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MRI-guided high-intensity focused ultrasound thalamotomy for recurrent tremor: Case series and retargeting utilizing DTR deterministic tractography and computerized stereotactic atlases

Alexander Fleisher, Gordon Baltuch *

Department of Neurological Surgery, Columbia University Irving Medical Center, New York-Presbyterian Hospital, New York, NY, United States

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ABSTRACT

Introduction: Magnetic resonance-guided high-intensity focused ultrasound (MRgHIFU) is an incisionless neurosurgical procedure to treat essential tremor (ET) and tremor-dominant Parkinson's disease (TDPD). While MRgHIFU is an effective neurosurgical procedure to suppress tremor in ET and TDPD, recurrence of tremor symptoms after a first MRgHIFU ablative procedure have been reported. We present 3 cases to report the utilization of deterministic tractography and digitized stereotactic atlases to identify variables that contribute to recurrent tremor and to plan retreatment MRgHIFU thalamotomies.
Objective: We present 3 cases to report the utilization of deterministic tractography and digitized stereotactic atlases to identify variables that contribute to recurrent tremor and to plan retreatment MRgHIFU thalamotomies.
Methods: 2 patients with ET and 1 patient with TDPD initially underwent a successful and complication-free MRgHIFU thalamotomy procedure with standard indirect targeting. All 3 patients had recurrent tremor at 1–6 months post-ablation. Following this period, all patients received postoperative magnetic resonance imaging (MRI) scans with dentato-rubro-thalamic-tract (DRTT) two-tensor deterministic tracking (FT2) and a computerized stereotactic atlas superimposed onto the lesion site of thermoablation.
Results: In the TDPD patient, the DRTT was shown to be anterior to the high-intensity focused ultrasound (HIFU) lesion from the first ablation. Retreatment with anterior targeting permanently suppressed tremor. In 2 patients, the DRTT partially or fully reconstituted after the first ablation. The original target was retreated with increased-temperature sonications, resulting in permanent tremor suppression.
Conclusions: Postoperative image processing with DRTT deterministic tractography and computerized stereotactic atlases is an effective way to plan MRgHIFU thalamotomies for recurrent tremor. The target for TDPD may be anterior to the standard ventral intermediate nucleus (VIM) thalamotomy coordinates.

Introduction

Magnetic-resonance-guided high-intensity focused ultrasound (MRgHIFU) is a growing neurosurgical procedure to treat movement disorders such as essential tremor (ET) and tremor-dominant Parkinson's disease (TDPD) [1,2]. ET is among one of the most diagnosed movement disorders worldwide, reducing the quality of life (QOL) for approximately 7 million Americans [3]. Additionally, a large retrospective study found that TDPD (44%) is the most common subtype of Parkinson's disease compared to akinetic-rigid (29%), mixed (18%), and gait difficulty (9%) [4]. MRgHIFU offers an alternative to deep brain stimulation (DBS) in treatment for these disorders because MRgHIFU is incisionless, in most circumstances requires no anesthetic practices, and an outpatient procedure [5]. An increasing number of patients with ET and TDPD are choosing MRgHIFU further because of its treatment effectiveness, advantages over DBS, and faster recovery time [6].

Clinical evidence has demonstrated the lasting effects of MRgHIFU, reporting 50% improvement in combined hand ET and motor scores 4–5 years post-treatment [7]. Additional studies show the short-term and lasting effects of MRgHIFU tremor suppression in TDPD patients [8,9]. Intracranial MRgHIFU utilizes a helmet-like device that includes hundreds of ultrasonic emitters to deliver precisely targeted sound waves

* Corresponding author at: Department of Neurological Surgery, Columbia University Irving Medical Center, New York-Presbyterian Hospital, 710 West 168th St., 4th Floor, New York, NY 10032, United States.
E-mail addresses: alexander.fleisher@nyulangone.org (A. Fleisher), gb2774@cumc.columbia.edu (G. Baltuch).

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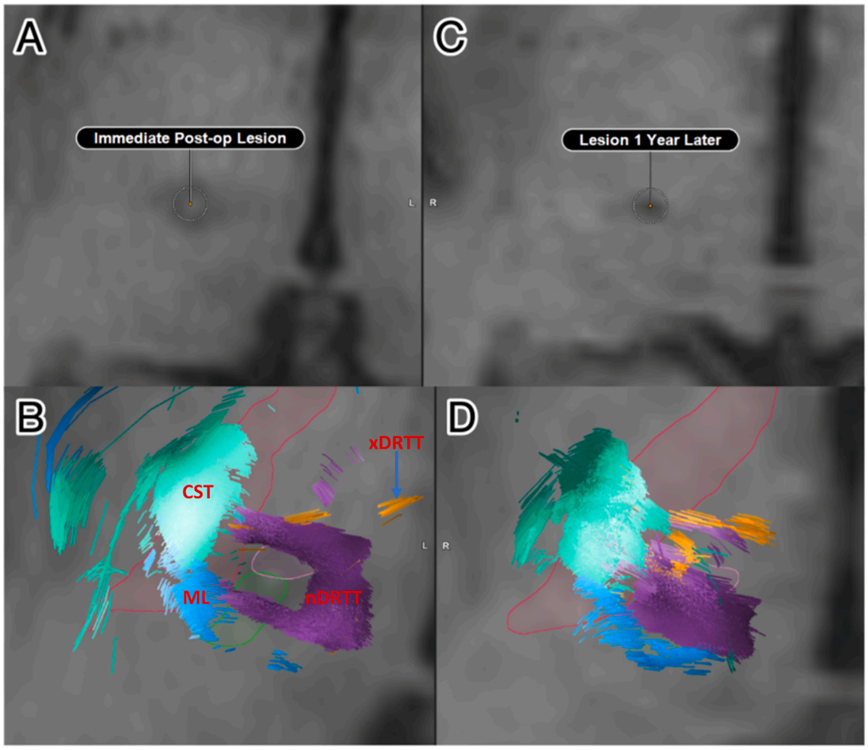

Fig. 1. Axial T1-weighted images of lesion sites in a 66-year-old right-handed female with ET. (A) Immediately post-op lesion core with surrounding edema. (B) FT2 tractography overlay with superimposed stereotactic atlas immediately post-op. The nDRTT (*purple*), xDRTT (*orange*), medial lemniscus (*blue*), and corticospinal tract *(green*) are shown. Atlas registration shows the internal capsule (*red* outline), VPL (*green* outline), and VIM (*pink outline*). (C) Ablation site 1-year post-op. Lesion core is no longer observed, showing a decrease in size. (D) FT2 tractography overlay with superimposed stereotactic atlas 1-year post-op. The nDRTT (*purple*), xDRTT (*orange*), medial lemniscus (*blue*), and corticospinal tract (*green*) are shown. Atlas registration shows the internal capsule (*red* outline) and VIM (*pink* outline). Abbreviations for key structures are displayed on the images in bold red text for clarity.

through the skull and create a thermal lesion in the thalamus. These waves converge at a single area, deep in the brain, and heat neural tissue to generate a lesion without the need for invasive surgery (thermoablation). The procedure is performed in an MRI scanner, which offers real-time imaging to guide the procedure and allows intraoperative adjustments based on clinical examination findings and real-time thermometry. The central target to treat these movement disorders through MRgHIFU is the dentato-rubro-thalamic-tract (DRTT) at its intersection with the ventral intermediate nucleus (VIM) of the thalamus. Although, consensus coordinates of thermoablation are utilized for this procedure, studies have shown that incorporating advanced-imaging techniques, such as diffusion tensor imaging (DTI) tractography and computerized stereotactic atlases, can be used to improve lesion precision and targeting [10,11]. This can result in increased tremor suppression while avoiding eloquent neural structures, reducing the risk of adverse events. Previous studies report that TDPD coordinates are more anterior compared to classic, indirect VIM targeting coordinates to result in a more pronounced clinical effect [12].

While MRgHIFU is an effective neurosurgical approach for reducing tremor in ET and TDPD patients, recurrence of tremor symptoms following the initial ablative procedure have been reported [13–15]. This case series presents 2 cases of recurrent ET and 1 case of recurrent TDPD after a successful, initial MRgHIFU ablative procedure. We use two-tensor deterministic tracking (FT2) and superimposed, computerized stereotactic atlases to gain insight into MRgHIFU factors associated with tremor recurrence and to guide a retreatment procedure. This case series shows how FT2 tractography and computerized stereotactic atlases can be used in conjunction with standard, indirect targeting to improve MRgHIFU treatment outcomes, optimizing the procedure for ET and TDPD patients.

Methods

Patient selection and initial MRgHIFU treatment

Patients were selected based on the identification of medically recurrent tremor symptoms for ET and TDPD after an initial MRgHIFU ablative procedure that successfully suppressed the tremor. 3 patients fit these criteria and were selected for this case series: 2 patients with ET and 1 patient with TDPD. The 2 ET patients consisted of a 66-year-old right-handed female and 72-year-old right-handed male. The TDPD patient selected was a 62-year-old right-handed male. All 3 patients developed recurrent tremor symptoms 1–6 months post-op. The recurrent tremor had a similar severity to the pre-ablation tremor for the corresponding pathology. The central target of initial lesioning for all patients was the VIM contralateral to the dominant hand for tremor suppression. Initial lesion targeting utilized standard, indirect targeting: 13–15 mm lateral to the midcommissural point (MCP), 25% of anterior commissural-posterior commissural (AC-PC) distance posterior to the MCP, and 1.5 mm superior to the AC-PC plane. Intraoperative MRI sequences were also obtained throughout each ablation to guide the placement of the lesion and see it in real time. All patients underwent a successful MRgHIFU ablative procedure, and immediate tremor suppression was achieved, as evidenced by intraoperative and immediately post-operative Archimedes spiral testing. There were no complications observed in any of the MRgHIFU procedures including post-operative gait ataxia and paresthesia.

MRI analysis and planning for retreatment

For each patient, comparative MRI imaging sequences were obtained for optimal and thorough ablation analysis. MRI sequences considered

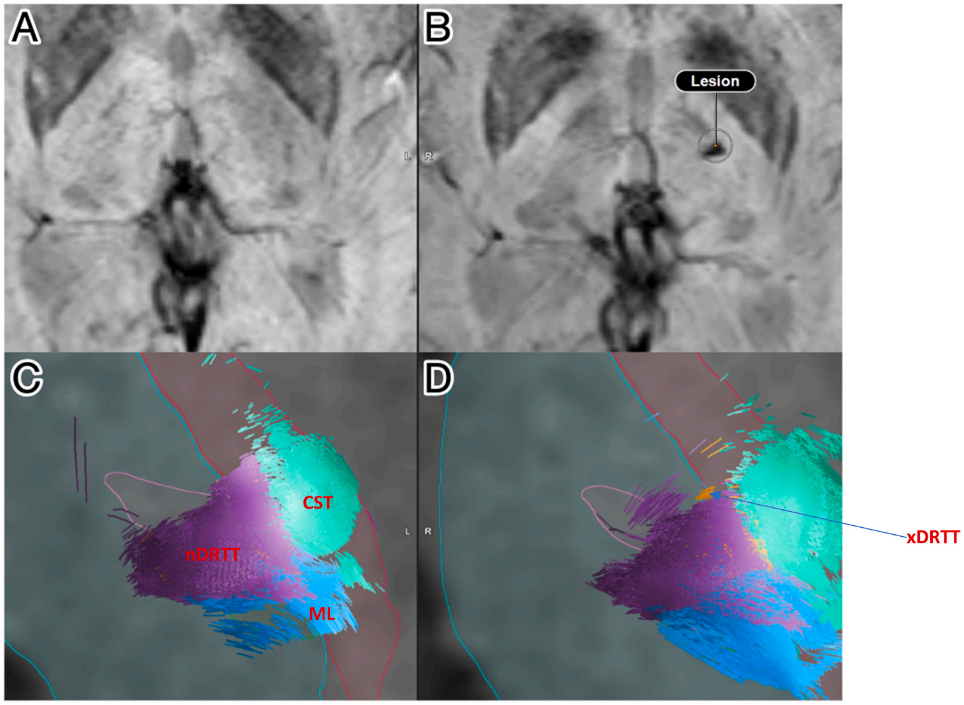

Fig. 2. Lesion sites and image processing in a 72-year-old right-handed male with ET. (A) Pre-op SWI. (B) Immediate post-op SWI of the ablation site. A triangular-shaped lesion is observed. (C) FT2 tractography overlay with superimposed stereotactic atlas on pre-op axial T1-weighted image. The nDRTT (*purple*), medial lemniscus (*blue*), and corticospinal tract (*green*) are shown. The xDRTT could not be successfully tracked. (D) FT2 tractography overlay with superimposed stereotactic atlas on immediately post-op axial T1-weighted image. The nDRTT (*purple*), xDRTT (*orange*), medial lemniscus (*blue*), and corticospinal tract (*green*) are shown. Atlas registration shows the internal capsule (*red outline*), thalamus (*blue* outline), and VIM (*pink* outline). Abbreviations for key structures are displayed on the images in bold red text for clarity.

for the 66-year-old right-handed female with ET were axial T1-weighted images of the lesion site immediately post-op and 1-year post-op. Susceptibility-weighted sequences (SWI) of the 72-year-old right-handed male with ET were considered in the pre-ablation and post-ablation stages for lesion presentation. Axial T1-weighted images of each ablation stage were also included for advanced imaging analysis. As well, axial T1-weighted images of pre-op and post-op lesion sites for the 62-year-old right-handed male with TDPD were considered. Per patient, we compared these two sequences to identify causes of recurrent tremor and to plan retreatment MRgHIFU thalamotomies. For MRI imaging comparison analyses, we employed the use of Brainlab Elements (Brainlab, Munich, Germany). Brainlab® is a broadly utilized, FDA-approved neurosurgical planning software platform that supports precision targeting in procedures such as DBS and MRgHIFU. Brainlab Elements Fibertracking was used for FT2 tractography, based on obtained DTI studies for each patient, to visualize whiter matter bundles of importance. White matter bundles were selected based on four-tract tractography targeting [16]. Four-tract tractography targeting is beneficial because it allows for precise visualization and differentiation of critical white matter pathways that are relevant to tremor suppression. By identifying and mapping tracts such as the decussating dentato-rubro-thalamic-tract (xDRTT) and non-decussating dentato-rubro-thalamic-tract (nDRTT), corticospinal tract (CST), and medial lemniscus (ML) we could potentially identify recurrent tremor variables, as variations of four-tract tractography targeting have shown to be useful in retreatment MRgHIFU procedures for recurrent tremor [13]. Additionally, Brainlab Elements was used for neuroanatomical mapping to predict the locations of structures on and near the lesion site to create customized stereotactic atlases. Atlas structures were also rendered according to the tractography regions of interest (ROIs). Once the atlas and tractography were established, the tractography was superimposed onto the atlas for each patient. Each image set was then qualitatively evaluated based on tract changes and lesion placements.

Results

In all patients, post-operative imaging studies show successful MRgHIFU ablation, four-tract tractography analyses, and rendered atlases. An immediate post-ablation T1-weighted sequence for the 66-year-old right-handed female with ET shows an observable lesion core and outer rim area (Fig. 1A). The superimposed neuroanatomical atlas of this lesion shows that the lesion overlaps with the VIM and ventral posterolateral nucleus (VPL) of the thalamus (Fig. 1B). This patient experienced no adverse events associated with an ablated VPL or ML such as gait imbalance, ataxia, and numbness or loss of sensation. Tractography analysis also reveals that the nDRTT, xDRTT, and ML are discontinued when the lesion overlaps with the VIM. However, as evidenced by 1-year post-ablation T1-weighted sequences, the lesion faded over time and lost an observable core (Fig. 1C). The nDRTT, xDRTT, and ML are also reconstituted at this point (Fig. 1D). A permanent lesion was then placed with a retreatment procedure including increased-temperature sonications. SWI imaging of the 72-year-old right-handed male with ET shows the emergence of a lesion after an initial MRgHIFU procedure (Fig. 2A and 2B). Tractography analysis shows a partial discontinuity in the nDRTT in the post-ablation stage compared to the pre-ablation stage (Fig. 2C and 2D). The ablation also partially overlaps with the VIM. Increased-temperature sonications in a retreatment procedure resulted in lesional temperatures that created a persistent lesion and permanent tremor suppression. In the 62-year-old right-handed male with TDPD, T1-weighted imaging shows the placement of a lesion post-ablation with an observable core and outer rim area (Fig. 3A and 3B). Tractography analysis demonstrates that the nDRTT was disrupted post-ablation compared to pre-ablation, overlapping with the VIM (Fig. 3C and 3D). However, the nDRTT is found to be anterior to the lesion site of ablation. A more pronounced clinical effect was obtained in a retreatment procedure with anterior targeting.

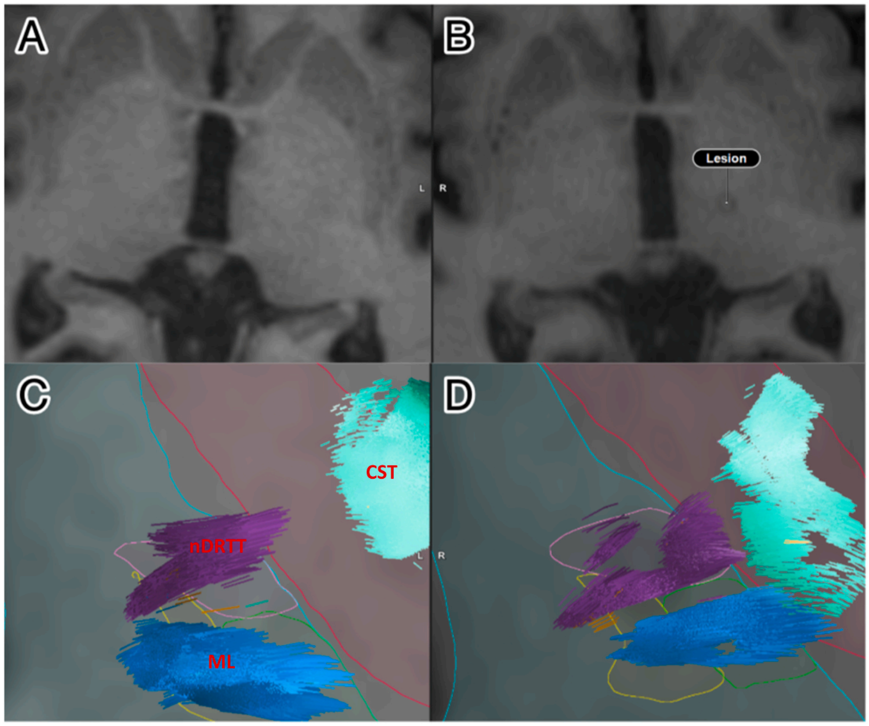

Fig. 3. Axial T1-weighted images of lesion sites in a 62-year-old right-handed male with TDPD. (A) Pre-op. (B) Immediate post-op ablation site. Lesion core and surrounding edema is observed. (C) FT2 tractography overlay with superimposed stereotactic atlas pre-op. The nDRTT (*purple*), medial lemniscus (*blue*), and corticospinal tract (*green*) are shown. The xDRTT could not be successfully tracked. Atlas registration shows the internal capsule (*red* outline), thalamus (*blue* outline), and VIM (*pink* outline), VPL (*green* outline), and ventral posteromedial nucleus (VPM; *yellow* outline). (D) FT2 tractography overlay with superimposed stereotactic atlas immediately post-op. The nDRTT (*purple*), medial lemniscus (*blue*), and corticospinal tract (*green*) are shown. The xDRTT could not be successfully tracked. Atlas registration shows the internal capsule (*red* outline), thalamus (*blue* outline), and VIM (*pink* outline), VPL (*green* outline), and VPM (*yellow* outline). Abbreviations for key structures are displayed on the images in bold red text for clarity.

Discussion

The 66-year-old right-handed female with ET who experienced recurrent tremor after an initial MRgHIFU ablation show evidenced lesion fading 1-year post-op. Previous studies demonstrate that MRgHIFU-induced lesions can shrink overtime, with lesion shrinkage linked to a higher risk of tremor recurrence [17]. The initial lesion comprises of a necrotic central core, surrounded by cytotoxic and perilesional vasogenic edema. This edema suppresses neural transmission in and around the VIM. This can be seen using the computerized stereotactic atlas. As edema resolves overtime, surrounding intact tremorgenic pathways may recover, contributing to tremor recurrence [18]. So, early tremor suppression may reflect transient functional suppression. Once the edema resolves, residual tremor circuits may reemerge. This is evidenced in this study where the nDRTT reconstituted 1-year post ablation, promoting tremorgenic pathways. The retreatment procedure resulted in a permanent lesion that was placed with increased-temperature sonications, so this suggests decreased temperature efficiency for the initial MRgHIFU procedure. Studies show that there is a strong correlation between thermal dose and sustained tremor improvement ($r = 0.73$) [19]. This is because sonication reaching 55–60°C induce coagulative necrosis, irreversibly disrupting tremor-generating circuits in the VIM such as the nDRTT and xDRTT. Faster neural tissue heating reaches the threshold for coagulative necrosis more reliably within targeted intracranial nuclei, creating larger lesions that are more centered on critical tremor pathways. So, high temperatures ensure optimal ablation early on, leading to a more robust lesion formation and permanent tremor suppression [20].

In the 72-year-old right-handed male with ET, there is an observable lesion on SWI imaging immediately post-operatively. The tractography demonstrates that the nDRTT is discontinued post-op, indicating ablation. However, the lesion is not visible on the T1-weighted sequence with the atlas and tractography overlay. This also suggests decreased temperature efficiency, similar to the previously discussed case, during the initial MRgHIFU procedure because sonications delivered at higher temperatures achieved the thermal threshold necessary for permanent lesioning, resulting in long-term tremor suppression. Also, there is only partial disruption of the nDRTT which could indicate incomplete DRTT ablation. One proposed mechanism is that only partial interruption of DRTT pathways initially suppresses tremor, but alternate routes – like the pallidothalamic tract – can compensate overtime, allowing tremor signals to accumulate again [21]. Also, MRgHIFU lesions that partially intersect the DRTT leave residual, functional fibers of the tract intact [22]. These spared fibers can continue to propagate tremor signals, leading to partial or transient clinical effects. A prospective MRgHIFU cohort study demonstrated that greater overlap between the ablation site and posterior DRTT white matter was significantly associated with durable tremor suppression [23]. Lesions that failed to intersect these critical fibers only led to partial or short-term clinical benefits.

In the 62-year-old right-handed male with TDPD, tractography revealed that the nDRTT was located anterior to the ablation site. A more pronounced clinical effect was obtained with anterior targeting, suggesting that TDPD may be generally more anterior compared to classic indirect targeting coordinates. Previous studies suggest different anatomy in TDPD tremor circuits, where the TDPD efficacy peak is significantly anterior to ET target [12]. Accordingly, targeting slightly anterior to classic indirect coordinates yields better clinical response in TDPD, likely reflecting the distinct spatial organization of tremor-conducting tracts in this patient group. Future studies should prospectively evaluate anterior versus conventional targets, ideally using tractography to confirm DRTT engagement and correlate lesion location with long-term tremor suppression. Incorporating individual connectomic data may further refine patient-specific targeting strategies for the TDPD treatment group for MRgHIFU. Although this study shows the efficacy of using four-tract tractography targeting in conjunction with computerized stereotactic atlases, the use of this method alone should not replace classic indirect targeting due to error possibilities behind the planning software algorithms [24]. Importantly, in the example patient described, the initial lesioning was performed using standard indirect targeting, and thus these advanced imaging tools should be interpreted as complementary adjuncts rather than primary determinants of targeting. Reliance solely on 'new and digitalized' planning features may introduce inaccuracies, and integration with established stereotactic principles remains essential. Additionally, tractography outputs are dependent on ROI selection and user-defined parameters, which can significantly influence the resulting visualization of white matter pathways. Superimposed atlas structures and tractography findings may not always correspond precisely with intra-operative neurophysiological data (e.g., microelectrode recordings in DBS procedures). Therefore, these tools should be interpreted cautiously and used as complementary adjuncts to established stereotactic targeting methods and clinical judgment. For example, the 66-year-old right-handed female with ET showed an ablated ML with lesion overlap into the VPL immediately post-op. However, the patient experienced no symptoms associated with ML ablation extended into the VPL. This case series indicates that FT2 tractography, when combined with computerized stereotactic atlases and standard indirect targeting, can enhance the precision of MRgHIFU procedures and potentially improve treatment outcomes in both ET and TDPD patients.

Conclusions

We demonstrate that the use of DTI deterministic tractography and digitized stereotactic atlases yields valuable insight into recurrent tremor causes after a successful

MRgHIFU procedure in ET and TDPD patients. The use of tractography and stereotactic atlases on post-op image processing can also be used as a method to plan re-operations for recurrent tremor MRgHIFU cases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors of this manuscript have no acknowledgements to declare.

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