Diffusion Tensor Imaging and Colored Fractional Anisotropy Mapping of the Ventralis Intermedius Nucleus of the Thalamus

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BACKGROUND: The ventralis intermedius (VIM) nucleus of the thalamus is the primary surgical target for treatment of tremor. Most centers rely on indirect targeting based on atlas-defined coordinates rather than patient-specific anatomy, making intraoperative physiological mapping critical. Detailed identification of this target based on patient-specific anatomic features can help optimize the surgical treatment of tremor.

OBJECTIVE: To study colored fractional anisotropic images and diffusion tensor imaging (DTI) tractography to identify characteristic magnetic resonance appearances of the VIM nucleus.

METHODS: Four patients undergoing stereotactic surgery for essential tremor (ET) were retrospectively studied with analysis of magnetic resonance imaging-based colored fractional anisotropy (FA) images and fiber tractography. All were scanned with a 1.5-T magnetic resonance imaging unit, and all sequences were obtained before frame placement. Because the goal of this study was to identify the DTI characteristics of physiologically defined VIM nucleus, we selected and studied patients who had undergone DTI and had efficacious tremor control with intraoperative microlesioning effect and tremor reduction with less than 2.0-V stimulation.

RESULTS: Analysis of color FA maps, which graphically illustrate fiber directionality, revealed consistent anatomic patterns. The region of the VIM nucleus can be seen as an intermediate region where there is a characteristic transition of color. Presumptive VIM nucleus interconnectivity with sensorimotor cortex and cerebellum was identified via the internal capsule and the superior cerebellar peduncle, respectively. FA maps could also be used to distinguish segments of gray matter, white matter, and gray-white matter boundaries.

CONCLUSION: Analysis of DTI and FA maps on widely available 1.5-T magnetic resonance imaging yields clear identification of various structures key to neurosurgical targeting. Prospective evaluation of integrating DTI into neurosurgical planning may be warranted.

KEY WORDS: Deep brain stimulation, Diffusion tensor imaging, Fiber tractography, Fractional anisotropy, Ventralis intermedius

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The ventralis intermedius (VIM) nucleus, which, according to Hassler's classification, is a subdivision of the motor thalamus, is currently the most common target for the surgical treatment of tremor.[1-3] Most centers rely on indirect targeting based on atlas-defined coordinates rather than patient-specific anatomy, making intraoperative physiological mapping critical. Detailed identification of this target based on patient-specific anatomic features can help optimize the surgical treatment of tremor.

ABBREVIATIONS: DBS, deep brain stimulation; **DTI,** diffusion tensor imaging; **FA,** fractional anisotropy; **PILC,** posterior limb of the internal capsule; **VIM,** ventralis intermedius

The application of diffusion tensor imaging (DTI) has enhanced the ability to view anatomic detail beyond what is seen by conventional

magnetic resonance imaging (MRI) or computed tomography and has allowed in vivo imaging of fiber tracts in humans.[4-7] Water diffusion in white matter is directionally dependent, allowing the formation of anisotropic maps and evaluation of their movement vectors. Fiber tracts can be deduced by calculating the cumulative molecular water diffusion vectors. This type of imaging has been validated with many known fiber tracts and animal models.[8-10]

OBJECTIVE

Newer imaging modalities, such as DTI, can potentially help target the VIM nucleus more accurately, resulting in higher efficacy and fewer side effects and, in the case of deep brain stimulation (DBS), longer lasting generators. In this study, we studied colored fractional anisotropy (FA) images and DTI tractography to identify characteristic MRI appearances of the VIM nucleus.

METHODS

Of 392 patients who had undergone DBS from November 18, 1993 to February 18, 2010, we retrospectively reviewed 4 patients who had undergone DBS for tremor. Three of these patients had essential tremor and 1 had tremor-dominant Parkinson disease. DTI was performed in the 1.5-T Sonata (Siemens, Munich, Germany) intraoperative MRI suite before frame placement. Specific inclusion criteria included patients who had an intraoperative microlesioning effect and who had tremor reduction starting with less than 2.0 V during intraoperative stimulation. The selection criteria were intended to ensure that we only selected and studied patients in whom we were confident that the electrode was optimally placed in the intended target based on low-amplitude therapeutic stimulation. We presume that the closer the electrode location to the target of interest is, the lower the voltage threshold is for efficacious treatment and the fewer the side effects. Including patients who required higher voltages for therapeutic efficacy might have increased the uncertainty and specificity of the maps obtained using DTI. There were a total of 4 electrodes placed, 2 of which were repositioned intraoperatively. One was moved 2 mm deeper, as the most efficacious contact was the lowermost. Another electrode was moved 2 mm anterior because of significant sensory side effects.

DTI, T1, T2, fluid-attenuated inversion recovery source imaging acquisition was undertaken either preoperatively or intraoperatively before placement of the Leksell stereotactic frame. DTI data were acquired using single-shot spin-echo echo-planar imaging with TR = 10,000 ms, TE = 90 ms, acquisition matrix = 128 $\times$ 128 and field of view = 25.6 cm. A slice thickness of 2 mm with no gap was used. Diffusion-sensitizing gradient encoding was applied in 12 directions by using a diffusion-weighted factor b = 700 s/mm^2, and 1 image was acquired without the use of a diffusion gradient, ie, b = 0 s/mm^2. The DTI time was approximately 4 minutes. The Leksell frame was then placed parallel to Raid's line with the patients under sedation. The patients were then rescanned in the Sonata intraoperative MRI suite for frame registration. All stereotactic planning was performed on BrainLab's iPlan Stereotaxy 2.6 (Feldkirchen, Germany).

DBS electrode implantation was according to standard surgical procedures, independent of diffusion tensor maps described in this report. After standard sterilization and opening, the patient was awakened and a radiofrequency electrode with a 1.8-mm exposed tip was placed measuring impedance to target, which ranged from 390 to 540 Ω. Trial stimulation was then performed at 2 Hz and then 100 Hz with a pulse width at 100 ms. After adequate clinical response, the radiofrequency electrode was removed and the Medtronic 3387 lead was placed to target. If the clinical response was inadequate, the radiofrequency electrode was repositioned. Intraoperative stimulation was performed using Medtronic's (Minneapolis, MN, USA) 3628 stimulator with a pulse width of 90 ms and 160 Hz. After adequate clinical response, the electrode was secured using a Navigus cap (Image Guided Technologies, Inc., Boulder, Colorado). Postoperative computed tomography or MRI was performed to check placement of the leads. The implantable pulse generators were implanted at a later stage, typically about 2 weeks postoperatively. A detailed description of the stereotactic procedure as well as the imaging acquisition for targeting has been previously reported.[11,12]

BrainLab's iPlan Cranial 2.6, Stereotaxy 2.6, or RT 4.1 software was used in all the analyses. Eddy current correction and head motion correction (affine) was used in all patients. Colored FA maps were used to identify the VIM nucleus and surrounding structures using the Schaltenbrand-Wahren atlas information and MRI sequences such as T1, T2, spoiled gradient echo, and fluid-attenuated inversion recovery. Final electrode placement was analyzed postoperatively, and final trajectories were traced based on artifact location using postoperative MRI scans.[11] All image sequences were automatically fused and manually checked to confirm appropriate fusion using the software. The VIM nucleus as defined by the FA map was then compared with the VIM nucleus as defined by atlas and compared with the final electrode position.

Axial, coronal, and sagittal images of the colored FA map were analyzed for identification of consistent anatomy and structures across patients. A standard color scheme was used in the BrainLab software to encode the FA maps, with blue indicating superior-inferior, red indicating transverse, and green indicating anteroposterior. When key characteristics were identified, they were marked using the object creation tool. Anatomic correlation between these regions was then studied with the atlas as well as other MRI. Deterministic fiber tractography in BrainLab software was used in key regions of interest to better understand and demonstrate the anatomy and connectivity of the region.

RESULTS

Consistent patterns in colored FA maps across all patients improved visualization and identification of key anatomy in the region of the VIM nucleus. Fiber tractography demonstrated possible connectivity between the VIM nucleus and the sensorimotor cortex via the internal capsule as well as the cerebellum via the superior cerebellar peduncle.[13]

Gray-White Matter Delineation

Colored FA maps highlighted boundaries between major gray and white matter regions, which can sometimes be obscured on T1- or T2-weighted imaging. The boundaries between the posterior limb of the internal capsule, the thalamus, and the globus pallidus could be unambiguously delineated using color FA maps (Figure 1). Major white matter tracts helped in this delineation because of their confluent color. For example, the posterior limb of the internal capsule (PLIC) was mostly blue in color, representing a superior-inferior fiber direction. The same

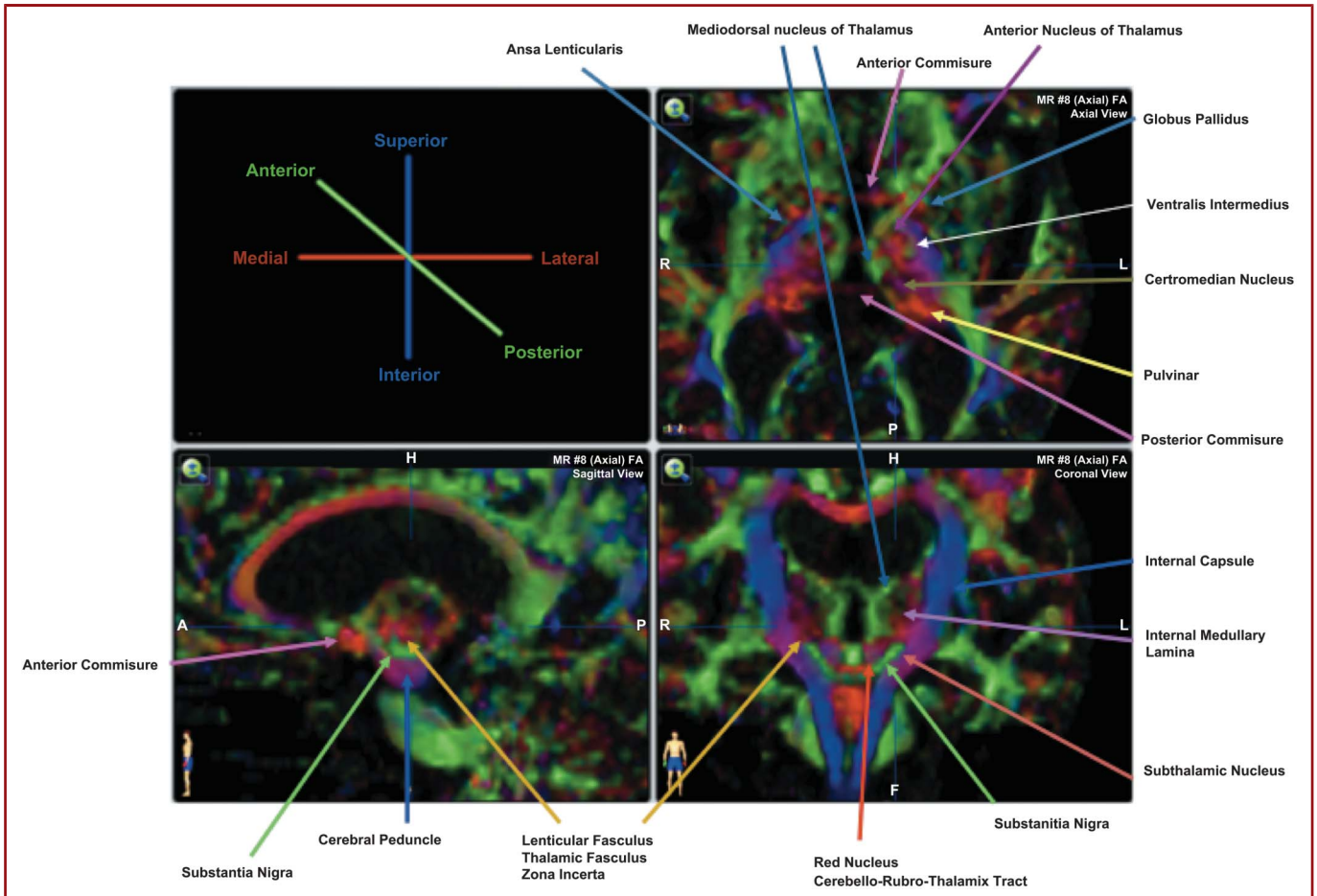

FIGURE 1. *Colored fractional anisotropy map. Colors indicate fiber direction (red = medial-lateral, blue = superior-inferior, green = anterior-posterior). Various structures have been identified and labeled in the image obtained on 1.5-T magnetic resonance imaging. Note the differential appearance between white and gray matter and their distinguishing boundaries. Anterior and medial regions of thalamus have green color appearance, consistent with frontal projections. The posterior thalamus in the region of the pulvinar nucleus demonstrated lateral projections, which merged with posteriorly projecting fibers of optic radiations. The portion of the thalamus where the ventralis intermedius nucleus (VIM) is located has a transitional color appearance. The VIM was located above bridging fibers below the thalamus seen on coronal and sagittal imaging, demonstrating cumulative effects of the corticospinal tracts, cerebellorubrothalamic tracts, nigral projections, and many smaller fibers including the central tegmental tract, thalamic fasciculus, and lemniscal fibers.*

was even true of smaller white matter tracts such as the ansa lenticularis. Conversely, regions such as the thalamus and globus pallidus containing gray matter demonstrated heterogeneity of color with regional variation.

White Matter Segmentation

FA maps also clearly distinguish between major white matter bundles that are not otherwise readily discernable on T1- and T2-weighted imaging. The internal capsule illustrates this concept well. Color changes are seen depending on anterior or posterior segments (Figure 1, upper right panel). The anterior limb of the internal capsule contains voxels with anteroposteriorly oriented fibers (green color), whereas the PLIC is dominated by voxels with superoinferiorly oriented fibers (blue color). Even within the PLIC, regional variations could be used to distinguish parts of the PLIC. Although the posterior portions of PLIC project toward the parieto-occipital lobe with green anteroposteriorly oriented fibers, the more anterior and central portions of PLIC project frontoparietally with blue-purple superoinferiorly oriented fibers (Figure 1, upper right panel).

Another notable area is the region below the thalamus containing major tracts that were distinguishable based on fiber directionality (color coding) (Figure 1, bottom right panel). One of these tracts was the internal capsule, which was most lateral on coronal imaging and typically a blue-purple color, indicating a mostly superoinferior tract direction. Immediately superior and medial to the internal capsule is a green region with fibers in an anteroposterior direction presumably containing the nigral projections. Again, immediately superior to this is another tract that most typically has transverse projecting fibers (ie, red) and likely

contains cerebellorubrothalamic tracts, lemniscal fibers, fibers of the thalamic fasciculus, and Forel's fields. This most superior tract also typically included a band projecting laterally to the internal capsule; this intersection also contained the zona incerta and was at the intercommissural plane.

Color coding could also be used to readily identify the other important areas such as the anterior commissure, posterior commissure, and corpus callosum (Figure 1).

Gray Matter (Thalamus) Segmentation

The thalamus itself also demonstrated characteristic internal FA patterns. The posterior thalamus near the region of the pulvinar is most often red (indicating transverse fiber orientation) with projections that entered posterior to internal capsule emanating into optic radiations (Figure 1, upper right panel). The mediodorsal nucleus of the thalamus was also clearly seen with green-colored anterior projections. Observation of the ventral posterior and ventral anterior thalamic regions consistently demonstrated a color-coded transitional region seen near the VIM nucleus (as defined based on the site of optimal DBS). The sensory thalamus, on the other hand, displays a more red-purple appearance, whereas the motor thalamus often has a more green-red coding (Figure 2). Clear separations of the thalamus could be seen secondary to the internal medullary lamina identifying the ventrolateral and ventroposterior from the mediodorsal nuclei.

Inspection of the VIM nucleus region, as defined by optimal site of DBS at low voltages, consistently revealed key thalamic FA features (Figure 2). On axial imaging, the key features were the transitional color of the VIM nucleus. Lateral to the internal medullary lamina contained the external and internal portions of the VIM nucleus. On coronal imaging, the electrode tip was consistently seen abutting a key signature region of white matter bundles described above. Last, sagittal images revealed a consistent red-purple line contained in the mid-to-posterior aspect of the thalamus creating a partition therein. The electrodes were typically seen just anterior to this line.

Diffusion Tractography

Region of interest was placed in the VIM nucleus as identified by the Schaltenbrand-Wahren atlas and efficacious electrode placement. Tractography of this region of interest demonstrated fibers entering or exiting the thalamus, incorporating the internal capsule and leading to the sensorimotor cortex as well as the cerebellum through the superior cerebellar peduncle (FA, 0.25 and minimum fiber length of 15 mm) (Figure 3). There was no major consistent difference in tractography seen comparing the Schlatenbrand-Wahren atlas as the region of interest, the DTI-based VIM nucleus, or the electrode location.

DISCUSSION

DTI, a method of visualizing white matter fiber fibers in vivo, has numerous applications in neurosurgery. This technology can readily identify major white matter tracts, but also has use in gray matter partitioning. Interestingly, some have documented parcellation of the thalamus into its subnuclei.[14,15] Still, colored FA maps and DTI to date have not been used to identify major tracts in the region of the VIM nucleus. We theorized that major tracts leading to and from the VIM nucleus would indicate the precise and specific signature of this region. We believe that this region was clearly identified even on 1.5-T MRI. Higher quality imaging and probabilistic tractography may further increase the precision for identification of this nucleus.

The VIM nucleus receives vestibular and cerebellar projections, proprioceptive inputs from limbs, and projects to cortical 3a and motor areas.[16,17] Interestingly, the VIM nucleus was visualized in our study contained in a colored transitional zone, similar to histological studies that have also identified a transitional appearance between ventro-oralis and ventrocaudalis, which was indicated by density and cell type.[13] Input and output connectivity, evident on FA maps, may be directly related to this cell density and type. Furthermore, physiological information obtained about the VIM nucleus and surrounding structures has also demonstrated a transitional electrophysiological signature.[18]

Other noninvasive studies with probabilistic parcellation of the PLIC have found projections to the sensorimotor cortex in the region of PLIC near its midpoint.[15] Also, the VIM nucleus was overlying a very complex region containing many distinct tracts. These tracts, including the cerebellorubrothalamic tract, nigral projections, lemniscal, internal capsule, zona incerta, thalamic fasciculus, and subthalamic fasciculus, have all been implicated in both the effects of DBS and many of the side effects encountered.[19]

The complexity of the thalamus and its connections to other portions of the brain cannot be simplified by any single modality. Clarity of anatomic junctions between white matter and gray matter are becoming increasingly apparent with higher quality imaging. It is clear, however, that white matter tracts in gray matter play a role in side effects of DBS. Shields et al[19] demonstrated through clinical data that the common side effect of eye deviation during subthalamic nucleus stimulation may be attributed to white matter fiber tracts being activated in the anterior limb of the internal capsule leading to the frontal eye fields.

Furthermore, overlap of the Schaltenbrand-Wahren atlas in DBS targeting can be difficult and user dependent. The atlas is not based on information that is specific to the patient, but on a cadaveric brain dissection. The variability of the scaling methods to improve the model is difficult to fully evaluate.[20] We, therefore, favor a multimodality assessment, using various sequences of MRI followed by use of the atlas. We believe that colored FA sequences increase the information available to the surgeon and enhance the precision needed on a patient-by-patient basis.

In this study, we demonstrated that 1.5-T MRI scanning can yield information that can guide critical decision making and precise DBS targeting. Although we have demonstrated a proof-of-concept in this retrospective series with imaging at 1.5 T, we acknowledge several shortcomings in analysis and interpretation and future directions for this line of investigation. A major issue is

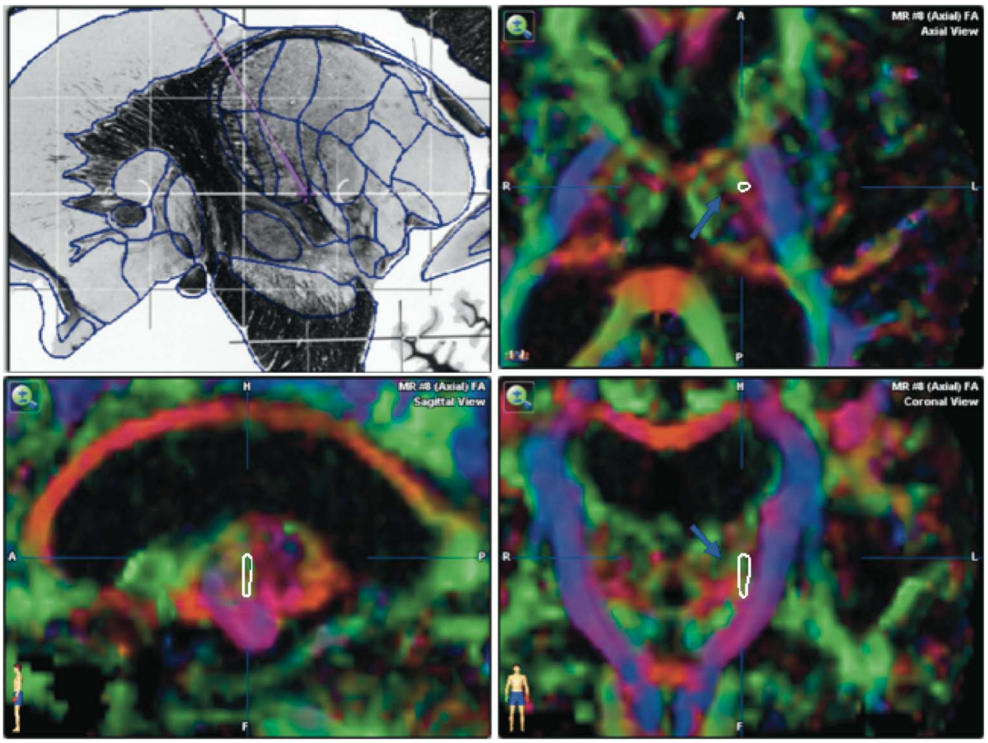

FIGURE 2. *The ventralis intermedius nucleus (VIM) of the thalamus in purple. Overlap of the final electrode position with Schaltenbrand-Wahren atlas fused to the fractional anisotropy (FA) map and drawn as an object (white) on color sequences. Imaging of a colored FA map demonstrated a consistent finding correlating with efficacious postoperative deep brain stimulation insertion. Note that the posterior limb of the internal capsule demonstrates a homogeneous color in its respective parts, green in the anterior limb and purple-blue in the majority of the posterior limb. Note that the most posterior portion of the posterior limb of the internal capsule the green appearance, demonstrating optic radiations. The thalamus itself demonstrated heterogeneity with the more posterior having a red-purple appearance at the level of ventral posterior nucleus, pulvinar, whereas the mediodorsal nucleus has a green appearance. The internal medullary lamina (blue arrow) can be seen separating the mediodorsal thalamus from ventral lateral nucleus and ventral posterior nucleus. The VIM nucleus is located in the transitional zone where the electrode tip is colored pink on axial, sagittal, and coronal FA images. Last, neighboring white matter tracts can be clearly distinguished by fiber directionality especially seen on the coronal images below the thalamus.*

that of imaging resolution. In the current study and in most image sequences, DTI sequences are acquired with voxels measuring $2 \times 2 \times 2$ mm^3. The spatial resolution and accuracy are further compromised by patient motion during prolonged image acquisition and eddy currents, which occur in the conductive parts of the magnet causing significant geometric distortions. Although these can be partially corrected for with retrospective corrections by registering the distorted diffusion image with a less distorted image acquired without diffusion weighting (usually the first acquired diffusion volume), there are residual artifacts (and therefore distortion) that cannot always be fully accounted for. Given the precision of stereotactic neurosurgery, the implications of this degree of spatial resolution and residual distortion is unclear; it may prove to be significant, especially when targeting small structures such as the VIM or subthalamic nucleus. Future studies with high-resolution DTI will need to be conducted in a prospective manner to better evaluate the importance of improved imaging spatial resolution. Imaging can no doubt further be improved with increased field strength (eg, 3 T or 7 T), acquiring increased number of directions, and using an increased number of channels on a dedicated head coil. However, these increases in resolution and specificity must be evaluated in light of the distortions that are introduced with such changes, especially as they pertain to increased field strength and B0 field inhomogeneities. Although a detailed analysis of the physics of these points is beyond the scope of this report, we are encouraged by these early findings that enhanced refinement of this technique will yield crucially important information. A prospective evaluation of the potential distortions introduced by different field strengths is particularly relevant for using DTI for stereotactic planning and targeting In addition, further use of computerized analytical methodologies may further our understanding of portions of the brain. Probabilistic DTI will be a crucial step in understanding this interconnectivity and defining regions of the brain.

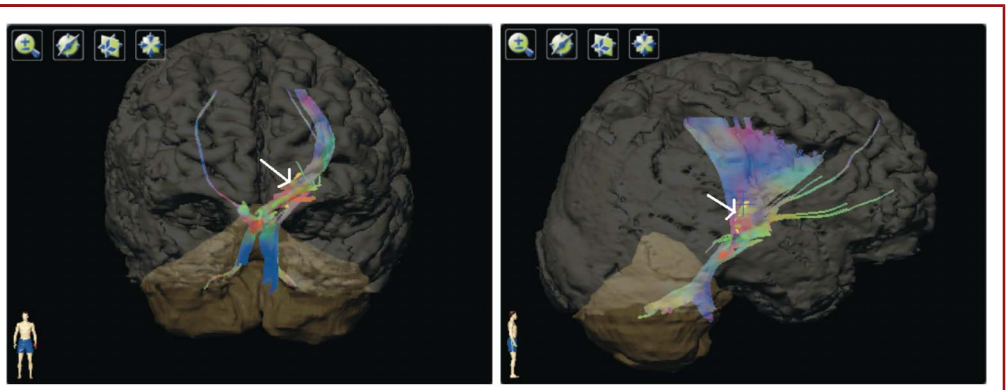

FIGURE 3. *Diffusion tensor imaging of the ventralis intermedius (VIM) nucleus. Demonstration of fibers emerging from thalamus entering the internal capsule and projecting to sensorimotor cortex as well as the cerebellum via the superior cerebellar peduncle. (Fractional anisotropy set at 0.25 and minimum fiber length at 15 mm). Yellow is the electrode drawn as an object passing through the VIM nucleus. White arrow indicates the region where the electrode enters the VIM nucleus.*

CONCLUSION

In this preliminary study, many regions of the brain seen on colored FA maps and DTI can be readily identified and even perhaps used for neurosurgical interventions. MRI is becoming widely available throughout the world and the practice of DBS is rapidly growing; making use of these technologies is key to surgeons. We feel confident that further analysis of these and other data will yield further enlightenment about the precise anatomic detail needed for DBS electrode placement, increasing beneficial effects, and reducing side effects to these patients while enhancing our understanding of brain function.

Disclosures

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COMMENTS

The authors present an original study using diffusion tensor imaging (DTI) and short- and long-range tractography to better delineate the boundaries of the ventralis intermedius (VIM) nucleus and thus facilitate the direct targeting for deep brain stimulation (DBS) electrode implantation. Although the parameters used for DTI (voxel resolution of $2 \times 2 \times 2$ mm^3 with only 12 diffusion gradient directions) do not allow a very detailed study

of the fiber tracts of interest, this methodology certainly improves on the commonly used anatomic analysis using regions of interest, not only for the VIM nucleus, but also for adjacent nuclei such as the ventralis caudalis, ventralia lateralis (Vop-Voa), centromedian, and anterior nuclei of the thalamus, all of which have been proposed as stimulation targets in the treatment of pain and movement disorders, as well as some forms of epilepsy.

We are certain that further refinements and extensions of DTI (in particular as imaging methods provide improvement in spatial and angular resolutions) will allow a detailed study of the fiber connectivity between the basal ganglia and cortical and brainstem structures in humans. This technique, coupled with functional magnetic resonance imaging and positron emission tomography, will perhaps provide important information on the physiology of basal ganglia and on the physiopathology of several neurological disorders.

On the other hand, the nucleus VIM has been considered part of the ventralis lateralis (Walker) and a separate nucleus by Hassler. However, it is not clear whether it is related to proprioceptive sensation as proposed by Jasper and Bertrand on the basis of microelectrode recordings back in the 1970s or to motor function as the rest of VL nuclei (Voa-Vop). Cerebellar fibers have been proposed to end in the posterior part of Vop and not in the VIM nucleus in humans (Tasker).

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The authors studied the utility of fiber tractography derived from DTI for the identification of the VIM nucleus of the thalamus. Color fractional anisotropy (FA) maps were analyzed retrospectively in 4 patients who had placement of DBS electrodes for the control of tremor and in whom low-amplitude stimulation was sufficient for that effect. The VIM nucleus was identified as a purplish zone of color transition between the internal capsule laterally, the internal medullary lamina medially, and surrounding thalamic nuclei.

FA maps of the thalamus and associated white matter tracts have been studied in normal subjects. The importance of this report lies in the lack of a characteristic appearance of the VIM nucleus on anatomic imaging. For purposes of surgical tremor control by lesioning or DBS, the VIM nucleus location is targeted based on ventricular landmarks and confirmed via intraoperative stimulation. Reasonably, the authors selected patients who had an excellent result from DBS, indicating that the electrodes were solidly in the VIM nucleus. Thus, the article can be accused of the circular reasoning that affects many studies of functional imaging, namely, that the FA maps clearly identify the VIM nucleus because that is where the nucleus is supposed to be.

However, this is a preliminary report and paves the way for prospective study of DTI tractography as a means of reliable identification of the VIM nucleus on imaging. If this can be demonstrated, it will be a very useful tool for surgical and possibly radiosurgical procedures for tremor control.

Of course the concept can be applied to other targets not easily identified on "standard" anatomic imaging alone. These images, acquired on a 1.5-T MRI and processed on a commercially available surgical navigation system, are within the reach of anyone doing stereotactic neurosurgery.

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