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Original Article

Dentato-rubro-thalamic tract tractography: Constrained spherical deconvolution versus diffusion tensor imaging for essential tremor deep brain stimulation targeting

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Received: 02 November 2024
Accepted: 10 April 2025
Published: 30 May 2025

DOI
10.25259/SNI_924_2024

Quick Response Code:

ABSTRACT

Background: This study aimed to compare diffusion tensor imaging (DTI) and constrained spherical deconvolution (CSD) techniques in the segmentation of the dentate-rubro-thalamic tract (DRTT), evaluating their anatomical accuracy and applicability for surgical planning in deep brain stimulation (DBS) for essential tremor surgery in two patients.

Methods: The images were acquired using two 1.5 Tesla magnetic resonance imaging protocols optimized for both DTI and CSD. Preprocessing included noise removal, artifact correction, and distortion adjustments. Segmentation was performed using region-of-interest definitions from specific atlases. CSD was applied with response function estimation, followed by fiber orientation reconstruction and tracking using the probabilistic improved fiber orientation distribution 2(iFOD2) algorithm. The DTI technique was conducted with tensor calculation and fractional anisotropy (FA) analysis. Volume and FA metrics were compared between techniques to evaluate segmentation accuracy for the DRTT.

Results: CSD-based segmentation showed significantly larger volumes in the left hemisphere compared to DTI, along with higher FA values. In the right hemisphere, the difference was not statistically significant. Dice similarity index analysis revealed very low correspondence between the techniques in both hemispheres, suggesting greater precision of CSD in DRTT segmentation.

Conclusion: CSD proved to be more effective in DRTT segmentation, with better angular resolution and greater detailing of axonal trajectories, especially in regions with fiber crossing.

Keywords: Constrained spherical deconvolution, Deep brain stimulation, Diffusion tensor imaging, Essential tremor, Tractography

INTRODUCTION

Essential tremor (ET) is a common neurological disorder characterized by action and postural tremors. The dentato-rubro-thalamic tract (DRTT) has been identified as a crucial white matter pathway involved in the circuits implicated in ET. Deep brain stimulation (DBS) targeting this tract has shown promising results in treating refractory cases of ET.[1]

Among the methods for performing tractography, diffusion tensor imaging (DTI) is widely used due to its ability to map the fractional anisotropy (FA) of white matter fibers.[2] However, DTI has intrinsic limitations, such as the inability to resolve multiple fiber directions within a single voxel, resulting in a limited representation of the complexity of axonal architecture.[2] The DTI technique is particularly challenging in fiber-crossing regions, where the accuracy of directional estimation is compromised.[16] Consequently, this limitation can lead to inaccurate information, potentially negatively impacting clinical outcomes in functional neurosurgery procedures, such as DBS.[16]

To overcome these limitations, advanced techniques like constrained spherical deconvolution (CSD) have been developed. CSD allows for the reconstruction of the fiber orientation distribution function (fODF), providing a more precise and detailed visualization of the multidirectionality of fibers within a voxel.[2] This approach is particularly beneficial in identifying and segmenting complex tracts such as the DRTT, which is crucial for accurate targeting in DBS for ET.[16]

The ventral intermediate nucleus (VIM) of the thalamus is the classic target in DBS for treating ET, generally determined by indirect targeting (commissural coordinates).[16] DRTT determination through CSD, by offering superior resolution of axonal trajectories, can refine target determination in DBS for ET, improving therapeutic efficacy and minimizing adverse effects.[2] In this study, we present a comparative analysis of two tractography methods (CSD and DTI) and illustrate the advantages of using DRTT through CSD in DBS planning for ET with two clinical cases.

MATERIALS AND METHODS

Image acquisition

Forty diffusion images at 7 Tesla resolutions from the Human Connectome Project (HCP) database were evaluated. The acquisition protocol for these images was as follows: repetition time (TR) of 7000 ms, echo time (TE) of 71.2 ms, b-values of 1000 and 2000 s/mm^2, and an echo spacing of 0.82 ms. Structural T1-weighted images were obtained using Siemens devices. The age range of the subjects was from 22 to 35 years, comprising 29 women and 11 men. All subjects had no brain pathology.

For the two clinical cases, the diffusion image acquisition protocol was carried out using two different 1.5 Tesla magnetic resonance imaging (MRI) systems. This dual-protocol approach was employed to ensure compatibility with different clinical settings and to validate the robustness of our methodology across different imaging parameters. Both clinical protocols were optimized to ensure adequate resolution and compatibility with the application CSD techniques, ensuring the necessary quality for subsequent tractographic analysis.

In the first clinical case, the acquisition was performed on a gradient echo (GE) scanner, where diffusion sequences were obtained with the following parameters: TR = 8,325 ms, TE = 0.1099 ms, acquisition matrix of 128 × 128, field of view (FOV) of 640 mm, slice thickness of 5 mm, and gradient with 33 directions. T1-weighted structural images were acquired with TR = 0.0086 ms, TE = 0.0034 ms, a 256 × 256 matrix, and a FOV of 256 mm. In the second clinical case, diffusion images were acquired with a Philips 1.5 Tesla scanner, using a sequence with TR = 3,291 ms, TE = 0.0934 ms, acquisition matrix of 90 × 90, FOV of 225 mm, slice thickness of 2.5 mm, and a gradient of 32 directions. The T1-weighted sequence was acquired with TR = 0.0088 ms, TE = 0.0041 ms, a 240 × 240 matrix, and a FOV of 120 mm.

Pre-processing

The diffusion images were subjected to pre-processing steps to enable DRTT tractographic segmentation. First, signal noise was removed using the dwidenoise tool, followed by the use of the mrdegibbs tool to eliminate potential acquisition artifacts. In addition, the images were processed with the help of the dwifslpreproc tool, which performs a pipeline for correcting distortions caused by susceptibility and motion.

The images from the HCP underwent preprocessing steps in their acquisition protocol, which included motion correction and distortion correction. Therefore, it was not necessary to subject this group of images to the preprocessing typically required for clinical images.

Definition of regions of interest (ROIs)

Tractography was performed using a ROI-based approach, with ROIs derived from atlases and used as targets for DRTT segmentation. For the inclusion of ROIs, the dentate nucleus of the cerebellum, defined by the Spatially Unbiased Atlas Template of the cerebellum and brainstem, was used as the seed region to initiate segmentation. In addition, contralateral hemisphere inclusion masks were selected to segment the DRTT as follows: The contralateral red nucleus, defined by the Parkinson's Disease 25 subjects histological atlas (PD25), the contralateral ventrolateral thalamic nucleus (PD25), and the contralateral primary motor cortex defined by the Juelich Cytoarchitectonic Atlas.

For exclusion ROIs, to remove the ipsilateral fibers of the dentate nucleus, the following masks were selected: the corpus callosum defined by the Johns Hopkins University International Consortium of Brain Mapping-DTI-81 white matter atlas, the corresponding bulb of the brainstem (manually defined with the assistance of the Harvard-Oxford Subcortical Structural Atlas), the ipsilateral ventrolateral thalamic nucleus, and the ipsilateral red nucleus. All ROIs were originally defined in the common space of the Montreal Neuroscience Institute. To be used in tractography directly within the native diffusion space of each patient, we

performed diffeomorphic non-linear co-registration using the Advanced Normalization Tools (ANTs) software package.

CSD technique

The CSD technique was implemented using the MRtrix3 software package[3,15] which provided us with a set of tools for structuring and processing the methodology. In this sense, we initially estimated the response function using the dwi2response tool, employing the D'hollander algorithm to identify single-fiber voxels. This identification is crucial as it defines the diffusion response function, a critical parameter for guiding deconvolution and accurately determining the fiber orientation in each voxel. Based on this estimation, the subsequent step was the reconstruction of the fODF using the dwi2fod tool, which provides a detailed profile of fiber directions within each voxel.

After the reconstruction of the fODFs, tractography was conducted using the probabilistic iFOD2 algorithm. This method was chosen for its ability to handle the complexity of fiber trajectories in regions with crossing or dispersing directions. The iFOD2 algorithm is particularly effective in resolving multiple fiber populations within a voxel, making it ideal for tracking complex white matter structures like the DRTT. Fiber tracking was parameterized to generate a total of 5,000 streamlines, trials 2000, max_attempts_per_seed 5000, angle 45°, and max_length 10000, ensuring a comprehensive representation of neural connections.

Finally, the obtained segmentation was subjected to cross-space registration using a diffeomorphic non-linear co-registration method through the ANTs software. This process was performed to align the segmented diffusion images with the anatomical space of each patient's T1-weighted sequences, ensuring spatial conformity between the structures of interest and surrounding areas [Figures 1 and 2].

DTI method

A deterministic tractography based on DTI was performed to compare with CSD-based tractography. For this purpose, the Tensor_Det deterministic algorithm from the MRtrix3 toolkit was used. In this approach, the dentate nucleus, the contralateral red nucleus, and the contralateral ventrolateral nucleus were defined as seed ROIs, while the corpus callosum, the contralateral dentate nucleus, and the ipsilateral red nucleus were set as exclusion ROIs. All ROIs were defined according to the atlases used for CSD tractography. The parameters were set with -maxlen 10000, -angle 45, and -seeds 2000000. All other tool options were left at default settings.

Stereotactic method

The stereotactic targeting methodology utilized the Eximius Med Software Stereotactic Module (Artis, Brasilia, Brazil).

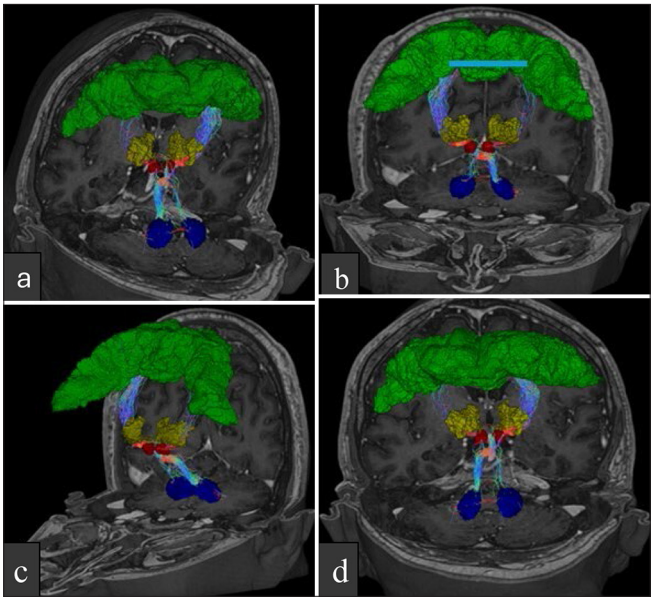

Figure 1: Three-dimensional reconstruction of the dentate–rubro–thalamic tract in patient 01. (a) Frontal view.(b) Frontal lateral view. (c) Posterior view.(d) Posterior-oblique view.

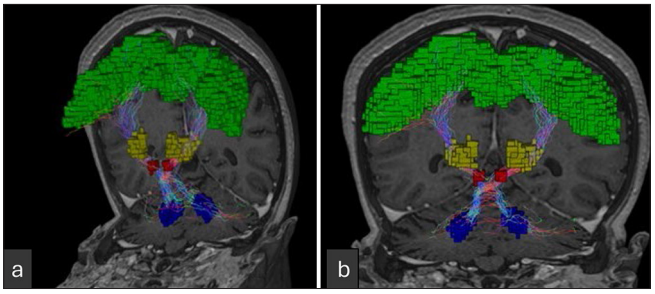

Figure 2: Three-dimensional reconstruction of the dentate–rubro–thalamic tract in patient 02. (a) Frontal view.(b) Frontal lateral view.

High-resolution MRI scans were acquired, and the anterior commissure - posterior commissure (AC-PC) plane was defined. These images were then co-registered with computed tomography CT scans taken with the stereotactic frame in place. A standardized human brain stereotactic atlas was overlaid onto the co-registered images to aid in identifying subcortical structures. The intersection between the VIM of the Thalamus and the DRTT was identified as the primary target for electrode placement. Cartesian coordinates (x, y, and z) of the target were calculated relative to the mid-commissural point and compared with standard VIM target coordinates.[10]

RESULTS

CSD versus DTI

The DRTT segmentation results from the HCP cases using CSD and DTI techniques revealed significant differences in volume and FA metrics, particularly in the left hemisphere. The

CSD technique showed a significantly larger segmented volume (10,230 mm^3) compared to DTI (3,708 mm^3; $P = 0.0035$), along with higher FA values (0.362 vs. 0.242; $P < 0.0001$) [Table 1]. These findings suggest that CSD is more accurate in identifying fiber architecture, especially in areas of complex crossing, where DTI tends to underestimate connectivity. No statistically significant differences in mean diffusivity (MD) were observed between the techniques ($P = 0.0842$), indicating that both methods are similar in estimating global diffusivity but differ in angular resolution and the ability to delineate more detailed axonal pathways. In the right hemisphere, there were no significant differences in volume ($P = 0.613$), fractional anisotropy values ($P = 0.0589$), or MD ($P = 0.4470$).

The similarity analysis between the volumes segmented by both techniques, measured by the Dice similarity index, showed low concordance in both hemispheres (0.013 on the left and 0.035 on the right). These values indicate a significant discrepancy between the techniques in DRTT delineation, highlighting the presumed superiority of CSD in tract reconstruction compared to DTI, which demonstrated limitations in identifying more complex axonal trajectories. Clinically, these findings suggest that CSD offers greater precision and detail in the segmentation of DRTT.

Clinical cases

Two patients, a 67-year-old man and a 70-year-old woman, both with action and postural tremors refractory to medical treatment (optimized doses of propranolol and primidone), underwent surgical treatment with DBS implantation targeting the DRTT. Instead of using the classic stereotactic coordinates for target definition in the VIM of the thalamus (VIM), we employed a direct targeting technique to position the electrodes along the DRTT trajectory that passes ventrally to the thalamus [Figures 3 and 4]. The Cartesian coordinates (x, y, and z) of the target were calculated relative to the mid-commissural point, with values obtained for two distinct patients. For Patient 1, the coordinates were x = −13.4, y = −4.5, z = 56.5 (right) and x = 13.5, y = −5, z = 56.5 (left). For Patient 2, the coordinates were more posterior and inferior: x = −15.8, y = −12.5, z = 45.5 (right), and x = −13.5, y = −11.5, z = 45.5 (left). The individual coordinates for patients 1 and 2 demonstrate how each patient's anatomical variation can impact location relative to the classical value. For tractography, we used the CSD algorithm with ROIs defined in an atlas.

After electrode implantation, intraoperative tests (macro-stimulation) were performed, resulting in tremor control at low stimulation amplitudes (<1 mA) and a broad therapeutic window (>3 mA) in both cases. Postoperatively, both patients demonstrated sustained tremor control without adverse effects or surgical complications.

DISCUSSION

The comparison between DTI and CSD suggests the superiority of CSD in DRTT segmentation and three-dimensional reconstruction. CSD not only showed significantly larger segmented volumes and higher FA values,

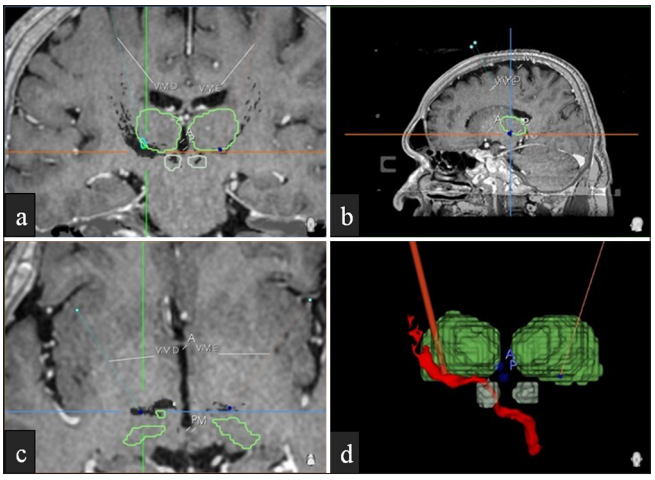

Figure 3: Multiplanar coronal, sagittal, and axial views showing the position of the electrode in the thalamic target tract for DBS in patient 1. Tractography demonstrates the surgical accuracy of electrode placement. (a) Coronal view displaying electrode position within the thalamic target.(b)Sagittal view highlighting the electrode trajectory. (c) Axial view showing cross-sectional electrode localization. (d) 3D tractography confirming the accuracy of electrode positioning relative to thalamic structures.

Table 1: Evaluation and Comparison of the Metrics of the DRTT Segmented using CSD and DTI Technique.

	Volume	FA	MD (x10-4)
CSD - left	10,230 (936, 14.521)	0.362 (0.388, 0.451)	5.08 (4.91, 5.26)
DTI - left	3,708 (0, 3,476)	0.242 (0.000, 0.385)	4.88 (0.0, 5.20)
Value of p**	0.0035	< 0.0001	0.0842
CSD - right	4,683 (0, 4,440)	0.260 (0, 0.443)	3.05 (0.0, 5.03)
DTI - right	3,077 (0, 4,229)	0.253 (0, 0.374)	3.36 (0.0, 5.10)
Value of *p***	0.6133	0.0589	0.4470

CSD: Constrained spherical deconvolution, DRTT: Dentato-rubro-thalamic tract, DTI: Diffusion tensor imaging, FA: Fractional anisotropy, MD: Mean diffusivity, Median (1st Q, 3rd Q), **Wilcoxon test.

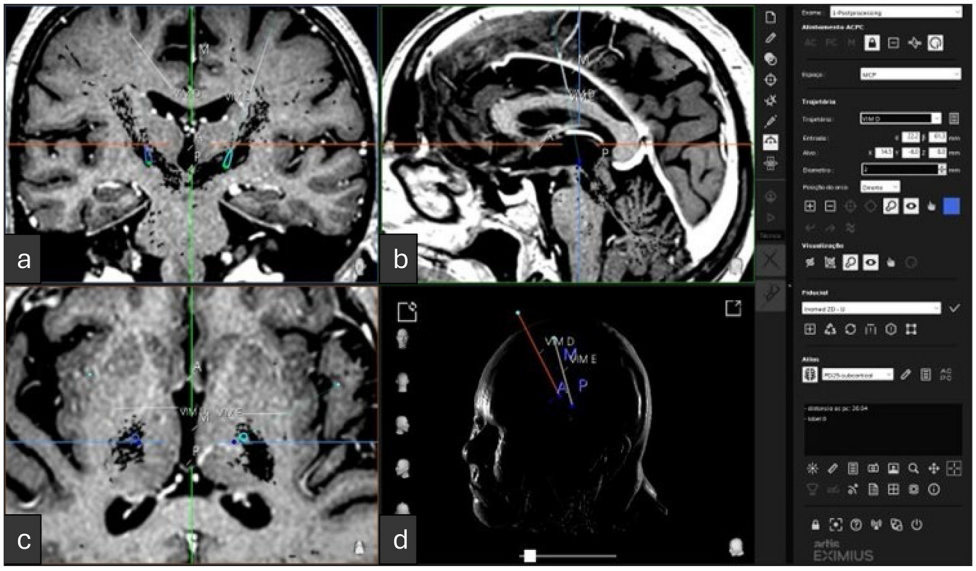

Figure 4: Multiplanar reconstruction demonstrating the electrode trajectory in the thalamic target region for DBS in patient 2. (a) Coronal view showing electrode placement within the thalamic area. (b) Sagittal view depicting electrode trajectory and alignment. (c) Axial view with crosshair indicating electrode location. (d) 3D reconstruction illustrating stereotactic coordinates and vector direction of electrode insertion.

especially in the left hemisphere, but also demonstrated greater precision in trajectory delineation, facilitating the anatomical identification of the VIM of the thalamus, which is the primary therapeutic target for DBS. In contrast, DTI systematically underestimated the volume and complexity of the DRTT, generating less detailed and potentially inadequate results for precise surgical planning.

The DRTT plays a central role in modulating tremors and is one of the most important targets for neuromodulation in DBS procedures for treating ET.[1] Precise identification of this tract is essential for therapeutic success, as proper segmentation and visualization of axonal trajectories are crucial for the effective placement of electrodes.[10]

Anatomically, the DRTT originates in the superior cerebellar peduncle, decussates, and projects anteriorly to the red nucleus before reaching the ventral thalamus, located in proximity to the medial lemniscus (LM).[9] This circuit participates in fine motor control and coordination. Studies such as those by Coenen *et al*. have demonstrated that precise stimulation of DRTT fibers at the level of the VIM results in more effective tremor modulation.[1,4,9] Mapping this tract optimizes the placement of DBS electrodes, avoiding adverse effects related to the stimulation of adjacent areas, such as the LM, as demonstrated by Morrison *et al*.[9]

Although the use of the DRTT in DBS planning for ET is not yet universally accepted, clinical studies suggest that this tract can play a central role in effectively treating tremors. Studies by Parras *et al*.[11] emphasize the importance of integrating DRTT mapping into preoperative planning, especially when advanced tractography techniques are used. The complex and narrow configuration of the DRTT relative to other critical pathways makes its segmentation particularly challenging, especially for traditional methods like DTI. Although widely used, the DTI technique has inherent limitations in its mathematical model, which assumes the presence of a single predominant diffusion orientation per voxel. In regions of crossing, juxtaposition, or fiber branching, as frequently occurs in the DRTT, DTI fails to distinguish axonal trajectories with multiple directions, resulting in a simplified and often inaccurate mapping of neural connectivity.[7,16]

The Dice similarity index between the two techniques highlighted this discrepancy, showing extremely low values for the correspondence between the segmented volumes (0.013 on the left and 0.035 on the right), suggesting that the representations obtained by DTI are insufficiently concordant with those generated by CSD. This difference reflects the limitation of DTI in identifying axonal trajectories in regions of complex crossing and curvature, underscoring the need for a more robust methodology, such as CSD, to ensure accurate tract visualization.[8]

In contrast, the CSD technique addresses these deficiencies by calculating the fODF distribution function, allowing for the precise identification of multiple bundle orientations within the same voxel. Using more detailed angular information and a deconvolution model that more accurately separates the directions of the bundles, CSD can segment the DRTT along its entire length, even in densely crossing regions, such as its anterior projection to the red nucleus and its entry into the

ventral thalamus.[13] This way, CSD provides a more detailed reconstruction of the DRTT, preserving the tract's natural continuity and curvature allowing for better visualization and segmentation of white matter fibers, which is crucial for precise and effective surgical planning in functional neurosurgery.[12]

Direct visualization of the VIM is insufficient in conventional imaging. Patients with anatomical variations benefit from the reconstruction of the DRTT through tractography techniques, such as DTI or CSD, as this fiber bundle can serve as a reference structure to guide the insertion of electrodes.[9]

Besides its applicability in treating ET, CSD shows great potential in other neurological conditions that require precise segmentation and accurate fiber visualization, such as Parkinson's disease, defining boundaries for glioma resection, and assessing compromised tracts in ischemic lesions.[5,13,14] This versatility demonstrates CSD's superiority not only in terms of spatial and angular resolution but also in its ability to support individualized surgical planning based on the patient's specific anatomy.

However, despite promising results, challenges associated with the use of CSD remain. These include variability between different reconstruction software, lack of standardization in applied quantitative metrics, and high computational demands that are not feasible on most current hardware. This heterogeneity can result in variations in outcomes, necessitating more comparative studies and clinical trials to validate CSD's superiority in different clinical scenarios and with larger populations. Until more evidence is consolidated, DTI remains the standard technique due to its simplicity and wide availability. Nonetheless, CSD stands out as an emerging methodology, offering a more robust and detailed resolution for segmenting complex tracts. It shows great potential to become the method of choice for planning neurosurgical interventions in anatomically complex regions, particularly as computational capabilities advance.[6]

As further studies consolidate these findings, CSD has the potential to become the preferred technique for tractography and planning neurosurgical interventions, such as DBS in patients with ET, gradually replacing DTI as the reference method in this context. These advancements in imaging and targeting techniques promise to significantly improve outcomes in functional neurosurgery, particularly in the treatment of movement disorders.

CONCLUSION

A comparative analysis between DTI and CSD techniques in DRTT segmentation suggests that CSD provides superior detailing of axonal trajectories, offering more precise reference points for VIM localization. The results indicate that CSD is capable of accurately delineating the anatomy of the tract, potentially enhancing surgical precision.

Ethical approval: The research/study approved by the Institutional Review Board at UNIVERSIDADE FEDERAL DE SERGIPE – UFS, number 77903624.0.0000.5546, dated May 21, 2024.
Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.
Financial support and sponsorship: Nil.
Conflicts of interest: There are no conflicts of interest.
Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirms that they have used artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript or image creations.

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How to cite this article: Menezes RF, Prudente RL, Freitas EL, Fernandes de Oliveira Santos B. Dentato-rubro-thalamic tract tractography: Constrained spherical deconvolution versus diffusion tensor imaging for essential tremor deep brain stimulation targeting. Surg Neurol Int. 2025;16:211. doi: 10.25259/SNI_924_2024