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Efficacy of Fiber Tractography in the Stereotactic Surgery of the Thalamus for Patients with Essential Tremor

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Abstract

Several targets and targeting methods are utilized in stereotactic surgery to achieve tremor suppression for patients with intractable tremor. Recent developments in magnetic resonance imaging, including diffusion tensor imaging, have enabled the setting of appropriate targets in stereotactic surgery. In this retrospective study, the optimal target to suppress tremors in stereotactic surgery was explored using diffusion tensor image-based fiber tractography. Four tracts were focused on in this study, namely: the cerebello-thalamo-premotor cortical fiber tract, cerebello-thalamo-primary motor cortical fiber tract, spino-thalamo-somatosensory cortical fiber tract, and pyramidal tract. In 10 patients with essential tremor, we evaluated the thalamotomy lesions and active contacts of the lead in thalamic stimulation by diffusion tensor image-based fiber tractography to reveal which part of the cerebral cortex is most affected by stereotactic surgery. Tremor suppression and adverse events were also evaluated in the patients involved in this study. Consequently, the good tremor suppression was achieved in all patients. There had been no permanent adverse events 3 months after surgery. Twelve lesions in thalamotomy patients or active contacts of the lead in thalamic stimulation patients were on the cerebello-thalamo-premotor cortical fiber tract (12/14 lesions or active contacts: 86%). In conclusion, the cerebello-thalamo-premotor cortical fiber tract may be an optimal target for tremor suppression. Diffusion tensor image-based fiber tractography may enable us to both determine the optimal target to achieve strong tremor suppression and to reduce the number of adverse events by keeping lesions or electrodes away from important fiber tracts, such as the pyramidal tract and spinothalamic fibers.

Key words: diffusion tensor image, essential tremor, fiber tractography, premotor cortex, thalamus

Introduction

Since Hassler reported in the 1950s that the ventral intermedius nucleus (Vim) is an optimal target for tremor in patients with Parkinson's disease, Vim in the thalamus has been targeted for intractable tremors in stereotactic surgery.[1)] It was also reported that stimulation of the ventro-oral posterior nucleus (VoP) or posterior subthalamic area is effective in controlling intractable tremors.[2,3)] Indirect targeting methods based on the relative position of the target to the midpoint between the anterior commissure (AC) and the posterior commissure (PC) are used in most cases. Despite the development of targeting methods, it remains unclear, however, if the targeted point is correct.

In anatomic terms, Vim receives fiber tracts from the cerebellum and projects fiber tracts to the primary motor cortex (M1).[4,5)] VoP receives fiber tracts from the globus pallidus internalis and projects fiber tracts to the premotor cortex (preM). In patients with essential tremor, Vim stimulation leads to increased cerebral blood flow and activation of M1.[6)] Visualization analyses of these fiber tracts could identify the nuclei in the thalamus.[7)] Through probabilistic tractography, the connection of Vim to M1 and VoP to PreM was clarified in 17 healthy volunteers.[8)]

Diffusion tensor imaging (DTI) is a type of magnetic resonance imaging (MRI) that can show axonal organization in the brain.[9)] Using DTI-based fiber tractography (DTI-FT), an individual fiber tract can be visualized. Visualization analyses on fiber tracts in the thalamus with DTI-FT may enable the detection of optimal targets for tremor suppression. The purpose of this study is to use DTI-FT to identify an optimal target to suppress tremors in stereotactic surgery. The lesions of thalamotomy and active contacts of the lead in deep brain stimulation (DBS)

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were evaluated with DTI-FT to reveal which area of the cerebral cortex may be most affected by stereotactic surgery in patients with intractable tremor.

Materials and Methods

Study design

This is a retrospective observational clinical study.

Patient characteristics

This study consisted of data from 10 consecutive patients with essential tremor who underwent stereotactic surgery (thalamotomy in 6 patients, thalamus DBS in 4 patients) between May 2011 and December 2013 (Table 1). All patients suffered from intractable tremor that could not be controlled by medication. The median patient age was 71.5 years (range: 45–76). The average duration of symptoms was 9.5 ± 4.6 years (range: 3–26). Unilateral thalamotomy or DBS was selected when a patient had laterality on tremor severity. Bilateral DBS was performed in cases with severe bilateral tremors that impaired activities of daily life.

MRI

Before surgery, MRI studies were performed without a stereotactic frame. MRI data were acquired on a 3T MRI system (GE, Signa Horizon 3.0) comprising an isotropic T2-weighted image, a three-dimensional (3D) T1-weighted image with a contrast medium, and DTI. A T2-weighted fast spin echo image was acquired with the following parameters: repetition time, 4800 ms; echo time, 92 ms; field of view, 220 mm; matrix, 512 × 256; slice thickness, 2 mm; and number of excitations (NEX), 3. The 3D-T1-weighted image was acquired after contrast injection with the following parameters: repetition time, 700 ms; echo time, 1.5 ms; flip angle, 12; field of view, 220 mm: slice thickness, 1.6 mm; matrix, 512 × 256; and NEX, 1. DTI was acquired with the following parameters: repetition time, 4800 ms; echo time, 86 ms; field of view, 260 mm; matrix, 128 × 128; b-value, 1000 s/mm^2; and directions, 20.

Computed tomography (CT)

Preoperative stereotactic CT imaging data were acquired using a 320-row multidetector scanner (Aquilion ONE ViSION Edition, Toshiba). The parameters were as follows: tube voltage, 120 kV; tube current, 300 mA; collimation, 80 × 0.5; tube rotation time, 1.0 s; PF, 0.673; matrix, 512 × 512; slice thickness, 2 mm; and increment, 1 mm.

Stereotactic surgery

A stereotactic frame (Leksell model G) was mounted on the patient's head under local anesthesia. The base of the frame was roughly parallel to Reid's base line. After stereotactic CT scans were performed, image data were transferred to a FrameLink 5.0™ workstation and fused to preoperative MRI data (T1- and T2-weighted). After confirming AC and PC, the tentative targets were set at 13 to 17 mm lateral to the midline, 5–6 mm in front of the PC, and 0–3 mm superior to the AC-PC line. Entry points were determined for a trajectory to avoid vessels, sulci, and the lateral ventricles. Burr holes were opened at 15–20 mm anterior and 35 to 40 mm lateral to the bregma. After two or three multi-track micro-recordings were performed, Vim was determined by the firing of tremor-related cells

Table 1 Patient characteristics and pre/postoperative tremor scores. Age, sex, side, and surgery of patients are shown with pre- and post-operative tremor scores

Case	Age	Sex	Side	Surgery	Preoperative FTM tremor rating scale					Postoperative FTM tremor rating scale				
					UE tremor		Writing	Drawing		UE tremor		Writing	Drawing	
					rt.	lt.		rt.	lt.	rt.	lt.		rt.	lt.
1	74	M	lt.	coagulation	3	–	4	3	–	0	–	1	1	–
2	76	M	lt.	coagulation	3	–	4	4	–	0	–	0	0	–
3	69	M	bil.	DBS	4	4	4	4	3	0	0	0	0	0
4	74	F	lt.	coagulation	4	–	3	4	–	1	–	0	0	–
5	75	M	rt.	coagulation	–	3	–	–	3	–	0	–	–	0
6	45	M	lt.	coagulation	3	–	4	4	–	1	–	0	0	–
7	75	F	lt.	coagulation	3	–	3	3	–	0	–	0	0	–
8	55	M	bil.	DBS	4	3	3	3	3	0	0	1	1	1
9	66	M	bil.	DBS	4	3	4	4	3	1	0	0	0	1
10	68	M	bil.	DBS	4	3	4	3	3	0	1	0	0	0

FTM: Fahn-Tolosa-Marin, DBS: deep brain stimulation, UE: upper extremity.

or the kinesthetic response, ventralis caudalis, caused by the alteration in touch sensation. After a microstimulation (frequency, 130 Hz; pulse width, 60–90 μs; amplitude < 6–7 mA) was performed to evaluate tremor suppression and adverse effects, a target was determined. In cases of thalamotomy, a test lesion was made at 40°C for 60 s using Elekta™ to confirm that there was no neurological deficit. Finally, a lesion was made at 70–80°C for 20–60 s. In DBS cases, an electrode (Medtronic 3389) was used with confirmation of appropriate electrode placement with C-arm. Pulse generators were placed under general anesthesia, after electrode placement.

Clinical assessment

The degree of tremors was assessed with three items of the Fahn-Tolosa-Marin (FTM) tremor rating scale (upper extremity (UE) tremor, Drawing B, Writing) before and 3 months after surgery. Perioperative adverse effects were also surveyed. Microsoft Excel 2010 software was used to calculate averages, percentages, and standard deviations. Wilcoxon signed-rank tests were performed with StatView software.

Fiber tracking

DTI-FT was performed on a workstation of the StealthViz™ DTI software application. The fractional anisotropy level was 0.2. Minimal fiber length was set to 5 mm. Seed density was held at 3.0. Maximal directional change of fibers was chosen to be 150 degrees. All fiber tracts were described by setting three voxels of interest (VOIs) on T1- or T2-weighted images. In this study, we sought to describe the following four tracts: the cerebello-thalamo-premotor cortical fiber tract (C-T-preM: red fibers), cerebello-thalamo-primary motor cortical fiber tract (C-T-M1: green fibers), spino-thalamo-somatosensory cortical fiber tract (Sp-T-S1: blue fibers), and pyramidal tract (Py: purple fibers) (Figs. 1 and 2). The VOIs were set as follows:

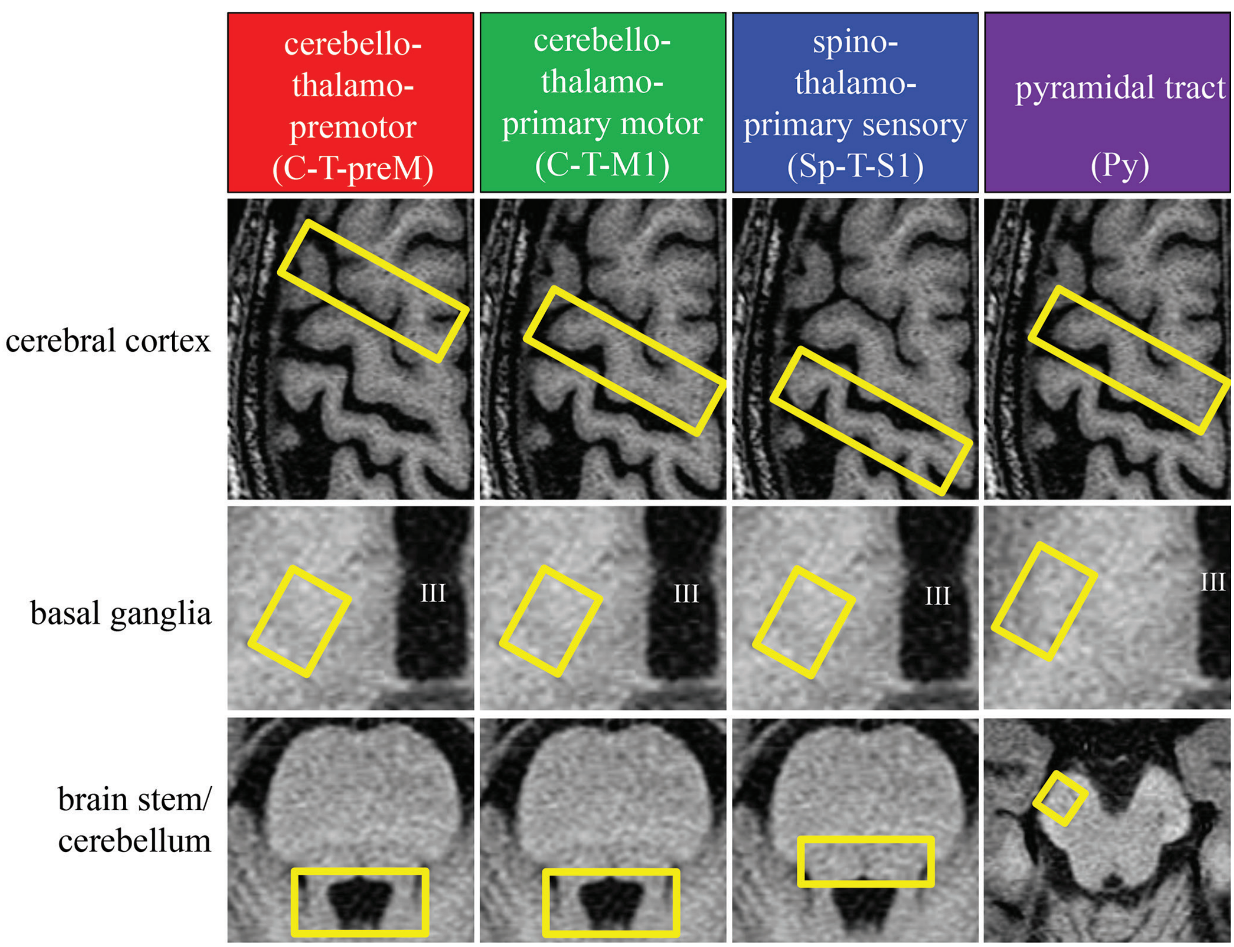

Fig. 1 Four fiber tracts evaluated in this study. Four fiber tracts are described by setting three VOIs. C-T-preM: superior cerebellar peduncle, thalamus on the AC-PC level, and preM; C-T-M1: superior cerebellar peduncle, thalamus on the AC-PC level, and M1; Sp-T-S1: medial lemniscus, thalamus on the AC-PC level, and S1; Py: cerebral peduncle, internal capsule, and M1.

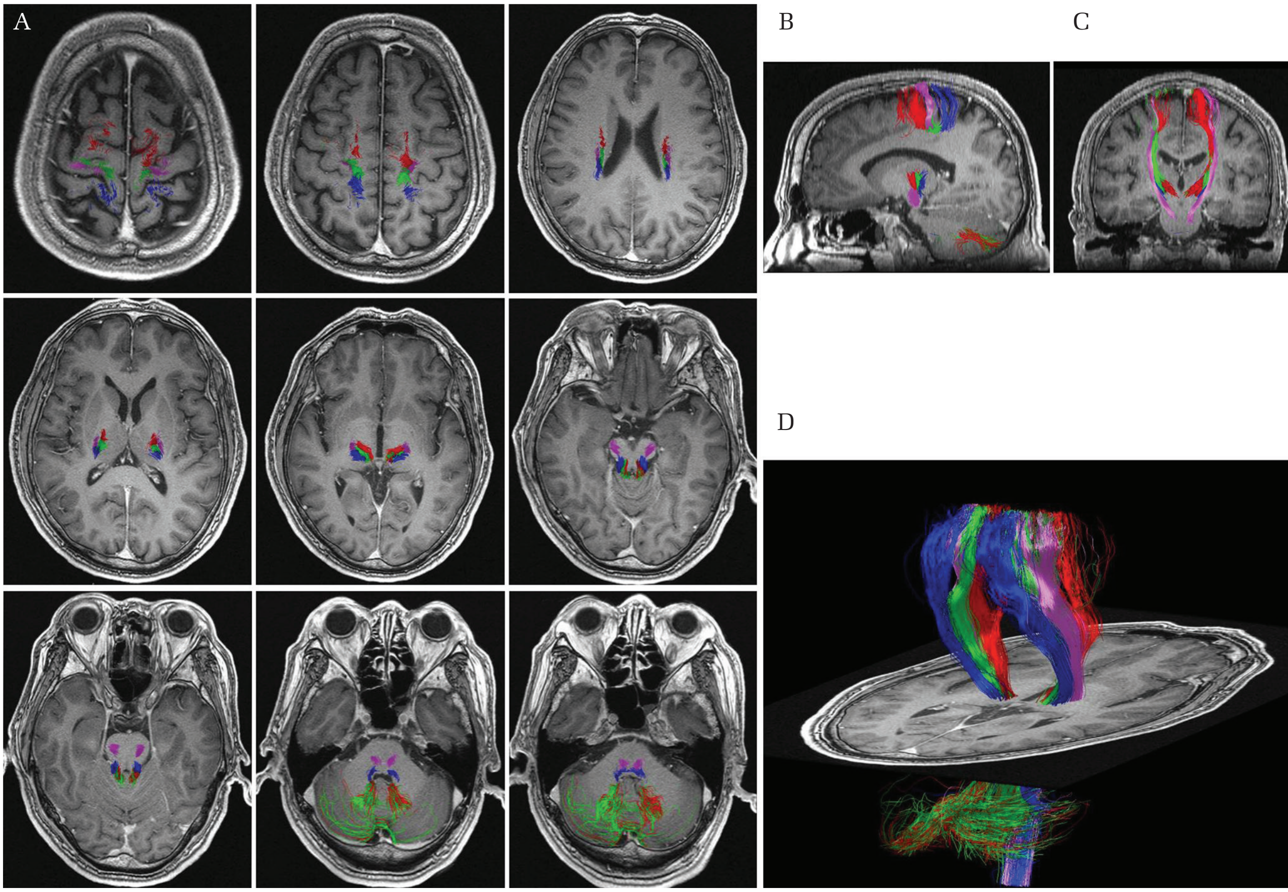

Fig. 2 Preoperative diffusion tensor imaging-based fiber tractography (DTI-FT). Consecutive axial (A), sagittal (B), coronal (C), and 3D (D) images of representative DTI-FT achieved preoperatively are shown.

C-T-preM: superior cerebellar peduncle, thalamus on the AC-PC level, and preM; C-T-M1: superior cerebellar peduncle, thalamus on the AC-PC level, and M1; Sp-T-S1: medial lemniscus, thalamus on the AC-PC level, and S1; Py: cerebral peduncle, internal capsule, and M1. Under these conditions, only fiber tracts that ran through all three voxels were described. Fiber tracts that were apparently non-existent were cropped. The four fiber tracts of interest are shown in 3D in Fig. 2.

Correlation between fiber tracts and lesions in thalamotomy cases

After MR scanning was performed 3 months after surgery, the image data of four patients who underwent thalamotomy were fused with the preoperative DTI-FT. The relationship between lesions and fiber tracts was examined. DTI-FT was carried out before and 3 months after surgery in two patients who underwent thalamotomy. The differences between preoperative and postoperative DTI-FT were examined.

Correlation between fiber tracts and active contacts of the lead in DBS cases

After CT scanning was performed 3 months after surgery, the image data of four patients who underwent DBS were fused with the preoperative DTI-FT. The placement of the active contact was evaluated with artifacts of contact in the postoperative CT image. Which fiber tract corresponded to the contact of the leads was examined in each case.

Results

Tremor suppression

Tremors were alleviated effectively in all cases (Fig. 3 and Table 1). The average preoperative and postoperative UE tremor score was 3.4 ± 0.51 and 0.29 ± 0.47 of 4, respectively. The average UE score was improved by 92%. The average Writing score was 3.7 ± 0.50 preoperatively, and 0.22 ± 0.44 postoperatively. The average Writing score improved by 94%. The average Drawing B score was 3.4 ± 0.50 preoperatively, and 0.29 ± 0.47 postoperatively.

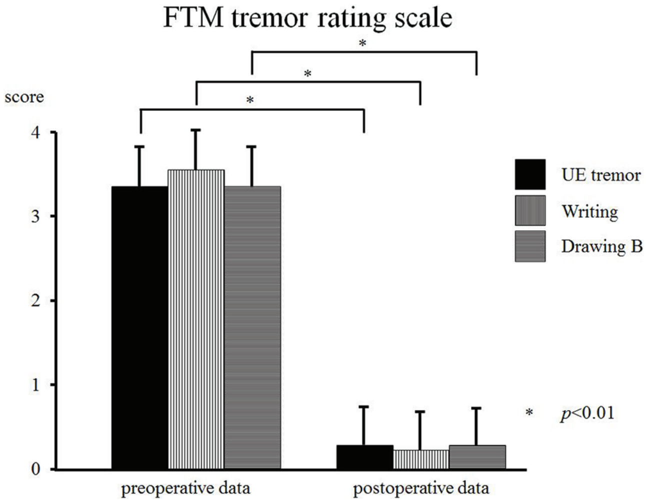

Fig. 3 FTM tremor rating scale. Three items of the FTM tremor rating scale (UE tremor, Writing and Drawing B) were evaluated before and 3 months after surgery. Patients who underwent thalamotomy or thalamus-DBS showed significant amelioration.

The average Drawing B score was improved by 92% (Fig. 3 and Table 1).

Adverse events

There were no perioperative permanent adverse events such as intracranial bleeding, ischemia, or infection in any case. In one patient who underwent thalamotomy, decreased tonus of extremities contralateral to the lesion was transiently observed. The symptoms completely disappeared 3 months after surgery. Mild dysarthria was observed in another case of thalamotomy. However, this symptom had also disappeared 3 months after surgery. In one case of DBS, transient paresthesia by electrical stimulation was observed.

Fiber tractography

C-T-preM is described as a fiber tract that passes from the cerebellum through the superior cerebellar peduncle via the red nucleus and the ventro-lateral thalamus to the preM (red fibers, Fig. 2). C-T-M1 is described as a fiber tract that passes from the cerebellum through the superior cerebellar peduncle via the red nucleus and the ventro-lateral thalamus to the primary motor cortex (M1) (green fibers, Fig. 2). Sp-T-S1 passes in front of the 4th ventricle (the medial lemniscus) and through the lateral midbrain, lateral posterior subthalamic area, and ventro-lateral thalamus with projection to the S1 cortex. Py is described as a thick fiber tract that passes from M1 via the posterior limb of the internal capsule through the cerebral peduncle (purple fibers, Fig. 2). C-T-preM and C-T-M1 were not clearly distinguished from the cerebellum to the red nucleus. From the red nucleus to the ventro-lateral thalamus, these two fiber tracts were meticulously and gradually separated from each other. Finally, in the ventro-lateral thalamus, C-T-preM and C-T-M1 were separated almost completely and projected parallel to the cortices. These fiber tracts passed through the white matter medially to Py. Sp-T-S1 got close to C-T-preM and C-T-M1 at the level of the superior cerebellar peduncle and then took a course to the lateral pons. Sp-T-S1 got close to C-T-M1 once again in the lateral area of the posterior subthalamic area at the level of the midbrain and passed into the posterior ventro-lateral thalamus. Finally, Sp-T-S1 projected to the S1 cortex in parallel with C-T-preM and C-T-M1.

Lesion position in thalamotomy cases

In all six cases of thalamotomy, lesions were clearly detected on T1- and T2-weighted images. The centers of the lesions were positioned on C-T-preM in all cases (Table 2). In the postoperative DTI-FT of two patients who underwent thalamotomy, C-T-preM was not described, and the postoperative C-T-M1 fiber tract was described as slightly different than the preoperative C-T-M1 (Fig. 4).

Position of active contacts of the lead in DBS cases

The centers of active contacts were on the C-T-preM or on the border between the C-T-preM and the

Table 2 The center of lesions or active contacts of the lead in all surgeries. Almost all fiber tracts passed the C-T-preM fiber

Case	Center of lesion or active contact
1	C-T-preM
2	C-T-preM
3 rt.	C-T-preM
3 lt.	Border
4	C-T-preM
5	C-T-preM
6	C-T-preM
7	C-T-preM
8 rt.	C-T-preM
8 lt.	C-T-preM
9 rt.	C-T-preM
9 lt.	C-T-preM
10 rt.	C-T-preM
10 lt.	C-T-M1

C-T-preM: cerebello-thalamo-premotor cortical fiber tract, C-T-M1: cerebello-thalamo-primary motor cortical fiber tract.

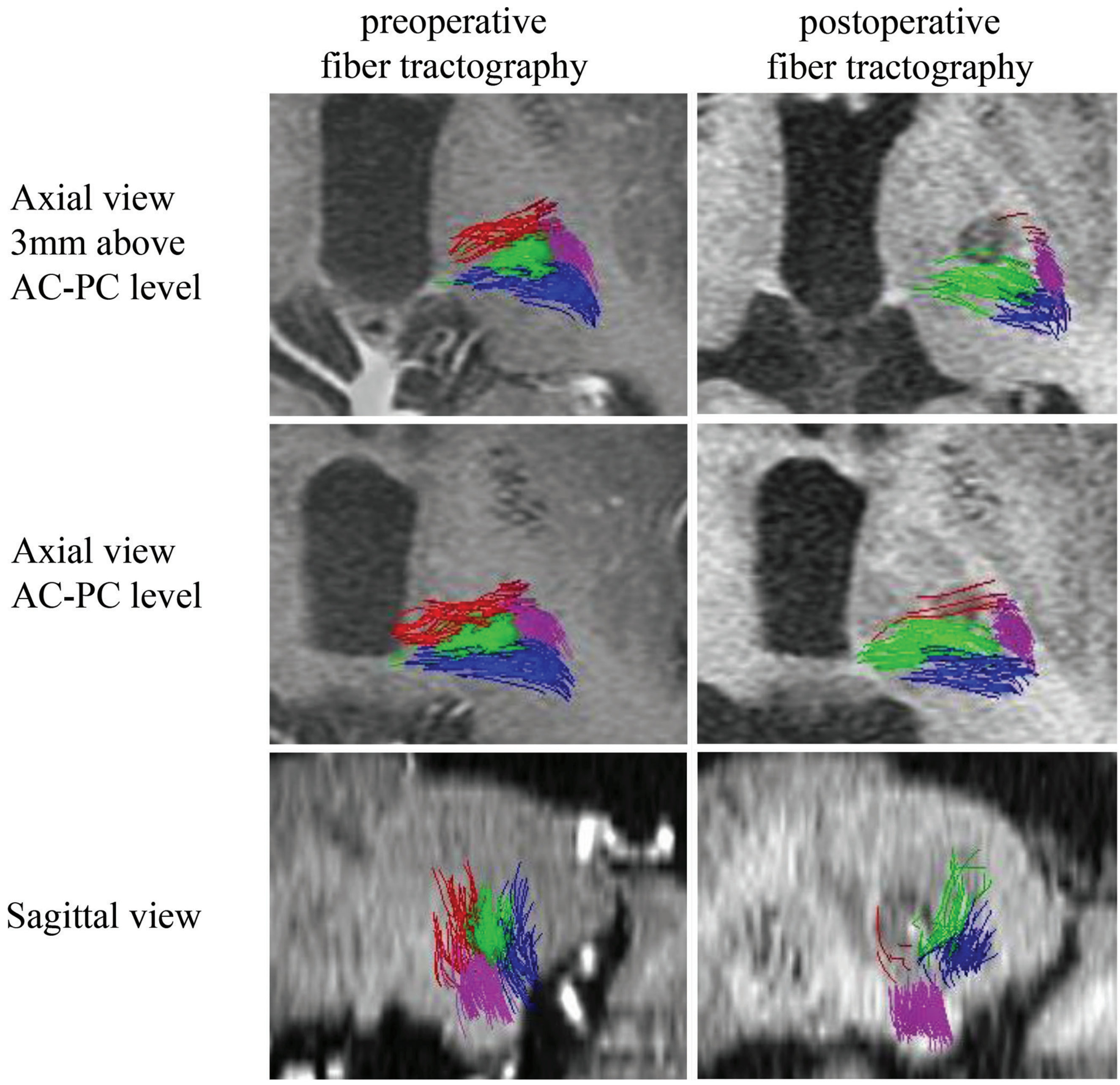

Fig. 4 Pre/postoperative DTI-FT after thalamotomy. This figure is pre- and postoperative DTI-FT of the representative case after thalamotomy. All four fiber tracts were described preoperatively. Postoperatively, C-T-preM was not described well at any level.

C-T-M1 (Fig. 5). The placement of the lead in regard to DTI-FT is shown in Table 2. In the thalamus, the tremor suppression effect seemed to be stronger if the lead was placed nearer the center of C-T-preM.

Discussion

In this study, tremor suppression was achieved in all 10 patients who underwent stereotactic surgery for thalamus without any permanent complications. With DTI-FT, four tracts of C-T-PreM, C-T-M1, Sp-T-S1, and Py were drawn. Lesions in thalamotomy patients or active contacts of the lead in DBS patients were positioned dominantly in C-T-PreM (12/14: 86%). This is the first report to use DTI-FT to demonstrate that C-T-PreM might be critical for tremor suppression.

Tremor suppression and adverse effects by surgery

Over 50 years have passed since Reichenbach reported stereotactic surgery for Parkinson's disease.[10)]

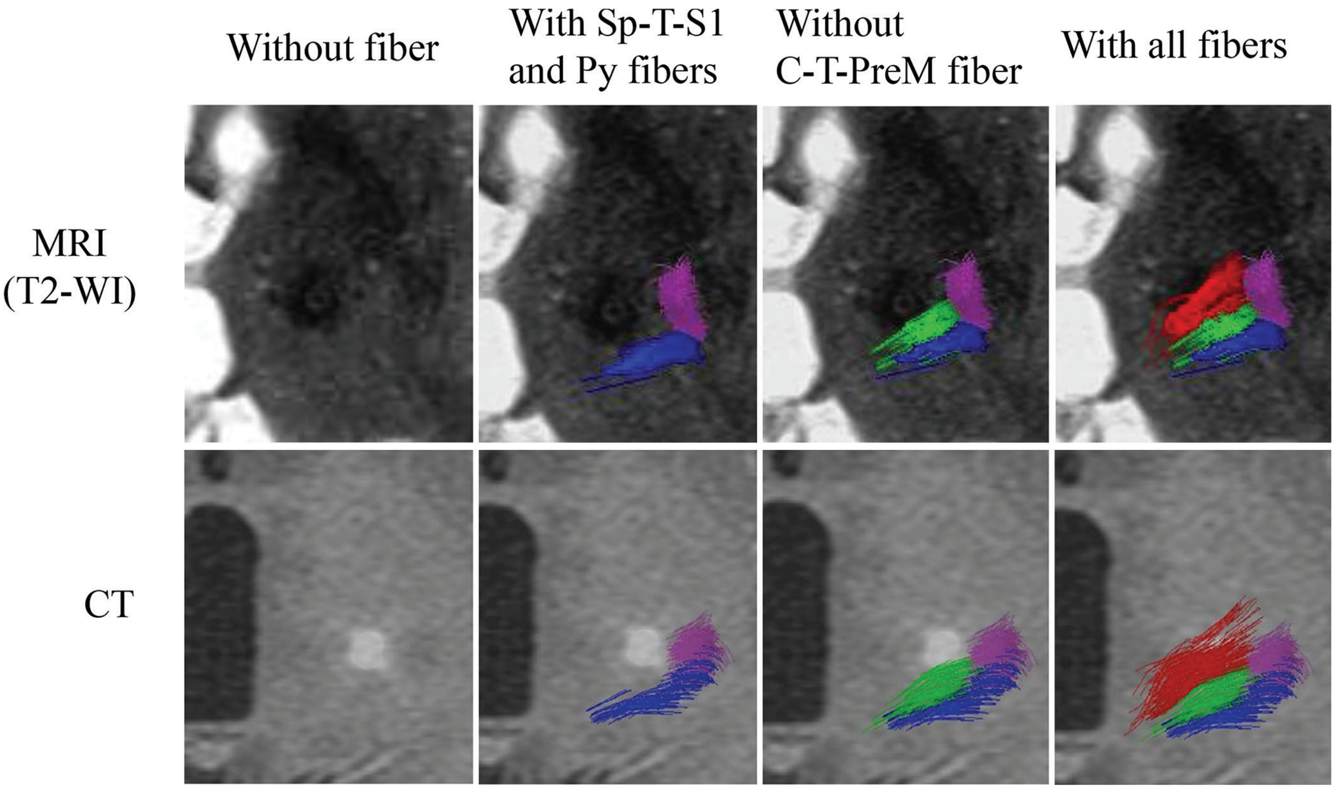

Fig. 5 Pre/postoperative DTI-FT after DBS. Preoperative DTI-FT was added in a step-by-step manner on preoperative T2-weighted image (*upper column*) and on postoperative CT (*lower column*), showing that C-T-PreM fibers were on the active contacts of the lead in DBS patients.

At that time, the mortality rate for stereotactic surgery was as high as 2%.[11] The technology for safe and precise stereotactic surgery has advanced notably. Thirty-six Parkinson's disease patients with intractable tremor underwent Vim thalamotomy with modern stereotactic techniques using microelectrode recording.[12] Over 90% of patients enjoyed symptomatic amelioration, although 13% suffered from permanent complications. During the same period, electrical stimulation of Vim was shown to be effective at controlling tremor, with 88% symptomatic relief for patients with Parkinson's disease or essential tremor.[13] Subthalamic nucleus stimulation was also reported to be effective in four patients suffering from intractable tremor without any permanent complications.[14] During the past 10 years, more than one electrode (e.g., Vim plus VoA and VoP) has sometimes been used to control intractable tremor.[2] In our study, tremor amelioration was achieved in all 10 patients. Tremor scores on three items were improved by over 90%. There were no permanent complications, although 3 of the 10 patients suffered from transient complications that had disappeared 3 months after surgery. The surgical outcomes in this study are favorable and show that thalamus-DBS and thalamotomy are effective for tremor suppression and are relatively safe, although further follow-up is needed.

Validity of DTI-FT

In our study, DTI-FT was performed with StealthViz™ DTI software in which fiber assessment by continuous tracking algorithm was incorporated. This algorithm is a computing method for deterministic fiber tractography that uses the diffusion anisotropy of water molecules. Water molecules move more easily along axonal bundles than perpendicular to them because fewer obstacles exist along the fibers. Thus, diffusion anisotropy refers to the direction of the axonal bundle in a voxel.[9,15,16] In deterministic tractography, fiber tracts are constructed by tracking the major directions of the diffusion anisotropy for every neighboring voxel. In our study, postoperative fiber tracts passing through lesions were not drawn in two cases of thalamotomy. This is because it is supposed that thalamotomy might break up neuronal axons and the anisotropy of lesion sites would be lost. Artifact by the lead might also affect the anisotropy in DBS cases, although we did not perform postoperative DTI after DBS. One of the existing issues of deterministic fiber tractography is the drawing of crossing or kissing fiber tracts. Although three VOIs were settled for each fiber tract in our study, meaningless tracts that might be crossing or kissing fiber tracts should be cropped by the examiner. It is thus impossible to avoid subjectivity completely, which might be a limitation of DTI-FT.

Tremor suppression target

Ever since Ohye reported that Vim might be a good target for tremor suppression, the best target for tremor suppression has been discussed.[17] Taira's review on tremor surgery showed the significance of Vim as a good target and the change in the trend for appropriate targets to suppress tremor.[18] The caudal zona incerta and posterior subthalamic area might be other good targets for tremor suppression.[19,20,21] Blomstedt revealed that re-operation of DBS on the caudal zona incerta achieved tremor suppression after unsatisfactory initial DBS for Vim.[19] The posterior subthalamic area was also demonstrated to be a safe and feasible target for tremor suppression.[20] Plaha showed the superiority of the caudal zona incerta in the rate of tremor control in PD patients compared to subthalamic nucleus (STN).[22]

Developments in DTI technology have revealed the critical fiber connections related to tremor suppression as well as the critical thalamic nuclei. The involvement of the dentatorubrothalamic tract has been demonstrated in several retrospective studies.[21,23] In the analysis of 11 patients who underwent DBS, all effective contacts were located inside or in proximity to the dentatorubrothalamic tract. The preoperative DTI-FT was fused with the postoperative CT image. In regard to the cerebellar involvement in patients with essential tremor, DTI technology is also significant. The mean diffusivity of the cerebellar gray matter of 67 essential tremor patients was significantly higher than that of healthy controls, which might indicate the presence of microstructural changes in the cerebellum of patients with essential tremor.[24] Furthermore, the other group showed long-term structural changes in the cerebelloruburothalamic tract after thalamotomy by DTI.[25]

In our study, four tracts (C-T-PreM, C-T-M1, Sp-T-S1, and Py) were focused on and the strong involvement of C-T-PreM was shown in 10 consecutive patients with essential tremor who underwent thalamotomy or thalamic DBS. A multi-institutional study of thalamic DBS using the probabilistic connectivity technique[26] showed that efficacious DBS contact for controlling tremor was highly co-localized with thalamic voxels demonstrating a high probability of connectivity with PreM.[27] The strong involvement of PreM was demonstrated by both DTI-FT in our study and by probabilistic connectivity technique in their study. It might be possible that C-T-preM and C-T-M1 described in our study showed afferents from the cerebellum passed through not only Vim, but also the area anterior to Vim, which might be VoP, although it remains unclear from our DTI-FT data. Additionally, there might be fibers coincided spatially in Vim connected to preM or M1. Further exploration in this field will confirm the most effective target to suppress tremor and improve the accuracy of stereotactic surgery.

Key perspectives and limitations

Recent studies on the pathophysiology of tremor showed the commonalities and differences between Parkinson's disease and essential tremor.[28,29] The cerebellothalamocortical circuit might be the center of the pathology of both pathological conditions. The switch in Parkinson's disease is, however, dopaminergic dysfunction with subsequent exacerbated activity in the cerebellothalamocortical circuit whereas the key in essential tremor lies in dysfunction of the cerebellothalamocortical circuit itself. DTI-FT technology might accelerate breakthroughs in this field.

In clinical practice, DTI-FT might change therapeutic strategy. The lesions in thalamotomy or active contacts of the lead in DBS might be determined mainly by DTI-FT, although analyses of the position of the lead in DBS have been difficult.[30] The positional relationship between the thalamic nuclei and the surrounding fiber tracts might differ from person to person, and individual DTI-FT is needed to identify the most promising target.[31] Very recently, King demonstrated that the electrophysiological findings within the Vim thalamus defined by tractography corresponded with the known microelectrode recording characteristics of Vim in patients with tremor.[32] As for thalamic pain, the spinothalamocortical tract was described in DTI and integrated into the stereotactic treatment planning for DBS. Three of four patients reported more than 40% pain relief 1 year after surgery. This is the first report of DTI-FT-guided DBS.[33] Coenen also reported good short-term outcomes for two patients who underwent bilateral DBS in the STN with the electrodes traversing the dentatoruburothalamic fiber using DTI-FT.[34] The combined stimulation of the two targets might be ideal and appropriate for patient symptoms. A randomized controlled trial related to this strategy is ongoing (https://clinicaltrials.gov/show/NCT02288468), and the results are awaited. In the future, we expect that appropriate targets for patients with various types of tremors might be individually determined by DTI-FT.

Conclusions

In our study, good tremor suppression was achieved in all patients. The lesions and the active contacts of the lead were dominantly on the C-T-preM fiber tract in patients who underwent stereotactic surgery. C-T-preM fiber tracts might be an optimal target for tremor suppression. Further research could determine an optimal target for tremor in accordance with tremor type. Individual fiber tracts can be drawn with DTI-FT. DTI-FT enables the identification of the optimal target to achieve strong tremor suppression and also reduces the number of adverse events by keeping lesions or electrodes away from important fiber tracts, such as Py and Sp-T-S1.

Acknowledgment

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Conflicts of Interest Disclosure

All authors declare that we have no COI to be disclosed related to this manuscript. Additionally, the authors who are members of JNS have registered online Self-reported COI Disclosure Forms through the website for JNS members.

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