Correlation of diffusion tensor tractography and intraoperative macrostimulation during deep brain stimulation for Parkinson disease

Clinical article


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Object. The purpose of this study was to investigate whether diffusion tensor imaging (DTI) of the corticospinal tract (CST) is a reliable surrogate for intraoperative macrostimulation through the deep brain stimulation (DBS) leads. The authors hypothesized that the distance on MRI from the DBS lead to the CST as determined by DTI would correlate with intraoperative motor thresholds from macrostimulations through the same DBS lead.

Methods. The authors retrospectively reviewed pre- and postoperative MRI studies and intraoperative macrostimulation recordings in 17 patients with Parkinson disease (PD) treated by DBS stimulation. Preoperative DTI tractography of the CST was coregistered with postoperative MRI studies showing the position of the DBS leads. The shortest distance and the angle from each contact of each DBS lead to the CST was automatically calculated using software-based analysis. The distance measurements calculated for each contact were evaluated with respect to the intraoperative voltage thresholds that elicited a motor response at each contact.

Results. There was a nonsignificant trend for voltage thresholds to increase when the distances between the DBS leads and the CST increased. There was a significant correlation between the angle and the voltage, but the correlation was weak (coefficient of correlation \( R = 0.36 \)).

Conclusions. Caution needs to be exercised when using DTI tractography information to guide DBS lead placement in patients with PD. Further studies are needed to compare DTI tractography measurements with other approaches such as microelectrode recordings and conventional intraoperative MRI-guided placement of DBS leads.

Key Words • diffusion tensor tractography • deep brain stimulation • functional neurosurgery

Deep brain stimulation (DBS) is recognized as an effective surgical intervention for the motor symptoms of Parkinson disease (PD) that are refractory to medication or induced by medication. Deep brain stimulation typically targets the subthalamic nucleus (STN), globus pallidus internus (GPi), or ventral intermediate nucleus (Vim) of the thalamus. Contemporary stereotactic technique typically involves MRI-guided planning and intraoperative validation/confirmation of the therapy. The DBS leads are initially positioned based on direct target visualization on MR or standard coordinates relative to the anterior commissure–posterior commissure line. Subsequent intraoperative testing is performed in the awake patient to estimate the efficacy of stimulation and the proximity to neighboring structures that can produce side effects. The threshold for corticospinal or corticobulbar tract activation can be used to approximate the location of the DBS lead relative to the GPi and Vim targets. The patients are observed for a motor response to stimulation and asked to report any sensations as the voltage is increased. Depending on the motor threshold, the leads are deemed to be either in a correct
position or too close to or too far from the corticospinal tract (CST). If needed, the leads can be moved medially or laterally to adjust the position relative to the CST in order to achieve the best clinical response while minimizing side effects.\textsuperscript{14} Other approaches to confirm the adequate location of the DBS leads include microelectrode recordings for the identification of single-cell firing characteristics of neurons within the target nucleus.\textsuperscript{15}

Recent emphasis on improved MRI visualization of subcortical nuclei with 3-T MRI\textsuperscript{16} and enhanced visualization of deep brain white matter tracts with diffusion tensor imaging (DTI)\textsuperscript{4} has raised the possibility of anatomically guided DBS, which would obviate the need for patients to be awake. The ability to map the CST by using DTI and tractography with stereotactic precision could potentially expedite the placement of the DBS leads, reduce the need for repositioning, decrease operating time, and improve overall patient experience and outcome.

The purpose of this study was to investigate whether DTI of the CST is a reliable surrogate for intraoperative macrostimulation through the DBS leads. We hypothesized that the distance on MRI from the DBS lead to the CST as determined by DTI would correlate with intraoperative voltage thresholds for macrostimulation activation of motor responses through the same DBS lead.

**Methods**

**Study Population**

The institutional review board of the University of Virginia approved this retrospective study, in compliance with the Health Insurance Portability and Accountability Act, with a waiver of consent.

We considered for our study all patients with PD who underwent placement of DBS leads between June 2010 and June 2011. We included all patients in whom the same model of DBS electrodes was used (Medtronic model 3387), and hence the same contact geometry. In these patients, targets were the GPi or the Vim. Patients undergoing Vim targeting were treated because they presented a strong tremor-dominant subtype of PD by the Jankovic\textsuperscript{7} formula. Patients undergoing STN targeting were excluded because of reliance on microelectrode recording instead of increasing amplitude with macrostimulation to detect motor threshold. On the contrary, macrostimulation is performed in every instance for GPi and Vim targeting. The Vim target is located farther away from the internal capsule compared with the GPi target. The variation in the target distance provided a wider range of potential distances to test our hypothesis.

**Magnetic Resonance Imaging**

All patients included in the study underwent an MRI with DTI on the day prior to DBS placement. The MRI was performed for operative planning purposes and included the following sequences: volumetric 3D T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) studies covering the whole brain in 1-mm axial slices (TI 1900 msec, TR 900 msec, TE 2.34 msec, matrix 512 × 512, NEX 1); volumetric 3D T2-SPACE (T2-weighted sampling perfection with application-optimized contrasts using different flip angle evolutions) sequences covering the whole brain in 1-mm sagittal slices (TR 3200 msec, TE 402 msec, matrix 512 × 512, NEX 1); and DTI in 4-mm axial slices (TR 4100 msec, TE 93 msec, matrix 768 × 768, NEX 1). The DTI was performed using 20 diffusion directions.

All patients underwent a postoperative MRI session including the same sequences except for the DTI, which would have been of limited quality because of the artifacts created by the DBS leads. The postoperative MRI studies demonstrated the DBS leads in their final position. All pre- and postoperative imaging was performed at 3 T.

**Surgical DBS Placement and Macrostimulation Through DBS Leads**

All DBS procedures were performed by the same neurosurgeon. Frame-based MRI–guided targeting was used for all cases. The DBS procedures targeting the Vim were performed without sedation to maximize the occurrence of tremor for testing during surgery. Surgical procedures targeting the GPi all used intravenous dexmedetomidine for sedation, which was discontinued after the bur holes were made. This allowed the patient to remain awake during the intraoperative testing. Inhalational anesthetics were not used.

Once the bur hole had been made and the lead positioned, macrostimulation through the DBS lead was initiated. The DBS lead used has 4 contacts labeled 0–3. The contact closest to the tip of the lead is labeled “0” by convention, whereas the contact closest to the source is labeled “3.” The distance from the tip to the first contact is equal to 1.5 mm. Each contact measures 1.5 mm. The space between contacts is also equal to a distance of 1.5 mm. The total distance from the electrode tip to the top of contact 3 is equal to 12 mm. The DBS lead diameter is 1.27 mm.

Intraoperative testing was performed using monopolar configuration at 130 Hz with a pulse width of 60 μsec for consistency while continuously interacting with the patient and assessing response and side effects. The voltage was increased until a symptom or side effect was recognized. Neurological responses to intraoperative voltage increases applied to different contacts were recorded by the neurosurgical team. Symptom relief was noted as well with the alleviation of tremor or the improvement of bradykinesia and rigidity. Paresthesias were reported and noted to be transient or persistent. Motor activation of the face or appendages was used to identify the motor threshold for each contact. The DBS leads with motor thresholds of less than 2 V are assumed to be too close to the CST. Those with motor thresholds of more than 4 V may be too lateral to the target region of the GPi. Final placement also depends significantly on the demonstration of clinical efficacy with high-frequency stimulation. Only the threshold for motor activations was used for analysis in the current study; we compared our MRI distance measurements to the voltage threshold required to elicit CST activation because it was easily tested and provided an appropriate proof of concept based on one tract involving concrete motor function.
Diffusion tensor tractography in deep brain stimulation

Processing of MR Images

Based on the preoperative MRI study, DTI tractography of the CST was performed using the posterior arm of the internal capsule and the cerebral peduncle as seeding regions. The DTI tractography was performed according to a probabilistic approach by using an open-source processing software package called Camino. Subsequently, we performed a rigid registration of the preoperative DTI data set to the preoperative 3D T1-weighted MPRAGE data set, and a rigid registration of the preoperative 3D T1-weighted MPRAGE data set to the postoperative 3D T1-weighted MPRAGE data set. The latter step produced the composite transformation on which the reconstructed tracts were mapped to the space of the 3D T1-weighted MPRAGE, yielding a data set that included the leads in their final position adjacent to the mapped CST (Fig. 1). All registrations were performed using the open source ANTs (Advanced Normalization Tools) software. Visual examination of the final coregistered data sets was performed to verify adequate quality of the manipulated data.

Using the registered images, which included anatomical detail of the CST adjacent to final lead position, the minimum euclidean distance transform was calculated by an automated computer algorithm to measure the shortest distance from each lead contact to the CST. These distances for each contact on each lead were recorded, as well as the angle described by the euclidean segment to the CST (Fig. 2).

Statistical Analysis

Data Description. The voltage thresholds and the distance (in millimeters) and angle measurements (in degrees) were summarized by the mean, SD, median, interquartile range, and the range of the measurement distribution.

Measurement Variability Analyses. The “between-patient” and “within-patient” variance components associated with the variability in the voltage, distance, and angle measurements were estimated using random-effects models according to the principles of restricted maximum likelihood estimation. In addition to the variance component estimates, measurement variability was summarized for each variable by computing the percentage of the total variability in the measurements explained by between-patient and within-patient measurement variability. The software of the MIXED procedure of SAS version 9.2 (SAS Institute, Inc.) was used to conduct the measurement variability analyses.

Relationship Between Voltage, Distance, and Angle. Gaussian generalized estimating equation (GEE) regression models were used to assess linear and nonlinear relationships between the voltage thresholds (outcome) and the distance and angle measurements (predictors). The GEE method is a standard approach that is used to analyze clustered data with inherent correlation, which is applicable in our case because each lead in each patient has several contacts, and therefore several correlated voltage, distance, and angle measurements were obtained in each patient. In regard to model specification, restricted cubic spline functions of the distance and angle measurements were used as predictors of voltage. The restricted cubic spline functions allowed linear and nonlinear associations to be examined. Distance by angle interaction was also considered. The “ols” function of the “Hmisc” library of Spotfire Splus version 8.2 (TIBCO, Inc.) was used to conduct the GEE regression analyses.

Study Population

We identified 60 patients with PD who underwent an MRI study of their brain with DTI prior to DBS lead
placement. Among those 60, we excluded patients undergoing STN targeting (n = 19), and we retained only those in whom DBS targeted the GPi (n = 27) or the Vim (n = 14), for a total of 41. From this group of 41 patients we excluded those with insufficient MRI quality for DTI and/or registration processing (n = 9) and patients lacking adequate intraoperative testing data (n = 5) as well as patients in whom the DBS lead was adjusted intraoperatively after the initial macrostimulation through the DBS lead (n = 10).

Our final study population consisted of 17 patients (10 men and 7 women; mean age 63 years, range 38–77 years). Six patients had both right and left DBS leads, which were considered separately. There were a total of 23 DBS leads in our 17 patients, with a total of 54 contacts tested intraoperatively (54 voltage thresholds).

**Voltage, Distance, and Angle Measurements**

The voltage thresholds for motor activation during the macrosimulation through the DBS lead, and the distances and angles measured between the DBS leads and the CST as defined on DTI tractography for each contact are reported in Table 1.

Measurement variability with respect to the voltage, distance, and angle measurements is summarized in Table 2. For the voltage thresholds, the within-patient variability accounted for 51.8% of the variation of the recorded values, and the between-patient variability accounted for 48.2% of the variation of the recorded values. For the distance measurements, the within-patient variability accounted for 38.1% of the variation of the recorded values and the between-patient variability accounted for 61.9% of the variation of the recorded values. For the angle measurements, the within-patient variability accounted for 77.9% of the variation of the recorded values and the between-patient variability accounted for 22.1% of the variation of the recorded values.

**Relationship Between Voltage, Distance, and Angle**

We tested different GEE regression models by using the voltage thresholds required to elicit motor activation during the macrosimulation through the DBS lead as outcomes, and a combination of one or several of the following as predictors: distances and angles measured between the DBS leads and the CST as defined on DTI tractography, as well as an interaction term between distance and angle.

The model that most accurately predicted the voltage thresholds was one including the angles measured between the DBS leads and the CST as defined on DTI tractography, including a nonlinear term (Table 2). There was a nonsignificant trend for voltage thresholds to increase when the distances between the DBS leads and the CST increased (Fig. 3). There was no significant interaction between distance and angle. Even this best model (voltage/angle) had a relatively poor predictive value, as indicated by a coefficient of correlation (R) of 0.36 (Table 3). This reflected a wide spread of the voltage thresholds plotted against the angle values (Fig. 4). We repeated the same analysis exclusively in the patients in whom DBS targeted the GPi (28 contacts in 10 patients), and the results were similar.

**Discussion**

Our results did not identify a significant relationship between the motor thresholds at each contact during macrosimulation through the DBS lead and the distance from these contacts to the CST as determined by DTI. The statistical analysis of the voltage thresholds against the distance showed a significant variability, suggesting a more complex relationship than a simple linear one, including a contribution of the angle to the relationship with the voltage motor threshold. These negative results were unexpected and counterintuitive, and we considered different explanations for them.

All the distances and angles were measured automatically by a computed algorithm, which eliminates the possibility of a human bias. The only possible error in the distance measurements was introduced by the susceptibility around the DBS lead contacts. The metallic nature of the contacts created a susceptibility blooming artifact on the MR images that made them look slightly larger than they really are (1.28 mm in diameter per the manufacturer’s specification). This could result in distance estimates between the contacts and the CST that are slightly smaller than actual. This susceptibility artifact explains why there were a couple of distance measurements of zero—a zero distance did not necessarily indicate that the DBS lead was impinging on the CST). The susceptibility artifact, however, was the same for all lead contacts in all patients, and the potential bias would have been consistent across cases; hence, it should not have masked a relationship between voltage and distance. Also, voltages, distances, and angles displayed similar contributions to within-patient and between-patient variations, supporting the robustness of our measurements.

<table>
<thead>
<tr>
<th>TABLE 1: Data summary for the dependent and independent variables in 17 patients who underwent DBS for PD*</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>voltage thresholds (V)</td>
</tr>
<tr>
<td>distance (mm)</td>
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<tr>
<td>angle (°)</td>
</tr>
</tbody>
</table>

* Table headings are defined as follows: SD denotes the standard deviation of the measurement distribution; 25th and 75th percentiles denote the interquartile range of the measurement distribution; and min (minimum) and max (maximum) denote the range of the measurement distribution.
Another possible explanation for our results was a shift of the brain tissue after the DBS surgery compared with the preoperative DTI study. Such a shift might have interfered with the accurate measurement of distances to the CST, despite the registration of pre- and postoperative MRI studies. Our registration algorithm was automated, and the accuracy of the registration was confirmed visually in all study patients.

The intraoperative macrostimulation through the DBS lead may also have contributed to the observed results. In our study, we limited our evaluation to motor responses to maintain consistency. Intraoperative threshold data were obtained by observing and asking patients for a motor response that would indicate CST stimulation. In most cases, a definite motor response was elicited and the appropriate applied voltage inducing the response was documented. In a few cases, however, the patient's motor response might have been in reaction to a sensation or stimulation of a higher-order motor system. These nonspecific motor responses may have contributed to the lack of a linear relationship between the recorded voltages and the distances measured. That being said, in the pallidotomy era, motor thresholds were routinely used to optimize lesion location as a proxy for proximity to the internal capsule. Even in the era of DBS, macrostimulation is still used to confirm that the DBS leads are not too close to the internal capsule.

The shortest contact-to-CST distance was used as a predictor variable for the voltage required to elicit a CST response based on the assumption that current follows the path of least resistance, which should theoretically be the shortest path in a uniform environment. However, if a voltage source is located in a nonuniform environment, the path of least resistance is not necessarily the shortest distance from the source to a specific point. The intracerebral tissue environment in which a DBS lead tip is located is most certainly not a uniform environment based on tissue characteristics. There are likely to be alternative current pathways that may vary from patient to patient depending on postplacement tissue characteristics. This is yet another contributing factor that may explain the weak correlation and absent statistical significance in our data set.

We acknowledge several limitations to our study. Our study was retrospective in nature and involved a relatively small number of patients, which opens the study to Type II errors related to insufficient power. We compared DTI tractography measurements to macrostimulation through the DBS lead. There are other approaches to confirm the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Summary</th>
<th>Voltage Estimate</th>
<th>Distance Estimate</th>
<th>Angle Estimate</th>
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<tbody>
<tr>
<td>between-patient variability</td>
<td>SD (σ_{between})</td>
<td>0.96 V</td>
<td>1.45 mm</td>
<td>6.16°</td>
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<tr>
<td>within-patient variability</td>
<td>SD (σ_{within})</td>
<td>1.39 V</td>
<td>1.44 mm</td>
<td>16.99°</td>
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<tr>
<td>between-patient variability</td>
<td>% of total variation</td>
<td>48.2%</td>
<td>61.9%</td>
<td>22.1%</td>
</tr>
<tr>
<td>within-patient variability</td>
<td>% of total variation</td>
<td>51.8%</td>
<td>38.1%</td>
<td>77.9%</td>
</tr>
</tbody>
</table>

**Table 2: Measurement variability—analysis of the between-patient and within-patient variability in voltage, distance, and angle**

**Fig. 3.** Graph showing the relationship between voltage thresholds required to elicit motor activation during macrosimulation through the DBS lead, and distances measured between the DBS leads and the CST as defined on DTI tractography.
appropriate location of the DBS leads, including microelectrode recordings for the identification of single-cell firing characteristics of neurons within the target nucleus. These recordings require highly sensitive and expensive equipment and substantial expertise in electrophysiology. Despite these high-fidelity recordings, microelectrode recording has yet to be proven superior in direct comparative studies with other intraoperative validation techniques such as macrostimulation through the DBS electrode or intraoperative imaging localization. Also, there is a possibility that the margins defined by DTI were “conservative” in comparison with actual anatomy. In other words, the DTI tracts are within the CST, but the anatomical margins may “feather” a bit beyond the borders defined by the computer. Finally, myelinated fibers may show different thresholds depending on axon size and the quality of the myelin sheath; however, this is something that we cannot ascertain by clinical imaging.

Conclusions

At this point, because no strong correlation could be shown with the conventional macrostimulation technique, caution needs to be exercised when using DTI tractography information to guide DBS lead placement in patients with PD. The DTI data may be better suited to delineate the nuclei in question rather than only examining the proximity to the CST. Further studies are needed to compare DTI tractography measurements with other approaches such as microelectrode recordings and conventional intraoperative MRI–guided placement of DBS leads.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Wintermark, Said, Elias. Acquisition of data: Wintermark, Said, Elias, Raghavan, Cupino, Frysinger. Analysis and interpretation of data: Wintermark, Said, Elias, Raghavan, Cupino, Tustison, Frysinger. Drafting the article: Wintermark, Said. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Wintermark. Statistical analysis: Wintermark, Cupino, Tustison, Patrie, Xin. Administrative/technical/material support: Wintermark. Study supervision: Wintermark.

References


![Fig. 4. Graph showing the relationship between voltage thresholds required to elicit motor activation during the macrosimulation through the DBS lead, and angles measured between the DBS leads and the CST as defined on DTI tractography.](image)
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