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Clinical Study

Typical variations of subthalamic electrode location do not predict limb motor function improvement in Parkinson's disease

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ABSTRACT

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for patients with medically refractory Parkinson's disease (PD). The degree to which the anatomic location of the DBS electrode tip determines the improvement of contralateral limb movement function has not been defined. This retrospective study was performed to address this issue. Forty-two DBS electrode tips in 21 bilaterally implanted patients were localized on postoperative MRI. The postoperative and preoperative planning MRIs were merged with the Stealth FrameLink 4.0 stereotactic planning workstation (Medtronic Inc., Minneapolis, MN, USA) to determine the DBS tip coordinates. Stimulation settings were postoperatively optimized for maximal clinical effect. Patients were videotaped 1 year postoperatively and assessed by a movement disorder neurologist blinded to electrode tip locations. The nine limb-related components of the Unified PD Rating Scale Part III were tabulated to obtain a limb score, and the electrode tip locations associated with the 15 least and 15 greatest limb scores were evaluated. Two-tailed *t*-tests revealed no significant difference in electrode tip location between the two groups in three-dimensional distance ($p = 0.759$), lateral–medial (x) axis ($p = 0.983$), anterior–posterior (y) axis ($p = 0.949$) or superior–inferior (z) axis ($p = 0.894$) from the intended anatomical target. The range of difference in tip location and limb scores was extensive. Our results suggest that anatomic targeting alone may provide the same clinical efficacy as is achieved by "fine-tuning" DBS placement with microelectrode recording to a specific target.

1. Introduction

Parkinson's disease (PD) is characterized by the loss of dopaminergic cells in the substantia nigra pars compacta.[17] Although levodopa (L-dopa) therapy generally provides excellent clinical response for years, most patients eventually develop progressive worsening and disabling motor fluctuations.[9,30] Dose escalation is typically limited by disabling peak-dose dyskinesias.[30]

For medically refractory patients with disabling motor fluctuations, stimulation of the subthalamic nucleus (STN) or the pars internus of the globus pallidus through deep brain stimulation (DBS) is the most beneficial surgical intervention.[10,14,25,27,43] The STN is an oblong deep brain nucleus that is essential to the extrapyramidal motor system.[17,33] With DBS, high frequency stimulation of a nuclear target (via the implantation of electrodes) produces a very similar effect to lesioning that target, with the advantages of reversibility and modulation.[4,5,7,21]

The electrode tip is 1.27 mm in diameter and is presumed to produce a current spread of less than 4 mm.[29,40] The STN is about 5 mm in diameter.[18] Electrode tip position relative to the motor portion of the STN is presumed to determine the clinical efficacy of stimulation therapy. Stereotactic atlases (created from a small number of human brains) have defined the relationship of the subcortical nuclei to the intercommissural midpoint (ICM),[41] the point half way between the anterior commissure (AC) and the posterior commissure (PC).

Physiological localization using microelectrode recording (MER) is performed to map the STN boundaries and tailor DBS placement[44] to compensate for anatomical variations and possible intraoperative brain shifting.[6,45] Detailed MER mapping of STN boundaries requires multiple electrode passes through the brain. In comparison to image-guided placement (target defined relative to the individual patient's ICM), MER mapping increases the risk of hemorrhage and frontal lobe trauma, increases operative time,

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and requires specialized, technologically advanced equipment and a physiologist trained in microelectrode recording interpretation.[10,15,16]

In contrast, stereotactic MRI-based (or CT scan/magnetic resonance-based) image-guided placement requires less operative time, fewer electrode penetrations of the brain, and obviates the need for physiologic equipment and interpretation.[15] The disadvantage of image-guided placement is that accuracy may be compromised by mechanical inaccuracies of the frame, individual patient variation from the available human stereotactic atlas coordinates, inaccurate setting of the stereotactic apparatus, shifting of the frame relative to the patient's head, and intraoperative brain shift.[20,48]

STN stimulation in PD patients using current methods of implantation provides consistent clinical benefit,[13,19,27] can reduce dopamine replacement therapy requirements by 50% to 60%,[28,50] and improves contralateral limb function.[11,24,38] However, there is no consensus regarding how critical it is for electrodes to be implanted precisely where they are targeted. Although studies have correlated the accuracy of electrode placement with the clinical outcome (Unified Parkinson's Disease Rating Scale [UPDRS] motor examination subscale) of the implanted patients,[1,31,40,49] these have been based on global assessments of the overall benefit of bilateral STN stimulation. Attempting to assess the clinical efficacy of a single electrode might be achieved more accurately by examining a unilateral limb motor effect. Thus, we retrospectively examined the DBS electrode tip locations based on postoperative MRI relative to intended location, and correlated this with the response of the contralateral limb motor function to STN stimulation as measured by the UPDRS Part III.[12]

2. Materials and methods

2.1. Patient selection

Between January 2000 and February 2001, 21 patients (14 men, 7 women) with advanced PD underwent bilateral STN DBS placement at our institution. Patients were selected by the operating surgeon and a neurologist specializing in the treatment of movement disorders (BF). Selected patients had longstanding dopamine-responsive PD with motor fluctuations that consisted of periods of severe immobility ("offs"), periods with good motor function ("good on"), and L-dopa-induced dyskinesias despite optimal medication adjustment.[14] Twenty patients underwent a bilateral simultaneous implantation, and 1 patient underwent a staged procedure. The mean age of the patients at the time of surgery was 57.9 years (range 43–73 years), and the average duration of PD was 14.4 years (range 4–27 years). Of our 21 patients, 5 had undergone a previous operation for PD (3 unilateral pallidotomies, 1 bilateral pallidotomy, and 2 fetal tissue transplants; 1 patient underwent both a unilateral pallidotomy and a fetal tissue transplant).

2.2. Stereotactic planning

A functional Cosman-Roberts-Wells (CRW) stereotactic frame (Radionics; Burlington, MA, USA) was used for all 21 patients. We attempted to align the stereotactic ring with the orbitomeatal plane. We obtained a volumetric T1-weighted axial MRI that included the region of the AC–PC plane with 1.5 mm or 2 mm slice thickness, but this did not allow the STN to be visualized directly. For the first 9 patients, the Radionics Stereoplan platform was used for surgical planning, with the initial target calculated relative to the ICM (4 mm posterior, 4 mm inferior, and 12 mm lateral), adjusting for any tilt in all three planes. For the subsequent 12 patients, we used Stealth Framelink 2.0 (Medtronic Inc.; Minneapolis, MN, USA), with the FrameLink 2.0 program reformatting the MRI to the AC–PC plane in order to yield the calculated coordinates for the STN.

2.3. Neurophysiologic localization

Our MER criteria for implantation have been described.[42] Briefly, high impedance tungsten microelectrodes (range: 200-700 kOhm) 24 mm long with a tip size of 20-25 μm (FHC; Bowdoinham, ME, USA) were advanced to the end of the guide tube, located 30 mm above the calculated anatomic target. Impedence at 1000 Hz was measured at 3 mm and 20 mm after the microelectrode left the cannula. Subsequently, the recording microelectrode was advanced to the target by an electronic stepper microdrive and the electrical signals from single neuronal units and background activity were filtered at 100 Hz to 3000 Hz, preamplified and amplified to 10,000 to 50,000 times, digitized, and sent to an oscilloscope and audio system for real-time monitoring, and to a digital recording device for off-line analysis. The MER coordinate positions, Fourier transforms of discharge frequencies, and action potential morphologies of single units, fiber activity, and background changes were quantified and recorded. Typically, bursting cells of the anterior thalamus were encountered followed by electrically quieter regions that corresponded to the fields of Forel and zona incerta. Proceeding ventrally, an area of increased background noise and irregularly firing neurons (often responsive to movement) were detected, corresponding to the STN. Further ventrally, below the STN, a region of more rapidly and regularly firing neurons that corresponded to the substantia nigra pars reticulata (SNpr) was detected. The average STN height along the first microelectrode track was 5.0 ± 0.6 mm (range 4.3-6.4 mm).

The height and depth of the STN and the depth of the SNpr were compared to a track through the target point on the stereotactic atlas along the known angle of the trajectory.[41] If these data indicated that the trajectory was as expected in the central region of the STN (including a minimum of 4-mm length of STN), we used these results for DBS placement. The first MER track satisfied these criteria on the first side in 9 of 21 implants. However, in these patients we placed the DBS 1 mm anterior to the calculated target path. In the remaining 12 first-side implants, we performed one or more parallel MER tracks until the central region of the STN had been adequately identified. On the second side, 19 of 21 implants were done with a single MER track. Typically, this track was along the same laterality from the midline as the implanted electrode on the first side. The surgery for one of the two second-side implants that required more than a single MER track was performed separately (intentionally staged). The other patient had the second-side electrode implanted 1 mm posterior to the first-side settings because of a relatively short STN on the initial MER track. Thus, we adjusted the intended target in this study from the image-calculated target (based on MER results) by 1 mm anterior (3 mm posterior to the ICM) in most patients (24/42 electrodes). Interestingly, 16 were adjusted no more than 1 mm away from the image-calculated target, 1 was adjusted by 1.5 mm and 1 was adjusted by 2.5 mm. The distal electrode contact was placed at the physiologically defined ventral boundary of the STN.

We did not attempt to target the STN precisely in each patient, our use of MER was mainly to make sure that we were well within the STN. Although we presume that the final target was near the center of the STN, our methodology does not confirm this for each electrode because of presumed individual variation in the distance of the STN from the ICM. However, our targeting assumed that the relationship of the STN to adjacent structures (SNpr, thalamus, zona incerta) is well predicted by the stereotactic atlas.

After removing the MER guide cannula, we placed the DBS electrode (Medtronic; models 3387 or 3389) by first positioning a longer guide cannula in the desired trajectory (as determined by previous MER recordings) and advancing it to the appropriate depth (about 15 mm above the ventral STN). The DBS electrode was then advanced to the desired depth (generally with the distal electrode intended to be within 1 mm of the inferior STN boundary). Excessive proximity to the medial lemniscus and internal capsule was evaluated by macrostimulation via the DBS electrode. Macrostimulation[31] between the deepest and most superficial electrodes did not produce sustained sensory symptoms or dystonic muscle contractions in any patient, nor did it change the electrode position of any patient in this series. Nine patients were implanted with model 3387 electrodes. The remaining 12 patients were implanted with model 3389 electrodes, because the implanting surgeon felt that the advantage of multiple contacts being within the 5 mm diameter STN outweighed the potential advantage of a greater span in the z axis. The desired electrode location was confirmed by postoperative T1-weighted axial MRI within 48 hours of the implant. Implantation of the lead extension wire and pulse generator (neurostimulator) was carried out 1 to 2 weeks later under general anesthesia.

2.4. STN stimulator settings

Typically, pulse generators were programmed initially 1 to 2 weeks after the DBS electrode implant. Subsequent extended programming was typically conducted at the 1 month and 3 month follow-up visits, with the patient in an "off" (medication withdrawal) state. The final settings were those that produced the greatest improvement of tremor (if present), bradykinesia and rigidity, without bothersome side effects. Stimulator setting data were obtained from chart review.

2.5. Merging of preoperative and postoperative MRI

The postoperative and immediate preoperative MRI for all patients were transferred via digital audio tapes to the Stealth Workstation. The Stealth FrameLink 4.0 program was used to manually merge the frame-based (preoperative) and the postoperative volumetric MRI (using 8-10 anatomical landmarks). The accuracy of the merge was confirmed using the "Split" format, which allows the user to carefully examine two overlapping images by sweeping across the screen to convert from one to the other. The mean "point-to-point" matching error was less than 1.0 mm, with an excellent overlap in all 3 planes of view. The mean error of merging for all 21 patients (22 total merges because 1 patient had implants performed on 2 separate days) was 0.39 mm (range 0.12-0.83 mm). Following the merge, we set the Blend Setting to 0% on the merged image, which displayed only the preoperative image with its fiducial markers (not the DBS artifact seen on the postoperative images). We then obtained the coordinates for the CRW fiducial frame. The mean fiducial error for all 21 patients was 0.73 mm (range 0.39-0.97 mm).

2.6. Calculation of STN target (manually vs. FrameLink 4.0)

The MRI was reformatted to the AC–PC plane by identifying the anterior and posterior commissures and 3 midline landmarks (to correct for tilt). The AC–PC distance was recorded for each patient. We then selected the center of the electrode artifact by shifting the Blend Setting from 0% to 100% (to visualize the postoperative MRI only), and then used all planes of view to determine the center at the tip of the electrode MRI artifact. Besides calculating the stereotactic frame coordinates of the point itself, we calculated its coordinates relative to the ICM ("AC–PC coordinates"). Therefore, there were 4 sets of coordinates for each patient: DBS tip frame and AC–PC coordinates for left and right. We then obtained the FrameLink 4.0 station's calculated STN target coordinates for the left and right side of each patient (the corresponding AC–PC coordinates are always 12 mm lateral, 4 mm posterior and 4 mm inferior to the ICM). This procedure for determining the DBS tip coordinates was performed by 3 separate observers (SM, PBS, RRG) to test the interobserver reliability of the: (i) definition of AC–PC distance, (ii) manual coordinates, and (iii) computer coordinates (partly reliant on each observer's definition of the AC–PC distance).

2.7. Calculation of intended STN coordinates (intended DBS target)

We used the CRW arc and ring angles relative to the AC–PC plane, the x and y axis shifts from the CRW target and the depth of the electrode placement to calculate the intended DBS tip target for each patient. The arc angles for the 21 patients was from 9° to 21° (mean 16.4°). The forward ring angle relative to the AC–PC plane was 30° for each electrode.

We then used the FrameLink 4.0 workstation with the OR adjustments (i.e. the x axis and y axis shifts and the depth of placement) to determine the intended target for the electrode tip, in relation to the midpoint of the patient's AC–PC plane. Meticulous care was taken to identify the posterior edge of the AC and the anterior edge of the PC and to precisely correct for any tilt off the vertical. We adjusted the initial y coordinate (4 mm posterior to the midcommissural point [MCP]) by a factor of cosine 30°, which equals 0.866 (we used 0.9). For example, if a patient had an operating room (OR) adjustment of 1.5 mm anterior in the y axis, this value was adjusted by 1.5/0.9 = 1.7. If the OR adjustment was anterior, than the value was added to the initial y coordinate, and if it was negative, it was subtracted from that coordinate. Therefore, in this example, if the OR adjustment was anterior, the FrameLink 4.0 adjustment in the y axis for the AC–PC coordinate would be $-4.0 + 1.7 = -2.3$. If the OR adjustment was posterior, than the FrameLink 4.0 adjustment would be $-4.0 - 1.7 = -5.7$. We were able to determine the corresponding AC–PC coordinates for the desired STN, which was determined in the OR for each patient. A similar adjustment was made for the x axis, using the angle of 30° relative to the AC–PC plane.

2.8. Determination of the difference between intended and MRI-determined DBS tip target

We compared the AC–PC tip coordinates of each by subtracting the intended AC–PC coordinates from the MRI determined AC–PC coordinates in each plane (x, y, and z) for all 21 patients. From the resulting numbers, we then calculated the distance between the tip coordinates in 3D space for each patient by taking the square root of $(x^2 + y^2 + z^2)$. Therefore, there were eight values for each patient: right x, y, and z and right 3D coordinate; left x, y, and z, and left 3D coordinate. These values were obtained by three independent observers to determine the interobserver reliability, and repeated by one observer (RRG) in a subset of patients to determine intraobserver reliability.

2.9. Clinical outcome

Postoperative evaluation consisted of neurologic examination using the Core Assessment Program for Intracerebral Transplantations (CAPIT) protocol, postoperative MRI and assessment of PD symptoms and medications, as described.[26,31] All patients were videotaped at baseline and at 1 year postoperatively. The videotaped exams were assessed by a movement disorder neurologist (SJF) blinded to stimulation status (electrode tip locations), with upper and lower extremity rigidity evaluated by a nonblinded

Table 1
Limb components of the Unified Parkinson's Disease Rating Scale (UPDRS) (Part III) motor scores

UPDRS limb-specific components (unilateral)	Maximum score (total = 28)
1. Rest tremor – hand	4
2. Rest tremor – foot	4
3. Action tremor	4
4. Rigidity – upper extremity	4
5. Rigidity – lower extremity	4
6. Finger tapping	4
7. Hand gripping	4
8. Hand pronation/supination	4
9. Leg agility	4

examiner.[13] The nine limb-related components of the UPDRS Part III (Table 1) were tabulated to obtain a limb score [(off-stimulation, off-medications) – (on-stimulation, off-medications)] indicative of contralateral limb response to stimulation, resulting in a total of 42 limb scores (one per electrode implanted). The electrode tip locations associated with the 15 least and 15 greatest limb response scores were compared to optimally assess the relationship between the anatomic location of the electrode tip and postoperative limb function. Additionally, the difference between electrode tip location and intended target (for each of the three blinded observers) was compared between these groups to evaluate the existence of a consistent trend separating one group from the other (see Table 3). The coordinates in the x-axis were adjusted to make negative x-values correspond to increasing laterality. This was done to account for the difference between the definition of laterality in left-sided and right-sided electrodes.

2.10. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 10 (SPSS; Chicago, IL, USA) and GraphPad Software (San Diego, CA, USA). Each series of comparisons between outcome measures was conducted using paired two-sample *t*-tests for approximately normally distributed data, and nonparametric Wilcoxon signed-rank tests for discrete outcomes. Nonparametric measures of correlation were performed using Kendall's tau and Spearman's rho. Differences between proportions were examined using Fischer's exact test. To identify outcome predictors, regression analyses were performed.

Table 2
Location of electrode tips relative to intended target (in millimeters)

Side/axis	Right (n = 21) Mean ± SD	Left (n = 21) Mean ± SD	Right (n = 21) Range	Left (n = 21) Range
x	−1.2 ± 1.2	+1.3 ± 1.3	−3.0 to +2.5	−0.4 to +5.1
y	−0.2 ± 1.3	−0.5 ± 1.4	−3.4 to +2.0	−4.1 to +1.2
z	+1.9 ± 1.6	+1.7 ± 1.7	−0.2 to +6.6	−1.1 to +5.2
3D	+2.9 ± 1.4	+2.9 ± 1.5	+0.7 to +6.7	+1.0 to +5.9

Negative values = leftward on x axis (medial on right x, lateral on left x) and posterior on y axis; positive values = rightward on x axis (lateral on right x, medial on left x) and anterior on y axis.
3D = three dimensional, SD = standard deviation.

3. Results

3.1. Electrode tip locations

3.1.1. Difference between location of electrode tips and intended target

The mean difference between electrode tip location and intended target for all 21 patients was less than 2 mm in all axes regardless of laterality, with a relatively small range of tip locations (Table 2). The mean absolute deviation of electrode tip location from target was 1.4 mm in the x axis, 1.0 mm in the y axis and 1.9 mm in the z axis. In the x axis,[35] of the 42 electrodes (18 right, 17 left) were located no further than 2 mm from the intended target, 38/42 (19 right, 19 left) in the y axis, and 25/42 (12 right, 13 left) in the z axis. Analysis comparing the 5 patients who underwent previous PD surgery versus the 16 patients who did not revealed no statistically significant difference in any axis with regard to electrode placement.

3.1.2. Measurement of interobserver and intraobserver reliability

The interobserver reliability of the electrode tip coordinates among the three observers was assessed. Reliability was extremely high for every coordinate, as the interclass correlation coefficient was never less than 0.71, regardless of laterality or axis. Intraobserver reliability (in all axes and 3D distances) was calculated using the coordinates of one observer (RRG). No intraclass correlation coefficient was less than 0.65, except for the z axes (right = 0.00, left = 0.53).

3.2. Clinical outcome

3.2.1. Electrode contacts used for stimulation

Stimulator settings were available for all 42 electrodes (range 2–14 months postoperative);35 electrodes used a monopolar configuration, and 7 were programmed to a bipolar setting. For most electrodes, contacts 1 or 2 were "active" (used for stimulation), similar to previous reports.[13,31,48] From the distribution of active programming electrode contacts used for stimulation, only one patient (described previously[31]) had a bipolar programming with a number 3 electrode (right and left) as a negative contact. In four of the six electrodes with 2 months of follow-up, the stimulation settings did not change at 1 year follow-up. However, in the other two electrodes, the settings did change at 1 year compared with 2 months of follow-up, with the active electrode changing from 1 to 0 in the first, and in the second from 1 and 2 to 0 only.

Table 3
Evaluation of electrode tip location versus intended target related to improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score

Absolute value of tip-target differential (mm)	Limb improvement on UPDRS blinded review	n	Mean	Standard deviation	p value (mean)	Variance	Sample size needed for 80% power to detect significant difference
x	Limited	15	−1.11	0.81	0.983	1.93	118,000
	Maximal	15	−1.10	0.92		1.92	118,000
y	Limited	15	−0.09	0.88	0.949	1.80	22,270
	Maximal	15	−0.06	1.34		0.85	22,270
z	Limited	15	1.86	1.69	0.894	1.62	7,113
	Maximal	15	1.93	1.27		2.94	7,113
3D	Limited	15	2.62	1.41	0.759	1.39	1,355
	Maximal	15	2.76	1.18		1.99	1,355

3D = three dimensional.

3.2.2. Blinded videotape comparison of least and most improved contralateral limb motor function

Videotape reviews were performed at 1 year postoperatively in all 21 patients and clinical outcomes were graded by a movement disorder neurologist (SJF) who was blinded to the electrode tip location. Evaluation of upper and lower extremity rigidity was made by a nonblinded examiner, as described previously.[13] Blinded videotape analysis is a highly objective evaluation of clinical outcome, which may result in a more modest improvement in recorded UPDRS scores than previously reported by studies in which videotape evaluators were not blinded.[13]

From the blinded videotape analysis, the change in the limb-specific components of the UPDRS Part III motor scores (Table 1) that compared on-stimulation, off-medication to off-stimulation, off-medication at 1 year was determined, yielding a limb score that corresponded to each electrode implanted (42 scores total). The mean limb score was 4.31 ± 5.5 (range −2.5 to 22.5), where a greater score indicated a larger improvement in UPDRS motor scores. A correlation analysis between all 42 limb scores and electrode locations in the x, y, and z axes revealed no significant correlations in any axis (absolute value of all correlation coefficients <0.2). Limb scores of $\leqslant$1.5 were segregated into a minimal stimulation responsive group, whereas limb scores of $\geqslant$5 segregated into a maximal stimulation responsive group. Of the 42 limb scores, 15 were classified as minimally (limited) responsive to stimulation (mean = −0.37; SD = 1.3; range = −2.5 to 1.5), and 15 were deemed maximally responsive (mean = 10.2; SD = 5.0; range = 5 to 22.5, $p < 0.0001$) (Fig. 1). As with the range of limb scores, the range of differences in tip location (x axis = 2.5 mm lateral to 5.1 mm medial; y axis = 4.1 mm posterior to 2 mm anterior) relative to the intended target was significant. The significance of this result is that it optimizes the likelihood of finding a relationship between the location variation and the clinical effect.

The electrode that had the greatest single-axis deviation from the intended target (5.1 mm medial) was associated with inadequate tremor suppression, although the overall limb score was in the intermediate range. This electrode was replaced 2 years after initial implantation, and the new electrode provided effective tremor suppression (4 mm lateral to previous electrode). There were no significant differences between the electrodes of the 5 patients with previous PD surgery versus the 16 patients without previous surgery.

The electrodes comprising the minimal and maximal responder groups were compared with corresponding preoperative L-dopa test results for the limb-specific components of the Part III UPDRS motor score (mean ± SD; minimal group score = 4.7 ± 3.3; maximal group score = 5.1 ± 2.8). The preoperative L-dopa data were available for 11 of the 15 electrodes in each group.

This comparison revealed no statistical difference between the two groups to indicate a predictive value of preoperative L-dopa results on postoperative limb motor function. There were likewise no statistical differences between the limited and maximal responder groups with regard to patient age or PD duration. However, 11/15 minimal responder electrodes were model 3387 (versus model 3389), whereas only 4/15 of the maximal responder electrodes were model 3387 ($p = 0.03$).

The two groups were similar in electrode tip location ($p > 0.05$) with regard to 3D distance ($p = 0.759$), lateral-medial (x) axis distance ($p = 0.983$), anterior–posterior (y) axis distance ($p = 0.949$) or superior–inferior (z) axis distance ($p = 0.894$) from the intended anatomical target (Table 3). This finding was highly correlated among the 3 observers, as was the variance of electrode location distributions between the two groups (Table 3). Additionally, the intended target coordinates between groups was compared, revealing no significant difference in any axis between the two groups (Table 4). A power analysis of our results demonstrated that for the differences between the means of the 2 groups (Table 3), at 80% power, a sample size of 1355 electrodes in each group would be needed to detect a significant difference with regard to 3D distance.

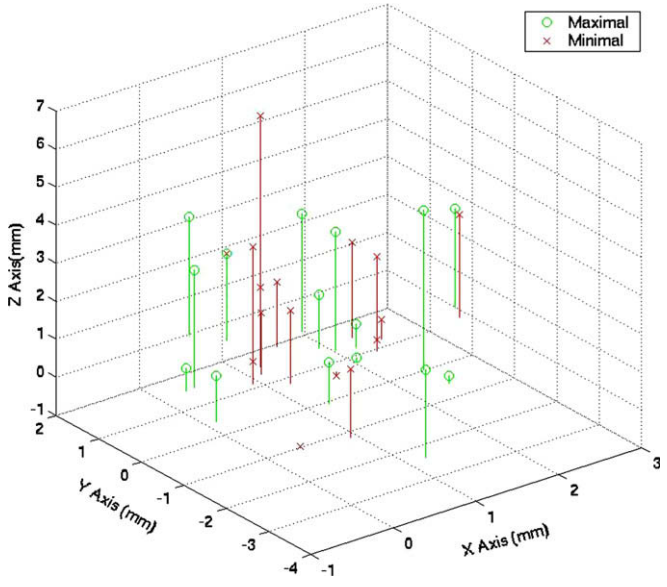

Fig. 1. Three-dimensional scatterplot of the locations of the deep brain stimulation electrode tips (determined by Robert R. Goodman) versus the intended target. The intended target location is (0,0,0): (○) = the 15 electrodes associated with the maximally responsive limb scores; (×) = the 15 electrodes associated with the minimally responsive limb scores. This figure is available in colour at www.sciencedirect.com.

4. Discussion

4.1. Electrode tip locations

Although Brice and McLellan described successful DBS in humans as early as 1980 for alleviation of tremor in multiple sclerosis,[8] it was Benabid et al. in the early 1990s who demonstrated the effectiveness of STN stimulation for the treatment of PD.[3,36] STN stimulation is considered the most efficacious surgical method for the symptomatic treatment of advanced PD.[22,23,34]

The role of MER in guiding DBS electrode implantation in the STN, performed since the prototype protocol,[3] is based on the hypothesis that MER improves the accuracy of electrode placement above that provided by image and macrostimulation guidance alone.[2,18,37,46,47,52] It is widely believed that electrode position optimizes clinical outcomes, yet few studies have confirmed the anatomic location of implanted electrodes.[1,31,40,46] We showed that the location of the electrode tip was consistently within 2 mm of the intended target in all axes,[31] and our findings suggested that a DBS electrode placed anywhere within a 6 mm diameter cylinder centered at the intended STN target (3 mm radius from the target) provides equivalent clinical efficacy as measured by blinded videotape review of UPDRS motor scores and patient questionnaire data.[31]

In the present study we used MER guidance only to confirm that the electrode was within the STN, without attempting to define the target as the motor or dorsolateral portion of the STN. Because MER guidance did not significantly alter our target from the image-defined target, the final electrode placement of electrodes in this study might provide significant variation relative to the motor portion of the STN; thus, the best limb improvement scores would lie

Table 4
Comparison of intended target coordinate between limited responder and maximal responder groups (in millimeters)

Direction (axis)	Limited (n = 15) Mean ± SD	Maximal (n = 15) Mean ± SD	Limited (n = 15) Range	Maximal (n = 15) Range
Lateral (x)	11.5 ± 0.5	11.3 ± 0.3	11.0–12.5	11.0–12.1
Posterior (y)	4.6 ± 0.9	4.7 ± 1.0	2.3–5.5	3.3–6.7
Inferior (z)	6.2 ± 0.6	6.3 ± 0.7	4.9–7.0	5.3–7.5

SD = standard deviation.

within the motor STN and the worst would lie outside the motor STN. Furthermore, because of the relatively stable relationship between the motor STN and the ICM, the average relationship of the "motor STN electrodes" to the ICM would be expected to differ from the average "non-motor STN electrodes". However, our results contradict this assumption.

The variability of the electrode tip location represents the measurable discrepancy from the intended brain target, not the variation expected from adjustment of the target by MER results. In these patients, as with most implants reported by high volume centers, the target adjustment based on MER data involved relatively small distances for all electrodes: most electrodes were implanted 1 mm anterior to the image-calculated target, and all but one were within 1.5 mm of this target. The average variation of the measured target from the intended target in this series is greater than the MER-guided adjustment from the image-calculated target. The variation of one electrode from the intended target did correlate with a suboptimal clinical outcome. Although the overall limb score for this electrode was in the intermediate range (not in the minimally or maximally responsive groups), it was ineffective for tremor suppression. This single/anecdotal experience suggests that the placement needed for certain clinical benefits (i.e. improved L-dopa responsiveness) may be distinct from the placement required for optimal tremor control.

To further elucidate the impact of anatomic electrode tip location on clinical outcome, we specifically examined the relationship between electrode tip location and contralateral limb motor function, since the improvement provided by STN stimulation for contralateral limb motor function is well known.[11,24,38,39,51] We used the AC–PC calculated coordinates based on T1-weighted imaging, and did not directly visualize the STN. If the STN could be adequately and accurately visualized by an MRI, it might allow more accurate targeting than using the AC–PC coordinates. This would also lessen the need for MER by eliminating one of its uses (the individual variation of the STN relative to the ICM). Most surgeons still do not rely on either the calculated target or direct STN visualization alone, but supplement this with MER to confirm targeting, presumably to correct for other causes of error (i.e. brain or frame shift or mechanical inaccuracies). The MRI of the postoperative electrode tip location is our measure of the electrode tip's relation to the intended target, and is not attempting to directly assess the location of the tip in relation to the 3D conformation of that individual STN. Based on our technique and the electrode tip locations in this study (within 2 mm of the intended target in all axes), our DBS tip locations (relative to the MCP and intended target) are similar to those obtained by other DBS implanters.[3,10,13,27,31]

4.2. Contralateral limb motor outcome

Blinded videotape analysis of 21 patients 1 year postoperatively using the components of the UPDRS pertaining to limb motor function (Table 1) was tabulated to obtain a limb score corresponding with each electrode implanted. The 42 limb score changes were not correlated with the variation of DBS tip location from the intended target, but the scores allowed a segregation of maximal (most positive) and minimal (least positive) scores that represented the degree of contralateral limb motor improvement with stimulation (n = 15 in each group). Additionally, the coordinates of the intended targets were not different between groups, indicating that differences between the groups could not be explained by differences in STN targeting.

In comparing the proportion of bipolar versus monopolar settings between the two outcome groups, results (Fischer's exact test) revealed no difference in settings between the two groups, indicating no increased likelihood of suboptimal electrode placement in the minimally stimulation-responsive group. The lack of a significant difference in stimulation parameters between the two groups (including the active contacts) suggests that variation in the z axis does not explain the difference in clinical benefit.

Of the minimally responsive electrodes, 11/15 were model 3387, whereas only 4/15 maximally responsive electrodes were 3387. Other than contacts 1 and 2, the most likely active contact for the model 3387 electrodes was contact 3, whereas it was contact 0 for the 3389 electrodes. Because both models were placed at similar depth, the efficacy difference might result from model 3387's superior coverage or from the difference in inter-electrode spacing. The uppermost electrode of the 3387 implants was possibly stimulating an anatomic area (and providing some clinical benefit) not effectively stimulated by the 3389 contacts. Our study does not provide conclusions on the possible advantage of one of these electrodes. Further investigation of electrode differences might be warranted.

Preoperative L-dopa test results were not predictive of which STNs would be minimally or maximally responsive to stimulation with regard to limb motor function. The reason for this finding is unclear.

The MRI-determined DBS tip locations in these two groups were statistically examined to assess the contribution of each axis to limb motor outcome, and the tip locations in these two groups did not differ significantly in any axis. Therefore, the degree of contralateral limb motor function improvement, within the range of electrode tip locations in this study, was not due to the proximity of the DBS electrode to the intended target in the STN. In addition to comparing these extreme response groups, analyzing all 42 electrodes yielded no evidence of a correlation between variation of location and limb motor score improvement. An analysis of the anatomic location of the electrodes used for stimulation, rather than the electrode tip, might provide a better indicator of the location required for optimal clinical efficacy. Electrodes 1 and/or 2 were the active contacts in most patients. These electrodes have a fixed relationship to the electrode tip, and thus analyzing the tip location is essentially the same as analyzing the location of the active contacts; this consistent relationship of the active contacts to the tip is slightly more lateral, anterior and superior (relative to the ICM) than the tip. Furthermore, the tip location depends most critically on the x and y dimensions, since in the z axis, 4 contacts are available that allow compensation for an error in that dimension. Even if motor outcome does not appear to be strongly influenced by small differences in electrode tip location, nonmotor effects might be impacted (i.e. stimulation-induced side-effects). However, side effects are also not strongly related to small variations in electrode tip location.[32]

A limitation of this study is the relatively small sample size per group, which could limit the statistical power required to differentiate the relatively small differences between these groups. This is particularly problematic since we are using our results to assert a negative relationship of variation in tip location to clinical efficacy. However, given that the differences observed between groups in this study would require a minimum of 1355 electrodes in each group (minimum of 22,270 electrodes per group if examining purely the x or y axes; Table 3), to demonstrate significance ($p < 0.05$) at 80% power, a larger sample size (even with a multicenter trial) would probably still be inadequate. Our previously published maximal clinical outcomes are comparable to those reported for STN surgery,[13] which supports the assumption that the DBS leads in these patients were accurately placed.

Another limitation is that the optimal stimulation parameters used for these patients may allow too much current spread to reveal significant variations in clinical effect. Although we are not claiming that the threshold for clinical effect did not differ based on electrode location, the results from this study clearly indicate that electrodes were able to provide similar clinical benefit at well-tolerated stimulation settings.

Our patients had significant variability in limb motor response to stimulation, but limited variation of the DBS electrode tip locations relative to the intended target (<2 mm). The mean DBS tip location discrepancies were essentially identical for the maximal and limited limb response groups. Removing the MER from the brain and then placing the DBS electrode does not mean that the DBS electrodes are placed precisely in the MER track because brain shift, or some other mechanical inaccuracy of the frame, could cause the DBS electrode to end up in a different position. This could occur even when placing the DBS electrode along the last MER track. This problem can be overcome only if the DBS electrode is placed through the same guide sleeve as the microelectrode without making any mechanical adjustment between the last MER pass and the introduction of the DBS electrode. However, this would be feasible only if the guide sleeve used for MER ends close to the target depth, in order to minimize the chance that the DBS electrode could deviate in the brain. Fortunately, the data in this series suggest that the variability of the DBS electrode placement from the intended target was not large enough to compromise the limb motor response in these patients.

Variable placement within the STN volume may produce variable limb motor response based on the distance from a specific STN subregion. To address this hypothesis, the intended target would have to be a specific STN subregion. Our intended target was at a consistent location relative to the patient's ICM. If there is variation in the relationship of the STN to the ICM, then the variation may be explained by the "maximal" and "limited" responders having a consistently different relationship (e.g. their STN centers). Previous reports have indicated a relatively limited variation of this target relative to the patient's ICM.[3,10,46] Direct examination of this variation may now be possible, using high strength (3 Tesla) MRI. These images will allow the determination of the image-defined STN center relative to each patient's ICM. The possibility that STN targeting[3,25,46] would avoid the variability of limb motor response scores could also be tested by applying our method of DBS tip location analysis to such a series of patients. We acknowledge that defining the electrode placement in the STN relative to the motor STN may have yielded different results than those from the method used in this study (i.e. defining electrodes as being within a large part of the STN).

Another potential limitation is that our main analysis placed the clinical outcome in groups, rather than as a strict 1:1 correlation. Although we did analyze for correlation, the potential for mismatch between DBS electrode placement and clinical outcome in the setting of a somatotopically organized STN could potentially have compromised the results from this study. An additional limitation was our usage of two different electrodes in the study (models 3387 and 3389), which could have potentially confounded our results.

Another explanation for our observations could be that electrode location within the STN does not determine the limb motor response. Other factors may influence this response, such as variable current spread to surrounding structures, biologic variability between individuals, or that disease variations influence the limb motor response. Limb motor response is only one measure of potential clinical benefit from stimulation. STN stimulation has many other effects (such as reduction of dyskinesias and reduction of "off" severity and duration) and this report is not intended to suggest that limb motor response is an accurate representation of a PD patient's overall clinical response to STN stimulation therapy.

5. Conclusion

The results of this study support our prior conclusions that optimal clinical efficacy allows a range of tolerance for variability in STN lead location.[31] We have examined this variability with respect to the intended anatomical target (AC–PC coordinates). This does not directly examine the relationship to each individual's STN. It is unclear whether this range of tolerance (relative to AC–PC coordinates) will obviate the need to adjust electrode placement according to individual variations of the STN. Depending on the range of variability tolerated, anatomic targeting alone (either indirect or possibly directly via improved MRI) may provide the same clinical efficacy as that achieved by "fine-tuning" DBS placement with MER to a specific target within the STN.

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