Deep brain stimulation (DBS) is an effective option for treatment-refractory essential tremor (ET).4,21,26 Apart from other targets, the dentatorubrothalamic tract (DRTT) has been suggested as the anatomical substrate for stimulation-induced tremor alleviation based on deterministic diffusion tensor imaging (DTI) tractography results.11,12,25,31

Current knowledge about the anatomical course of the DRTT is mainly derived from data in monkeys.2,27 The DRTT projects from the deep cerebellar nuclei mainly...
to the contralateral thalamus, courses through the superior cerebellar peduncle, decussates, and passes through and anterior to the red nucleus (RN) before reaching the ventral thalamus. In humans, important knowledge about the anatomical course of the DRTT in the subthalamic region comes from a microanatomical analysis of the postmortem brain by Gallay and coworkers\(^{18}\) and Morel’s atlas of the human thalamus and basal ganglia\(^ {22}\) (according to their nomenclature, the DRTT is named “fasciculus cerebellothalamicus” [fct]). In previous studies, different methods for DTI-based fiber tracking of the DRTT have been described; however, the fiber tracking data obtained using these different methods have been evaluated in only a limited number of patients, and it is not known to what extent the tracked fibers correspond to the anatomical DRTT.\(^ {11,12,19,31}\) This may have an impact on the comparability between different study results and their corresponding conclusions. Furthermore, the DRTT is anatomically close to the medial lemniscus (ML) at the level of the midbrain. Therefore, fiber tracking results aiming to represent the DRTT must reliably respect anatomical segregation from the ML.

Given previous studies reporting different methodologies for fiber tracking of the DRTT, the objective of our study was to systematically investigate the results of different tractography approaches using commercially available software, for surgical planning. The tractography methodologies and their results are assessed in terms of feasibility and accuracy in displaying the DRTT as well as its relation to the ML in each patient. Additionally, tracking results are correlated to both the anatomical DRTT based on the Morel atlas and the clinical outcome measure.

**Methods**

**Patients**

We retrospectively analyzed 6 patients (2 male, 4 female; mean age 70 ± 10 years) with ET who had undergone bilateral implantation of DBS electrodes into the ventral intermediate nucleus (Vim) of the thalamus. All patients provided written informed consent before the entire procedure. The study protocol was approved by our local ethics committee.

**Magnetic Resonance Imaging**

Preoperative imaging was performed with a 3-T MRI system (MAGNETOM Trio Tim, Siemens). Multiecho, fast spin echo T2-weighted sequences were obtained using the following parameters: 28 contiguous coronal slices, slice thickness 2 mm, FOV 220 mm, acquisition matrix 128 × 128, TR 2000 msec, and multiple TEs ranging from 12 to 96 msec in 12-msec steps. These sequences were coregistered with the DTI sequences acquired in each patient: gradient directions 12, slice thickness 2.2 mm, 55 slices, TR 10,100 msec, TE 88 msec, FOV 280 mm, matrix 256 × 256, and b value 1305 sec/mm\(^2\).

**Fiber Tracking**

The anterior commissure (AC) and posterior commissure (PC) were identified manually, and images were adjusted according to the AC-PC line. Deterministic fiber tracking based on DTI was performed using iPlan NET 3.0 software (Brainlab AG). The T2-weighted and diffusion-weighted sequences were fused by applying a rigid fusion algorithm. The DTI sequences were automatically corrected for eddy current distortions and head motion. The software allows one to define an arbitrary number of regions of interest (ROIs) and to adjust the minimum fiber length as well as the minimum value of fractional anisotropy (FA).

Fiber tracking of the bilateral pyramidal tract (PT) was performed. Three ROIs were anatomically defined based on T2-weighted sequences: a cuboid box was constructed covering the precentral gyrus, identified according to the Yousry criteria\(^ {35}\) (Fig. 1A); a second cuboid box was constructed covering the genu and the posterior part of the ipsilateral internal capsule at the level of the striatum; and a manually segmented ROI constituting the ipsilateral lateral two-thirds of the cerebral peduncle was selected. Minimal fiber length was set at 40 mm, and the FA value was set between 0.29 and 0.37, resulting in the depiction of only 1 homogeneous fiber bundle.

The ML was tracked by applying 3 ROIs: a cuboid box was constructed along the postcentral gyrus, analogous to the box constructed for the ROI for tracking the PT; a second cubic box including the posterior crus of the ipsilateral internal capsule and a third semilunar-like ROI were constructed on axial slices at the level of the inferior colliculus covering the lateral aspect of the tegmentum, posterolateral to the substantia nigra and RN (Fig. 1H). Minimal fiber length was set at 40 mm and FA was set between 0.28 and 0.33, depending on the tracking results in each individual patient, leaving exclusively 1 homogeneous fiber bundle within all 3 ROIs and ignoring fibers passing into the cerebellum. In the text sections below, the abbreviation “ML” will be used to refer to fiber tracking results of the medial lemniscus, as opposed to “ml,” which will refer to the Morel atlas–based medial lemniscus.

Fiber tracking of the DRTT was performed according to 4 different approaches adapted in part from previous work by other groups.

**Method 1**

Three different ROIs were defined: the manually segmented dentate nucleus of the ipsilateral cerebellum, the ipsilateral superior cerebellar peduncle, and a cubic box including the ipsilateral precentral gyrus (Fig. 1A, C, and D). The ROIs as well as the tracking parameters were adapted from the previous work of Coenen et al.\(^ {11,12}\) Minimum fiber length was set at 20 mm, and the FA value was primarily set at 0.2 and, consequently, was adapted to display only 1 homogeneous fiber bundle included in all 3 ROIs while ignoring anatomically implausible fibers.

**Method 2**

Three different ROIs were defined based on T2-weighted images: first, the manually segmented contralateral dentate nucleus based on all axial slices showing its contours; second, the manually segmented contralateral superior cerebellar peduncle on sagittal slices; and, third, a cubic box covering the ipsilateral RN (Fig. 1C–E). The ROIs as well as the tracking parameters were adapted from pre-
previous work by Kwon and coworkers,\textsuperscript{20} as well as Schlaier et al.\textsuperscript{31} The minimum fiber length was set at 30 mm, and the FA value was primarily set at 0.15 and, consequently, was adjusted to display only 1 homogeneous fiber bundle.

Method 3

Two different ROIs were defined on T2-weighted imaging: the manually segmented dentate nucleus of the ipsilateral cerebellum and a second manually segmented ipsilateral region in the posterior subthalamic area (PSA). The area was defined in the axial plane at the level of the maximum diameter of the RN to include the white matter anterolateral to the RN and medial-posterior to the subthalamic nucleus (STN) corresponding to the caudal zona incerta and fct as described in the Morel atlas\textsuperscript{22} (Fig. 1F). Minimum fiber length was set at 30 mm, and the FA value was adjusted to display 1 homogeneous fiber bundle included in both ROIs.

Method 4

This approach was equal to method 3, except that a third ROI comprising the ipsilateral precentral gyrus including the hand notch was introduced (Fig. 1A, D, and F). Minimum fiber length was set at 30 mm, and the FA value was adjusted to display 1 homogeneous fiber bundle included in all 3 ROIs.

Image Analysis

The anatomical course and position of the fibers in each patient were analyzed with respect to their spatial relationship to the STN and the RN. Both structures were used to define the PSA on axial T2-weighted slices at the level of the maximum diameter of the RN (Fig. 2).

The lateral (LAT) and anteroposterior (AP) stereotactic coordinates with reference to the midcommissural point of the center of the different fiber bundles were determined at 3 different levels: 3.6 mm below the AC-PC line (vertical [VERT] $-3.6$ mm), 1.8 mm below the AC-PC line (VERT $-1.8$ mm), and at the level of the AC-PC line (VERT 0 mm). The mean position of the center of each fiber bundle, as well as its corresponding 95% confidence interval, was calculated and projected onto axial planes of the Morel atlas at the corresponding levels (VERT $-3.6$, $-1.8$, and 0 mm)\textsuperscript{38} and compared with the position of the fct.

Target Planning and Active Contact Determination

Targets were visually identified on axial T2-weighted slices based on anatomical landmarks in the PSA, according to the method of Blomstedt et al.\textsuperscript{5} The postoperative active contact position was determined as previously described by our group.\textsuperscript{24} The distance between the active electrode contact and the center of each DRTT tractography model was analyzed in each patient.

Correlation Between Clinical Outcome and Distance From DRTT to Active Contact

Specialized movement disorder neurologists assessed in a nonblinded fashion the preoperative off-medication and 12-month postoperative on-stimulation/off-medication tremor severity by using the Fahn-Tolosa-Marin tremor rating scale (TRS). Part A and B subscores were determined separately for each side of the body. The improvement in the compound Part A and B TRS subscores for each side of the body was correlated to the distance between the active contact position and each of the 4 DRTT tracking method results for the corresponding contralateral hemisphere.
Statistical Analysis

Data were analyzed using Prism 6 software (GraphPad). The Shapiro-Wilk normality test was used to test for normal distribution of data sets. A 2-way ANOVA was performed for statistical analysis of the mean positions of the different fiber bundle centers at the 3 investigated levels (VERT = −3.6, −1.8, and 0 mm). Post hoc analysis was performed by applying Tukey’s multiple comparison test. A paired 2-sided t-test was applied to test for differences between method 1 tracking results and ML tracking results. Data are presented as the mean ± standard deviation or 95% confidence intervals. A p value < 0.05 was considered statistically significant.

Results

Tracking Results for the PT and ML

Both the PT and ML could be displayed in 100% of the cases. The mean FA value to visualize the PT was 0.32 ± 0.03. Fiber tracking of the ML required a mean FA value of 0.34 ± 0.05. Tractography results for the PT projected onto the internal capsule at all 3 vertical levels of the Morel atlas (Fig. 3A–C). The mean position of the tracked ML was anatomically close to the ml based on atlas data at the level VERT = −3.6. At the level VERT = −1.8 mm, ML tractography results were displayed anterior to the atlas-based ml. At VERT 0 mm, the tracked ML projected onto the somatosensory part of the thalamus.

Fiber Tracking of the DRTT and Variability in the FA Value

The 4 different methodologies to track the DRTT led to macroscopically plausible and implausible tracking results (Fig. 4). Different FA values were required to visualize the DRTT (Table 1). The lowest FA values had to be selected in method 2 (0.16 ± 0.06) to display crossing fibers. The FA values were higher and typically in the range of 0.2–0.46 for the 3 other tracking methods, which did not display crossing fibers.

DRTT Stereotactic Coordinates and Projection Onto the Morel Atlas

Stereotactic coordinates for the center of each fiber bundle were determined at 3 different VERT levels. The mean values for each tracking methodology are presented in Table 2. Two-way ANOVA revealed statistically significant different mean LAT and AP coordinates for the tracked fibers at the different levels (p < 0.001 LAT coordinate, p = 0.002 AP coordinate) and for the 4 different tracking methods (p < 0.001 LAT coordinate, p = 0.02 AP coordinate; Table 3). Post hoc analysis by applying Tukey’s multiple comparison test revealed statistically significant differences in the mean LAT coordinates between all methods except between methods 2 and 3 (Fig. 3D). With respect to the mean AP coordinates of the tracked fibers, a statistically significant difference was only found between methods 1 and 2 (Fig. 3E).

The mean tract position and 95% confidence interval for the LAT and AP directions were projected onto axial slices at the corresponding levels on the Morel atlas. At VERT = −3.6, the mean center of method 1 tracking results projected lateral to the atlas-based fct and covered parts of the internal capsule and the STN (Fig. 3A). Further, the mean fiber position came close to the tracking results for the ML. At the more superior levels (VERT = −1.8 and 0), the tracking results for method 1 kept the anatomical relation mainly at the lateral aspect of the atlas-based fct and covered large parts of the somatosensory thalamus (ventral posterolateral nucleus [VPL]) as well as the ventrolateral posterior part of the thalamus (VLp) corresponding to the Vim.
Tracking results of method 2 covered parts of the RN as well as large parts of the atlas-based fct at the level VERT −3.6 mm (Fig. 3A). At VERT −1.8 mm, tractography results covered the anterior aspect of the atlas-based fct. At VERT 0 mm, tractography results almost exclusively covered the ventrolateral anterior part of the thalamus (VLa) and the VLp (corresponding to the Vim).

Method 3 tracking results covered the atlas-based fct.
at the lower levels VERT −3.6 and −1.8 mm (Fig. 3A–C). At VERT 0 mm, the mean fiber bundle position was located mainly anterior to the atlas-based fct and projected mainly onto the atlas-based medial nucleus of the thalamus (VM).

Tracking results of method 4 corresponded to the atlas-based fct at all 3 vertical levels (Fig. 3A–C). The mean fiber bundle position was projected onto the posterior part of the atlas-based fct at VERT −3.6 and passed progressively anterior at more superior levels to reach and almost entirely cover the VLp (corresponding to the Vim) at VERT 0.

**Individual Fiber Anatomy With Respect to the PSA**

Analysis of individual fiber anatomy related to the PSA in each patient showed that fiber bundles tracked using method 1 passed the PSA in 50%, while fibers tracked using methods 2, 3, and 4 passed the PSA in 58%, 58%, and 67% of cases, respectively (Table 4).

**Preoperative Target and Active Contact Position**

The mean preoperative target coordinates were LAT 10.38 ± 0.92, AP −5.27 ± 0.89, and VERT −3.05 ± 0.22 mm. The mean active contact positions were LAT 10.31 ± 1.26, AP −4.39 ± 0.66, and VERT −2.23 ± 1.65 mm.

**Clinical Outcome and Correlation With DRTT Tractography Results**

The mean preoperative combined (bilateral) TRS score was 51.2 ± 15.1. The mean postoperative combined TRS score was significantly reduced to 21.3 ± 12.9 (p = 0.004). Unilateral improvement scores were not significantly correlated to the distance between the active contact and any of the 4 DRTT tracking method results for the corresponding contralateral hemisphere. Method 1 tracking results showed the highest variability in the distance to the active contact, ranging from 0.8 to 6.1 mm, as compared with method 2 tracking results, which had the least variability, ranging from 0.9 to 3.3 mm (Fig. 5). Furthermore, unilateral improvement scores were not significantly correlated to the distance between the active contact and the most plausible of the 4 tracking results with respect to MRI-based anatomical landmarks of the PSA (Spearman’s r = 0.34, p = 0.28).

**Discussion**

Our study results show that different methods can be applied for deterministic DTI-based fiber tracking to model the DRTT. The application of different fiber tracking parameters led to statistically significant divergent results in the anatomical course of the displayed fibers. The anatomical differences were detectable on both the individual MR images for each patient and projections of the tracts on the stereotactic atlas of Morel. Plausible tracking results could not be achieved in every patient by using any of the presented methods. None of the presented methods produced results that were correlated to clinical outcome. The most robust and accurate tracking results in the area of interest (PSA) considered for DBS electrode implantation for the treatment of tremor seemed to be obtained using method 4; however, this method does not display crossing fibers, a known feature of the anatomical DRTT.

In our 4 different methods aimed at displaying the DRTT, we used different sets of tracking parameters, that is, minimum fiber length, minimum FA value, and different ROIs. The FA value constitutes a metric of the level of anisotropy within voxels ranging from 0 (isotropic) to 1 (anisotropic). As DTI measures the directionality of the diffusion process of water molecules, voxels containing axons of the same orientation will have a high FA value.

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**TABLE 1. Variability in the FA value for successful tracking results of the DRTT using 4 different methods**

| Tracking Method | Mean FA Value | FA Value Range |
|-----------------|---------------|----------------|
| 1               | 0.32 ± 0.06   | 0.24–0.42      |
| 2               | 0.16 ± 0.06   | 0.10–0.26      |
| 3               | 0.34 ± 0.05   | 0.25–0.46      |
| 4               | 0.31 ± 0.06   | 0.20–0.41      |

Values expressed as the mean ± standard deviation, unless indicated otherwise.

**TABLE 2. Lateral and anteroposterior coordinates of the center of the fiber bundles displayed in 4 different tracking methods**

| Method | VERT −3.6 mm | VERT −1.8 mm | VERT 0 mm |
|--------|--------------|--------------|-----------|
| LAT    | AP           | LAT          | AP        | LAT       | AP          |
| 1      | 12.79 ± 3.1  | −6.16 ± 2.96 | 14.2 ± 2.59 | −5.81 ± 2.28 | 15.65 ± 2.46 | 6.56 ± 3.22 |
| 2      | 6.60 ± 2.89  | −4.98 ± 2.33 | 9.80 ± 1.93 | −4.54 ± 1.70 | 12.55 ± 2.38 | −4.33 ± 1.64 |
| 3      | 8.14 ± 1.53  | −6.35 ± 1.64 | 9.46 ± 1.94 | −6.09 ± 1.42 | 10.46 ± 2.77 | −2.79 ± 1.60 |
| 4      | 10.13 ± 2.4  | −7.05 ± 2.07 | 12.03 ± 2.5 | −6.36 ± 1.66 | 13.94 ± 2.84 | −4.25 ± 0.90 |

Values expressed as the mean ± standard deviation.
Thus, the FA value threshold acts as a constraint on displayed fibers along voxels with a homogeneous directionality. The minimum fiber length and the selection of specific ROIs confine the display of fibers to these applied volumes of interest. Adjustment of these parameters has implications on the selectivity and course of the displayed fibers. The role of different sets of tracking parameters in the tractography results for large fiber bundles has been demonstrated before.\textsuperscript{8,10,33}

Fiber tracking results using method 1 had a close anatomical relation to the medial lemniscus based on both atlas-based data (ml) and tractography results (ML). On an individual patient basis, fibers tracked using method 1 passed the PSA in 50% of cases, while they were posterior and lateral to the PSA in 50% of the cases. Method 2 aims to display crossing fibers. According to anatomical and electrophysiological data, the DRTT projects from the deep cerebellar nuclei mainly to the contralateral thalamus.\textsuperscript{2,27} Low FA values in the range of 0.10–0.26 must be selected to display plausible tracking results. Still, no fibers or anatomically implausible fibers were displayed in 42% of cases, indicating the difficulty with and the limitations of DTI-based fiber tracking in displaying crossing fibers in the cerebellum and midbrain. However, the tracking results seemed accurate based on the Morel atlas data at all 3 investigated levels and in 58% of the cases with reference to MRI-based anatomical landmarks. Method 2 tracking results showed the least variability in the distance to the active contact and were not correlated to clinical outcome.

When method 3, the only method based on 2 ROIs, was applied, it frequently displayed fibers running to the orbitofrontal cortex and through the mammillary bodies. Adding a third ROI covering the precentral gyrus (method 4) increased the accuracy of the tracking results based on both the Morel atlas data and anatomical landmarks in each patient. The tractography results of both of these methods were not correlated to clinical outcome.

The importance of reliable modeling of the DRTT is

| Position Relative to PSA | Method 1 | Method 2 | Method 3 | Method 4 |
|--------------------------|----------|----------|----------|----------|
| w/in PSA                 | 50%      | 58%      | 58%      | 67%      |
| Pst to PSA               | 25%      | 25%      |          |          |
| Lat to PSA               | 25%      | 8%       | 8%       |          |
| Medial to PSA            | 17%      | 17%      |          |          |
| Ant to PSA               | 25%      | 17%      |          |          |

Ant = anterior; pst = posterior.

*FIG. 5.* Regression analysis and the correlation between unilateral TRS scores, and the distance between the active contact position and the center of the tracked DRTT by method 1 (A), method 2 (B), method 3 (C), and method 4 (D). There was a nonsignificant inverse correlation between the unilateral TRS score, and the distance between the active contact and the tracked DRTT of method 1 and method 2 (Spearman’s $r = -0.09$, $p = 0.76$; and Spearman’s $r = -0.07$, $p = 0.88$; respectively). There was a slightly positive correlation between the unilateral TRS score, and the distance between the active contact and the tracked DRTT of method 3 and method 4 (Spearman’s $r = 0.54$, $p = 0.71$; and Spearman’s $r = 0.55$, $p = 0.06$; respectively).
based on growing interest in this tract for DBS surgery and research. Deep brain stimulation of the PSA,\textsuperscript{5,30} the caudal zona incerta,\textsuperscript{29} or the prelemniscal radiations\textsuperscript{7} has shown promising results in the treatment of ET. In these cited studies, the DRTT was already proposed as the underlying neural substrate. Recent work supports the concept of better tremor control in patients whose active contact is localized closer to the DRTT.\textsuperscript{15,34} Various groups have described their different methods for representing and delineating the DRTT using deterministic DTI-based fiber tracking.\textsuperscript{1,3,11,31} However, the accuracy and reliability of DTI-based tractography of the DRTT, as well as its implications for clinical outcome, are still matters of debate. For example, Schlaier et al. were unable to show that contacts closer to the DRTT provided better tremor control than distant contacts in the intraoperative setting.\textsuperscript{31} Coenen and coworkers demonstrated the tendency of clinically effective active contacts to be located closer to the modeled DRTT than the less effective active contacts;\textsuperscript{12} however, this inverse correlation failed to be statistically significant. In line with this finding, tractography results for any of the methods applied in our series of patients were not correlated to clinical outcome. In contrast to previous work by Schlaier et al. and Coenen et al., who targeted the Vim, we found that both the target and the active contact position were located within the PSA in our patients. Consequently, our retrospective analysis of tractography results aimed to display the DRTT in relation to the stimulation site failed to demonstrate a clear correlation with clinical outcome at both the level of the thalamus and the PSA. Whether DRTT tractography results serve as a clinical prognosticator or whether tractography-based targeting improves clinical outcome is far beyond the scope of this study. However, our results contribute to the important issue of individualized targeting. Contrary to stereotactic atlas-based targeting, MRI-based targeting allows one to consider a patient’s individual anatomy. Current MRI sequences are appropriate to display landmarks in the subthalamic region but fail to visualize the Vim. Diffusion tensor imaging–based fiber tracking of the DRTT may help to define the target for DBS to treat tremor depending on the accuracy of the tractography results. Promising results that strengthen the concept of tractography-guided targeting of DBS contacts for tremor have come from previous work. Sammartino and coworkers\textsuperscript{28} presented a novel tractography-based algorithm to target the Vim of the thalamus. Interestingly, tracking the ML and PT was first used to define an ROI at the level of the thalamus, which was then used to track the DRTT in a second step. According to the authors, this tractography-based targeting approach differed significantly from a conventional targeting approach and yielded accurate results. Furthermore, Fenoy and Schiess presented a prospective series of 20 patients undergoing DRTT tractography-based DBS device implantation at the level of the thalamus.\textsuperscript{14}

Our study has some limitations. The fiber tracking results were based on deterministic DTI. Deterministic fiber tracking constructs 1 streamline that starts at a selected seed volume ROI and is propagated along neighboring voxels with similar diffusion directions until it reaches voxels of low anisotropy. This streamline presumably represents the best solution for the fiber path. Known shortcomings of DTI are its low signal/noise ratio and its sensitivity to artifacts caused by motion, thermal noise, and eddy currents.\textsuperscript{3,6} In our series, the applied field strength was 3 T, the slice thickness 2.2 mm, and the in-plane resolution 1.1 × 1.1 mm\textsuperscript{2}. In part, parameters were chosen to deal with the trade-off of obtaining high-resolution images while maintaining an acceptable signal/noise ratio and an image acquisition time that is pragmatic in everyday clinics. The effect of the applied magnetic field strength on the accuracy of the DTI-based fiber tracking results was analyzed previously by Ford and coworkers.\textsuperscript{37} They could demonstrate high accuracy of fiber tracking results in cases of ultra–high-field strengths (11.1 T) and an isotropic high resolution of 0.333 mm. In their study, however, an excised human brainstem was investigated. Until now, these sophisticated imaging techniques have not been applicable for routine clinical use in preoperative targeting for DBS. According to their results, the corticospinal tract and ML seemed to be artificially enlarged at lower resolutions of 1 and 2 mm, which are currently used in everyday clinics.

Furthermore, a low angular resolution of only 12 directions was applied in our series to be compatible with the Brainlab tracking algorithm, which fails in cases in which a higher number of orientations are used.\textsuperscript{32} However, these technical limitations have implications for depicting small fiber tracts: in cases of multiple fiber populations with different orientations contained in 1 voxel, their contribution to the signal is averaged and information about fiber orientation is lost.\textsuperscript{23} Tensor calculation and the assumption that the largest diffusion axis corresponds to the fiber orientation fail in cases of voxels containing 2 or more fiber tracts with different orientations. Theoretically, the use of a higher angular resolution, according to Coenen et al., should be more accurate in displaying crossing fibers—a hypothesis that must still be proven.\textsuperscript{11,12}

Furthermore, fiber tracking results have been shown to be dependent on the tracking algorithm applied and the software package used.\textsuperscript{39} As a matter of fact, this affects the comparability of results found in different studies using different software. We decided to use Brainlab software for fiber tracking analysis since it is used in many centers for surgical planning.

Probabilistic fiber tracking is reported to overcome some of the limitations of deterministic fiber tracking. A thorough comparison of deterministic and probabilistic fiber tracking algorithms can be found in Fillard et al. and Daducci et al.\textsuperscript{13,16} In probabilistic tractography, a seed volume of interest is chosen and a map of streamlines is constructed by building a connectivity distribution between the seed volume and every other voxel based on the most probable diffusion direction. Recently, Sammartino and coworkers have shown that probabilistic fiber tracking to display the DRTT did indeed result in better visualization of crossing fibers compared with that obtained with deterministic fiber tracking.\textsuperscript{32} However, probabilistic tractography did not provide a more accurate target definition, which is eminently important in stereotactic neurosurgery. In line with these findings, Schlaier et al.\textsuperscript{32} compared deterministic and probabilistic tractography...
approaches to display the DRTT. Indeed, probabilistic fiber tracking yielded more sensitive and robust tracking results; however, the authors found a complete overlap between probabilistic and deterministic tracking results in the majority of patients. Furthermore, the computational complexity leading to excessive data acquisition and time expenditure (4.5–33 hours) relativizes the potential benefits and limits the current role of probabilistic fiber tracking, which is not approved for clinical practice. Taken together, these results emphasize that deterministic fiber tracking approaches for target definition are more reliable for clinical use.

Conclusions

There is no one-size-fits-all approach for DTI-based tractography to model the DRTT, and different methods can yield results with good anatomical approximation. We recommend using 3 ROIs including the dentate nucleus of the cerebellum, the PSA, and the precentral gyrus. Tracking results must be cautiously evaluated for anatomical plausibility and accuracy in each patient. More recent alternatives to DTI need to be studied with respect to potentially greater anatomical accuracy and improvements in displaying crossing fibers.

References

1. Anthofer J, Steib K, Fellner C, Lange M, Brawanski A, Schlaier J: The variability of atlas-based targets in relation to surrounding major fibre tracts in thalamic deep brain stimulation. Acta Neurochir (Wien) 156:1497–1504, 2014
2. Asanuma C, Thach WR, Jones EG: Anatomical evidence for segregated focal groupings of efferent cells and their terminal ramifications in the cerebellothalamic pathway of the monkey. Brain Res 286:267–297, 1983
3. Bastin ME, Armitage PA, Marshall I: A theoretical study of the effect of experimental noise on the measurement of anisotropy in diffusion imaging. Magn Reson Imaging 16:773–785, 1998
4. Benabid AL, Pollak P, Gao D, Hoffmann D, Limousin P, Gay E, et al: Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 84:203–214, 1996
5. Blomstedt P, Sandvik U, Tisch S: Deep brain stimulation in the posterior subthalamic area in the treatment of essential tremor. Mov Disord 25:1350–1356, 2010
6. Calamante F, Porter DA, Gadian DG, Connelly A: Correction for eddy current induced B, shifts in diffusion-weighted echo-planar imaging. Magn Reson Med 41:95–102, 1999
7. Carrillo-Ruiz JD, Velasco F, Jiménez F, Castro G, Velasco AL, Hernández JA, et al: Bilateral electrical stimulation of prelemniscal radiations in the treatment of advanced Parkinson’s disease. Neurosurgery 62:347–359, 2008
8. Catani M, Thiebaut de Schotten M: A diffusion tensor imaging tractography atlas for virtual in vivo dissections. Cortex 44:1105–1132, 2008
9. Christidi F, Karavasilis E, Samiotis K, Bisdas S, Papanikolaou N: Fiber tracking: A qualitative and quantitative comparison between four different software tools on the reconstruction of major white matter tracts. Eur J Radiol Open 3:153–161, 2016
10. Clark CA, Barrick TR, Murphy MM, Bell BA: White matter fiber tracking in patients with space-occupying lesions of the brain: a new technique for neurosurgical planning? Neuroimage 20:1601–1608, 2003
11. Coenen VA, Allert N, Mädler B: A role of diffusion tensor imaging fiber tracking in deepbrain stimulation surgery: DBS of the dentato-rubro-thalamic tract (drt) for the treatment of therapy-refractory tremor. Acta Neurochir (Wien) 153:1579–1585, 2011
12. Coenen VA, Allert N, Paus S, Kronenbürger M, Urbach H, Mädler B: Modulation of the cerebellothalamo-cortical network in thalamic deep brain stimulation for tremor: a diffusion tensor imaging study. Neurosurgery 75:657–670, 2014
13. Daducci A, Canales-Rodríguez EJ, Descoteaux M, Garyfallidis E, Gur Y, Lin YC, et al: Quantitative comparison of reconstruction methods for intra-voxel fiber recovery from diffusion MRI. IEEE Trans Med Imaging 33:384–399, 2014
14. Femeny AJ, Schiess MC: Deep brain stimulation of the den tato-rubro-thalamic tract: outcomes of direct targeting for tremor. Neuromodulation 20:429–436, 2017
15. Fiechter M, Nowacki A, Oertel MF, Fichtner J, Deboe I, Lachenmayer ML, et al: Deep brain stimulation for tremor: is there a common structure? Stereotact Funct Neurosurg 95:243–250, 2017
16. Fillard P, Descoteaux M, Goh A, Goultard S, Jeunissen B, Malcolm J, et al: Quantitative evaluation of 10 tractography algorithms on a realistic diffusion MR phantom. Neuroimage 56:220–234, 2011
17. Ford AA, Colon-Perez L, Tripplett WT, Gullett JM, Mareci TH, Fitzgerald DB: Imaging white matter in human brainstem. Front Hum Neurosci 7:400, 2013
18. Gallay MN, Jeanmonod D, Liu J, Morel A: Human pallido-thalamic and cerebellothalamic tracts: anatomical basis for functional stereotactic neurosurgery. Brain Struct Funct 212:443–463, 2008
19. Groppa S, Herzog J, Falk D, Riedel C, Deuschl G, Volkmann J: Physiological and anatomical decomposition of subthalamic neurostimulation effects in essential tremor. Brain 137:109–121, 2014
20. Kwon HG, Hong JH, Hong CP, Lee DH, Ahn SH, Jang SH: Dentatorubrothalamic tract in human brain: diffusion tensor tractography study. Neuroradiology 53:787–791, 2011
21. Lozano AM: Vim thalamic stimulation for tremor. Arch Med Res 31:266–269, 2000
22. Morel A, Maghin M, Jeanmonod D: Multiarchitectonic and stereotactic atlas of the human thalamus. J Comp Neurol 387:588–630, 1997
23. Mori S, Zhang J: Principles of diffusion tensor imaging and its applications to basic neuroscience research. Neuron 51:527–539, 2006
24. Nowacki A, Fiechter M, Fichtner J, Deboe I, Lachenmayer L, Schüpbach M, et al: Using MDEFT MRI sequences to target the GPi in DBS surgery. PLoS One 10:e0137868, 2015
25. Oertel MF, Schüpbach WM, Ghika JA, Stieglitz LH, Fiechter M, Kaelin-Lang A, et al: Combined thalamic and subthalamic deep brain stimulation for tremor-dominant Parkinson’s disease. Acta Neurochir (Wien) 159:265–269, 2017
26. Perlmuter JS, Mink JW: Deep brain stimulation. Annu Rev Neurosci 29:229–257, 2006
27. Rouiller EM, Liang F, Babalian A, Moret V, Wiesendanger M: Cerebellothalamicocortical and pallidothalamocortical projections to the primary and supplementary motor cortical areas: a multiple tracing study in macaque monkeys. J Comp Neurol 345:185–211, 1994
28. Sammartino F, Krishna V, King NK, Lozano AM, Schwartz ML, Huang Y, et al: Tractography-based ventral intermediate nucleus targeting: novel methodology and intraoperative validation. Mov Disord 31:1217–1225, 2016
29. Sandvik U, Hariz GM, Blomstedt P: Quality of life following DBS in the caudal zona incerta in patients with essential tremor. Acta Neurochir (Wien) 154:495–499, 2012
30. Sandvik U, Koskinen LO, Lundquist A, Blomstedt P: Thalamic and subthalamic deep brain stimulation for essential
tremor: where is the optimal target? Neurosurgery 70:840–846, 2012
31. Schlaier J, Anthofer J, Steib K, Fellner C, Rothenfusser E, Brawanski A, et al: Deep brain stimulation for essential tremor: targeting the dentato-rubro-thalamic tract? Neuromodulation 18:105–112, 2015
32. Schlaier JR, Beer AL, Faltermeyer R, Fellner C, Steib K, Lange M, et al: Probabilistic vs. deterministic fiber tracking and the influence of different seed regions to delineate cerebellar-thalamic fibers in deep brain stimulation. Eur J Neurosci 45:1623–1633, 2017
33. Stieglitz LH, Lüdemann WO, Giordano M, Raabe A, Fahlbusch R, Samii M: Optic radiation fiber tracking using anteriorly angulated diffusion tensor imaging: a tested algorithm for quick application. Neurosurgery 68:1239–1251, 2011
34. Sweet JA, Walter BL, Gunalan K, Chaturvedi A, McIntyre CC, Miller JP: Fiber tractography of the axonal pathways linking the basal ganglia and cerebellum in Parkinson disease: implications for targeting in deep brain stimulation. J Neurosurg 120:988–996, 2014
35. Yousry TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buetter A, et al: Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. Brain 120:141–157, 1997

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Conception and design: Nowacki, Schlaier, Pollo. Acquisition of data: Nowacki, Debove. Analysis and interpretation of data: Nowacki, Pollo. Drafting the article: Nowacki. Critically revising the article: Schlaier, Pollo. Reviewed submitted version of manuscript: Debove. Approved the final version of the manuscript on behalf of all authors: Nowacki. Administrative/technical/material support: Schlaier, Debove, Pollo.

Correspondence
Andreas Nowacki: University Hospital Inselspital Bern, University of Bern, Switzerland. neuro.nowacki@gmail.com.