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Microelectrode Recordings Validate the Clinical Visualization of Subthalamic-Nucleus Based on 7T Magnetic Resonance Imaging and Machine Learning for Deep Brain Stimulation Surgery

BACKGROUND: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a proven and effective therapy for the management of the motor symptoms of Parkinson's disease (PD). While accurate positioning of the stimulating electrode is critical for success of this therapy, precise identification of the STN based on imaging can be challenging. We developed a method to accurately visualize the STN on a standard clinical magnetic resonance imaging (MRI). The method incorporates a database of 7-Tesla (T) MRIs of PD patients together with machine-learning methods (hereafter 7T-ML).

OBJECTIVE: To validate the clinical application accuracy of the 7T-ML method by comparing it with identification of the STN based on intraoperative microelectrode recordings.

METHODS: Sixteen PD patients who underwent microelectrode-recordings guided STN DBS were included in this study (30 implanted leads and electrode trajectories). The length of the STN along the electrode trajectory and the position of its contacts to dorsal, inside, or ventral to the STN were compared using microelectrode-recordings and the 7T-ML method computed based on the patient's clinical 3T MRI.

RESULTS: All 30 electrode trajectories that intersected the STN based on microelectrode-recordings, also intersected it when visualized with the 7T-ML method. STN trajectory average length was 6.2 ± 0.7 mm based on microelectrode recordings and 5.8 ± 0.9 mm for the 7T-ML method. We observed a 93% agreement regarding contact location between the microelectrode-recordings and the 7T-ML method.

CONCLUSION: The 7T-ML method is highly consistent with microelectrode-recordings data. This method provides a reliable and accurate patient-specific prediction for targeting the STN.

KEY WORDS: Deep brain stimulation, Microelectrode recordings, Subthalamic nucleus, Image-based targeting, Machine learning, High-field MRI, Surgical planning, Validation

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Deep brain stimulation (DBS) of the subthalamic nucleus (STN) region is an established therapy for the management of the motor symptoms of advanced Parkinson's disease (PD).^{1–4} Outcomes are highly dependent on the location of the stimulating electrode

with respect to the STN.^{2,5–12} However, accurate identification of the STN and its exact boundaries on a standard clinical magnetic resonance (MR) image can be challenging. Typically, clinical magnetic resonance imaging (MRIs) for DBS targeting are acquired with 1.5 or 3 Tesla

ABBREVIATIONS: 3D, 3-dimensional; ASM/AAM, active shape models and active appearance models; DBS, deep brain stimulation; DLOR, dorsolateral oscillatory region; FGATIR, fast gray matter acquisition T1 inversion recovery; FLAIR, fluid attenuation inversion recovery; MER, microelectrode recordings; ML, machine learning; MR, magnetic resonance; MRI, magnetic resonance imaging; PD, Parkinson's disease; SD, standard deviation; STN, subthalamic nucleus; SWI, susceptibility-weighted imaging; T, Tesla; RMS, root mean square; VTA, volume of tissue activated

(T) magnets and implementing T2-weighted, susceptibility-weighted imaging (SWI), fast gray matter acquisition T1 inversion recovery (FGATIR), or fluid attenuation inversion recovery (FLAIR) imaging protocols. Historically, 2 methods have been used and are often combined, to estimate the STN location: (1) indirect targeting, and (2) direct targeting. The *indirect* approach was used as the preferred method prior to the routine use of T2 weighted MR images. It refers to the selection of targets based on nearby anatomic landmarks. This method is inherently inaccurate as atlases do not account for variability in the patients' anatomy.^{13,14} Moreover, Pallavaram et al¹⁵ have reported that there is significant intersurgeon variability in the selection of relevant anatomic points. *Direct* targeting is performed based on visually identifying the target. The STN is usually best seen on a T2 weighted, SWI, FGATIR or FLAIR MR sequence where hypointense areas lateral to the red nucleus indicate the STN and the substantia nigra.¹⁶ The borders of target structures may however often be unclear and the target nuclei may appear in only 1 or 2 slices. Furthermore, there is an ongoing debate regarding the most effective target.^{16,17} Last, a recent study suggests that the STN representation on SWI does not correspond to electrophysiological STN borders.¹⁸ To cope with individualized anatomy in the face of suboptimal imaging, some groups have utilized deformable 3-dimensional (3D) digital atlases to estimate the patients' individual anatomy.¹⁹⁻²³

Given the anatomic variability and inconsistent identification of major landmarks on imaging,¹⁵ microelectrode recordings (MER) of the STN are often utilized for electrophysiological verification of the STN. The Parkinsonian STN has unique electrophysiological features that help facilitate its identification and may be useful in predicting clinical outcomes.²⁴⁻²⁹ Until recently, MER has also necessitated expertise in the use and interpretation of physiological data and has been associated with extended operative time. Although this is changing with new software tools to MER analysis like HaGuide (Alpha Omega Engineering, Nazareth, Israel), many have continued to question the routine use of MER³⁰⁻³⁵ preferring to rely on image-based targeting alone.

Ultrahigh-field, 7 T anatomic MRI of the human brain can exhibit rich informational content that facilitates the segmentation of the STN³⁶⁻⁴² (Figure 1). However, the availability of 7 T MRI is limited to only a few research institutions. We developed a method for the automatic creation of a patient-specific, 3D anatomic model of the STN based on the patient's own clinical MR image (Figure 2; 1.5T or 3T; T2-weighted or FLAIR). This method incorporates a machine-learning (ML) method "trained" on a database of ultrahigh field (7 T) MRI to predict the shape and position of the patient's STN on the clinical image.⁴³ The predicted patient-specific STN has been shown to be highly accurate when compared to the same patient's 7 T data.⁴³

The definition of the STN based on MER has been previously compared to its definition based on standard imaging methods.⁴⁴⁻⁴⁸ Studies have reported that 40% to 50% of the MER tracks may detect STN-like activity at 1.5 mm or more

FIGURE 1. Axial views of the midbrain of one Parkinson's disease patient as observed with a standard clinical 3T MRI (left) and a high-field 7 T MRI (right), both are T2-weighted images.

FIGURE 2. Visualization of the midbrain of one Parkinson's disease patient as observed with a standard clinical 3T MRI (left) and the 7 T-ML method applied on the same image, T1-weighted (up) and T2-weighted (down).

from the borders of the MRI-defined STN (using 1.5T and 3T T2).⁴⁴⁻⁴⁶ Verhagen et al⁴⁷ have recently compared 1.5T, 3T, and 7 T T2 MRIs with MER. They observed that the lateral border was significantly more medial (~2 mm on average) on 1.5T and 3T MRI than in the MER-based STN; this difference was not found in the 7 T group. They concluded that increasing MRI field strength to 7 T might improve DBS targeting. Rasouli et al⁴⁸ have compared STN lengths estimated on quantitative susceptibility mapping images using 3T MRI to those computed based on MER and observed a 0.5-mm difference on average.

In this study, we compare the image-predicted STN location, to the STN as defined by intraoperative MER. MER is the gold standard for high fidelity definition of the STN based on the functional properties of the tissue. Note that the image-predicted STN location was not incorporated in the planning of the MER trajectory. MERs and MRI scans were acquired at one center in Jerusalem, while the MRI-based predictions of the STN were computed at another center in Twin Cities and each center was blinded to the other's results. We show that the predicted STN computed on the patient's clinical MRI strongly agrees with the MER data.

METHODS

Study Participants

We retrospectively analyzed the data of 16 consecutive PD patients who underwent STN DBS surgery (14 bilateral and 2 unilateral surgeries with a total of 30 implanted leads and electrode trajectories). Patients' average age at time of DBS surgery was 58 ± 9 yr old. Average disease duration was 7.5 ± 2.7 yr. The patients' cohort consisted of 8 women and 8 men. Rest tremor was observed in 9 patients, of whom 3 were defined as "tremor dominant" that are patients with relatively mild akinetic symptoms.

Surgical Procedure and MER

This study was approved by the institutional review board. All patients met accepted clinical inclusion criteria for DBS surgery and gave their written informed consent for the study. All surgeries were performed at Hadassah Medical Center (Jerusalem, Israel) by the neurosurgeon Z. I. using the CRW stereotactic frame (Radionics, Burlington, Massachusetts). The STN target coordinates were chosen with direct targeting based on T2-weighted MR images using Framelink 5 software (Medtronic, Dublin, Ireland). The surgical trajectory was based on 3T T1-weighted gadolinium enhanced (T1-Gd) images fused to the T2-weighted MR images using the same software. The surgical targeting was performed with no assistance of the image-predicted STN location (see below). MRI was acquired with a 3T Trio scanner (Siemens, Munich, Germany). T1-weighted imaging parameters were as follows: repetition time = 1900 ms, echo time = 2.27 ms, 256×256 voxels per slice and voxel size $0.49 \times 0.49 \times 1$ mm³. T2-weighted imaging parameters were as follows: repetition time = 3230 ms, echo time = 66 ms, 320×220 voxels per slice, and voxel size $0.375 \times 0.375 \times 2$ mm³. Surgery was performed with the patients awake, not sedated and off dopaminergic medications (>12 h). MRI and the surgical plans were fused to a stereotactic CT scan on the morning of surgery.

MER data were collected with the MicroGuide system (AlphaOmega Engineering, Nazareth, Israel) and incorporating polyamide coated tungsten microelectrodes (AlphaOmega). We have recorded a mean impedance of 0.43 ± 0.28 M Ω (mean $\pm$ SD) measured at 1 kHz. The original signal was amplified by 10 000. Then, a hardware 4-pole Butterworth band-pass filter in the range of 250 to 6000 Hz was applied and the signal was sampled at 48 kHz. Starting with the more severely affected hemisphere, 2 parallel microelectrodes recorded the intracranial multiunit activity, starting at 10 mm above the STN target as defined on the clinical image. One electrode was aimed at the center of the dorsolateral STN. The other electrode was placed 2 mm in parallel and anterior

or posterior to the central electrode. The trajectory was carefully selected to avoid the cortical sulci, the ventricles and major blood vessels based on the T1-Gd image sequences. The 2 electrodes were advanced in steps of between 0.4 and 0.1 mm at the same time. A typical recording duration was ~ 8 s in each step.

For clinical purposes, the neurophysiologist H. B. identified entry into and exit from the STN as a large change in the MER background activity. Moreover, the neurophysiologist has identified typical pattern of STN discharge to confirm microelectrode location within the STN. The root mean square (RMS) of the MER signal was normalized by its value prior to entry into the STN in a noncellular area. The normalized RMS was used to estimate the multiunit background activity and to detect the MER depths at which the electrode crossed the dorsal and ventral borders of the STN. Spectrograms that present oscillatory activity at tremor frequency (4-8 Hz) and/or beta ranges (13-30 Hz) provided further verification that the electrode was within the STN.^{26,28,29} For this study, the STN boundaries were defined automatically using a custom method that incorporates the RMS and spectrograms of the MER.^{27,28} The boundaries were then verified by the neurophysiologist H. B.. The final position of the DBS electrode was decided in the operating room based on the MER data and intraoperative assessment of the benefits and/or side effects observed during stimulation with a macroelectrode at the lower border of the STN dorsolateral oscillatory region (DLOR).²⁶⁻²⁸ The chronic lead was positioned such that contact #1 (second from the tip, electrode model Medtronic-3389) was placed in an effective location (as identified by both MER and stimulation effects) within the STN, usually with its distal border at the distal border of the DLOR. All leads were fixated with the Stimloc device (Medtronic).

The geometry of the four contacts of the chronic lead were then "overlaid" on the MER RMS plots (Figure 3A) and classified into: (1) outside and dorsal to the STN, (2) inside the STN, and; (3) outside and ventral to the STN. A contact was classified as "inside" if most of it (50% or more) was inside the STN. Otherwise, it was classified as "outside." Note that there can be some minor uncertainty in definition of the precise STN entry/exit point based on MER. For example, the STN entry was associated with an increase of 20% in neural activity, while a threshold of 50% would result in a 0.1 mm lower entry point and 0.3 mm higher exit points. The uncertainty in MER definition of STN entry and exit points in our setup is estimated to be ± 0.25 mm.²⁶ Comparing the contacts locations with respect to the STN based on intraoperative MER and postoperative CT provides a clinical-relevant insight. Specifically, it estimates if the clinical efficacy observed with contacts placed based on MER guidance, would be similar to those placed using the 7 T-ML method. This is based on the reported association between stimulation location and treatment efficacy.

High-Field 7 T Database and ML Prediction of the STN

At the University of Minnesota (Twin Cities, Minnesota), we established and validated a database of high-field 7 T MR images (T1, T2, and SWI) of 46 PD patients that underwent DBS therapy in the Department of Neurology, University of Minnesota.³⁷ The subcortical structures were manually segmented on each of the 7 T images. The inter- and intrastructure geometrical relations of the segmented structures and the relations between image intensities and segmented structures were simultaneously analyzed through a unified approach for combining active shape models and active appearance models (ASM/AAM).⁴⁹ Once all the PD patients datasets were received at the Twin Cities from Jerusalem, the shapes and positions of the STNs from each patient were estimated

using the ASM/AAM analysis and a custom ML algorithm (hereafter 7 T-ML).^{43,50,51} The method and algorithms have previously been described in greater detail.⁴³ The 7 T-ML method overlays the estimated position and 3D shape of the STN on the PD patients' clinical MR image (Figure 3B).

The actual locations of the chronic DBS electrodes and their contacts were extracted from a postoperative CT scan performed several days after surgery. A typical CT image dataset contained 210 axial slices of 500×500 voxels per slice and voxel size of $0.49 \times 0.49 \times 1$ mm³. Note that DBS stimulation surgery may be associated with introduction of intracranial air. However, movement of the distal contact, targeting error, and clinical outcomes are not affected by intracranial air according to Bentley et al.⁵² Furthermore, we have ensured that the frontal lobe shift along the anterior-posterior axis in our dataset is less than 5 mm. Based on another unpublished study in our group, this ensures a less than 0.5 mm electrode tip migration. The CT scans were registered to the preoperative MRI such that the electrode contact locations and the segmented STN reside on the same coordinate system. The registration incorporates a region of interest mask in the basal ganglia zone to further eliminate the possible effect of a brain shift on the measurements accuracy. Then, the contacts were classified based on their locations relative to the STN borders, as observed with multiple 3D views, and compared to the classification based on MER. The entire process was performed automatically using in-house developed software (Surgical Information Sciences, Minneapolis, Minnesota) and incorporating registration modules of advanced normalization tools.^{53,54} The accuracy of the method was validated visually using the 3D Slicer.⁵⁵

Statistical Analysis

Paired *t*-test was applied to test the null hypothesis that the means of STN lengths measured with MER and with 7 T-ML are equal. For reporting the variability in STN lengths, we computed their standard deviation (SD). These measures were computed with Microsoft Excel, Version 14.7.3, 2011. Last, we calculated the number of contact classifications that match and those that mismatch between the MER and 7 T-ML to estimate a more clinically relevant measure.

RESULTS

Figure 3 presents a typical result where the 7 T-ML method accurately predicted the MER detected STN and correctly classified the location of individual contacts. All 30 implanted electrode trajectories that intersected the STN based on MER, also intersected it using the 7 T-ML method (Figure 4). The average span of STN as per MER was 6.2 ± 0.7 mm and 5.8 ± 0.9 mm for the 7 T-ML for the identical trajectory (Table 1). STN lengths measured with MER were not significantly different from those measured with the 7 T-ML method ($P > .05$; *t*-test). Moreover, the 2 measures were significantly correlated ($r = 0.41$, $P < .01$). The regression equation is $y = 0.52x + 2.6$, where *x* and *y* are the STN length per MER and 7 T-ML, respectively. We observed 93% (112/120) agreement with MER regarding contact location with respect to the STN, using the 7 T-ML method (Table 1). Interestingly, using the 7 T-ML method all of the 8 (out of 120 examined) misclassified contacts were at the dorsal border of the STN (contact #2; Figure 4C).

The actual clinical benefits of incorporating the 7 T-ML method in presurgical planning of DBS surgery are yet to be investigated and are outside of the scope of this study. However, note that 3 out of 30 (10%) MER trajectories were adjusted during the surgery (P03-L undocumented change, P05-L 2 mm posterior, and P06-L 2 mm anterior). In all of these cases, the contacts classification based on the revised MER matched the contacts classification based on 7 T-ML. Moreover, 6 electrodes (20%) were implanted on a trajectory that is 2 mm posterior (5) or anterior (1) and parallel to the central one. The differences between the planned and actual electrode location may be related to several factors, including a change of trajectory based on unexpected cortical anatomy, brain shift, or the uncertainty in the definition

of the STN on the 3T MRI. Note that a higher uncertainty is expected for 1.5T MRI. Thus, the above data provide more evidence for the need and the potential of the 7 T-ML method described here.

DISCUSSION

The goal of this study was to validate the accuracy, and its clinical relevance, of a novel method, called 7 T-ML, for visualizing the STN on standard clinical MRI. The validation is performed via a comparison of the imaging-based 7 T-ML method to intraoperative neurophysiological MER data. Here, we tested the imaging-based 7 T-ML method, using clinical 3T data and under the full intraoperative DBS setup, in contrast to our previous study that compared the 7 T-ML method results to ground-truth high-resolution 7 T MRI acquired of the same subject.⁴³ Furthermore, the 7 T-ML method evaluated here incorporates real-life intraoperative sources of error. Our new approach for the visualization of the STN, based on a 7 T MR image database combined with an ML approach, facilitates highly accurate localization of DBS contacts within the STN. The results suggest that incorporation of a 7 T MRIs database and ML method provides an accurate estimation of STN location and shape. The 7 T MRI facilitates the accurate segmentation and modeling of subcortical structures and their geometric relations. The ML method accurately portrays the variability of the STN shape and position. This provides a validation of the clinical accuracy of the new approach under the full DBS surgical setup.

The slope of the linear regression between the STN lengths per MER and 7 T-ML was 0.52, while a slope of 1 represents a perfect match. One possible explanation for this observation may be related to the STN length measurement errors in the MER and MRI. To test this theory, we simulated ($n = 1000$) an error by adding a random error with distribution of $\sim N(0,$

2) ($2 = 1.5$ mm for MRI and 0.5 mm for MER) to the MER measurements. Then, we checked the effect of the simulated error on the regression and the Pearson correlation coefficients. The mean regression slope was 0.97 ([SD] = 0.53, range -0.87 to 2.85). The mean Pearson correlation coefficient was 0.33 (SD = 0.17, range -0.36 to 0.73). Note that the observed slope of 0.52 is about the average minus one standard deviation. Therefore, the observed slope may be explained by the STN's length measurement error. Another possible explanation may be related to possible differences between anatomic appearance in MRI and electrophysiological function spatial distribution.

As noted in the results, the 8 misclassified contacts (out of 120) using the 7 T-ML method were at the dorsal border of the STN (contact #2). In 6 cases, the MER indicated the contact is mostly inside, but the suggested 7 T-ML method indicates it is mostly outside. These misclassified contacts may be explained by possible differences between electrophysiology and imaging defined borders. The dorsal entry to the STN was defined in part by an increase of at least 20% in the normalized RMS of the MER signal. Increasing the threshold to 40%, for example, would result in a ventral shift of the STN dorsal border that could change the classification of contact #2 from "inside the STN" to "outside and dorsal to the STN." Moreover, the average absolute difference between the MER and 7 T-ML STN lengths was 0.75 mm (SD = 0.59 mm), which approaches the limits of possible accuracy considering an image of 1-mm voxel resolution. Other possible sources of error are brain shift,⁵⁶ preprocessing image manipulation and normalization errors, image fusion and registration errors that may led to inaccurately defining the STN.

Methods that estimate the volume of tissue activated (VTA) have the potential to predict the optimal stimulation parameters to be used for each patient.⁵⁷ However, they rely on the accurate estimation of contact locations within and around the target, requiring visualization of both the shape and borders of

TABLE Detailed Experimental Results.

Patient # R/L	STN length (mm)		Contacts inside STN (Contacts #)	
	MER	7 T-ML	MER	7 T-ML
P01, R	7.1	7.1	2, 1, 0	2, 1, 0
P01, L	7.0	6.9	1, 0	2, 1, 0
P02, R	6.1	5.3	2, 1, 0	2, 1, 0
P02, L	7.2	7.2	2, 1, 0	2, 1, 0
P03, R	5.0	4.2	2, 1, 0	2, 1, 0
P03, L	6.3	5.0	2, 1, 0	2, 1, 0
P04, R	5.7	6.0	2, 1, 0	1, 0
P04, L	5.7	7.2	2, 1, 0	2, 1, 0
P05, R	5.4	4.8	2, 1, 0	2, 1, 0
P05, L	5.5	5.1	2, 1, 0	2, 1, 0
P06, L	6.7	6.1	2, 1, 0	2, 1, 0
P07, R	6.7	5.8	2, 1, 0	2, 1, 0
P07, L	7.2	5.5	2, 1, 0	2, 1, 0
P08, R	6.1	6.1	2, 1, 0	1, 0
P08, L	7.3	6.5	1, 0	2, 1, 0
P09, R	5.1	4.5	2, 1, 0	2, 1, 0
P09, L	6.1	4.4	2, 1, 0	2, 1, 0
P10, R	5.5	5.6	2, 1, 0	2, 1, 0
P10, L	6.9	6.0	2, 1, 0	2, 1, 0
P11, R	6.5	6.4	2, 1, 0	2, 1, 0
P11, L	6.1	4.9	2, 1, 0	1, 0
P12, R	7.1	5.5	2, 1, 0	1, 0
P12, L	5.1	7.3	1, 0	1, 0
P13, R	5.9	6.8	2, 1, 0	2, 1, 0
P13, L	6.0	6.3	2, 1, 0	1, 0
P14, L	6.0	6.4	2, 1, 0	1, 0
P15, R	5.5	5.6	2, 1, 0	2, 1, 0
P15, L	5.0	4.6	2, 1, 0	2, 1, 0
P16, R	6.2	4.9	2, 1, 0	2, 1, 0
P16, L	6.5	5.7	2, 1, 0	2, 1, 0
Average (SD)	6.2 (0.7)	5.8 (0.9)	# Consistent with MER 120	112

the anatomic structure of each patient. By incorporating the 7 T-ML method, the surgical team will be better able to visualize the location of the STN in 3D stereotactic space allowing greater accuracy in targeting this structure when implanting DBS leads. Better placement should lead to optimal clinical benefit and a reduced incidence of side effects. Moreover, more accurate postoperative localization of individual contacts may improve the efficacy of existing systems used to estimate the VTA, leading to shortened programming times and better outcomes.

Limitations

Study limitations are as follows. The preferred position of contacts and the accuracy of implanting the electrodes at the intended location varies among neurosurgeons.¹⁷ The thresholds for defining exact STN entry and exit have not been standardized. Here, we used an automatic method for the detection of the STN borders and subdomains.^{26,27,58} Since this is a single center study, the variability of contacts locations was relatively small

(Figure 4). For example, all contacts 0 and 1 were inside the STN based on MER since that is the preferred method in our center. A larger scale study comparing the 7 T-ML method to MER datasets of other centers will strengthen the validation. Another assumption inherent in this study is that STN defined borders based on MER match those defined by MRI. Although it is unclear to what extent the functional (MER) and anatomic (MRI) properties of the STN coincide, these results suggest that there is a strong correspondence between the 2. Last, DBS lead artifacts may cause error in electrode segmentation influencing the ultimate accuracy of the fusion data.

In this study, we have tested the 7 T-ML method accuracy, but not yet its clinical utilization. Nevertheless, we have considered related aspects and addressed them in a recent FDA 510k clearance.⁵⁹ 7 T MRI has shown advantages for basic science since of its capabilities to visualize, in fine details, the anatomic structures of the basal ganglia. However, the availability of 7 T systems is sparse and only available in selected academic and research institutions. In this work, we investigate if it is possible to utilize the technology and knowledge obtained from the 7 T data and apply it to the general population that don't have access to 7 T and are using the standard clinical data for their DBS surgeries. The method described in this work lays the groundwork for developing new tools that will provide 7 T-like capabilities based on software-only and without the need of a large capital investment for a 7 T system.

Ho et al⁶⁰ have compared awake versus asleep DBS for PD in a meta-analysis study. They have concluded that DBS under general anesthesia is associated with lower complication rates overall, but awake DBS is associated with less treatment-induced side effects. However, Brodsky et al⁶¹ reported superior speech fluency and quality of life in PD patients that underwent asleep DBS in comparison to awake DBS PD patients, while other motor outcomes were comparable. One possible reason for the variability in reported outcomes may be related to the various imaging protocols that are utilized in the different centers. We foresee that 7 T-ML may further improve asleep DBS procedures by reducing the variability in identified STN locations.

CONCLUSION

The outcomes of DBS therapy are highly related to the location of the DBS lead. Intraoperative recordings with microelectrodes and intraoperative imaging techniques provide a form of validation regarding the correct placement, yet the pre- or postoperative methods used to identify the STN on clinical images remains a challenging task. Recently, developed 3D deformable atlas-based registration methods may improve accuracy.⁶² Here, we present the next generation method that incorporates ML and a high-field 7 T MR database to accurately predict the STN shape and position on the clinical image. Accurate lead implantation and postoperative localization of DBS contacts may improve outcomes and reduce DBS programming time.

Disclosures

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COMMENTS

The methods used for stereotactic targeting have evolved over time, from an era of indirect targeting to one of direct targeting. Despite the significant advances enabled by MR structural imaging, commonly available clinical MRI sequences still sometimes do not allow visualization of small regions-of-interest or internal anatomy of subcortical structures, due to limitations in spatial resolution, signal-to-noise ratios (SNT), and contrast-to-noise ratios (CNR). The most commonly sought solutions have been to design and evaluate superior MR imaging sequences, such as SWI and FGATIR. Advances in neuroimaging and, perhaps more importantly, image analysis techniques necessitate critical evaluation of even more novel methods for using advanced neuroimaging to define stereotactic targets. In this report, the authors critically evaluate a novel image segmentation algorithm to define subject-specific subthalamic nuclei (STN) using machine learning algorithms that utilize a database of high-quality 7 T MRI with predefined STNs. This is a highly novel approach that integrates machine learning techniques that are becoming commonplace in the basic science world of signal analysis and classification and applying and integrating these methods into the clinical domain. All too often, this translation from basic science to clinical application takes far too long. In this case, the approach takes advantage of the higher spatial resolution and SNR/CNR of 7 T imaging while facing the reality that acquisition of 7 T magnets at most facilities is not likely to occur in the near future. The value of this approach will ultimately depend on anatomic and, more importantly, clinical validity. The results are preliminarily promising and show relatively good prediction value, on average across a population of subjects. But as Figure 4 reminds us, there can be considerable variation between MER and the 7 T-ML method in individual subjects. The authors attribute this measurement error in the length of STN, reminding us that even MER may be an imperfect science. Still, as far as defining STN anatomy, it remains our gold standard. Therefore, a more comprehensive dataset should be sought to directly compare MER-defined and 7 T-ML-predicted STN trajectory lengths to validate the validity of this technique for predicting STN anatomy, perhaps even in a prospective fashion. More importantly, this innovative team will have to consider how to determine the clinical value of this approach, likely with prospective trials to determine whether the 7 T-ML method can be relied upon to predict efficacious deep brain stimulation outcomes. In an era of value-based medicine, this will have to be critically compared to the growing literature of "asleep" DBS implantation outcomes, that suggest current imaging may in fact be sufficient. Still, there are few that argue that more information, especially in stereotactic surgery, is not better. I therefore look forward to further validation and testing of this method, as well as application of these types of machine learning approaches to other applications in neurosurgery.

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The authors present a very interesting study, which tested how well a machine learning algorithm compares to intraoperative microelectrode recording (MER) for predicting the location of the STN for implantation of DBS leads. Surgeries were performed in a standard fashion and the span of STN recorded along the implantation trajectory was faithfully noted. Post-op CT scanning was employed to localize the implanted lead within the 7 T model and the span of STN determined by each method was compared. Of note is that the 7 T-ML predicted target was not used as the initial anatomical target for the surgery.

The authors claim a high degree of agreement between the 2 data sets (MER and 7 T-ML), suggesting that this targeting method may present a viable alternative to intraoperative recordings for the placement of STN DBS electrodes. Overall, this is a nicely designed and executed study, which demonstrates the potential power of 7 T-MRI-based atlases and machine-learning algorithms to assist surgeons in the implantation of DBS electrodes; however, I disagree with the authors concerning how well the span of STN measured with the algorithm correlated with the MER data. The *P* value for the linear regression is just .5, the slope of the regression line is also just 0.5 (a true 1:1 correlation would yield a regression line with a slope of 1), and an *r* of 0.4 is not particularly robust. According to the scatter plot, an MER-derived STN span of 6 mm may be seen with 7 T-ML measurements ranging from <5 mm to >7.5 mm, an enormous variance on a percentage basis for such a small target. It is important to remember that for these comparisons,

averages and trends are not important, 1:1 concordance for a given patient is.

Finally, given that 30% of the leads were implanted along trajectories other than that which was originally intended by the surgeon, it would be interesting to know how the 7 T-ML derived STN targets compared to the operating surgeon's and how both compared to the final, MER-derived target. Such a comparison would tell us whether 7 T-ML is truly superior to the surgeon in predicting the final target. It is conceivable that such a comparison would yield an uncomfortable result and that, like John Henry, the powerful railway worker of lore, who lost his job to the steam engine, stereotactic neurosurgeons may be facing their obsolescence.

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