See the Editorial and the Response in this issue, pp 99–100.

J Neurosurg 106:101–110, 2007

Statistical determination of the optimal subthalamic nucleus stimulation site in patients with Parkinson disease

Dominique Guehl, M.D., Ph.D.,[1] Roderick Edwards, Ph.D.,[2] Emmanuel Cuny, M.D., Ph.D.,[3] Pierre Burbaud, M.D., Ph.D.,[1] Alain Rougier, M.D.,[3] Julien Modolo, M.Sc.,[4] and Anne Beuter, Ph.D.[4]

[1]Service de Neurophysiologie Clinique, [3]Service de Neurochirurgie, et Service de Neurologie, Hôpital Pellegrin, Université de Bordeaux; [4]Institut de Cognitique, Université Victor Segalen Bordeaux, Bordeaux, France; and [2]Department of Mathematics and Statistics, University of Victoria, British Columbia, Canada

Object. The subthalamic nucleus (STN) is currently recognized as the preferred target for deep brain stimulation (DBS) in patients with Parkinson disease (PD). If there is agreement in the literature that DBS improves motor symptoms significantly, the situation is less clear with respect to the side effects of this procedure. The goal of this study was to correlate the coordinate values of active electrode contacts with the amplitude of residual clinical symptoms and side effects using a mathematical approach.

Methods. In this study the investigators examined a cohort of 41 patients with PD who received clinical benefits from DBS after stimulating electrodes had been implanted bilaterally into the STN. The combined scores of residual clinical symptoms plus side effects, including speech disturbance, postural instability, and weight gain, were fitted by using either inverted ellipsoidal exponentials or smooth splines.

These analyses showed evidence of lower combined scores for stimulating contacts at an x coordinate approximately 12.0 to 12.3 mm lateral to the anterior commissure–posterior commissure (AC–PC) line and at a z coordinate approximately 3.1 to 3.3 mm under the AC–PC line. There was insufficient evidence for a preferred y coordinate location.

Conclusions. The authors propose a "best" therapeutic ellipse area that is centered at an x, z location of 12.5 mm, −3.3 mm and characterized by an extension of 1.85 mm in the x direction and 2.22 mm in the z direction. Therapeutic electrode contacts located within this area are well correlated with the lowest occurrence of residual symptoms and the lowest occurrence of side effects independent of STN anatomical considerations. The lack of a significant result in the y direction remains to be explored further.

Key Words • Parkinson disease • deep brain stimulation • subthalamic nucleus • side effect

The STN is currently recognized as the preferred target for DBS in patients with PD. Deep brain stimulation significantly improves parkinsonian symptoms (tremor, rigidity, and akinesia) as well as the severe motor fluctuations frequently associated with dyskinesias.[13,17] The effectiveness of STN stimulation depends on several selection criteria (patient age, motor response to levodopa therapy, normal cognitive functions, and normal findings on MR images of the brain) as well as on the phenotype of PD, the anatomical localization of active contacts, and neurological follow-up examinations for adjustment of stimulation settings. Although there is relative agreement in the literature that DBS improves motor symptoms (by ~ 60–75%),[11,13,26] the situation is not so clear for side effects. Indeed, to our knowledge, no study has been reported in the literature in which the amount of residual symptoms and the amount of side effects were examined concomitantly when DBS was turned on and off.

If we consider that for a given medical center, patient selection and follow-up examinations follow similar criteria, we can hypothesize that the phenotype of PD and the topography of electrode contacts can be used to explain to some extent the variability of DBS effectiveness and side effects observed among patients. Although it remains difficult at this time to clearly determine the "best" candidate for surgery on the basis of PD phenotype, it is interesting to determine the location of active contacts within and/or around the STN that will provide the largest motor improvement while producing the least side effects. This question has been addressed by other groups previously but remains open.[3,9,19,25,27,29] Indeed, neurophysiological and imaging techniques are

Abbreviations used in this paper: AC = anterior commissure; DBS = deep brain stimulation; MR = magnetic resonance; PC = posterior commissure; PD = Parkinson disease; RAT = rigidity, akinesia, tremor; RMS = root mean square; STN = subthalamic nucleus; UPDRS = Unified Parkinsons Disease Rating Scale.

commonly used to define the optimal site for electrode implantation,[1,4,10,12,19,20,22,28] but there is little evidence to date regarding the optimal site for permanent stimulation. To determine this optimal site, some authors have proposed correlating the positions of active electrode contacts with the dorsal boundary of the STN defined electrophysiologically.[3,7,12] However, correlating electrode position with anatomical landmarks such as the dorsal boundary of the STN is difficult because the variability across individual persons is large. This interindividual variability combined with the relatively small size of the target makes this correlation difficult to establish. In addition, stimulation of regions surrounding the STN also appears to be associated with positive effects.[9,27]

We propose that the determination of optimal coordinates of electrode contacts for DBS should take into account both the amplitude of residual clinical symptoms and the most frequent side effects in patients with PD. In this study, we correlated the coordinates of active electrode contacts to residual clinical symptoms while taking into account any side effects by using a mathematical approach in a cohort of 41 patients with PD who received bilateral implantation of electrodes in the STN without considering any correlation to STN anatomy.

Clinical Material and Methods

Patient Population and Clinical Assessment

The study population consisted of 41 patients (24 men and 17 women) who were considered for surgery based on the following criteria: 1) idiopathic PD with no significant comorbidities; 2) age younger than 70 years; 3) no cognitive impairment (Mattis Score[14] $>$ 130) and no psychotic side effects due to medication or past psychiatric history; 4) significant motor disability assessed on Part III of the UPDRS;[5] 5) a satisfactory motor response to levodopa (a decrease of $\geq$ 50% on the UPDRS Part III); 6) disabling motor fluctuations associated with "on" – "off" periods and/or severe dyskinesia refractory to appropriate treatments; and 7) MR imaging findings that were within normal limits.

To determine the effectiveness of STN stimulation alone, patients were tested 12 months after surgery under two successive conditions: "DBS on" (after withdrawal of $\geq$ 12 hours of antiparkinsonian medication[s] but during a stimulation period that had already lasted $\geq$ 12 hours), and "DBS off" (after $\geq$ 12 hours' withdrawal of antiparkinsonian medication[s] and after stimulation arrest for $\geq$ 60 minutes).

Patients were clinically assessed using Part III of the UPDRS.[5] Three subscores were extracted from this scale: a rigidity score (Item 22; score range 0–20), an akinesia score (Items 23–26 and 31; score range 0–36), a tremor score (Items 20 and 21; score range 0–28), and an axial score (Items 18 and 19, 27–30, and neck rigidity cited in Item 22; score range 0–28). A "RAT" score (that is, the sum of the patient's rigidity, akinesia, and tremor scores) was computed and reflected the effectiveness of STN stimulation on the parkinsonian triad. To distinguish the therapeutic effect of the right- and left-sided electrode contacts on the patient's contralateral symptoms, left- and right-sided RAT scores were calculated, taking into account independently the rigidity, akinesia, and tremor scores for each hemibody. The axial score is not based on unilateral aspects of neuromotor function, but we suppose that it could be influenced separately by the left and right electrode contacts and is the sum of contributions from the left and right. Thus we attribute half the axial score to the stimulator on each side (axial score/2 = right-sided axial score/2 + left-sided axial score/2), which is only an approximation as the contributions from the left and right electrode contacts may be unequal. The level of residual symptoms after STN stimulation was calculated from the clinical scores in the DBS-on condition (RAT + axial score/2): the lower the residual scores, the better the motor benefit derived under STN stimulation.

The most frequently reported side effects during STN stimulation were assessed clinically.[6] They included speech disturbance (dysarthria/hypophonia), postural instability, and weight gain. The severity of speech disturbance and that of postural instability were quantified using Items 18 and 29 of the UPDRS Part III, respectively (score range 0 [normal]–4 [severe]). To determine whether DBS was responsible for these two side effects, we calculated the difference between two postoperative scores: score in the DBS-on condition − score in the DBS-off condition. Thus, larger values (which may be negative) corresponded to a worsening of the symptoms related to STN stimulation. For weight gain, the patient's weight measured preoperatively was subtracted from the weight measured 12 months after surgery, allowing the following categories: 0, no weight change; 1, a weight increase of less than 5 kg; 2, a weight increase of 5 to 15 kg; and 3, a weight increase of greater than 15 kg. The combined scores were calculated by adding the residual symptom and side-effect scores.

Stereotactic Coordinates of Therapeutic Contacts

Quadripolar DBS electrodes were used to deliver bilateral monopolar stimulation. For the first 14 patients in this series, a cerebral computed tomography scan was obtained 3 days after electrode implantation. This scan was fused with a preoperative MR image, and the positions of the active contacts used in each patient was determined in relation to the AC–PC reference system described by Cuny et al.[4] For the other 27 patients, an MR image was obtained the day after electrode implantation. On this MR image the positions of active contacts used in each patient according to x, y, and z directions (corresponding to the lateral, anteroposterior, and vertical axes, respectively) were again determined and referred to the PC in the AC–PC reference system. Because brain sizes vary among individuals, a scaling factor was applied to compensate for the varying lengths of individual AC–PC lines. In addition, absolute values of the lateral (x) coordinates were used so that the left and right sides of the brain could be directly compared. Finally, for 28 of 41 patients in whom there were two active contacts on one side, the position of the reported therapeutic contact was defined as the midpoint between the two contacts.

Statistical Analysis

The therapeutic effect of bilateral STN stimulation on clinical symptoms was evaluated using a paired Student t-test to compare the scores obtained during the DBS-off and DBS-on conditions 12 months after surgery (Table 1).

Mathematical Analyses

To determine the stereotactic location of the active elec-

trode contacts allowing the best benefit with the least side effects, we proposed to take into account both the amplitudes of residual motor symptoms (right- and left-sided RAT scores, plus axial score/2 in each case) and the amplitudes of the most frequently encountered side effects (weight gain, speech disturbance, and postural instability). To obtain a sensible and global side-effect score, we added gains in speech disturbance and postural instability scores to the weight gain score. Therefore larger values were worse and smaller values were better. The mathematical models used in this study were applied to a combined score including residual symptoms and amplitudes of side effects related to STN stimulation. Two types of model fitting were attempted on the combined data.

Model 1. The first model is an inverted ellipsoidal exponential, which corresponds to the hypothesis that symptoms and side effects will be minimal when the stimulating contact is placed at some specific point within the STN, and that they will increase the farther away from that point the stimulating contact is placed, but only up to some maximum amount. The "nls" (nonlinear least squares) function in S-Plus (MathSoft) was used to fit the model parameters. One drawback of this model is that the rate at which the therapeutic effect of the contact diminishes with distance from the ideal point is assumed to be dependent on the x, y, and z axes directions, but from the point of view of the STN these axes are arbitrary. In our first version of this model, we also assumed that the combined score decreases to zero at the ideal point, which it may or may not do in practice. However, these assumptions are not so restrictive when the high level of noise in the data is taken into account. Also, there are already seven parameters in the model, and too many additional parameters could result in overfitting.

In a second version of the first model, we allowed for a nonzero optimum, but ignored the y direction, which does not seem to provide significant information. In this version there are six parameters.

Model 2. In the second model, the "gam" (generalized additive model) function in S-Plus is applied, which does not assume a functional form from the outset but instead attempts to fit relatively smooth splines to the data. Details can be found in publications by Hastie and Tibshirani[8] or Venables and Ripley.[23] An advantage of using this approach is that there is no a priori assumption of a point that minimizes the symptoms and side effects. If such a minimum exists it should in principle be discovered by the spline fit.

Results

A visualization of the contact locations in 3D space and their associated scores is shown in Fig. 1. The electrodes were not placed exactly in symmetrically equivalent spots for the left and right hemispheres (Fig. 1 *upper*), and the scatter of points representing contact locations appears slightly larger than the scatter of points reported by McClelland and associates[15] (see Fig. 1 in their paper on 26 patients). In Fig. 1 *lower*, the residual symptom score is indicated by color (dark blue represents the lowest and red the highest residual symptom scores), and the disk size represents the side effects (the larger the disk size the worse the side effects). Therefore, a small dark blue disk is the best result and a large red disk is the worst result. As can be seen in Fig. 1 *lower*, the smallest clinical scores are not necessarily located in the center of the scatter of points and the smallest side effects are not necessarily located at the periphery of the scatter of points.

TABLE 1

*Twelve-month postoperative scores showing the effectiveness of STN stimulation on motor symptoms**

Score	DBS-Off Period	DBS-On Period	Improvement (%)	p Value†
rt-sided RAT	14.7 ± 5.7	3.6 ± 3.0	71.2	<0.0001
lt-sided RAT	15.4 ± 6.8	4.7 ± 3.9	63.7	<0.0001
axial	10.8 ± 5	6.0 ± 3.7	41.1	<0.0001

* Values are expressed as means ± standard deviations. An explanation of scores and DBS-on and DBS-off periods can be found in *Clinical Material and Methods*. Probability values were determined using a paired Student t-test.

† Statistically significant.

The Ellipsoidal Exponential Model

The nls function in S-Plus was used to fit the data of the combined score to the nonlinear (exponential ellipsoidal) model given by the following function:

$$S = A(1 - \exp[-B\{x - x_0\}^2 - C\{y - y_0\}^2 - D\{z - z_0\}^2]). \quad \text{(Eq. 1)}$$

With "reasonable" starting values of the seven parameters, these values converge to the following (Table 2):

$A = 8.71$, $B = 0.70$, $C = 0.01$, and $D = 0.16$,

as well as

$x_0 = 11.99$ mm lateral to the AC–PC line;
$y_0 = 5.55$ mm anterior to the PC; and
$z_0 = -3.35$ mm with respect to the AC–PC line (that is, under the AC–PC line).

The last three parameters (x_0, y_0, and z_0) provide an estimate of the "ideal" 3D location for the stimulating contact; however, the fit is not particularly good because the symptom scores vary quite wildly. The residual standard error of the fit is 4.83 and the RMS of residuals is 4.62, which is not that much smaller than the size of the combined scores themselves, which range from −1 to 22.75 but with a mean of 6.88.

The effect of allowing the minimum point of the fitted function to be greater than zero was investigated by fitting instead to the following function:

$$S = A - E\exp(-B[x - x_0]^2 - C[y - y_0]^2 - D[z - z_0]^2).$$

If E were equal to A, then this equation would be equivalent to Equation 1, but if not, then the minimum fitted score would be A − E, which in that case would not be zero. However, this function did not produce a valid fit when using the nls function in S-Plus, probably due to the influence of the y variable, which appears to have no correlation with the scores. Thus, we applied the function again but without the y variable by using:

$$S = A - E\exp(-B[x - x_0]^2 - D[z - z_0]^2). \quad \text{(Eq. 2)}$$

Now the fitted parameter values (Table 3) are:

$A = 9.26$, $B = 0.41$, $D = 0.14$, and $E = 6.61$,

as well as

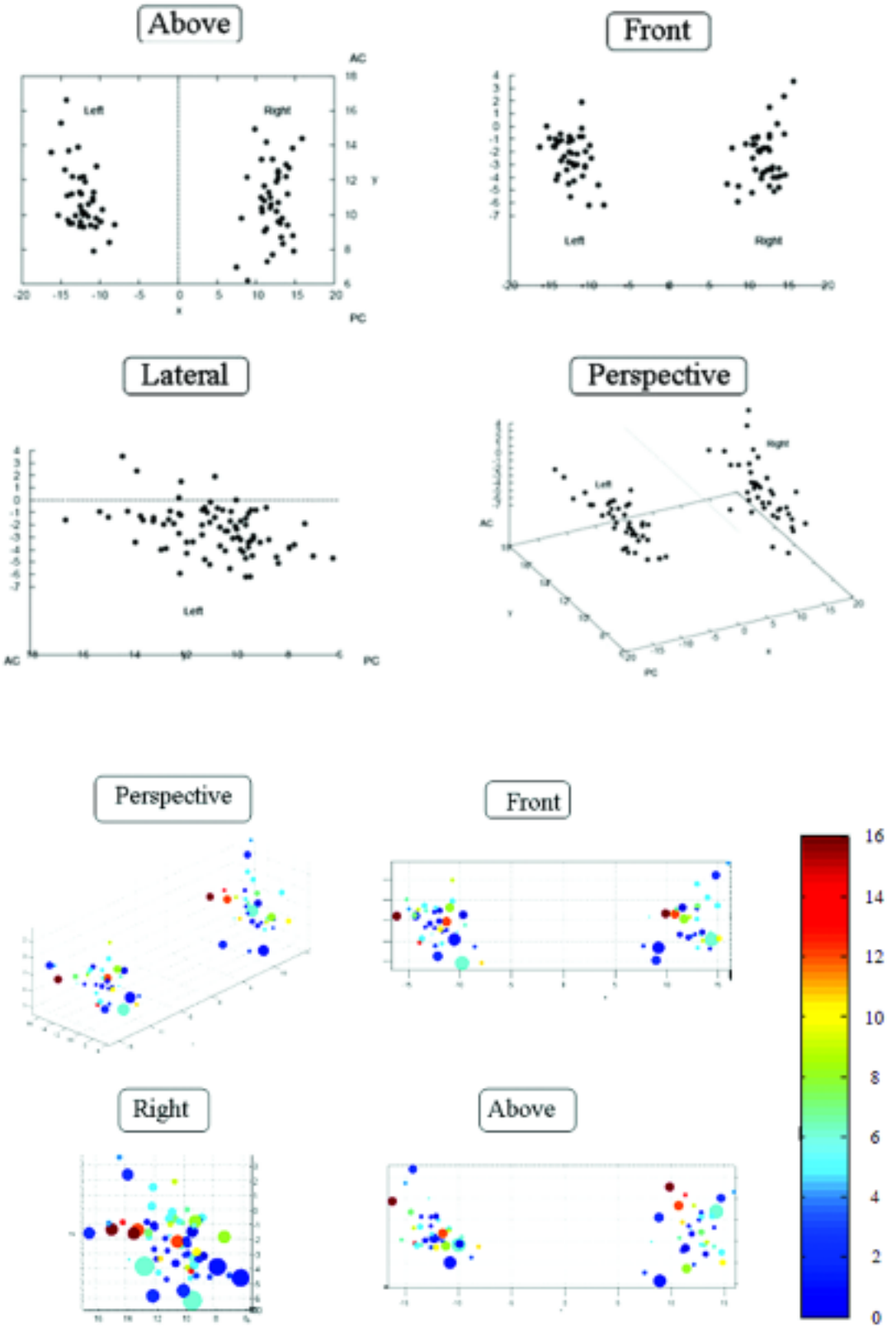

FIG. 1. *Upper:* Front, top (Above), lateral, and perspective views of the scatter of points corresponding to the 3D coordinates of the contacts. In the Above, Front, and Perspective panels, the right hemisphere is on the right side. *Lower:* A 3D representation of the x, y, and z coordinates of contacts in the DBS-on condition in which color represents the residual symptom scores (dark blue indicates the lowest residual symptom scores, with scores increasing through light blue, green, yellow, and orange to red, which indicates the highest residual symptom scores) and disk size represents the side effects (smallest disks are best and largest disks are worst).

TABLE 2
*Parameters fitted to Equation 1 using the nls function in S-Plus**

Parameter	Value	Standard Error	t	p Value
A	8.71	0.93	9.42	<0.0001†
B	0.70	0.49	1.41	0.157
C	0.01	0.03	0.28	0.779
D	0.16	0.15	1.03	0.305
x_0	11.99	0.24	49.53	<0.0001†
y_0	5.55	10.22	0.54	0.583
z_0	−3.35	0.76	−4.40	<0.0001†

* The residual standard error is 4.833 with 75 degrees of freedom.
† Statistically significant.

TABLE 3
*Parameters fitted to Equation 2 using the nls function in S-Plus**

Parameter	Value	Standard Error	t	p Value
A	9.26	1.16	7.99	<0.0001†
B	0.41	0.31	1.32	0.186
D	0.14	0.13	1.05	0.294
E	6.61	1.81	3.64	0.0002†
x_0	12.15	0.29	42.37	<0.0001†
z_0	−3.14	0.68	−4.60	<0.0001†

* The residual standard error was 4.805 with 76 degrees of freedom.
† Statistically significant.

x_0 = 12.15 mm lateral to the AC–PC line; and
z_0 = −3.14 mm with respect to the AC–PC line.

In this case, the residual standard error of the fit was 4.81 and the RMS of the residuals was 4.63. The comparison with the model in which Equation 1 is used is of interest because the fit is not exceptionally strong in either case, and thus consistency of results would strengthen our confidence that a real trend is present. The fitted minimum in the model in which Equation 2 is used is 9.26 − 6.61 = 2.65, and thus the function is considerably flatter than before, despite rising to a higher maximum of 9.26. The central point has not shifted much, however; both x_0 and z_0 are only slightly higher. Thus, the estimation of the "ideal point" does not appear to be too sensitive to the form of the model.

The Generalized Additive Model

We also used a generalized additive model (gam function in S-Plus), which does not impose a functional form but allows the data to determine the shape of the "effectiveness" function, by fitting relatively smooth splines to the data from the combined scores. When the gam function in S-Plus is applied, some indications of a dip in combined scores emerge, particularly in the x and z directions but not in the y direction (Table 4). This minimum—at least a local minimum—of the fitted score function occurs at approximately the following coordinates:

x_0 = 12.3 mm lateral to the AC–PC line (see Fig. 2);
y_0 = 11.9 mm anterior to the PC (the little dip in Fig. 3); and
z_0 = −3.3 mm with respect to the AC–PC line (see Fig. 4).

In x, the only minimum in the fitted curve is the one approximately 12.3 mm lateral to the AC–PC line (Fig. 2). The x direction effect is the clearest of the three direction effects.

In y, there could be a slight minimum approximately 11.9 mm anterior to the PC (Fig. 3), but it is not clear that scores do not get even lower for y values at either extreme. However, the drop in the fitted curve at either end is due to a few extreme points at which the symptoms were reduced to low values, but not lower than others throughout the y range, so not much confidence can be placed on this aspect of the fit (Fig. 3). In fact the y contribution to the fit is not significant.

In Fig. 4, showing the spline fit in z, the drop at large values of z ($z > 2.5$) is due entirely to one data point. In only one patient was a stimulating contact placed at a location at which z was greater than 2.5 mm and only on one side (at x = 15.85 mm, y = 14.40 mm, z = 3.53 mm), and in this case the combined score was reduced to a very low value (1.5). It would be unwise to base too much on this case, however; in another patient harboring the stimulating contact at a very similar position, although slightly lower in the z direction (x = 15.10 mm, y =1 4.27 mm, z = 2.43 mm), the combined score was reduced only to 15.0, and both patients had similar symptom scores (not including side effects, of course) in the DBS-off condition (21.5 and 26.0, respectively). On the other hand, the minimum at a z of −3.3 mm was based on many data points and is therefore more reliable. Thus, it is reasonable to conclude that there is evidence for lower combined scores for a stimulating contact near the coordinates x = 12.3 mm lateral to the AC–PC line and z = −3.3 mm with respect to the AC–PC line, but no sufficient evidence for a preferred y location. The RMS of the residuals was 3.87, and thus the location effect (essentially the depth of the minima in the fitted curves) was still not overwhelmingly large in relation to the noise; nevertheless, we can conclude that there is a location that improves the probability of effective treatment.

Figure 5 shows the plot of fitted combined scores as they depend on the two significant directions (x and z). Visually it reveals a hollow centered on the optimal x and z values where the result is best.

Overall Results

The overall results suggested by these analyses are that there is a slight tendency for symptoms to be reduced to lower levels with a minimum of side effects when the stimulating contact is located near an x of 12.0 to 12.3 mm lateral to the AC–PC line and a z near −3.1 to −3.3 mm with respect to the AC–PC line. Most of the data points for stimulating contact locations within 1 mm of any of the aforementioned estimated ideal points actually have low symptom and side-effect scores (and thus, low combined scores). Nevertheless, there were a few patients with stimulating contact locations close to these points who had higher com-

TABLE 4
*Values of the F statistic for nonparametric effects in the generalized additive model fit**

Intercept	Npar F	p Value
x_0	6.261	0.0008†
y_0	0.801	0.4979
z_0	2.931	0.0396†

* Npar = nonparametric.
† Statistically significant.

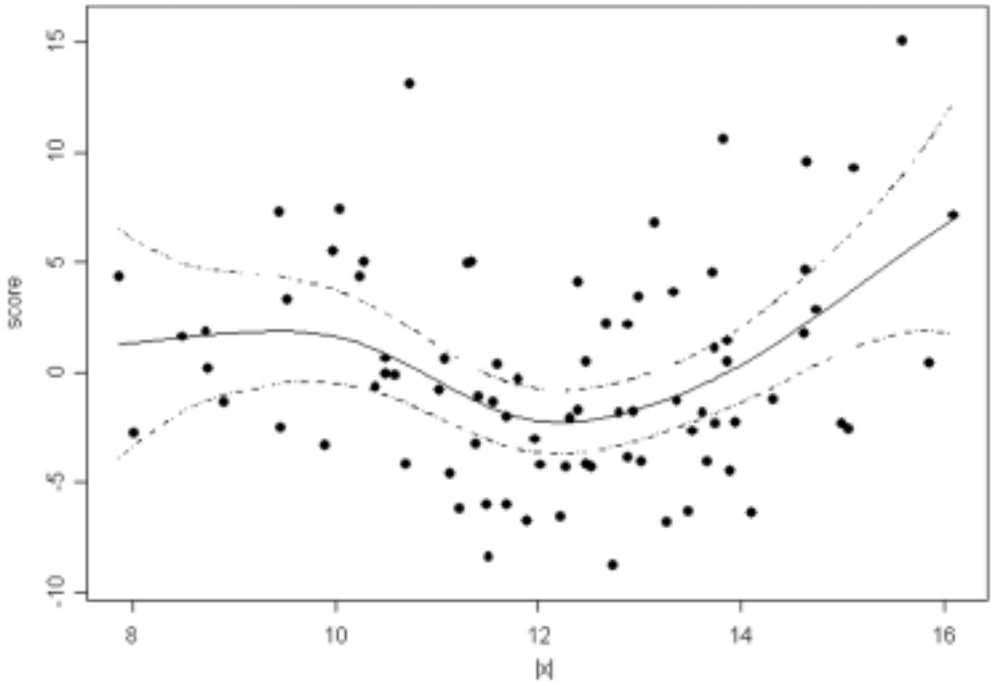

FIG. 2. Scatterplot showing the scaled generalized additive model—the "gam" fit—with a smooth spline function in x. The solid line shows the fitted x-dependent spline function, that is, s1(x) in fitted.score = intercept + s1(x) + s2(y) + s3(z). The dotted lines show pointwise twice-standard-error curves. The points are residuals added to s1(x), showing how well s1(x) can be used to explain the part of the actual score data not accounted for by s2(y), s3(z), and the intercept. More precisely, the points are located at s1(x) + residual, which is equal to (actual score) − s2(y) − s3(z) − intercept. The vertical axis has score units but represents only the x-dependent contribution to the score. The intercept was 7.48.

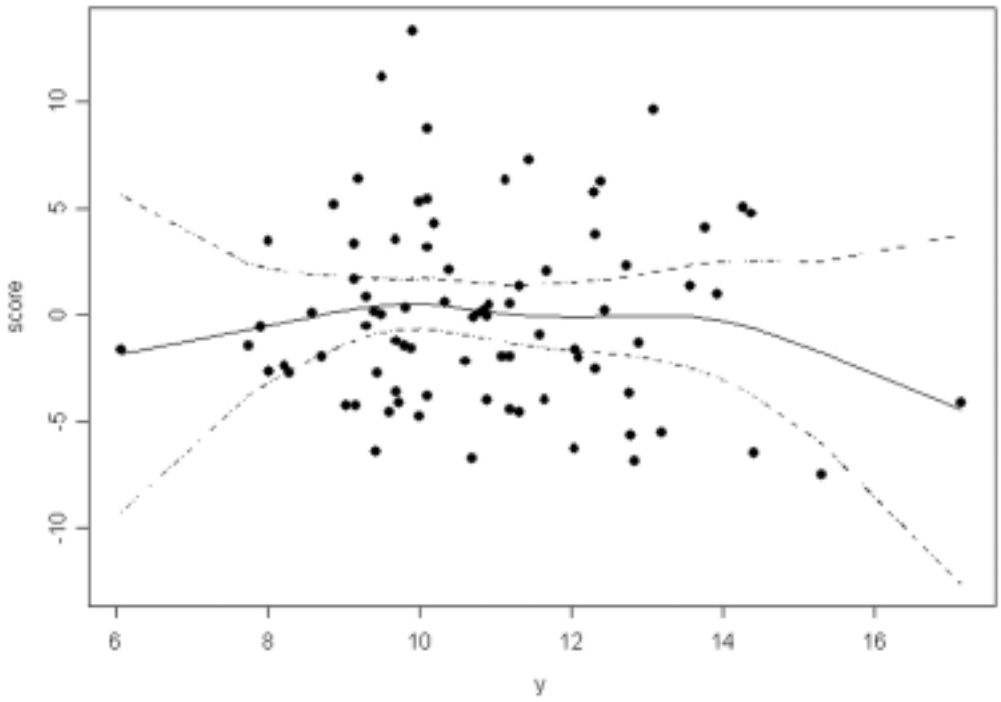

FIG. 3. Scatterplot showing the scaled generalized additive model—the "gam" fit—with a smooth spline function in y. The solid line shows the fitted y-dependent spline function, that is, s2(y) in fitted.score = intercept + s1(x) + s2(y) + s3(z). The dotted lines show pointwise twice-standard-error curves. The points are residuals added to s2(y), showing how well s2(y) can be used to explain the part of the actual score data not accounted for by s1(x), s3(z), and the intercept. More precisely, the points are located at s2(y) + residual, which is equal to (actual score) − s1(x) − s3(z) − intercept. The vertical axis has score units but represents only the y-dependent contribution to the score. The intercept was 7.48.

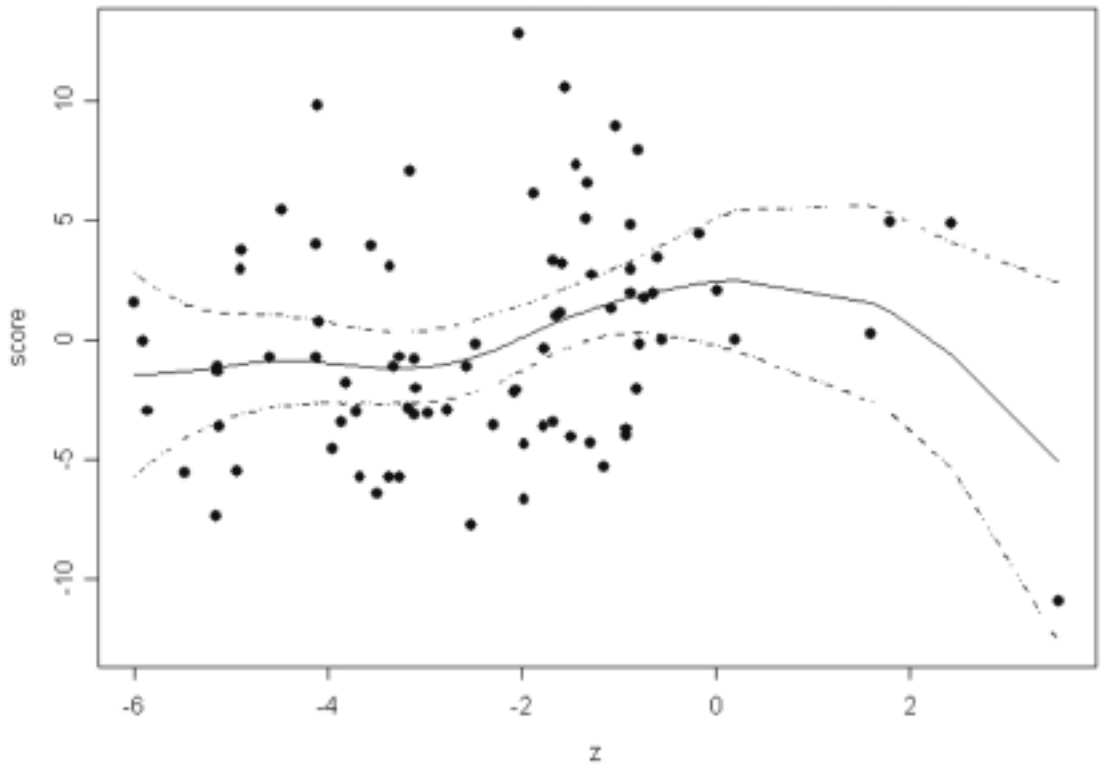

FIG. 4. Scatterplot showing the scaled generalized additive model—the "gam" fit—with a smooth spline function in z. The solid line shows the fitted z-dependent spline function, that is, s3(z) in fitted.score = intercept + s1(x) + s2(y) + s3(z). The dotted lines show pointwise twice-standard-error curves. The points are residuals added to s3(z), showing how well s3(z) can be used to explain the part of the actual score data not accounted for by s1(x), s2(y), and the intercept. More precisely, the points are located at s3(z) + residual, which is equal to (actual score) − s1(x) − s2(y) − intercept. The vertical axis has score units but represents only the z-dependent contribution to the score. The intercept was 7.48.

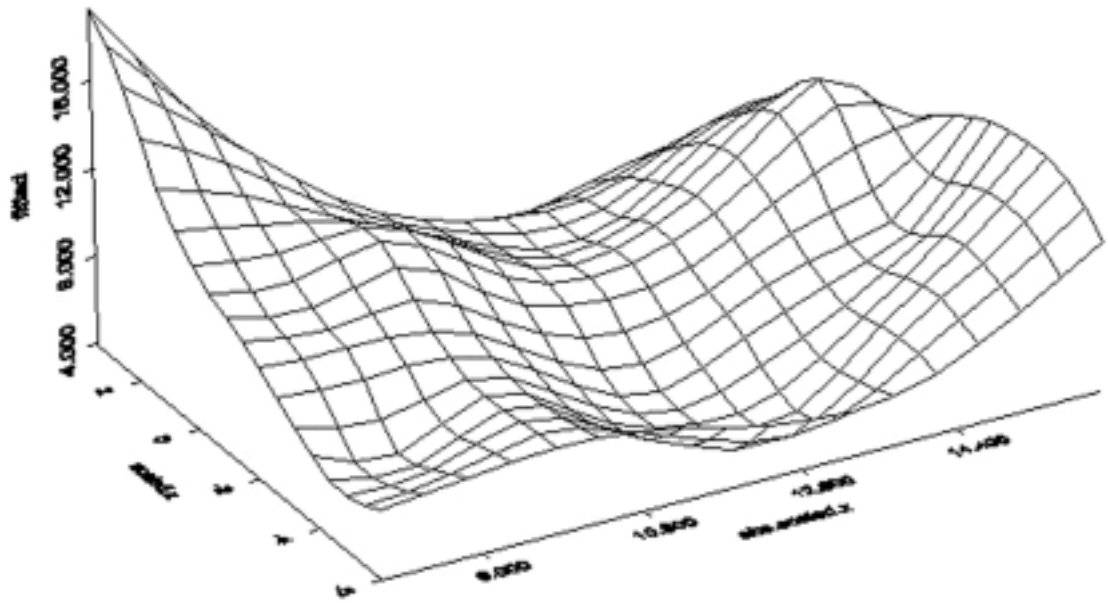

FIG. 5. Graph demonstrating the x and z coordinates of the best site, the generalized additive model "gam" with smooth spline functions, which reveals a hollow centered on the optimal x and z values.

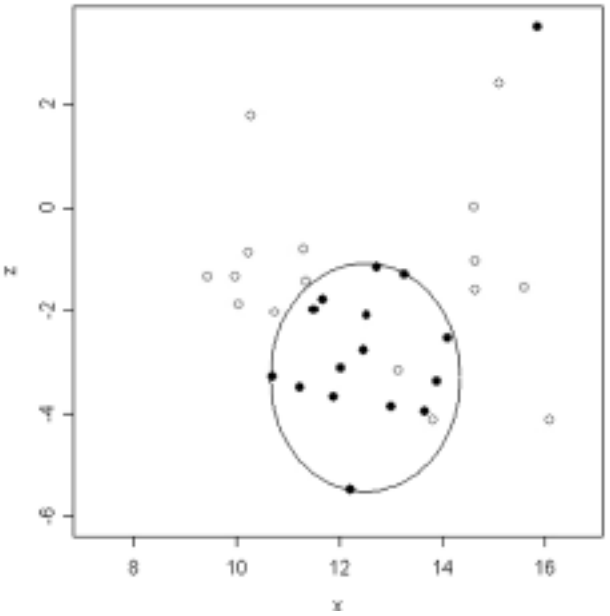

FIG. 6. Two-dimensional plot of contact locations with low combined scores (< 2.25, *black dots*) and high combined scores (≥ 11.5, *open dots*). An ellipse that has semimajor axes of lengths 1.85 mm in the x direction and 2.22 mm in the z direction, and is centered at an x value of 12.5 mm and a z value of −3.3 mm, contains most of the low combined scores. Sixteen of the 17 cases with low scores had contacts that lie inside the ellipse (two dots are superimposed). Only two cases in which there were high scores lie inside the ellipse.

bined scores. For example, one patient with a stimulating contact located at the x, y, and z coordinates of 13.15, 10.11, and −3.15 mm, respectively, had a combined score of 13.0. Two others—one with a contact located at the x, y, and z coordinates of 12.99, 8.88, and −3.55 mm, respectively, and the other with a contact at 12.67, 13.76, and −3.37 mm, respectively—had combined scores of 9.25 and 7.75, respectively. All other points within 1 mm of an approximate average "ideal x_0, z_0 point" of 12.25, −3.2 mm were associated with combined scores of 4.5 or lower.

Another confirmation of the reality of the minimum of the fitted score function comes from considering all the cases for which the combined scores were less than 2.25 (17 of 82 cases). In all but one of these cases the site of the contact lay within an ellipse with semimajor axes of length 1.85 mm in the x direction and 2.22 mm in the z direction, and whose center is at an x of 12.5 mm and a z of −3.3 mm (Fig. 6). This broadly matches the results of the curve-fitting exercises and could, in fact, be said to account for them. The y values for these cases ranged between 7.75 and 12.84 mm, which is a range centered at 10.3 mm with a half-width of 2.55 mm, wider than those for x or z, but in any case we do not have a significant y effect. The one exception for cases with combined scores lower than 2.25 was a patient (Case 38) already mentioned, in whom on one side the stimulating contact had the x, y, and z coordinates of 15.85, 14.40, and 3.53 mm, respectively (an extreme location), but in whom the combined score was 1.5. Furthermore, many other points within the specified elliptical area did not have such successful results, but in the most successful cases (score < 2.25) the contact sites were almost invariably located in this area. In fact, although in 16 (94%) of 17 cases with combined scores lower than 2.25 the contacts lay within this ellipse, in only 21 (32%) of 65 cases with combined scores of 2.25 or greater did the contacts lie within this ellipse, and in only one (9%) of the 11 cases with combined scores greater than 13 did they lie within the ellipse. Figure 6 shows the ellipse, the sites of contacts associated with combined scores lower than 2.25, and the sites of contacts associated with combined scores of 11.5 or greater. Thus, placing the stimulating contact in this region is by no means a guarantee of good results, but it does increase the probability of good results.

Discussion

The optimum site for therapeutic DBS is the subject of an ongoing debate. In this study, the fitting of a nonlinear model (the ellipsoidal exponential) or generalized additive model (smooth splines) to the combined scores based on residual motor symptoms and side effects provided precise coordinate values of the therapeutic area to target during STN surgery for PD. This model suggests that there is evidence for lower symptom and side-effect scores when a stimulating contact is located near the x coordinate of 12.0 to 12.3 mm lateral to the AC–PC line and the z coordinate between 3.1 and 3.3 mm under the AC–PC line. Most of the data points for stimulating contact locations within approximately 2 mm of this estimated ideal point were associated with combined low symptom and side-effect scores. However, the model was not able to identify an optimum value for the y coordinate.

The location of the STN is generally identified in relation to the AC–PC line (whose reported length is 25.8 mm on average). The size of the STN, according to Voges and associates,[24] is approximately 3 × 8 × 12 mm (coronal [x] × sagittal [y] × axial [z] axes) in humans. As indicated by Richter et al.,[18] the size and position of the STN are highly variable and differ systematically on MR images and on plates in atlases. These authors found the size of the STN to be 3.7, 5.9, and 5 mm for the x, y, and z coordinates, respectively. Surprisingly, in a different study, McClelland et al.[15] presented a 3D plot (similar to our Fig. 1 *upper* but with a smaller scatter of points) and compared the actual electrode locations to the intended electrode locations in the STN, which had been determined using electrophysiological studies and postoperative MR imaging for 26 individuals. All their contacts were within less than 2 mm of the intended target in all axes. This is surprising given the variability in the y and z directions across studies.

In the present study a region with less side effects and less residual symptoms can be located precisely using our model and, since stimulation inside the STN is associated with beneficial effects, the question arises: are we stimulating the STN, the border of the STN, or just outside of it? The values derived from MR imaging for the positions of the borders of the STN vary up to several millimeters.[18] Therefore it is currently impossible to answer this question.

Neurophysiological and imaging techniques are commonly used to define the optimal site for electrode implantation. Some authors have proposed to correlate the position of active electrode contacts with the dorsal or dorsolateral boundary of the STN defined electrophysiologically.[7,9,12] Zonenshayn and colleagues[29] have suggested that the opti-

mum region for stimulation is found in the anterior dorsolateral region. Hamel et al.[7] reported that nearly 70% of active electrode contacts were located near or within the dorsal border of the STN. The relation between the STN boundary and electrode location varies for two reasons: 1) there is some variability in the clinical evaluation of patients and in the precise localization of the electrode contact on the MR image; and 2) localization of the STN on the MR image is difficult. The average coordinates of the active contact found by Hamel and coworkers were 12.8 ± 1.0 mm in the x direction, 1.9 ± 1.4 mm in the y direction, and 1.6 ± 2.1 mm in the z direction in relation to the midcommisural point. Lanotte et al.[12] gave a mean position of the central point of the most effective electrode contact with respect to the midpoint of the AC–PC line as 12.3 ± 0.9 mm in the x direction, 1.7 ± 0.9 mm in the y direction, and 1.7 ± 1.5 mm in the z direction. Authors of other studies have reported similar results.[19] These two teams concluded that the most effective electrode contacts are located in the upper portion of the STN recording area or just above it. We suggest, however, that the conclusion reached by Lanotte et al. must confront the issue of variability mentioned earlier (for example, variability in measurement methods, across individuals, and of reference systems, particularly the validity of scaling of the AC–PC line).

In light of these data, the location of active contacts in our study in the lateral direction (x = 12–12.3 mm) is similar to the most effective contacts reported by these groups. On the other hand, the position of our active contacts in the vertical direction (z = −3.1 to −3.3) appears more ventral than that cited in previous studies. Interestingly our values are similar to those reported by Benabid and colleagues[2] and Starr[21] in larger series of patients in which different procedures were used. The location of the contact leading to the best clinical result was based either on ventriculography measures[2] or on findings of MR imaging.[21] The coordinates were as follows: 12.1 mm in the x direction and −3.16 mm in the z direction for the study by Benabid and colleagues, and 11.8 mm in the x direction and −3.9 mm in the z direction for the study by Starr. Nevertheless, it is very difficult to determine if the best contact lies in the STN or just above it. To answer this question it would be necessary to quantify the interindividual variability of the anatomical location of the STN, which has not yet been quantified precisely.

One remaining question lies in the fact that the model could not be used to identify an optimum value for y. This may mean that the range of electrode contact locations in the anteroposterior direction used in practice is not large enough to observe a clear drop in effectiveness. Thus we were unable to locate the anteroposterior boundary of the region where the location of the electrode contact provided the best clinical results. Interestingly, authors of studies in which an electrophysiological approach was used to target the STN have not reported values for the anteroposterior axis (y), probably because of the dorsoventral orientation of the electrode track used during the implantation procedure. The absence of a preferred y location appears to be a new result. In previous studies, Zonenshayn et al.,[29] Saint-Cyr et al.,[19] and Weinert et al.[25] found the mean location of clinically effective contacts for the y coordinate to be 1.62, 0.5, and 2.3 mm posterior to the midcomissural point, respectively. This inconsistency may suggest that the stimulated area is isotropic with regard to clinical effects as opposed to side effects along the anteroposterior axis and is anisotropic along the x and z directions.

The location of our ellipse defined in the x and z directions was determined independently of anatomical, imaging, or stereotactic considerations of the STN. Does this imply that it would be possible to realize preoperative targeting without any STN visualization or stereotactic determination? This question cannot be answered within the scope of this study, but will be the focus of further investigations because targeting the STN is a difficult aspect of intracerebral stimulation in PD. Nevertheless, this ellipse may in fact represent a part of the STN. This is supported by the fact that this ellipse is somewhat superimposed on a 3D STN representation that is centered at values proposed by Herzog et al.[9] and relies on the volumes proposed by Richter et al.[18] and Voges et al.[24] One limitation of the present study is that the right and left STN were treated together by using absolute values in the x direction. By doing so we might have cancelled out some asymmetries if they exist, as suggested in a recent study.[16] However, given the limited number of participants in this study (41 patients), we opted for not separating the two STNs.

Conclusions

In summary, independently of any anatomical and stereotactic considerations, it is possible to reconstruct mathematically, in two of three dimensions, the most effective region in which electrodes must be inserted to provide optimal clinical results while causing the least amount of side effects. The mathematical model we used could be refined by increasing the number of patients, decreasing the sources of variability, and exploring possible nonlinearities in side effects. This approach may provide a way for us to aim at an optimal target without having to deal with the difficulty of localizing the STN boundary using MR imaging.

References

1. Bejjani BP, Dormont D, Pidoux B, Yelnik J, Damier P, Arnulf I, et al: Bilateral subthalamic stimulation for Parkinson's disease by using three-dimensional stereotactic magnetic resonance imaging and electrophysiological guidance. **J Neurosurg 92:**615–625, 2000
2. Benabid AL, Koudsie A, Benazzouz A, Piallat B, Krack P, Limousin-Dowsey P, et al: Deep brain stimulation for Parkinson's disease. **Adv Neurol 86:**405–412, 2001
3. Butson CR, Cooper SE, McIntyre CC: Deep brain stimulation of the subthalamic nucleus: patient-specific analysis of the volume of tissue activated. **10th Annual Conference of the International FES Society,** July, Montreal, Canada, 2005
4. Cuny E, Guehl D, Burbaud P, Gross C, Dousset V, Rougier A: Lack of agreement between direct magnetic resonance imaging and statistical determination of a subthalamic target: the role of electrophysiological guidance. **J Neurosurg 97:**591–597, 2002
5. Fahn Y, Elton R: Unified Parkinson's disease rating scale, in Fahn S, Marsden C, Calne D, Goldstein M (eds): **Recent Developments in Parkinson's Disease, Vol 2.** Florham Park, NJ: Macmillan, 1987, pp 153–163
6. Guehl D, Cuny E, Benazzouz A, Rougier A, Tison F, Machado S, et al: Side-effects of subthalamic stimulation in Parkinson's disease: clinical evolution and predictive factors. **Eur J Neurol 13:** 963–971, 2006
7. Hamel W, Fietzek U, Morsnowski A, Schrader B, Herzog J,

Weinert D, et al: Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: evaluation of active electrode contacts. **J Neurol Neurosurg Psychiatry 74:**1036–1046, 2003
8. Hastie TJ, Tibshirani RJ: **Generalized Additive Models.** London: Chapman and Hall, 1990
9. Herzog J, Fietzek U, Hamel W, Morsnowski A, Steigerwald F, Schrader B, et al: Most effective stimulation site in subthalamic deep brain stimulation for Parkinson's disease. **Mov Disord 19:** 1050–1054, 2004
10. Houeto JL, Damier P, Bejjani PB, Staedler C, Bonnet AM, Arnulf I, et al: Subthalamic stimulation in Parkinson disease: a multidisciplinary approach. **Arch Neurol 57:**461–465, 2000
11. Iansek R, Rosenfeld JV, Huxham FE: Deep brain stimulation of the subthalamic nucleus in Parkinson's disease. **Med J Aust 177:** 142–146, 2002
12. Lanotte MM, Rizzone M, Bergamasco B, Faccani G, Melcarne A, Lopiano L: Deep brain stimulation of the subthalamic nucleus: anatomical, neurophysiological, and outcome correlations with the effects of stimulation. **J Neurol Neurosurg Psychiatry 72:** 53–58, 2002
13. Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D, et al: Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. **N Engl J Med 339:**1105–1111, 1998
14. Mattis S: **Dementia Rating Scale. Professional Manual.** Odessa, FL: Psychological Assessment Resources, 1988
15. McClelland S III, Ford B, Senatus PB, Winfield LM, Du YE, Pullman SL, et al: Subthalamic stimulation for Parkinson's disease: determination of electrode location necessary for clinical efficacy. **Neurosurg Focus 19(5):**E12, 2005
16. Nowinski WL, Belov D, Pollak P, Benabid AL: Statistical analysis of 168 bilateral subthalamic nucleus implantations by means of the probabilistic functional atlas. **Neurosurgery 57 (4 Suppl):** 319–330, 2005
17. Pollak P, Fraix V, Krack P, Moro E, Mendes A, Chabardes S, et al: Treatment results: Parkinson's disease. **Mov Disord 17 (3 Suppl):**S75–S83, 2002
18. Richter EO, Hoque T, Halliday W, Lozano AM, Saint-Cyr JA: Determining the position and size of the subthalamic nucleus based on magnetic resonance imaging results in patients with advanced Parkinson disease. **J Neurosurg 100:**541–546, 2004
19. Saint-Cyr JA, Hoque T, Pereira LC, Dostrovsky JO, Hutchison WD, Mikulis DJ, et al: Localization of clinically effective stimulating electrodes in the human subthalamic nucleus on magnetic resonance imaging. **J Neurosurg 97:**1152–1166, 2002
20. Starr P, Feiwell R, Marks W Jr: Placement of deep brain stimulators into the subthalamic nucleus: technical approach. **Stereotact Funct Neurosurg 72:**247, 1999
21. Starr PA: Placement of deep brain stimulators into the subthalamic nucleus or Globus pallidus internus: technical approach. **Stereotact Funct Neurosurg 79:**118–145, 2002
22. Sterio D, Zonenshayn M, Mogilner AY, Rezai AR, Kiprovski K, Kelly PJ, et al: Neurophysiological refinement of subthalamic nucleus targeting. **Neurosurgery 50:**58–69, 2002
23. Venables WN, Ripley BD: **Modern Applied Statistics with S-PLUS, ed 2.** New York: Springer, 1997
24. Voges J, Volkmann J, Allert N, Lehrke R, Koulousakis A, Freund HJ, et al: Bilateral high-frequency stimulation in the subthalamic nucleus for the treatment of Parkinson disease: correlation of therapeutic effect with anatomical electrode position. **J Neurosurg 96:**269–279, 2002
25. Weinert DM, Hamel W, Müller D, Herzog J, Deuschl G, Volkmann J: Electrophysiology and deep brain stimulation of the subthalamic area in Parkinson's disease: where are the active macroelectrode contacts? **Society for Neuroscience: Program No. 1012.9,** San Diego, CA, 2005 (Abstract)
26. Welter ML, Houeto JL, Tezenas du Montcel S, Mesnage V, Bonnet AM, Pillon B, et al: Clinical predictive factors of subthalamic stimulation in Parkinson's disease. **Brain 125:**575–583, 2002
27. Yelnik J, Damier P, Demeret S, Gervais D, Bardinet E, Bejjani BP, et al: Localization of stimulating electrodes in patients with Parkinson's disease by using a three-dimensional atlas-magnetic resonance imaging coregistration method. **J Neurosurg 99:**89–99, 2003
28. Zonenshayn M, Rezai AR, Mogilner AY, Beric A, Sterio D, Kelly PJ: Comparison of anatomic and neurophysiological methods for subthalamic nucleus targeting. **Neurosurgery 47:**282–294, 2000
29. Zonenshayn M, Sterio D, Kelly PJ, Rezai AR, Beric A: Location of the active contact within the subthalamic nucleus (STN) in the treatment of idiopathic Parkinson's disease. **Surg Neurol 62:** 216–226, 2004

Manuscript received May 19, 2006.
Accepted in final form July 14, 2006.
This study was funded by a contract from EC: Life Sciences, Genomics and Biotechnology for Health, Network of Excellence (Contract No. 005137, BIOSIM) to partner Dr. Beuter, and by a grant from the Natural Science and Engineering Research Council of Canada to Dr. Edwards.

Address reprint requests to: Anne Beuter, Ph.D., Institut de Cognitique (bâtiment 2A), Université Bordeaux 2, 146 rue Léo Saignat, 33076 Bordeaux, France. email: beuter@idc.u-bordeaux2.fr.