Determining the position and size of the subthalamic nucleus based on magnetic resonance imaging results in patients with advanced Parkinson disease

ERICH O. RICHTER, M.D., TASNUVA HOQUE, B.S., WILLIAM HALLIDAY, M.D., ANDRES M. LOZANO, M.D., PH.D., AND JEAN A. SAINT-CYR, PH.D.

Department of Neurosurgery, University of Florida, Gainesville, Florida; Department of Surgery, University of Toronto; Toronto Western Research Institute; and Department of Neuropathology, University of Toronto, Ontario, Canada

Object. The subthalamic nucleus (STN) is a target in surgery for Parkinson disease, but its location according to brain atlases compared with its position on an individual patient’s magnetic resonance (MR) images is incompletely understood. In this study both the size and location of the STN based on MR images were compared with those on the Talairach and Tournoux, and Schaltenbrand and Wahren atlases.

Methods. The position of the STN relative to the midcommissural point was evaluated on 18 T2-weighted MR images (2-mm slices). Of 35 evaluable STNs, the most anterior, posterior, medial, and lateral borders were determined from axial images, dorsal and ventral borders from coronal images. These methods were validated using histological measurements in one case in which a postmortem examination was performed.

The mean length of the anterior commissure–posterior commissure was 25.8 mm. Subthalamic nucleus borders derived from MR imaging were highly variable: anterior, 4.1 to 3.7 mm relative to the midcommissural point; posterior, 4.2 to 10 mm behind the midcommissural point; medial, 7.9 to 12.1 mm from the midline; lateral, 12.3 to 15.4 mm from the midline; dorsal, 0.2 to 4.2 mm below the intercommissural plane; and ventral, 5.7 to 9.9 mm below the intercommissural plane.

The position of the anterior border on MR images was more posterior, and the medial border more lateral, than its position in the brain atlases. The STN was smaller on MR images compared with its size in atlases in the anteroposterior (mean 5.9 mm), mediolateral (3.7 mm), and dorsoventral (5 mm) dimensions.

Conclusions. The size and position of the STN are highly variable, appearing to be smaller and situated more posterior and lateral on MR images than in atlases. Care must be taken in relying on coordinates relative to the commissures for targeting of the STN.

KEY WORDS • subthalamic nucleus • magnetic resonance imaging • movement disorder • Parkinson disease • surgery

Chronic high-frequency electrical stimulation of the STN is an increasingly important treatment option in patients with advanced PD. Many groups use ventriculography or MR imaging indirectly to target the STN relative to the AC and the PC. This indirect targeting is often based on coordinates derived from standard brain atlases, which are often scaled to a patient’s neuroimaging-derived AC–PC length in an attempt to improve the fit of the atlas coordinates to the patient. Note, however, that the stereotactic atlases are based on a relatively small number of brains; the Talairach and Tournoux atlas is based on one brain, and the Schaltenbrand and Wahren atlas uses one brain for the frontal series and a second for the axial and sagittal series. Furthermore, the position and size of the STN varies among atlas series. Little is known about the relative position of the borders of the STN or its size in these standard brain atlases compared with these factors in the general population or in patients with PD. We examined the size of the STN and the position of its borders relative to the AC and PC based on MR imaging results obtained in a population undergoing surgery for PD, and compared these features with the size and position of the STN in the Talairach and Tournoux, and Schaltenbrand and Wahren brain atlases. We are aware of a now-obsolete probabilistic atlas (Andrew and Watkins), in which STN limits have been reported based on a plane passing through the PC and the foramen of Monro and which is never used in stereotactic guidance. By transposing these data into AC–PC coordinates, we calculated that their representation of the STN was much more anterior and dorsal than in any current atlas and incongruent with any currently reported coordinates used in stereotactic surgery. Consequently, we did not further consider these data in our study.

Materials and Methods

Patient Population

All patients had given informed consent to participate in the research before any procedure was undertaken, and all MR images were obtained as part of the routine clinical care of the patients.

Eighteen patients with advanced PD (Table 1) were evaluated with the aid of MR imaging (1.5-tesla Sigma magnet; General Elec-
The AC–PC length derived from MR images is commonly longer than that obtained from the atlases. Many groups attempt to improve the fit of the atlas coordinates by scaling measurements of the AC–PC distance. The most anterior extent of the STN was measured on each axial slice relative to the anteroposterior position of the midcommissural point. The most anterior of these measurements was recorded in a database. The posterior border was similarly evaluated from the axial series (Fig. 1 upper). Dorsal and ventral borders were measured on coronal images (Fig. 1 lower) relative to the intercommissural plane. Medial and lateral border measurements were expressed in millimeters from the midline and could be obtained from either the axial or coronal series. When compared, measurements obtained from the axial and coronal series were found to vary minimally. The axial data set was used for the final analysis of medial and lateral borders.

The size of the nucleus was calculated in the anteroposterior, mediolateral, and dorsoventral dimensions. In each patient, the maximal value of each dimension was calculated as the distance (in millimeters) between the appropriate boundary measurements; for example, the dorsoventral height was the distance between the dorsal and ventral boundaries in each patient.

The STN measurements were geometrically corrected for pitch (range 0–17°) and yaw (range 0–6.5°). The effect of roll (range 0–8°) was below the spatial resolution of the MR images and therefore no roll correction was applied to the medial and lateral coordinates of the STN or to the height or depth relative to the AC–PC line.

**Statistical Analysis**

The AC–PC length determined from neuroimaging studies to those in the atlas. To investigate the validity of such scaling, we calculated correlation coefficients for the AC–PC distance with each of our MR imaging measurements. We found no significant correlation between any of our measurements and the AC–PC distance. The inability to correlate a relationship between the AC–PC distance and the position or size of the STN calls into question the validity of scaling to the AC–PC distance. Accordingly, we did not normalize our measurements to the AC–PC distances of the atlases.

The data set for each border was evaluated using SigmaStat (SPSS Science, Chicago, IL) to determine if it met the criteria for parametric statistical evaluation as normally distributed data. All data sets for the position of the borders of the STN based on MR images met these criteria except for the anterior border, which did not because of a single outlier. The mediolateral size data were normally distributed, but the anteroposterior and dorsoventral size data were not. Because these data could not be reliably evaluated in a uniform fashion by using parametric significance testing, we analyzed the relationship of each measurement to the atlas descriptively, calculating the percentile of the MR imaging data set into which each atlas observation fell. For example, when the position of a border in an atlas fell between the 34th and 35th observations for the position of that border in the MR imaging data set (number of STNs 35), that atlas value was described as less than the 3rd percentile compared with the MR imaging measurements. When the position in the atlas fell entirely outside the extremes of the positions measured on MR images, that atlas measurement was described as less than the 1st percentile compared with the MR imaging measurements.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean Value (range)</th>
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<tr>
<td>age (yrs)</td>
<td>54.9 ± 8.7 (39–68)</td>
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<tr>
<td>sex (M/F)</td>
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<tr>
<td>disease duration at age</td>
<td>12.2 ± 3.8 (6–19)</td>
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<td>time of surgery (yrs)</td>
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* Values are presented as the mean ± standard deviation.

**TABLE 2**

<table>
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<th>Parameter</th>
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<td>imaging study type</td>
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</tr>
<tr>
<td>TE</td>
<td>90 msec</td>
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<td>echo train</td>
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<td>gap</td>
<td>0 mm</td>
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<td>matrix</td>
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</tr>
<tr>
<td>bandwidth</td>
<td>3.29 kHz</td>
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</table>
Position and size of the subthalamic nucleus based on MR imaging

**Results**

Values are presented as the means ± standard deviations. As measured on axial MR images, the AC–PC lengths in the 18 studied brains were a mean 25.8 ± 1.6 mm (range 23.5–29.9 mm). The geometric center of the STN was at a mean distance of 3.8 ± 1.3 mm (range 0.5–6.1 mm) posterior to the midcommissural point. The mean lateral distance of the center was 12.2 ± 0.9 mm (range 10.1–13.7 mm) from the midline. The mean ventral distance from the intercommissural line was 5.1 ± 0.7 mm (range 4.2–6.6 mm). The positions of the nucleus borders were highly variable (note ranges in Table 3).

**Anterior and Posterior Borders**

The position of the anterior border of the STN was the most variable, ranging from 4.1 mm anterior to the midcommissural point to 3.7 mm posterior to the midcommissural point on MR images (Table 3). The mean value of the anterior border on MR imaging was 0.9 mm posterior to the midcommissural point (Fig. 2 upper). The anterior margin of the STN on MR imaging was 3.9 mm behind the position of the anterior border in the Talairach atlas and in the sagittal series in the Schaltenbrand atlas, and 4.65 mm behind the position of the anterior border in the axial series of the Schaltenbrand atlas. The values for the position of the anterior border of the STN derived from the brain atlases were at all the extreme of the distribution of positions for the anterior border obtained from the MR images, with only 1 of 35 MR imaging measurements being more anterior. Thus, the atlas measurements were at less than the 3rd percentile compared with the MR imaging data.

The posterior border of the STN in our patients ranged from 4.2 to 10 mm behind the midcommissural point. The mean position of the posterior border was 6.8 mm posterior to the midcommissural point. This position was similar to the posterior borders in the atlases (Fig. 2 upper). The mean value and 95% CI of the position of the anterior and posterior borders derived from the MR images are plotted onto a representation of the 12-mm lateral plate of the Schaltenbrand and Wahren atlas in Fig. 3.

**Medial and Lateral Borders**

The position of the medial border of the STN on MR images ranged from 7.9 to 12.1 mm lateral to the midline, with a mean of 10.3 mm (Table 3). This was a position significantly more lateral (4.55–6.3 mm) than the medial border in the brain atlases, all of which fell well below the 1st percentile from the MR imaging data set (Fig. 2 center).

The position of the lateral borders of the STN on the MR images ranged from 12.3 to 15.4 mm, with a mean of 14.1 mm. This position was similar to the lateral border in both the Talairach atlas (14 mm) and in the coronal series in the Schaltenbrand atlas (14.5 mm), although it was situated 1.65 mm more medial (< the 1st percentile) than the lateral border in the axial series in the Schaltenbrand atlas (Fig. 2 center).

**Dorsal and Ventral Borders**

On MR images, the position of the dorsal boundary ranged from 0.2 to 4.2 mm below the intercommissural plane, with a mean of 2.6 mm below the intercommissural plane (Table 3). This position was below (< the 9th percentile) the dorsal boundary in the Talairach atlas (0.5 mm below the intercommissural plane) and in the coronal series in the Schaltenbrand atlas (0.75 mm below), but it was significantly (< the 1st percentile) ventral to the dorsal border in the sagittal series in the Schaltenbrand atlas (at the intercommissural plane; Fig. 2 lower).

The position of the ventral border on MR images ranged from 5.7 to 9.9 mm below the intercommissural plane, with a mean of 7.6 mm below this plane. The mean position of the ventral border based on MR images was similar to the position of the ventral border in the sagittal series and coronal series in the Schaltenbrand atlas (7.75 mm), but was significantly (< the 3rd percentile) different from the position of the ventral border in the Talairach atlas (6 mm; Fig. 2 lower).

**Size of the STN**

The mean length of the STN was smaller on MR images than in any of the atlas series in the anteroposterior, mediolateral, and dorsoventral dimensions (Table 4).

Based on MR imaging, the anteroposterior length ranged from 3.4 to 9.7 mm (Fig. 4 upper), with a mean of 5.9 mm. The mean anteroposterior length derived from MR imaging

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### Table 3

<table>
<thead>
<tr>
<th>Border (mm)</th>
<th>Anterior</th>
<th>Posterior</th>
<th>Medial</th>
<th>Lateral</th>
<th>Dorsal</th>
<th>Ventral</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR images (range)</td>
<td>−0.9 (4.1 to −3.7)</td>
<td>−6.8 (−4.2 to −10)</td>
<td>10.3 (7.9 to 12.1)</td>
<td>14.1 (12.3 to 15.4)</td>
<td>−2.6 (0.2 to 4.2)</td>
<td>−7.6 (−5.7 to −9.9)</td>
</tr>
<tr>
<td>Position in Talairach atlas†</td>
<td>3 (&lt;3%)</td>
<td>−6 (NS)</td>
<td>5.5 (&lt;1%)</td>
<td>14 (NS)</td>
<td>−0.5 (&lt;9%)</td>
<td>−6 (&lt;3%)</td>
</tr>
<tr>
<td>Position in sagittal series in Schaltenbrand atlas†</td>
<td>3 (&lt;3%)</td>
<td>−8.5 (NS)</td>
<td>NA</td>
<td>NA</td>
<td>0 (&lt;1%)</td>
<td>−8.5 (NS)</td>
</tr>
<tr>
<td>Position in axial series in Schaltenbrand atlas†</td>
<td>3.75 (&lt;3%)</td>
<td>−6.25 (NS)</td>
<td>5.75 (&lt;1%)</td>
<td>15.75 (&lt;1%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Position in coronal series in Schaltenbrand atlas†</td>
<td>NA</td>
<td>NA</td>
<td>4 (&lt;1%)</td>
<td>14.5 (NS)</td>
<td>−0.75 (&lt;9%)</td>
<td>−7.75 (NS)</td>
</tr>
</tbody>
</table>

* The position of the anterior and posterior borders is relative to the midcomissural point; the medial and lateral borders are relative to the midline; and dorsal and ventral borders are relative to the intercommissural plane. Abbreviations: NA = not applicable; NS = atlas values that fell within the 95% CI of the MR imaging measurements.
† In parentheses next to each atlas value is its percentile rank comparison to the MR imaging data set.
was shorter than its length in the Talairach atlas (9 mm, the 9th percentile) or the axial series (10 mm, the 1st percentile) or sagittal series (11.5 mm, the 1st percentile) in the Schaltenbrand atlas.

In the mediolateral dimension (Fig. 4 center), the STN was much narrower based on MR imaging measurements (2.5–5.3 mm) than in any atlas series (8.5–10.5 mm, the 1st percentile).

The average dorsoventral height (Fig. 4 lower) of the STN derived from MR imaging measurements (5 mm) was similar to its height in the Talairach atlas (6.5 mm), but was shorter than the height in the coronal series of the Schaltenbrand atlas (7 mm, the 9th percentile) or the sagittal series in the Schaltenbrand atlas (8.5 mm, the 3rd percentile).

**Comparisons Based on Patient Sex and STN Orientation**

We compared the STN in male patients with that in female patients and the orientation of the STN, that is, the left compared with right side. No significant difference was observed using the Student t-test with a Bonferroni correction for multiple comparisons. Coordinates for right compared with left STNs had positive correlations for posterior (p < 0.05), medial (p < 0.05), dorsal (p < 0.01), and lateral (p < 0.01) coordinates only. The mediolateral and dorsoventral dimensions of the right and left STN centers correlated significantly at a probability value less than 0.05. Therefore, the anterior borders and AC–PC centers of the right and left STNs were not correlated (that is, neither the same nor systematically offset).

**Correlates With Patient Age**

We compared the location of STN and the age of the 18 patients by using a Spearman rho correlation coefficient. We only found a significant negative correlation (p < 0.01) between the dorsal border of STN and patient age.

**Comparison of MR Imaging–Based Measurements and Histological Measurements**

Although we analyzed only one case, the MR imaging–derived dimensions and location of the STN agreed to within 1 mm of the three-dimensional histological reconstructions, which were cross-validated with microelectrode recording data (Saint-Cyr and Halliday, unpublished observations).

**Discussion**

Unlike some targets in stereotactic surgery, the STN is visible on MR imaging. There is, however, disagreement as to whether this information should be used in target selection. Other investigators have looked at the center or laterality of the STN on MR imaging, but there has been no systematic report on all nuclear borders by using

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**FIG. 2.** Upper: Box-whisker plot demonstrating the position of the anterior (dark gray) and posterior (light gray) borders of the STN. The MR imaging data are compared with data obtained from standard brain atlases. The boxes represent the SD; the line in the box is the median value; the whiskers represent the 95% CI; and measurements falling outside the 95% CI are represented by single crosses. Center: Box-whisker plot demonstrating the position of the medial (dark gray) and lateral (light gray) borders of the STN. Lower: Box-whisker plot exhibiting the position of the dorsal (dark gray) and ventral (light gray) borders of the STN. MCP = midcommissural point; sag = sagittal; SW = Schaltenbrand and Wahren atlas; TT = Talairach and Tournoux atlas.

**FIG. 3.** Anterior and posterior borders from MR imaging plotted against a representation of the 12-mm lateral plate from the Schaltenbrand and Wahren atlas (dotted outline). The squares represent the mean position of the anterior and posterior borders by MR imaging. The error bars demonstrate the 95% CI. The triangle represents the position of the most anterior outlier for the anterior border, and the circle mark the most posterior outlier for the posterior border. All measurements are in millimeters relative to the midcommissural point on axial images. The inner, solid nuclear outline is the nuclear shape scaled and shifted to match the mean values from MR imaging.
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...this technique; and neither has there been a statistical comparison between MR imaging measurements and those on commonly used atlases.

We found that on T₂-weighted imaging with a low bandwidth, the STN could be reliably evaluated in all but one of 18 patients. In all patients, the positions of the borders of the STN were highly variable. In fact, the variation in the position of the borders was of a magnitude similar to the size of the nucleus. We examined the relationship between the position of the borders of the STN and the intercommissural length in each patient and could find no statistically significant correlation. Similarly, we found no statistically significant relationship between the intercommissural distance in each patient and the length of the STN in any dimension. With this imaging sequence, the nucleus appeared smaller in all dimensions than would be expected based on information either the Talairach or the Schaltenbrand atlas.

There are some limitations to our study. The anteromedial aspect of the STN on axial images is frequently difficult to distinguish from the substantia nigra, which appears similarly hypointense on these sequences. We believe that a careful review performed by multiple observers has reduced the impact of these factors on the reliability of our results. Nevertheless, the possibility does remain that the measurements of the anterior and medial borders in particular may have been affected by a systematic misinterpretation. On coronal MR images obtained in some patients, the ventral border of the nucleus may similarly blend into the substantia nigra, but this difficulty was encountered less often. The narrow distribution of values for the positions of the ventral and medial borders in comparison to the distribution of values for the positions of the anterior and posterior borders argues against the idea that these factors have led to a great degree of error in the ventral and medial borders, but it is difficult to know the extent to which the significant variability in the position of the anterior border is attributable to the difficulty in distinguishing it from the substantia nigra.

The typical limitations of MR imaging studies apply to this work as well. In particular, motion artifacts and other variables in the quality of clinical images contribute to imprecision. Both voxel size and volume averaging also affect the precision of the measurements. Our pixel size was 1.1 × 1.1 mm, and our slice thickness was 2 mm. Because all measurements were taken in the same planes as those in which the MR studies were obtained, the precision is most limited by the pixel size of 1.1 mm rather than the voxel size. Slice thickness can affect the precision of these measurements through volume averaging, but given the ovoid shape of the nucleus in the atlases, this is unlikely to add a significant degree of error. The effects of nonlinear MR imaging distortion on our results have not been directly addressed, but preliminary data from ongoing pathology/MR imaging correlation studies at our institution make us believe that these effects lead to a discrepancy of less than 1 mm. Finally, contrast levels and windowing have some influence on the appearance of the borders of the STN. Al-

<table>
<thead>
<tr>
<th>Width of STN</th>
<th>Anteroposterior</th>
<th>Mediolateral</th>
<th>Dorsoventral</th>
</tr>
</thead>
<tbody>
<tr>
<td>on MR imaging (range)</td>
<td>5.9 (3.4–9.7)</td>
<td>3.7 (2.5–5.3)</td>
<td>5.0 (2.9–9.4)</td>
</tr>
<tr>
<td>in Talairach atlas*</td>
<td>9 (&lt;1%)</td>
<td>8.5 (&lt;1%)</td>
<td>6.5 (NS)</td>
</tr>
<tr>
<td>in axial series in Schaltenbrand atlas*</td>
<td>10 (&lt;1%)</td>
<td>10 (&lt;1%)</td>
<td>NA</td>
</tr>
<tr>
<td>in sagittal series in Schaltenbrand atlas*</td>
<td>11.5 (&lt;1%)</td>
<td>NA</td>
<td>8.5 (&lt;3%)</td>
</tr>
<tr>
<td>in coronal series in Schaltenbrand atlas*</td>
<td>NA</td>
<td>10.5 (&lt;1%)</td>
<td>7 (&lt;9%)</td>
</tr>
</tbody>
</table>

* In parentheses next to each atlas value is its percentile rank comparison to the MR imaging data set.
though these factors have not been strictly controlled in this study, images were generally examined using parameters in a central range. Given that each patient’s MR image was optimized for clarity, there is some degree of uniformity across procedures. It is our experience that at the extremes of windowing, it is difficult to distinguish the STN from surrounding structures at all, but within the central range, variations in windowing make the borders of the nucleus more or less clear and do not substantially alter the size of the nucleus or the position of those borders. Again, a careful review performed by multiple observers should minimize the effect of these differences on our results.

Although STN cell counts have been reported to remain normal in patients with idiopathic PD6 cell packing and volume densities have not been reported, and the STN in patients with advanced PD may in fact be smaller as a result of the disease. Close agreement between the measurements obtained on MR imaging and those on histological analyses in our postmortem case support this hypothesis. With the caveat that one case should not be overgeneralized, the difference in the size of the STN, even between the two sides in an individual patient as we have observed using histological methods, also lends support to our conclusion that size is highly variable.

Results of previous studies based on microelectrode recordings have led to the conclusion that the position of the STN is variable enough that microelectrode data are important for the accurate placement of deep brain stimulation electrodes.6 Although some researchers have examined the center1 or laterality10 of the STN on MR imaging, our data represent both the first examination of the position of all borders of the STN and the first statistical description of the variability of these borders in a clinical population with PD. In addition, it is the first description of the dimensions of the STN based on MR imaging in this clinical population. It would appear that initial targeting might be better derived from an individual patient’s preoperative MR imaging results, rather than relying on indirect targeting based on the position of the AC and PC from ventriculography or MR imaging, and atlas-derived coordinates. Our data showing such marked variation in the position of the STN further underscores the need for microelectrode recording data to confirm the position of the STN and ensure optimal electrode placement. Currently, we are investigating the relationship between the position of the STN as predicted based on MR imaging and its position based on microelectrode recording.

Conclusions

We examined the size and position of the STN in a population of patients with advanced PD. Our MR imaging measurements were validated in a postmortem case. On MR images the position and size of the STN are highly variable and the nucleus is smaller than its size in either the Talairach or Schaltenbrand atlases, particularly in the mediolateral dimension. The inconstant relationship between the position of the STN and the commissures and between the position of the STN in patients and in standard atlases calls into question the practice of relying on the commissures or atlases for the selection of targets. The fact that there was no significant correlation between the position (and size) of the STN and the intercommissural distance calls into question the validity of scaling measurements from the atlas to the patient’s AC–PC length.

References