.97	1.92	3.11
SD	1.23	1.17	1.93	1.09	1.17	2.45

SD = standard deviation.

The values indicate the mean distance that electrodes were adjusted between the direct and final coordinates in cases in which MER data indicated their initial planned trajectory was not suitable. All values are presented as millimeters.

TABLE 5. Mean distance separating indirect (coordinate-derived) and final postoperative imaging-based electrode locations for 36 electrodes that were implanted in a location other than the initially planned image-based trajectory

Distance	Right Side			Left Side		
	X	Y	Z	X	Y	Z
Mean	1.90	1.24	3.27	2.21	1.48	3.15
SD	1.46	1.09	1.66	1.34	1.26	2.13

The values indicate the mean distance that electrodes were adjusted between the indirect and final coordinates in cases where microelectrode recording data indicated their initial planned trajectory was not suitable. All values are presented as millimeters.

FIG. 4. Axial T1-weighted MR image showing the DBS electrode artifact on the postoperative scan. Note the blooming effect with electrodes having an apparent 4–6 mm in diameter, while their actual diameter is 1.27 mm.

of electrode placement and allow for immediate correction of mis-targeting.

Conclusions

In conclusion, using our MRI method alone would be predicted to allow very good placement of DBS electrodes 80% of the time. For 20% of cases, targeting can be improved by obtaining electrophysiological recordings to characterize and validate the STN target region. If these findings are generalizable to other centers, our data suggest that preoperative imaging alone is insufficient and should be supplemented by a second-step validation using, for example, either intraoperative electrophysiology, as shown here, or perioperative imaging.^{6,8}

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Disclosures

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Conception and design: AM Lozano, CS Lozano. Acquisition of data: AM Lozano, CS Lozano, Ranjan, Boutet, Xu. Analysis and interpretation of data: all authors. Drafting the article: CS Lozano. Critically revising the article: AM Lozano, CS Lozano, Ranjan, Kucharczyk, Fasano. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: AM Lozano. Statistical analysis: CS Lozano, Ranjan, Boutet. Study supervision: AM Lozano.

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