Contrasting Connectivity of the Ventralis Intermedius and Ventralis Oralis Posterior Nuclei of the Motor Thalamus Demonstrated by Probabilistic Tractography

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BACKGROUND: Targeting of the motor thalamus for the treatment of tremor has traditionally been achieved by a combination of anatomical atlases and neuroimaging, intraoperative clinical assessment, and physiological recordings.

OBJECTIVE: To evaluate whether thalamic nuclei targeted in tremor surgery could be identified by virtue of their differing connections with noninvasive neuroimaging, thereby providing an extra factor to aid successful targeting.

METHODS: Diffusion tensor tractography was performed in 17 healthy control subjects using diffusion data acquired at 1.5-T magnetic resonance imaging (60 directions, b value = 1000 s/mm^2, 2 × 2 × 2-mm^3 voxels). The ventralis intermedius (Vim) and ventralis oralis posterior (Vop) nuclei were identified by a stereotactic neurosurgeon, and these sites were used as seeds for probabilistic tractography. The expected cortical connections of these nuclei, namely the primary motor cortex (M1) and contralateral cerebellum for the Vim and M1, the supplementary motor area, and dorsolateral prefrontal cortex for the Vop, were determined a priori from the literature.

RESULTS: Tractogram signal intensity was highest in the dorsolateral prefrontal cortex and supplementary motor area after Vop seeding ($P < .001$, Wilcoxon signed-rank tests). High intensity was seen in M1 after seeding of both nuclei but was greater with Vim seeding ($P < .001$). Contralateral cerebellar signal was highest with Vim seeding ($P < .001$).

CONCLUSION: Probabilistic tractography can depict differences in connectivity between intimate nuclei within the motor thalamus. These connections are consistent with published anatomical studies; therefore, tractography may provide an important adjunct in future targeting in tremor surgery.

KEY WORDS: Diffusion tensor imaging, Movement disorder surgery, Probabilistic tractography, Thalamus, Tremor

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The thalamus has been established as a target for alleviation of tremor since the middle of the 20th century.[1] Lesioning or continuous stimulation of the motor thalamus achieved reported improvements in essential tremor,[2-6] parkinsonian tremor,[5] Holmes tremor,[7,8] poststroke tremor,[9] and multiple sclerosis tremor.[5,10] The ventralis intermedius (Vim) is the commonest nucleus targeted within the motor thalamus, followed by the ventralis oralis posterior (Vop). The choice of thalamic motor nucleus to target remains controversial in certain circumstances. It is suggested that targeting the Vop is more efficacious for multiple sclerosis tremor[10] and that targeting the Vim in addition to the Vop may provide superior tremor relief in a variety of diseases.[9,11,12] Stereotactic functional neurosurgery depends on the accurate identification

ABBREVIATIONS: DLPFC, dorsolateral prefrontal cortex; **DTI,** diffusion tensor imaging; **PT,** probabilistic tractography; **SMA,** supplementary motor area; **Vim,** ventralis intermedius; **Vop,** ventralis oralis posterior

of anatomically and functionally distinct deep brain structures to maximize therapeutic benefits and to minimize adverse neurological sequelae of any intervention. The Vim and Vop are small nuclei within the ventrolateral thalamus and are intimately related to each other, which increases the challenge of targeting one over the other.

Diffusion tensor imaging (DTI) exploits the brownian motion of water molecules in neural tissue, as determined by brain microarchitecture, to resolve the dominant orientation of fibers in each voxel element.[13-17] The diffusion tensor is a mathematical representation in 3-dimensional space of the diffusion of water molecules in terms of magnitude and directionality.[15,18] The mean longitudinal direction of axons in white matter is represented by the greatest direction of diffusion measured by DTI.[19] Probabilistic tractography (PT) infers the most probable directionality and continuity of fiber paths from voxel to adjacent voxel to track and depict the whole white matter pathway on the basis of these orientation and magnitude data.[15] Although injected tracer studies remain the gold standard for fiber tracking, they are restricted to nonhuman subjects for obvious reasons. However, PT allows pathways within the human brain to be traced and visualized noninvasively. These images have the added advantage for surgeons in that they can be displayed intraoperatively and navigated with the use of stereotactic software. Diffusion tensor imaging has been carefully applied to the connections within the basal ganglia and the segmentation of the thalamus.[20-22]

The aim of this study was 2-fold: to test the ability of DTI PT to identify differences in connectivity between these 2 small, intimately related nuclei in different individuals and to delineate the currently recognized connectivity of the Vim and Vop nuclei in human control subjects with a view to supporting its use in aiding the planning and performance of stereotactic movement disorder surgery.

The nomenclature applied to the nuclear subdivisions of the motor thalamus has varied between authors and between species. On the basis of cytoarchitectural, myeloarchitectural, and chemoarchitectural criteria, Macchi and Jones[23] correlate the Hassler[24] Vop and Vim nuclei to the Hirai and Jones[25] anterior ventral lateral nucleus and ventral part of the posterior ventral lateral nucleus, respectively. There is debate as to whether the true connectivity of the Vim and Vop nuclei comprises more overlap than is recognized. Horseradish peroxidase conjugated to wheat agglutinin with biotinylated dextran amine injections in the macaque cerebellum anterogradely labeled predominantly the Olszewski oral ventral posterior lateral nucleus, embodying the Vim,[23] and area X, embodying the Vop nucleus, and, after pallidal injections labeling, was also seen in the Vim and Vop, albeit sparsely.[26] Hassler presumed that the Vop was the cerebellar receiving area,[24,27,28] whereas others dispute this.[23] The generally accepted wisdom is that the Vim is the cerebellar receiving area of the thalamus and the Vop is the pallidal receiving area.[23,29] Therefore, we hypothesized that seeding of the Vim would exhibit the highest probability of connections with the primary motor cortex and contralateral cerebellum and that seeding of the Vop would exhibit the highest probability of connections with the cortical destinations of the pallidofugal fibers, namely the supplementary motor area (SMA) and dorsolateral prefrontal cortex (DLPFC), and then the primary motor cortex.

METHODS

Diffusion-weighted data were acquired from 17 healthy control subjects who were specifically not known to have an underlying neurological diagnosis on a 1.5-T Siemens magnetic resonance imaging (MRI) scanner (echo-planar imaging; field of view, 256 × 208 mm; matrix, 128 × 104; slice thickness, 2 mm; in-plane resolution, 2 × 2 mm; repetition time, 15 seconds; echo time, 106.2 milliseconds). The diffusion weighting was isotropically distributed along 60 directions with a b value of 1000 s/mm^2. For each set of diffusion-weighted data, 5 volumes with no diffusion weighting were acquired at points throughout the acquisition. Three sets of diffusion-weighted data were acquired for subsequent averaging to improve the signal-to-noise ratio. The total scan time for the diffusion-weighted imaging protocol was approximately 45 minutes.

A high-resolution T1-weighted structural image was also obtained with a 3-dimensional FLASH sequence (repetition time, 12 milliseconds; echo time, 5.6 milliseconds; flip angle, 19°, with elliptical sampling of k space, giving a voxel size of 1 × 1 × 1 mm in 5.05 minutes). Images were analyzed with tools from the fMRIB Software Library (www.fmrib.ox.ac.uk/fsl).[30,31] Nonbrain tissue was extracted from the image with the brain extraction tool. Diffusion data were analyzed with the fMRIB diffusion toolbox as previously described.[32]

A movement disorder neurosurgeon (T.Z.A.) specified the location that would normally be targeted as the Vop and then the Vim nuclei. The stereotactic coordinates used were those historically used by our neurosurgical service to target the thalamic motor nuclei to treat tremor.[10,33] Relative to the midpoint of the anterior commissure-posterior commissure line, the Vop coordinates were 11 mm laterally (x), 0 mm anteroposteriorly (y), and 0 mm vertically (z); the Vim coordinates were 13 mm laterally (x), −4 mm anteroposteriorly (y), and 0 mm vertically (z). Figure 1 shows an example of these coordinates in a preoperative plan of a tremor patient. On the basis of these coordinates, 2 seed masks were plotted in each subject. The thalamus of the left hemisphere was studied in each patient. This procedure was then repeated separately for all subjects. Each seed was 1 voxel in size measuring 2 × 2 × 2 mm on the DTI. Nonlinear registration was used to warp the seed data into the correct area, thus avoiding the inclusion of streamlines from adjacent voxels in the results. The fMRIB diffusion toolbox was then run from each seed area with 5000 streamlines per seed voxel.

Transformation from diffusion space to standard space was performed with the ApplyXFM tool in the fMRIB Software Library. The resulting tracts were then combined and divided to give an average of tracts from both the Vim and the Vop seed areas. These were then overlaid onto the Montreal Neurological Institute 152 two-millimeter standard brain image. Tractograms were analyzed after thresholding between a minimum of 10 and maximum of 500 streamlines per voxel. The thresholding figures were chosen to aid visualization of the tracts.

A quantitative analysis was performed whereby the highest intensity (in arbitrary units) within the probabilistic tractogram at a point (highest intensity 2 × 2 × 2 mm voxel when overlaid on Montreal Neurological Institute 2 mm-slice standard brain) was recorded within each area: DLPFC, SMA, M1, and contralateral cerebellum. The quantitative

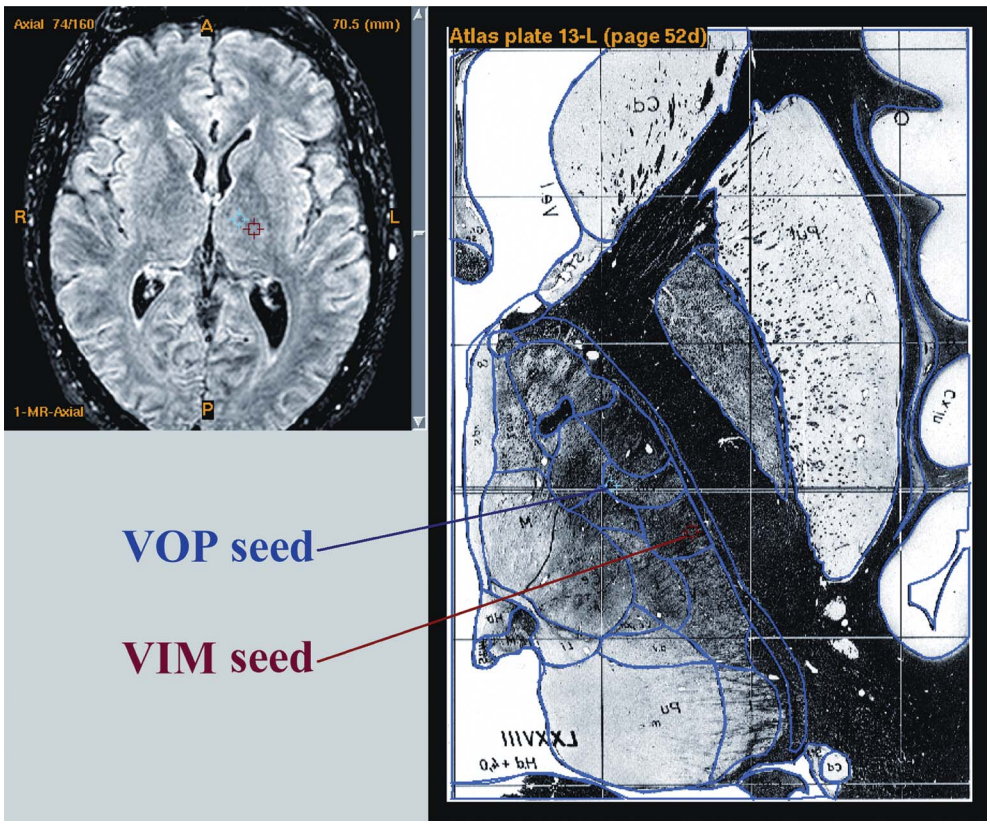

FIGURE 1. *Preoperative stereotactic plan (StereoPlan, Radionics Inc, Burlington, Massachusetts) in an illustrative case of a patient undergoing thalamic stimulation for intractable tremor. The locations of the ventralis oralis posterior (Vop) nucleus (blue target) and ventralis intermedius (Vim) nucleus (red target) are demonstrated on an axial preoperative T2 fluid-attenuated inversion-recovery magnetic resonance imaging (left) and Schaltenbrand and Wahren[24] atlas (right).*

analysis was performed with the individual tracts in each subject. In addition, to qualitatively reflect the consistency/reproducibility of the individual subject's results as a whole, the combined tracts for all subjects for both Vim and Vop seed sites were also prepared by combining all the tracts for each subject and dividing by the number of subjects to produce an average for each seed site. These were then overlaid onto the standard brain image.

Statistical Analysis

Data were analyzed with the Statistical Package for Social Sciences (SPSS) version 12. The means of PT intensity between the Vim-seeded and Vop-seeded tractograms for each subject in each of the 4 areas were compared. Statistical significance was accepted with a confidence level of 99%.

RESULTS

An example of the Vim and Vop seed locations is shown in a single subject in Figure 2A. The distribution of the probabilistic tractograms within the DLPFC, SMA, M1, and contralateral cerebellum after Vim and Vop seeding is presented graphically in Figure 2B through 2D. Figure 3 depicts the group-averaged results and shows the consistency with individual results for both seeds across all 17 subjects (a minimum threshold of 30 was used owing to the use of multiple tracts to aid visualization).

Data were assessed for normality with the Kolmogorov-Smirnov test, which demonstrated that the data were not normally distributed. The nonparametric Wilcoxon signed-rank test for related samples was therefore used to compare Vim-seeded vs Vop-seeded PT means within each area. In all subjects, Vop-seeded tractograms generated higher intensity compared with the Vim-seeded tractograms in the DLPFC and the SMA. The median ± SD highest intensity in the Vop-seeded tractograms compared with the Vim-seeded tractograms was 109.0 ± 206.7 (range, 11-894) vs 8.0 ± 33.7 (range, 0-95), respectively, in the DLPFC and 455.0 ± 286.0 (range, 77-1232) vs 20.0 ± 41.9 (range, 0-140), respectively,

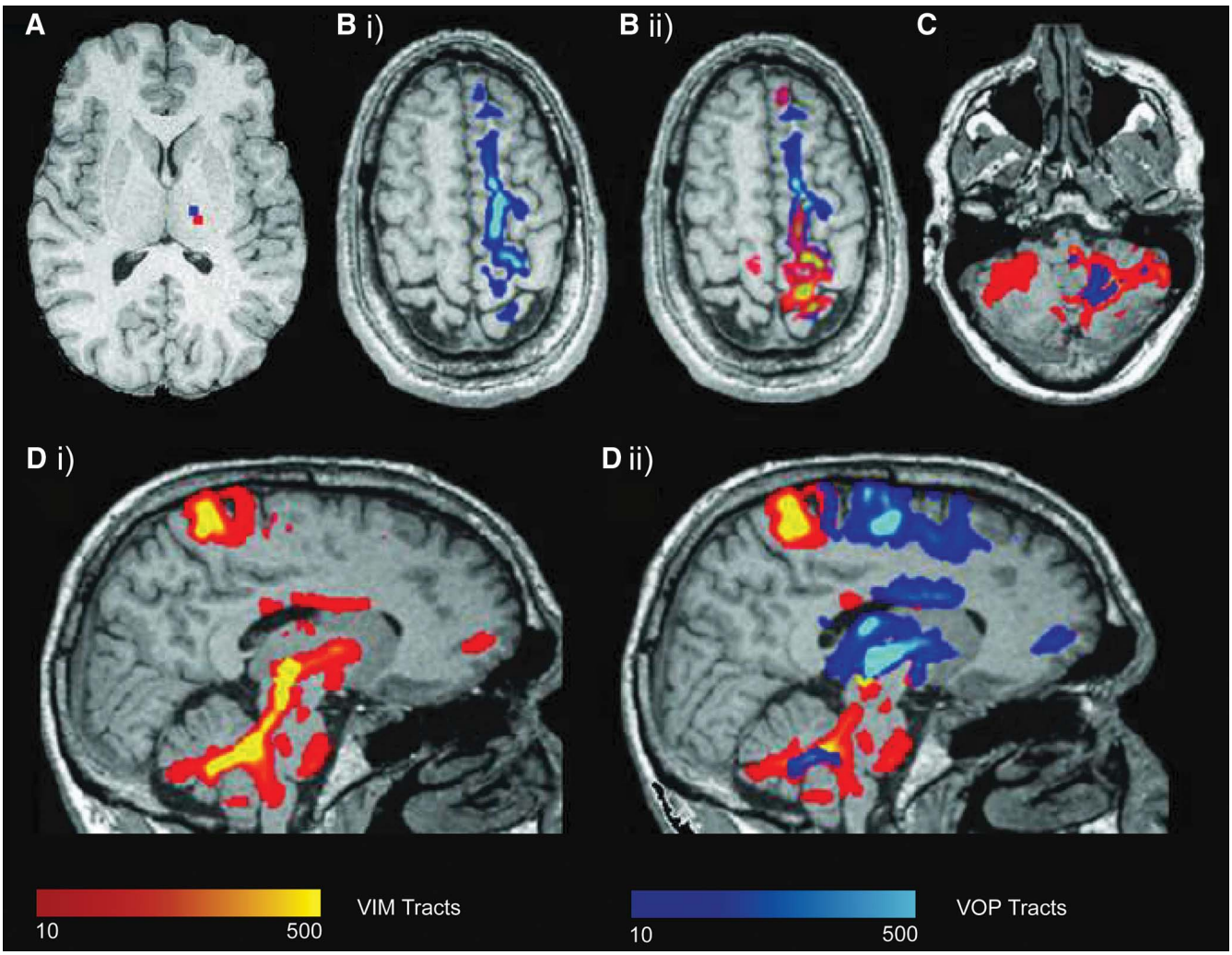

FIGURE 2. **A**, *axial T1 magnetic resonance image showing left ventralis intermedius (Vim; red) and ventralis oralis posterior (Vop; blue) seeds.* **B** *through* **D**, *probabilistic tractograms generated in 1 individual.* **B**, *axial sections after (i) Vop seeding with probabilistic tractography connections to primary motor cortex (M1), supplementary motor area (SMA), and area 9 of the prefrontal cortex and (ii) Vim seeding superimposed with tractogram connections predominantly in M1 and to a lesser extent in SMA.* **C**, *axial section demonstrating right contralateral cerebellar tractogram connections after Vim seeding only (left ipsilateral cerebellar connections are artifactual).* **D**, *sagittal sections after (i) Vim seeding showing tractogram connections in M1 and (ii) Vop seeding superimposed showing tractogram connections with SMA, prefrontal cortex, and to a lesser extent M1.*

in the SMA. These differences were highly statistically significant ($z = -3.622$, $P < .001$; and $z = -3.621$, $P < .001$, respectively). In all subjects, Vim-seeded tractograms generated higher intensity compared with the Vop-seeded tractograms in the M1 and the contralateral cerebellum. The median ± SD highest intensity in the Vim-seeded tractograms compared with the Vop-seeded tractograms was 894.0 ± 498.1 (range, 405-2209) vs 247.0 ± 193.6 (range, 18-619), respectively, in the M1 and 44.0 ± 40.2 (range, 0-145) vs 0.0 ± 16.2 (range, 0-50), respectively, in the contralateral cerebellum. These differences were highly statistically significant ($z = -3.621$, $P < .001$; and $z = -3.517$, $P < .001$, respectively; Table).

Both Vop and Vim seeds generated high intensity in the ipsilateral cerebellum; however, of the 4 cerebellar nuclei, it is known from anatomic studies that only the fastigial nucleus projects fibers to its ipsilateral and contralateral thalami (ventral lateral nucleus in monkeys).[23,27] It is unlikely that these tracts are dense enough to explain the PT intensity seen in our results. Because it is not expected to be strongly connected to the Vim or Vop nuclei in this a priori investigation, the ipsilateral cerebellum was not included in the analysis.

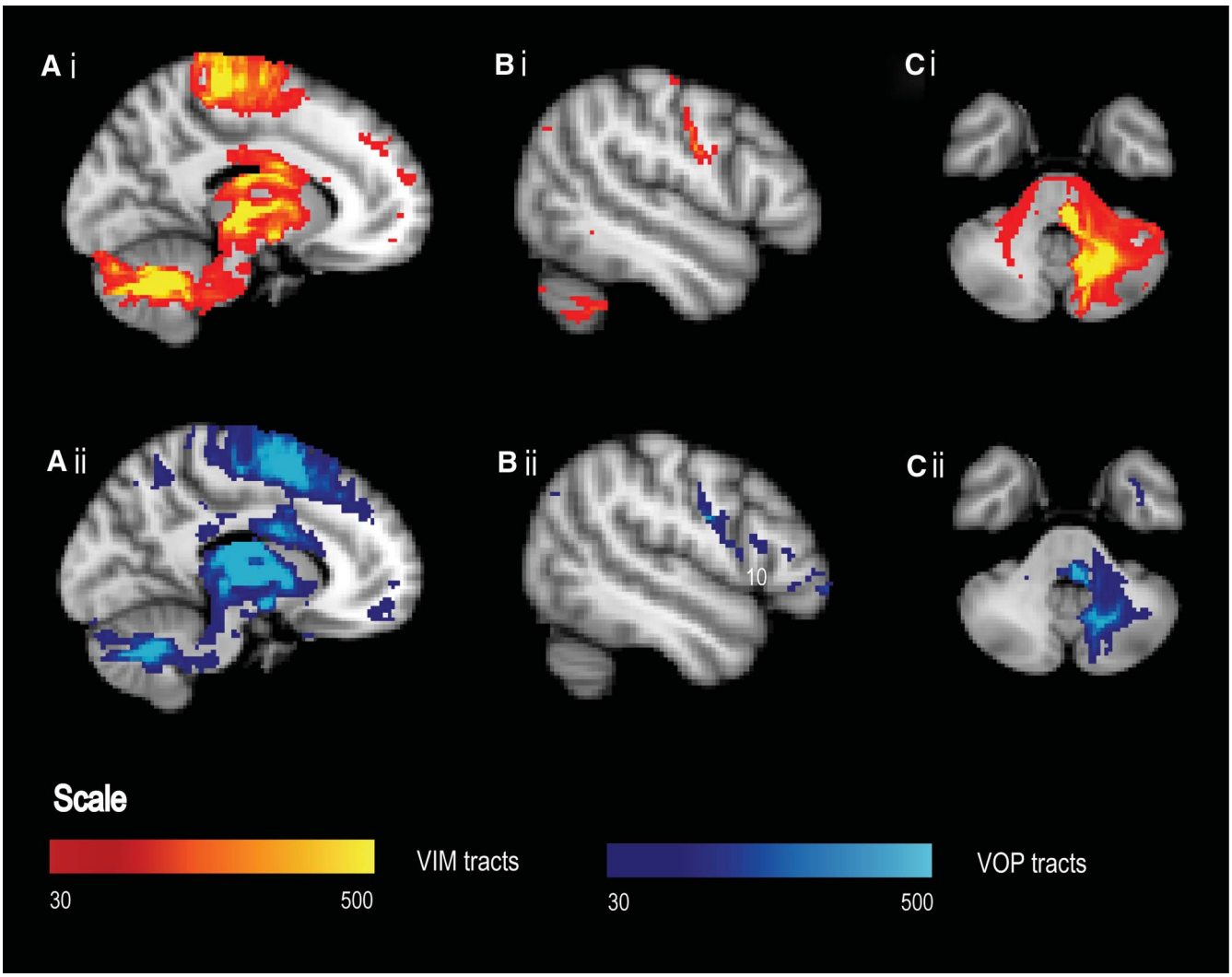

FIGURE 3. **A** *through* **C**, *probabilistic tractograms averaged across the group of 17 subjects.* **A**, *sagittal sections after (i) ventralis intermedius (Vim) seeding with tractogram connections to the primary motor cortex (M1) and (ii) ventralis oralis posterior (Vop) seeding with tractogram connections to M1 and the supplementary motor area (SMA).* **B**, *lateral view depicting greater tractogram connections to the dorsolateral prefrontal cortex after (ii) Vop seeding than (i) Vim seeding.* **C**, *axial sections after (i) Vim seeding showing greater contralateral (right) cerebellar tractogram connections than after (ii) Vop seeding.*

DISCUSSION

We have shown that DTI PT can identify differences in connectivity between the Vim and Vop nuclei despite their small size and anatomic intimacy. The thalamus has been studied in the past with DTI with the aim of providing new data on human brain connectivity[34]; however, in this study, we tested the ability of DTI to confirm human anatomic connections previously established using gold standard tracing techniques in nonhuman primates. We have accordingly also shown that the PTs generated from seeding the 2 nuclei showed connections to areas consistent with those already demonstrated by clinical and animal studies to indeed be connected to the Vim and Vop.

Seeding of the Vim in our study showed connections predominantly to the M1 and contralateral cerebellum compared with the results of Vop seeding, which is consistent with the published literature. The Vim is generally accepted to be the cerebellar receiving area of the thalamus before the fibers are projected to the primary motor cortex.[23,27,28] Retrograde transneuronal transport of herpes simplex virus-1 from M1 injections in macaques stains both the cerebellum and globus pallidus.[35] Seeding of the Vop in our study showed connections predominantly to the M1, SMA, and DLPFC cortexes. This

TABLE. Median Highest Intensities Within Probabilistic Tractograms After Ventralis Intermedius or Ventralis Oralis Posterior Nucleus Seeding[a]

	Median Highest Intensity (Range)		
	Vim	Vop	*P*
Dorsolateral prefrontal cortex	8.0 (0-95)	109.0 (11-894)	<.001[b]
Supplementary motor area	20.0 (0-140)	455.0 (77-1232)	<.001[b]
Primary motor cortex	894.0 (405-2209)	247.0 (18-619)	<.001[b]
Contralateral cerebellum	44.0 (0-145)	0.0 (0-50)	<.001[b]

[a]Vim, ventralis intermedius; Vop, ventralis oralis posterior.
[b]Significant.

distribution of connections is in agreement with animal studies. The Vop is recognized to be the thalamic relay for pallidofugal fibers. These fibers leave the globus pallidus as the ansa lenticularis and fasciculus lenticularis before combining to form the fasciculus thalamicus, which enters the thalamus[35,36] from where the pallidal output is projected to the cortex. Connections form the globus pallidus to the SMA[27,37-41] and DLPFC (Brodmann area 9 of the superior frontal gyrus and Brodmann area 46 of the middle frontal gyrus) and are well described in animal studies,[37,42] including the performance of cortical injections of viral tracers in macaques.[35]

In this study, although we did not use physical localization in individual cases and investigated control subjects rather than patients undergoing tremor surgery whose clinical outcomes we could later validate, we have used the same stereotactic coordinates used in our neurosurgical service, which have been shown to significantly improve tremor severity by up to 95%.[10,33] Generation of probability maps of cortical connectivity by selecting the entire thalamus is an alternative to the approach we have used.[34] Further study is required to test these methods in the other thalamic regions of surgical interest such as the sensory and anterior thalamic nuclei for pain and epilepsy surgery, respectively.

Tractography has been applied in the clinical neurosciences for several years; DTI has been used to predict outcome from neurological conditions such as intracerebral and pontine hemorrhage.[43,44] Tractography, together with functional MRI and magnetoencephalography, promises to play a vital role in the future of "functional neuronavigation" in which information illustrating not just the intracranial anatomy but also its functional significance in the individual is presented to the surgeon. Neurosurgical planning and performance for conditions such as glioma and cavernoma have already successfully incorporated tractography into its armamentarium in that subcortical eloquent white matter tracts can be revealed with the intention of minimizing the incidence of postoperative neurological deficits.[19,45-47] For example, knowledge of whether a tumor incorporates corticospinal tract or causes it to deviate around it has enormous implications for the resection strategy and the expectations of the extent of cytoreduction possible.

Large ipsilateral cerebellar connections were shown with both Vim and Vop seeding; however, the existing literature recognizes only a weak connection with the cerebellar fastigial nucleus in monkeys.[23,27] A number of explanations for this discrepancy are possible. It is perhaps possible that these connections in the studied human subjects were stronger than those predicted by animal studies. We take a conservative approach to the analysis of DTI data, however, and suggest that they may be inaccuracies in the predictions by the PT technique itself. The generated tractograms fundamentally reflect only the paths of least resistance to the movement of water molecules rather than necessarily actual neuronal pathways. Inherently, PT provides only a likelihood of a neuronal connection unlike tracer staining studies; hence, we performed an a priori analysis that considered only brain areas that have been accepted by prior literature to be connected to the Vim or Vop nuclei. Without such anatomic data to support the ipsilateral cerebellum being strongly connected to the motor thalamus, we refrain from making any claims regarding the importance or usefulness of these tractographic connections. It is possible that the ipsilateral cerebellar connections shown are artifacts secondary to interference by the large white matter tracts converging on the brainstem from other circuits. Given the size of the seed voxels, it is possible that some internal capsule fibers may have been included despite all efforts to ensure that seeds did not contain streamlines from adjacent voxels such as those of the internal capsule. This may have resulted in loss of voxel-to-voxel directionality at the corticopontocerebellar level, which may possibly also have accounted for the increased M1 connectivity of the more lateral Vim nucleus. Thresholding of tractographic data can be arbitrary in nature and adds another potential level of error to PT data. Accepting only tractograms at a higher probability threshold may have "removed" such ipsilateral cerebellar connections. However, we were careful to be consistent across all studied subjects, and exactly the same threshold levels were used before the quantitative analysis was performed in each case. An alternative explanation is that the seed voxels were indeed entirely intrathalamic and that directionality may have been lost elsewhere in the brainstem where multiple white matter tracts converge. The size of seed voxels used in this study was a limitation; however, it is reassuring that despite this limitation, the differential pattern of cortical connectivity from the Vim and Vop seeds was consistent with that predicted by the literature.

It is desirable that functional neurosurgery should exploit any new modality for the sake of patient benefit and safety and therefore should seize the advantages tractography promises. During targeting of the motor thalamus, the ability to discriminate between the Vim and Vop by use of their signature connection pattern rather than simply their appearance on MRI should greatly increase the chance of targeting the desired nucleus. Although there will inevitably be some

anatomic variation between individuals, this study has shown that within the cortical and cerebellar areas accepted to be connected to the respective nuclei, all subjects showed a convincing predominance in tractogram intensity for 1 nucleus over the other. Before the technique is embraced by the functional community, it is important that forthcoming investigation prospectively repeats this study with validation in patients undergoing tremor surgery, randomized to DTI or non-DTI targeting, allowing intraoperative and postoperative evaluation. This technique will be required to be efficacious and reliable as an additional targeting tool in tremor surgery before being widely applied clinically. The technology currently exists for this to be implemented with its incorporation into preoperative and intraoperative navigation methods in stereotactic functional surgery.

Disclosures

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COMMENTS

Functional neurosurgeons increasingly use structural magnetic resonance imaging (MRI) to visualize and directly target anatomic structures.[1-3] However, the subnuclei of the thalamus are not reliably identified on MRI at 1.5 T. Hyam et al present an interesting study that uses probabilistic tractography to examine unilateral thalamic connectivity in 17 healthy control subjects. Seed voxels were selected using atlas coordinates applied to structural MRIs at 1.5 T to estimate the location of ventralis oralis posterior and ventralis intermedius territories; the resulting connectivity patterns were then compared.

The utility of such an approach in delineating the thalamic target in functional neurosurgery is limited by a number of factors. The dispute concerning anatomic terminology and connectivity of thalamic subnuclei is mentioned in the article.[4,5] There is inevitable variability in seed voxel selection within the motor thalamus,[6] and the seed voxel size in this study approaches the widely accepted tolerance level for accurate stereotactic targeting in functional neurosurgery (2 mm).[7-9] Nevertheless, the motor thalamus may be more lenient to surgical inaccuracies than other brain targets with respect to clinical outcome.[10] Although the results of this study are broadly in keeping with known anatomic pathways, anomalies in connectivity strength with ipsilateral cerebellum reveal the limitations of the technique in its current format. Systematic parcellation of the human thalamus with tractography has offered an alternative approach when attempting to define thalamic subnuclei.[11,12]

Tractography certainly holds promise as a potential additional tool that may assist functional neurosurgeons when targeting relevant anatomical structures. Issues of MRI distortion and errors of fusion will need to be addressed if tractography data are to be incorporated into stereotactic target selection. Studies documenting added clinical value to patients are required before the functional neurosurgical community embraces such techniques in clinical practice.

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The authors show that with diffusion tensor imaging probabilistic tractography, the ventralis intermedius (Vim) ventralis oralis posterior (Vop) can be distinguished by their connectivity to the frontal lobe and cerebellum. Because, except for some recent studies of very high-field strength,[1] it is not possible to visualize Vop and Vim on magnetic resonance imaging scans, this provides a potential way to identify these nuclei definitively on imaging. Of course, it remains to be seen how well this technique can be implemented in routine clinical practice and its clinical results. In addition, the Vim is a relatively easy target for deep brain stimulation implantation with a variety of planning and neurophysiological control techniques, whereas Vop is a rarely targeted nucleus for deep brain stimulation. On the other hand, it may be underused and is a potential target for thalamotomy in Parkinson disease (eg, see Reference 2). Moreover, this technique might be extended to visualization of ventralis oralis connectivity, which may be of use in secondary dystonia.[3]

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