The Anatomical and Electrophysiological Subthalamic Nucleus Visualized by 3-T Magnetic Resonance Imaging

BACKGROUND: Accurate localization of the subthalamic nucleus (STN) is critical to the success of deep brain stimulation surgery for Parkinson disease. Recent developments in high-field-strength magnetic resonance imaging (MRI) have made it possible to visualize the STN in greater detail. However, the relationship of the MR-visualized STN to the anatomic, electrophysiological, or atlas-predicted STN remains controversial.

OBJECTIVE: To evaluate the size of the STN visualized on 3-T MRI compared with anatomic measurements in cadaver studies and to compare the predictions of 3-T MRI and those of the Schaltenbrand-Wahren (SW) atlas for intraoperative STN microelectrode recordings.

METHODS: We evaluated the STN by 3-T MRI and intraoperative microelectrode recordings in 20 Parkinson disease patients undergoing deep brain stimulation surgery. We compared our findings with anatomic cadaver studies and with the individually scaled SW atlas-based predictions for each patient.

RESULTS: The dimensions of the 3-T MR-visualized STN were very similar to those of the largest anatomic study (MRI length, width, and height: 9.8 ± 1.6, 11.5 ± 1.6, and 3.7 ± 0.7 mm, respectively; n = 40; cadaver length, width, and height: 9.3 ± 0.7, 10.6 ± 0.9, and 3.1 ± 0.5 mm, respectively; n = 100). The amount of STN traversed during intraoperative microelectrode recordings was better correlated to the 3-T MR-visualized STN than the SW atlas-predicted STN (R = 0.38 vs R = −0.17).

CONCLUSION: The STN as visualized on 3-T MRI corresponds well with cadaveric anatomic studies and intraoperative electrophysiology. STN visualization with 3-T MRI may be an improvement over SW atlas-based localization for STN deep brain stimulation surgery in Parkinson disease.

KEY WORDS: Deep brain stimulation, Electrophysiology, Magnetic resonance imaging, Microelectrode recording, Parkinson disease, Subthalamic nucleus

Deep brain stimulation (DBS) is a well-established surgical therapy for Parkinson disease. High-frequency electrical stimulation by DBS electrodes in the region of the subthalamic nucleus (STN) modulates the motor symptoms of Parkinson disease. Traditionally, surgical targeting of the STN has been performed with standardized stereotactic atlases, often with intraoperative confirmation of STN location through microelectrode recording (MER). In recent years, direct visualization of the STN with magnetic resonance (MR) imaging (MRI) has been used at both low (1.5 T) and high (3.0-9.4 T) magnetic field strength. However, some controversy remains regarding the relative merits of direct MR imaging and atlas-based targeting, particularly at 1.5 T, at which DBS targets may not be clearly visualized.

Ongoing developments in MRI technology, including increasing magnetic field strength, have improved the ability to visualize the basal ganglia. It is now possible to directly visualize the STN with 3-T MRI in a manner that assists DBS targeting.
and higher field strength appears to improve anatomic differentiation. Abosch et al\textsuperscript{7} used a 7-T MRI machine to visualize the STN and were able to see a clear boundary between the STN and the substantia nigra (SNR) in both the axial and coronal views; Massey et al\textsuperscript{16} confirmed this result with 9.4-T MRI. However, it remains to be shown whether the improved structural visualization with higher-field-strength MRI accords with anatomic measures of the STN or improves on atlas-based methods for localizing STN electrophysiological activity during intraoperative MER.

Proof that the MR-visualized STN has the same dimensions as the anatomic STN measured in cadaveric studies would be of considerable interest and importance to neurosurgeons\textsuperscript{9} because it indicates that the entirety of the STN is visualized clearly on MRI and sets the stage for the performance of noninvasive STN and DBS electrode localization studies. Furthermore, establishing that the electrophysiological STN as measured during intraoperative MER correlates better with the MR-visualized STN than atlas-based STN predictions would provide substantial foundation for MR-based preoperative or intraoperative targeting for DBS. In this study, we used 3-T MRI to visualize the STN. We first compared the dimensions of the MR-visualized STN at 3 T with the anatomic STN as measured in a cadaveric study of 100 specimens.\textsuperscript{17} We then evaluated both our MR-visualized STN and the Schaltenbrand-Wahren (SW) atlas-based predictions of STN against the electrophysiological STN observed during intraoperative MER. We find that the 3-T MR-visualized STN corresponds well to both the anatomic and electrophysiological STN.

**PATIENTS AND METHODS**

**Patient Selection**

We studied 20 consecutive patients with advanced idiopathic Parkinson disease who underwent STN DBS at our institution (16 men, 4 women; age, 61 \pm 7 years; range, 46-72 years). Selection criteria for DBS included a diagnosis of idiopathic Parkinson disease with the presence of motor fluctuations not optimally managed with medications or severe levodopa-unresponsive tremor. Patients with contraindications to 3-T MRI scanning, structural abnormalities on preoperative MRI, or dementia by neuropsychological testing were excluded. We performed the study in accordance with the policies of the Medical Institutional Review Board of the University of Michigan.

**DBS Procedure**

All patients underwent 3-T MRI as part of the baseline evaluation. This imaging included a high-resolution coronal imaging protocol designed to optimize visualization of the STN, illustrated in Figure 1. On the day of surgery, patients were fitted with a Leksell stereotactic frame (Elekta Instruments AB, Stockholm, Sweden) and underwent a preoperative 1.5-T MRI. The baseline 3-T MRI and preoperative 1.5-T MRI were coregistered by use of a mutual-information algorithm (Analyze 9.0; AnalyzeDirect, Inc, Overland Park, Kansas). Frame-based bilateral surgical targeting was then performed with commercial software (Framelink; Medtronic, Inc, Minneapolis, Minnesota). Initial indirect targeting at 12 lateral, 3 posterior, and 4 inferior to the midcommissural point was performed and then fine-tuned to the individual patient according to the MR-visualized STN. During surgery, an electrophysiologist (J.W.A.) performed MER, identifying the dorsal and ventral
borders of STN activity, and calculated the STN distance traversed. Once
STN localization was confirmed electrophysiologically, DBS leads were
placed under fluoroscopic visualization so that the tip of the DBS lead was
located near the ventral border of the electrophysiological STN. For our
study, we used the STN distance traversed during MER for these final lead
trajectories. A movement disorders neurologist (K.L.C.) activated the DBS
electrodes intraoperatively and evaluated the patient for symptom
improvements and side effects. After several weeks for intracranial air to
resolve, a high-resolution postoperative computed tomography (CT) scan
was performed to visualize the location of the DBS leads within the brain.
Nineteen patients underwent bilateral lead placement and 1 elected to have
unilateral placement for a total of 39 leads.

Image Analysis
Details of the 3-T MR and CT imaging protocols are given in Tables 1
and 2, respectively. The postoperative CT scan was coregistered to the 3-T
baseline MRI using a mutual-information algorithm (Analyze 9.0), as
illustrated in Figure 1B. After coregistration and scan orientation along
intercommisural and interhemispheric planes, STN dimensions (anterior-
posterior length, medial-lateral width, and superior-inferior height) were
measured from coronal slices, as described in the cadaveric study by
Bubnov,12 to allow direct comparison. Windowing of the MR data for
visualization was defined as centered at the level that maximized contrast
between STN and SNR and a width twice that amount to minimize
measurement variability. Simple windowing of CT data of DBS leads was
set to allow distinct visualization of individual contacts. Although more
sophisticated image processing of CT images is possible to reduce artifacts
caused by low Hounsfield units,13 these methods were not used in this
study. The length of MR-visualized STN traversed by the coregistered CT
image of the DBS electrode was then determined by identifying where the
DBS lead entered and exited the MR-visualized STN. The border between
the STN and SNR, when indistinct, was estimated by interpolation
between several adjacent coronal slices. All measurements were made while
blinded to the corresponding patient MER data to minimize measurement
bias. In some instances, the DBS lead as visualized on CT did not appear to
intersect the MR-visualized STN. In these instances, the distance traversed
was recorded as zero.

Atlas-Based Estimation
For atlas-based estimation, MR and CT data for each patient were fitted
to the SW atlas by use of commercially available software (Framelink). The
SW atlas length scaling was set by the location of the anterior and posterior
commissures. Atlas width and height were then scaled to optimize
correspondence to individual patient intracranial anatomy. The SW atlas-
predicted STN distance traversed by the DBS electrode was calculated
from STN entry and exit points of the DBS electrode on sagittal SW atlas
images. In some instances, the DBS lead as visualized on CT did not
appear to intersect the SW atlas-predicted STN. In these instances, the
distance traversed was recorded as zero.

Statistical Analysis
Statistical analysis was performed with commercially available software
(Excel; Microsoft Inc, Redmond, Washington). Results are expressed as
mean ± SD. To allow comparison of the strength of linear dependence
between MR and MER data, we used the Pearson product-moment
correlation coefficient, R. Sources of statistical variability in our data
include variability resulting from mutual information coregistration for
mixed-modality imaging, quantization effects caused by voxel representation
intrinsic to MR and CT imaging, targeting error between MER
and DBS lead placement, and general measurement accuracy.

RESULTS
Figure 1 illustrates the MR visualization of the STN at 3 T.
A comparison with an anatomic cadaveric study of 100 specimens
without central nervous system disease is shown in Table 3.17
The anterior-posterior length, medial-lateral width, and superior-
inferior height of the MR-visualized STN were 6.6 ± 1.6 mm
(range, 4.6-10.3 mm), 11.5 ± 1.6 mm (range, 9.1-14.3 mm),
and 3.7 ± 0.7 mm (range, 2.5-5.2 mm), respectively (n = 40).

### TABLE 1. Magnetic Resonance Imaging Protocol

<table>
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<th>Philips Achieva 3T Magnetic Resonance Imaging Scanner Settings</th>
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<td>Scan duration</td>
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*TE, echo time; TR, repetition time.*
For the same respective dimensions, cadaveric measurements were 9.3 ± 0.7 mm (range, 7-11 mm), 10.6 ± 0.9 mm (range, 8-14 mm), and 3.1 ± 0.5 mm (range, 2-5 mm). Note the striking similarity in not only the average dimensions but also the overall range of dimensions for the STN measurements between MR visualization of the STN at 3 T and anatomic specimens.

Figure 2 illustrates the correlation between the STN distance traversed by the DBS electrode and the STN distance for the same trajectory ascertained during intraoperative MER for both the MR-visualized STN (Figure 2A) and the SW atlas-predicted STN (Figure 2B). In a few instances, the MR-visualized and SW atlas-predicted STN did not intersect the CT-visualized DBS lead; therefore, they were assigned a value of zero. For the 37 final trajectories in the 19 patients for whom detailed MER records were available, STN distance traversed during MER recording was 4.2 ± 1.3 mm (range, 0.5-7.4 mm). MR-visualized STN distance traversed, as estimated from the CT-visualized lead, was 4.4 ± 1.6 mm (range, 0.0-7.0 mm). SW atlas-predicted STN distance traversed, as estimated from the CT-visualized lead, was 3.9 ± 2.2 mm (range, 0.0-7.4 mm).

The correlation for the 3-T MR-visualized STN to MER recording ($R = 0.38$) was superior to that for the SW atlas-based prediction ($R = -0.17$). Taken together, these comparisons between MR visualization and SW atlas-based estimates with intraoperative MER suggest that although average distance and range estimates may be similar to MER for the 2 methods, the correlation at the level of individual patients is superior for the MR-based method compared with the SW atlas-based estimation.

**DISCUSSION**

**Usefulness of STN Visualization With MRI**

Because the effectiveness of DBS for Parkinson disease symptoms depends on the accuracy of STN targeting, accurately visualizing the STN with MRI may improve surgical outcomes. Targeting the STN traditionally involves using an imaging method to define an initial target estimate and then using intraoperative MER, intraoperative stimulation, and clinical testing to optimally reposition the electrode. Because of multiple factors, including imaging imprecision, deflection of stereotactic frame components, deflection of the guide tubes, and brain shift, multiple MER trajectories and multiple passes of the DBS electrode may be necessary. A more accurate image-based method for STN localization would help to minimize the number of surgical passes required, reducing the potential risk of intracranial hemorrhage. Better imaging would also increase confidence in the precise localization of the STN, facilitating DBS surgery under general anesthesia. However, despite potentially more accurate anatomic localization with improved imaging, intraoperative testing of awake patients would continue to be required to confirm lead placement in an effective therapeutic location.

Accurate STN visualization may also be used for clinical research purposes. For instance, by coregistering postoperative CT images...
with high-resolution preoperative MRIs, it may be possible to visualize the DBS lead within the STN.\textsuperscript{22} If this can be done accurately, it would facilitate comparison of targeting methods and correlation of lead location to clinical outcome. Finally, validated STN visualization would enable MRI studies of interindividual STN variation and structure-function correlation.

**Controversy Over the Accuracy of MR-Based STN Visualization and Targeting**

There is considerable controversy over whether direct MRI visualization can accurately localize the STN. STN electrodes have been successfully placed with direct MRI visualization.\textsuperscript{5} Starr et al\textsuperscript{5} implanted 76 DBS leads and reported that they were able to directly visualize the STN on 1.5-T MRI 92% of the time. However, others have experienced difficulty with direct MRI visualization because of the small size and oblique shape of the STN.\textsuperscript{7} The limited resolution of conventional 1.5-T MRI also makes it difficult to distinguish the STN from the nearby SNR.\textsuperscript{24} Hamani et al\textsuperscript{24} found good correlation in general between the 1.5-T MRI-defined and the MER-defined STN except for the anterior-posterior axis, for which there was poor correlation. The authors discussed that one of the limitations of MRI localization was the low resolution of the STN on T2-weighted scans (obtained on a 1.5-T MRI scanner) plus the fact that nearby ganglia also had some hypointense signal intensity. Three other studies comparing multiple methods of STN targeting at 1.5 T found that direct MRI visualization was the least accurate.\textsuperscript{11,24,26} Similar studies have not yet been performed at higher field strength.

The alternative to direct MRI visualization is indirect visualization using anatomic landmarks and/or patient-specific atlases, but this method has drawbacks. For example, interpatient variability in STN size and location is a limiting factor of this method.\textsuperscript{9} Additionally, the most commonly used indirect markers are the MR-defined anterior and posterior commissures and the MR-defined red nucleus.\textsuperscript{24} Pallavaram et al\textsuperscript{32} found significant intersurgeon variability in the selection of commissure coordinates. In addition, Danish et al\textsuperscript{32} found that the red nucleus is an inconsistent marker for STN localization. Finally, multiple studies have found significant variation between the position of the directly visualized STN and atlas-based localization, although it is unclear whether the inaccuracy is with direct MRI-based localization or atlas-based localization because they were not tested against a third, accepted standard.\textsuperscript{38,29} Our study, by looking at the relationship between STN anatomy and MR visualization at higher 3-T MRI field strength, addresses some of these issues.

**Previous Anatomic and Histological Characterization**

The gold-standard method of localizing the STN is direct anatomic measurement. However, with the challenges inherent to cadaveric studies in humans, few studies have characterized the human STN by this method.\textsuperscript{13,17,30,31} The largest study to date in the literature is that by Bubnov.\textsuperscript{17} Bubnov examined 100 cadaveric specimens to determine averages and standard deviations for the positions and dimensions of the STN. Dimensions were measured along intercommisural, interhemispheric, and orthogonal coronal planes as summarized in Table 3. Lehman\textsuperscript{30} examined 40 brain specimens with coarse 5-mm coronal slice thickness, focusing on the location of the STN for targeting purposes. Among these studies, only that by Bubnov, to the best of our knowledge, contains sufficient numbers of human specimens for statistical comparison.

Dormont et al\textsuperscript{13} compared histological sections of cadaveric brains and MRIs to better understand the relationship between the MR-visualized STN and the anatomic STN. Areas of hypointense signal on MRI corresponded to the higher levels of iron present in the STN, and these regions of higher iron content correlated better with the anterior region of the STN from an atlas-based estimate. From these observations, the authors suggested that MRI might not visualize the posterior region of the STN well. In comparison, Bardinet et al\textsuperscript{32} developed an atlas registration methodology that is based on histological data and MR data and then compared the STN location obtained by this method with that of direct MRI and MER. This group found a strong correlation between all 3, with < 1-mm error, suggesting a closer correlation among modalities. More studies comparing imaging measurements with anatomic and MER measurements are needed to validate the imaging methods.

**Our Results**

In our study, the MRI-defined STN dimensions correspond very well to those defined by a large anatomic cadaver study.\textsuperscript{17} Our findings provide evidence that the STN can be accurately and completely visualized with high-field 3-T MRI and that the resolution is sufficient to accurately measure the STN in 3 dimensions. Our findings further suggest that the posterior portions of the STN may be better visualized on MRI at 3 T than at 1.5 T. One explanation for this may be that stronger field strength may allow greater visualization of STN areas with lower iron content or other forms of gray-white tissue differentiation. Although improved compared with visualization at 1.5 T, differentiation between STN and SNR remains challenging at 3 T. Recent studies suggest that still higher field strengths (7 and 9.4 T) may further improve delineation of STN and SNR.\textsuperscript{15,16} The clinical significance of this delineation for DBS lead placement remains uncertain.

In addition, we find a stronger correlation ($R = 0.38$ vs $R = -0.17$) between the MER-defined and the MRI-defined traversed STN distance than between the MER-defined and the SW atlas-based estimates of STN electrode-traversed distance. The average distance traversed for SW atlas-based estimates is similar to that observed intraoperatively by MER ($3.9 \pm 2.2$ vs $4.2 \pm 1.3$ mm, respectively). However, the correlation of SW-based estimates at the level of individual patients is poor. This important finding supports previous studies reporting that direct visualization of the STN with high-resolution MRI provides more accurate measurements of STN position (relative to MER measurements) than does indirect STN localization with an anterior-posterior commissure-based atlas.\textsuperscript{28,29} Our result extends these findings to 3 T.
Study Limitations

Our study did not compare the accuracy of direct STN visualization with 3-T MRI and that of STN visualization with 1.5-T MRI. Acar et al.15 compared atlas-based targeting from a 1.5-T MRI scanner and that of direct targeting with a 3-T MRI machine and found no significant difference in the calculated position of the STN; however, their study did not compare direct 1.5-T visualization with direct 3-T visualization. MRI technology is continuing to develop. The STN has been visualized with 7- and 9.4-T MRI machines.13,26 To maximize cost-effectiveness, it would be useful to compare higher-field MRI measurements with lower-field MRI measurements to see the extent to which high-field MRI has potential to improve localization accuracy in the presence of the anisotropic effects. In addition, measures of iron-containing structures like the STN and SNR may differ among high- and low-field-strength imaging systems owing to variable imaging distortion as a result of the presence of paramagnetic iron salts. In our study, such distortions may account for some of the differences between the MER-defined and MRI-defined traversed STN distances.

We took MER as a standard against which we measured the accuracy of direct localization and atlas-based localization. However, it is unclear whether this is an ideal choice of standard. Although some have referred to MER as a gold standard in STN localization, there is continued debate on the utility of MER.27 Because of its common use,34-36 it may be possible for a future study to perform intracranial anatomic- and MRI-based STN measurements, which could more definitively demonstrate the correlation (or lack thereof) of MRI-based STN localization and intraoperative MER. Furthermore, a well-defined anatomic STN on MRI may allow more confident DBS targeting and a better understanding of the relationship between electrode localization and therapeutic effects.

CONCLUSION

The development in MRI technology has made high-resolution visualization of the STN possible. We examined the accuracy of direct STN localization using high-field 3-T MRI by comparing it with anatomic cadaver measurements and MER measurements. Measurements obtained with direct STN targeting correlated well with those obtained by both anatomic cadaver studies and MER data. The correlation between direct STN measurements and MER measurements was stronger than that between SW atlas measurements and MER measurements. These results indicate that high-resolution MRI is an accurate method for locating the STN that may be an improvement over current SW atlas-based methods.

Disclosures

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REFERENCES


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**COMMENTS**

As magnetic field strength increases, many of the target regions used in functional neurosurgery can now be visualized. Visualization of the subthalamic nucleus (STN) is of particular interest because it is not consistently seen on 1.5-T images, and indirect targeting remains the mainstay of planning in these cases. The present study compares the dimensions of 3-T magnetic resonance (MR)-visualized STN and cadaveric STN measurements and finds remarkable similarities in the mean dimensions and the ranges of values. These data suggest that 3-T imaging accurately depicts the anatomical boundaries of the STN. As the authors acknowledge, these measurements may sometimes be limited by difficulty in discerning the border of STN with substantia nigra and the image distortion that occurs in iron-containing nuclei such as STN/ substantia nigra. These limitations may account for some of the variability seen in the correlations between the amount of STN obtained with intraoperative microelectrode recording and the amount of deep brain stimulation lead in STN on postoperative imaging. The correlation overall, however, was reasonable and was, not surprisingly, a dramatic improvement over that achieved with atlas-based predictions. The authors should be commended on their creative comparison of 3-T and cadaveric measurements and for providing preliminary evidence that 3-T borders generally correlate with intraoperative microelectrode recording findings.

The question that remains is how deep brain stimulation teams familiar with targeting on 1.5 T should incorporate 3-T direct targeting into their planning. That is, how much should surgeons who generally are able to confirm lead location with 1 or 2 microelectrode tracks alter their trajectories on the basis of the anatomical STN borders they see on 3-T MR? This determination will vary from center to center. On the basis of the data presented, at this point for groups new to 3 T, 3-T visualization probably is best used for fine-tuning of indirect coordinates, much as we use the borders of the red nucleus on 1.5-T MRs. As we better understand the relationship between electrode location in the anatomically visualized STN and therapeutic benefits, direct visualization will no doubt become increasingly valued. We look forward to future work on this topic from these authors.

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**The authors present their findings on the accuracy of 3-T magnetic resonance imaging for localizing the subthalamic nucleus (STN) using microelectrode recording as a gold standard. They also evaluate a linear-scaled Schaltenbrand-Wahren atlas, but this atlas can provide only an estimate of STN location. The dorsal border of the STN may be directly visualized against the contrast of subthalamic white-matter tracts on 3-T imaging. One must keep in mind that this contrast is created by T2 hypointensity from STN iron content, an effect that blooms at higher field strength. This hypointensity may not be confined to the anatomical boundaries of the STN. To reduce errors from image coregistration, a 3-T magnetic resonance imaging may be performed on the day of surgery with the Leksell frame in place. With improved imaging, confidence in the location of the STN is greater. However, it is important to consider that individual patients may benefit from customized positioning of the deep brain stimulation (DBS) lead within the STN. The use of intraoperative stimulation, preferably via the reference contact on the microelectrode, can confirm that anatomical and physiological placement within the STN provides the ideal therapeutic benefit. In our tremor-predominant patient population, we have found that placement of the DBS lead within the posterior tail of STN provides the ideal therapeutic benefit. Pooled patient outcomes in clinical studies may not have the resolution to highlight this unintended effect of performing DBS under general anesthesia using image-based targeting alone.

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