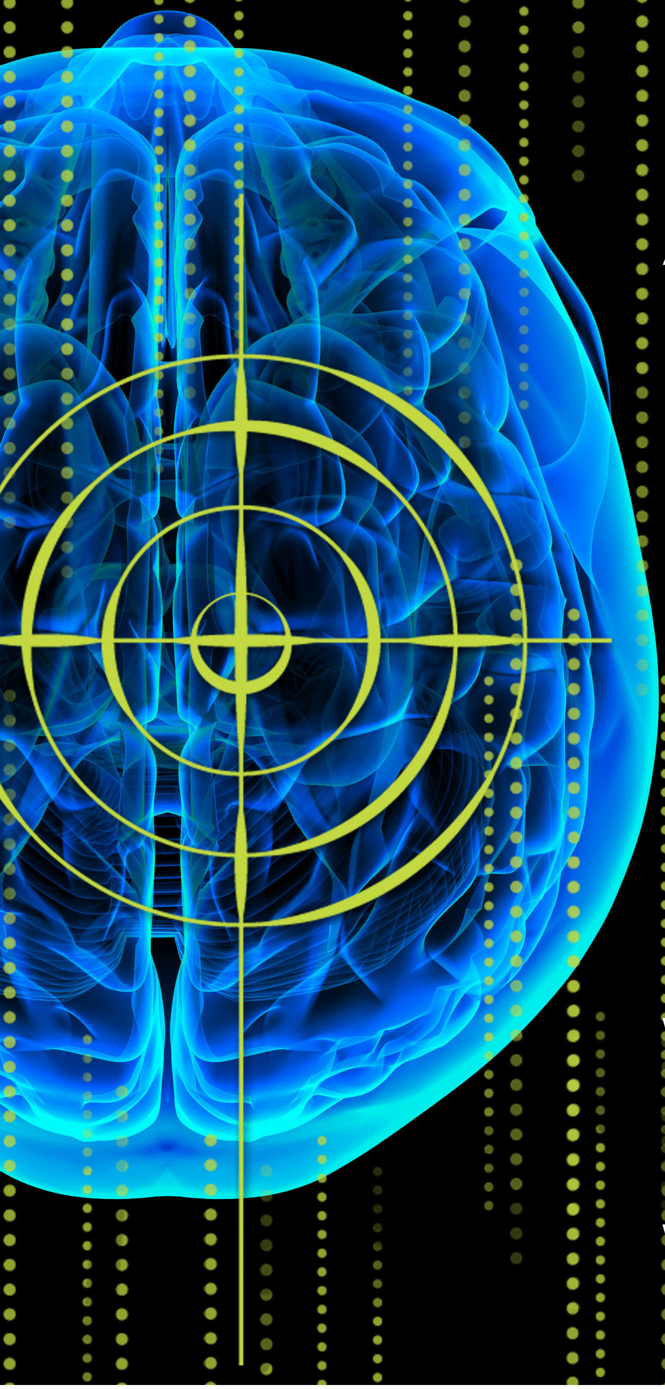


Brain Targeting

Focused Ultrasound Ablation for Essential Tremor

Workshop

13–14 September 2023

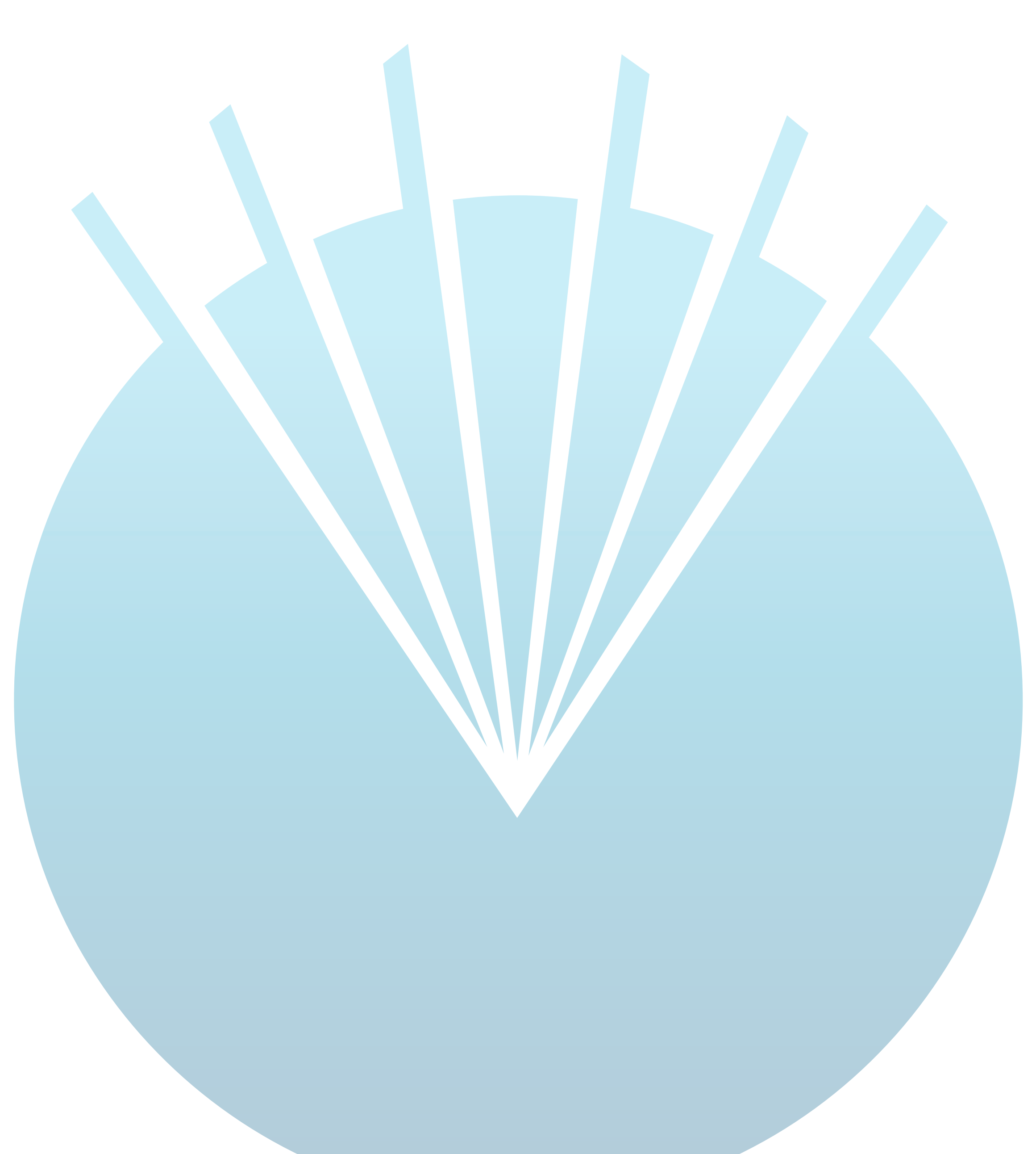
Renaissance Downtown

Washington DC

Sponsored by

Focused Ultrasound Foundation

INSIGHTEC



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Executive Summary

This white paper summarizes a one and a half-day workshop, "Brain Targeting: Focused Ultrasound Ablation for Essential Tremor," organized by the Focused Ultrasound Foundation and Insightec. The workshop began with presentations on the current state of the field and commercial landscape for focused ultrasound ablation treatment of essential tremor (ET).

This invite-only workshop brought together experts to present their knowledge and experience as well as discuss various approaches to maximize efficacy and decrease side effects, with a goal to improve patient experience and bolster the clinical credibility of the technology for ET ablation (driving further adoption and improving care).

There was agreement regarding uncertainty about what location is the best target and how to standardize localization into a method. Various approaches for optimal targeting included atlas-based targeting, direct targeting with white matter nulling MRI sequences, diffusion tensor imaging tractography, connectomics, and neuromodulation.

Collaborative efforts are needed to analyze and compare retrospective data across centers using different targeting methods. Standardizing imaging protocols, clinical outcomes, timing of assessments, and safety/efficacy metrics will be important to enable collaborative data analysis. Other key goals discussed were standardizing how to determine when the treatment is finished and clinical outcome measures.

Overall, the workshop highlighted the need to convene experts to determine the optimal standardized approach to focused ultrasound thalamotomy for essential tremor through data sharing and analysis and creating a roadmap to move the field forward.

Welcome and Background Introduction

Matt Eames, PhD, welcomed attendees and described the workshop goals:.

- Improve focused ultrasound (FUS) ET treatment outcomes by increasing efficacy, decreasing side effects, decreasing treatment time, and decreasing cost.
- Determine if there is a “best” standardized approach for targeting.
- Create a roadmap for future research and collaborations.
- Produce a white paper for the community.

Dr. Suzanne LeBlang, MD, presented results from a pre-meeting survey of attendees on their current practices for treating ET with FUS ablation. All respondents targeted the ventralis intermedius nucleus (VIM) to treat ET, but 30% also targeted the zona incerta, and 10% reported including the dentato-rubro-thalamic (DRT) tract or other areas. All respondents acquired pre-operative MRI. Most respondents (90%) reported using AC/PC coordinates for targeting. Most mentioned complementary techniques such as an atlas-based approach (40%), tractography (30%), connectomics (10%), or another method. Regarding optimal size of the necrotic lesion in Zones 1 and 2 in the axial plane, the majority responded 6–7 mm (70%), some reported 7–8 mm (20%) or 5–6 mm (10%). To monitor targeting, clinicians carefully observe clinical side effects in all patients (100%), as well as peak temperature (70%), clinical tremor (70%), thermal dose (60%), and non-thermal neuromodulation effects (20%). For the preferred/optimal number of sonications (including alignment, verification, and treatment) attendees responded with 7 (60%), 5 (20%), and 6 or 8 (tied, 10%). All sites collected T2-weighted images (100%), some collect diffusion-weighted images (DWI, 50%) or gradient echo sequences (GRE, 30%) following the procedure. The timing of post-treatment imaging varied across sites; immediately after the procedure (80% of sites), 24 to 48 hours after the procedure (50% of sites), and 1 to 3 months after the procedure (30% of sites). When asked what the acceptable occurrence of ataxia as a short-term side effect is, 50% answered 10% to 20%, 30% answered more than 20%, and 20% answered less than 10%. Most respondents felt that the acceptable occurrence of motor deficits was less than 2% (80%), some responded between 2% to 10% (20%). The acceptable occurrence of sensory deficits was between 2%–10% (50%), less than 2% (30%), or 10%–20% (20%).

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Presentations

Commercial Landscape – Insightec

Augusto Grinspan, MD, explained that Insightec is interested in increasing the consistency of brain targeting. In 2023, there were 143 magnetic-resonance guided FUS (MRgFUS) centers across 24 countries. There are 72 MRgFUS programs in the US, with 59 active programs and 13 in the process of launching. The number of procedures performed per year has increased from 262 in 2016 to 3,646 in 2022. There is still a lack of knowledge on the MRgFUS procedure for treating ET by clinicians, including the fact that follow-up data is available for more than 5 years for some patients. They hope to increase the presentations and posters at neuroscience meetings to increase awareness.

Current State of the Field

Essential Tremor

Vibhor Krishna, MD, discussed the current state of the field for ET and MRgFUS.[1] He described a trial in which patients were randomized to receive either MRgFUS thalamotomy or a sham procedure and found that patients treated with MRgFUS had improvement in contralateral tremor 3 months after the procedure.[1] After 1 year, there was a 40% improvement in contralateral tremor. However, there is a large degree of heterogeneity in outcomes because of target selection and the amount of tissue ablated during the procedure.[2,3] Safety data suggests that most adverse events were mild, with the most frequently occurring related to sensory deficits or balance.[4] To date, there have been 87 studies published on the use of MRgFUS for ET. In a survey of outcomes from these studies, tremor relief had a high heterogeneity with 40%–80% reduction in tremor severity. In terms of durability of outcomes, there is a 10%–20% reduction in tremor benefit, and 5%–15% of patients had a significant recurrence of tremor. Ataxia, gait disturbance, or imbalance were observed in 15%–90% of patients and typically resolved within 3–6 months but was persistent in 5%–30% of patients. Sensory and motor deficits were observed in 0%–30% of patients and usually resolved within 12 months.

Target coverage, including exact location and volume, is an important factor when determining optimal treatment technique. Limitations in the standard VIM-FUS ablation approach may result in a mismatch between the estimated target and actual tissue ablated, leading to tremor recurrence or side effects. The use of 3-D tractography for VIM-FUS ablation may increase accuracy. It is important to keep in mind that VIM is not a location in the brain, it is a volume. Using tractography, a prespecified volume of treatment can be planned (e.g., 70% of the VIM). A meta-analysis found that defining the VIM target reduced ataxia.[5] The use of 3D tractography for VIM-FUS ablation may increase specificity of treatment response, while limiting side effects.

It is unknown if T2-weighted imaging can accurately measure the extent of ablation. Post-operative, reversible edema can be a confounding factor. Post-operative diffusion MRI could be used to measure the extent of ablation.[6] The lesion volume is specific to the imaging sequence and the timing of acquisition.[6]

Question

Q. With respect to tremor recurrence, what percentage is caused by disease progression?

- In cases where there is a rapid deterioration after FUS, this occurs too quickly to be caused by disease progression or the procedure itself. ET is not a disease, but a phenotype. Progression occurs over years and large changes do not happen in a short time frame.
- A general rule of thumb is that tremor status 3 months post-procedure is typically the persistent effect. A smaller subset of patients may continue to see further improvements in tremor up to 4–5 months post-treatment.

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What is the Best Target for Focused Ultrasound Ablation for Essential Tremor?

Summary | Surveys of Targets

Wady Gedroyc, MD, discussed the heterogeneity of treatment for ET. VIM is the site for targeted treatment of tremor via multiple techniques including MRgFUS, deep brain stimulation (DBS), Gamma Knife radiosurgery, and radiofrequency ablation. There are important adjacent structures that increase the risk of adverse events such as the ventral caudalis nucleus (VC), associated with sensory side effects, and the internal capsule (IC) that may lead to motor side effects. The most accurate approach to targeting VIM is still under debate as it cannot be directly visualized on current clinical scanners.

The two commonly used methods of VIM targeting are anatomical, using adjacent landmarks to infer VIM position (anterior commissure-posterior line (AC-PC), third ventricle, and the IC), or with tractography using diffusion tensor imaging (DTI) to infer VIM position (DRT tract, medial lemniscus, and pyramidal tracts (PT)).

Dr. Gedroyc described a study that aimed to 1) assess various VIM targeting approaches used in MRgFUS thalamotomy and to 2) ascertain any trends in VIM targeting approach between 2019 and 2021. All MRgFUS centers were invited to participate. Results were analyzed regarding primary targeting method, any anatomical landmarks utilized, and utilization of tractography. In 2019, most centers were using anatomical targeting (96.2%, n=25) with only a few using tractography (3.8%, n=1) with similar findings in 2021. For the superior-inferior axis, there was a notable trend to lesion more superiorly over time with 40.9% targeting 2 mm above the medial commissure plane (MCP) in 2021 compared with only 16.0% in 2019. There was increased adoption of tractography over the study period. The utilization of tractography in targeting the VIM increased from 30.7% in 2019 to 60.8% in 2021. More research is needed to determine if targeting more superiorly within the VIM leads to better clinical outcomes and fewer adverse events.

What is the Best Target for MRgFUS in ET?

Rees Cosgrove, MD, described MRgFUS targeting in ET. The ideal goal of MRgFUS thalamotomy is complete and long-lasting tremor relief without any side effects. In practicality, the procedure results in a 75%–85% improvement in tremor without any permanent significant side effects. Accurate target selection and accurate lesion placement, along with adequate lesion size and extent result in effective tremor control. Thus, success is defined by both target location and volume. A lesion that is too small increases tremor recurrence, while a lesion that is too large will lead to permanent side effects.

Dr. Cosgrove described how he performs MRgFUS thalamotomy. Imaging is completed 24 hours post-operatively. Patients with a minimum of 1 year of follow-up data (n=200) were analyzed for tremor control. Analysis suggests that targeting slightly more anteriorly in the VIM leads to better tremor control and fewer side effects.

Panel Discussion

Moderator
Tom Gilbertson, PhD

Q. Where does the posterior subthalamic area (PSA) fit into this discussion?

- Dr. Cosgrove said that he does not target the PSA. He aims for the lesions to extend into the zona incerta just below the VIM.
- Dr. Bhavya Shah mentioned the idea of a 'football-shaped lesion' that extends from the VIM into the PSA or zona incerta that also ablates the decussating and non-decussating pyramidal-thalamic tract, and this lesion shape results in a better tremor response.[7] Directly lesioning the PSA is not a good idea, and is reported to increase side effects.
- Dr. Gedroyc shared that his group targets the zona incerta plus VIM, and they find that this results in good tremor control.

How is the "Best" Target Determined and How Can We Standardize Localization into a Method?

Optimized MRI Sequences for Visualization and Segmentation of Thalamic Nuclei for Targeting Applications

Manojkumar Saranthan, PhD, described MRI sequences to optimize MRgFUS. The structural MRI sequence MPRAGE with a white matter nulling (WMn) parametrization allows for improved visualization of anatomical boundaries in the brain. WMn-MPRAGE uses a similar idea to the Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR) sequence but borrows from earlier cortex-attenuated sequences and has been optimized for signal-to-noise, contrast, blur, and scan time. Using a radial-like acquisition allows motion robustness, improves contrast, and increases efficiency. The WMn-MPRAGE sequence was optimized for intra-thalamic contrast. A method known as THalamus Optimized Multi-Atlas Segmentation (THOMAS) was developed to automatically segment thalamic nuclei in WMn-MPRAGE images.[8,9] This sequence can work on a 3T MRI with a 15-minute acquisition time. The Dice score was 0.7 for most thalamic structures.

WMn-MPRAGE can be synthesized from T1 maps and then segmented using THOMAS, which offers improvements in image quality.[10] WMn can also be synthesized using deep learning from a standard T1 image.[11] In addition, WMn can also be synthesized robustly, without using deep learning, by using a cubic function to fit normalized intensity images. A manuscript is in preparation to compare several state-of-the-art methods for this.

An analysis of MRgFUS thalamotomy for ET responders (heat maps of lesions) was able to visualize overlap with VIM, and this seems to localize to the edge of the VIM (ventral edge).[12] Protocols are available for GE, Siemens, and Philips scanners for MPRAGE. THOMAS is opensource and available on GitHub.

https://github.com/thalamicseg/hipsthomasdocker

Question

Q. Is it possible to further improve THOMAS for VIM?

- The WMn sequence was not developed for specific nuclei and could be further refined in the regions of interest. There is a tool available that can select specific nuclei using a T1 map.

Atlas and Direct MR Imaging with WMn-MPRAGE

Rees Cosgrove, MD, described indirect atlas-based targeting during the early experience with MRgFUS for ET. Starting in 2019, the WMn sequence was used for procedure planning. It is important to remember that by fusing CT and WMn MRI, there will be a small errors from the fusion that may require adjustments. Visualization of thalamic nuclei greatly improved and allowed improved direct targeting with the use of WMn.

There will be an analysis of the targeting from before the targeting was applied and after. Intra-operatively, MR temperature imaging (MRTi) has been implemented to adjust lesion location and extent.[13]

Use of DTI in Targeting in MRgFUS Targeting for ET

Kristen Leeman, MD, presented on the use of DTI in MRgFUS targeting for ET. Traditional techniques use indirect targeting based off anatomic landmarks compared with stereotactic atlas coordinates, which do not account for interindividual anatomic variation. Traditional MRI sequences, as already discussed, do not provide the resolution or specificity needed for targeting thalamic nuclei. Their team uses a dual-approach to targeting with an initial independent target planning by the neurosurgeon (atlas based) and by a neuroradiologist (tractography-based targeting). The final target is chosen after comparison of DTI and stereotactic coordinates. The tractography is displayed on an independent workstation for reference during treatment. These methods are used in conjunction with clinical signs of tremor control for fine correction of the ablation site.

The initial assumptions for VIM targeting include:

- The streamlines produced from diffusion tractography approximate the actual white matter tracts in question.
- The DRT tract and the somatosensory tracts coursing through the ventral thalamus spatially correspond to the VIM and the VC nuclei, respectively.
- Targeting these tracts is clinically equivalent to targeting the nuclei through which they run.[14]

Using DTI-based coordinate selection, the epicenter of the DRT tract tends to lie slightly posterior and medial relative to atlas coordinates. While, anterior and medial sites are a safer starting point, a lesion that is too anteromedial may not produce a clinical response. Tractography at their institution is processed using the Brainlab Cranial planning software using a deterministic algorithm. A critical first step in processing, is the fine-tuned fusion of the anatomic sequences (3D T1 or T2) with the B0 DTI acquisition. In addition, the linear and nonlinear distortion correction automatically applied by the software, further aids in accurate fusion. Subsequently, the anatomic images are aligned/reformatted along the anterior commissure-posterior commissure plane.

For VIM targeting, there are 3 tracts that are connected or "seeded:"

- Corticospinal/pyramidal tract, connecting the precentral gyrus and the cerebral peduncle.
- Medial lemniscus, connecting the postcentral gyrus and the dorsal pons.
- DRT tract, connecting the precentral gyrus and ipsilateral red nucleus.

Intraprocedural imaging was optimized using a body coil and consists of an axial 2D T2 and axial DWI sequences.[15] Post-procedure imaging is done the same day as the procedure and consists of sagittal T1 or T2 for AC-PC localization, axial DWI, axial T2 through AC-PC plane, axial 3D susceptibility weighted imaging (SWI), and sometimes DTI if the patient is able to tolerate it.

Dr. Leeman described a re-treatment case where DTI was helpful. The initial ablation site was not visible 5 months after the procedure, which is not an uncommon finding. The DTI was repeated and there were some remaining fibers. However, she cautioned that DTI is a mathematical computation and can be manipulated, and parameters should be carefully managed. The re-treatment was planned based on the DTI, targeting the remaining fibers localized with tractography, and was successful. In summary, in their experience thus far, optimal ablation sites are selected based on the patient-specific location of the DRT tract as demonstrated by DTI (direct targeting) and correlated with traditional atlas-based measurements for thalamic VIM lesioning (indirect targeting).

Questions

Q. There was a comment that using DTI to guide the process seems to increase accuracy and reduce heterogeneity between cases.

Q. A participant noted that the re-treatment case had fibers remaining, and that DTI could be used to confirm the structural presence of the target.

- DTI is not used to ablate every fiber seen for the DRT tract, it is a combination of judgement and experience. Fiber tracking may be more useful for treating recurrence to allow visualization of remaining fibers, but for first-time treatments they do not try to ablate all DRT tract fibers, as this could result in unwanted side effects. Before using tractography, the neurosurgeon tended to treat more posteriorly if tremor control was not achieved, but with tractography we are tending to treat more anteriorly, especially in recurrent cases, if tremor persists.

Q. There was a question on using probabilistic targeting, and whether this would increase accuracy?

- Dr. Leeman responded that probabilistic targeting is very time consuming, and computationally complex. It provides information on the probability that a tract passes through a voxel, assigning a likelihood to different possible results thus reflecting the complex anatomy.
- Dr. Saranthan mentioned that instead of doing probabilistic targeting of the whole brain, it could be restricted to a certain area and may not take a long time to calculate.

Q. Have the successful cases been analyzed to see how much of the DRT tract fibers remain?

- Dr. Leeman responded that this could be worth assessing as they have a set of data for pre and post ablation DTI which could be compared with cases from other institutions without preoperative tractography.
- Participants discussed the potential for comparison between centers to compare cases with and without tractography.

Single Tract Deterministic Tractography to Guide VIM Thalamotomy

Dheeraj Gandhi, MD, presented on single tract deterministic tractography. Select cases were shared as an example of the advantages of this method. A 76-year-old patient with a cyst in the thalamus made them ineligible for DBS. Using DRT tract, the team found that subthalamic tract was not affected by the cyst and the patient underwent successful MRgFUS. An 82-year-old patient was evaluated who had previously had MRgFUS on the left side at another institution. The first attempt did not result in successful tremor treatment. Tractography was used afterwards and showed that the DRT tract was 2–3 mm lateral to the original location, which is not a typical location for treatment.

Dr. Gandhi uses FGATIR plus DTI. Fiber tracking parameters were described, and they perform deterministic fiber tracking on a Siemens Leonardo Task Card workstation that sits next to the Insightec system. The precentral gyrus and red nuclei are used as seed points for the DRT tract. Deterministic tractography has been done on 150 cases and takes about 7 minutes. This is a simple and straightforward approach that is computationally less invasive, commercially available, has fixed input parameters, provides consistent results, and is FDA-approved.

The tract location can vary greatly between patients. One reason for this is that older patients often have brain atrophy, and the location of brain areas can be extremely variable. Using only stereotactic coordinates may not allow accurate targeting. In general, there seems to be a high rate of side effects following MRgFUS for tremor control. DRT tractography has some potential pitfalls. It is a computational process that may not work for every patient. Patients with severe tremor may not have images suitable for tractography, and only atlas-based targeting can be done for these patients. Tracts from two different vendors will look different. The team is also creating an alternative approach for improved VIM targeting using synthetic MPRAGE (SynMPRAGE) images that can have good contrast with 3T.

Question

Q. How were the processing parameters created?

- Dr. Gandhi replied that these processing parameters are standard. Crossing fibers cannot be used with deterministic tractography, the computation must be made with ipsilateral seed points.

Multiparametric Approach for MRgFUS Targeting

Bhavya Shah, MD, discussed 4-tract tractography for targeting MRgFUS. Indirect targeting has been traditionally used for tremor control, but identifying the DRT tract was unclear. Software is used to identify the corticospinal tract and medial lemniscus to avoid unwanted side effects, and the DRT non-decussating and DRT decussating tracts are identified for targeting.[16] Direct versus indirect targeting is compared for every case.

Tract based targeting is generally located more anterior and more medial. The Essential Tremor Rating Assessment Scale (TETRAS) showed that 1 year average postural tremor reduction was 83%, and the average TETRAS kinetic tremor reduction was 84%.[17] They also found very few adverse effects, with 7.3% reporting paresthesia and 18.2% reporting transient imbalance 1 day following the procedure, but these resolved by 1 month.

Questions

Q. Attendees noted that this seems like a small amount of side effects for this procedure.

- Dr. Shah responded that this was only a case series of 20 patients.

Q. A question was asked about the volume of tissue ablated in these procedures.

- Dr. Shah answered that the lesions are very small and look like 'melted snowmen.' The second lesion is superior and slightly lateral to the first lesion. They use the tractography for intraprocedural targeting to avoid off-target effects. The RAS coordinates (Right, Anterior, Superior) remain the same across all software platforms and can be used to make sure that the area of targeting remains the same as the preplanned area on the workstation. They also avoid a third lesion unless there is an axial or voice tremor.

Q. Are there any potential side effects that have not been evaluated?

- Dr. Shah answered that there may be cognitive or proprioceptive fibers in the DRT tract, but this has not been observed in these patients. There may also be some overlap with the non-decussating DRT tract and the medial lemniscus and there may be some proprioceptive fibers in the most posterior portion of the DRT tract.

Q. There is a lack of ataxia in this group of patients. Given that there are certain factors that increase the risk of ataxia, are these patients excluded?

- So far there have been about 150 patients treated at the center, with follow-up data at 6 months and a few at 1-year post-procedure. Pre-existing gait issues increase the risk for ataxia. Patients with pre-existing gait issues, neuropathy, and joint replacement have an increased risk of long-term gait imbalance.
- The group discussed the importance of distinguishing between ataxia and transient imbalance after treatment. They also screen patients for small vessel disease in the cortico-ponto-cerebellar tract. This white matter tract helps prevent ataxia. Patients with disease in this tract are at high risk for developing ataxia after treatment.

Q. How reproducible is the target?

- Dr. Shah commented that the team did targeting research with cadaver data and found that the targeting was accurate.

Connectomics in Private Practice

Lloyd Zucker, MD, discussed functional targeting. Resting-state functional MRI (rs-fMRI) is used to correlate connections between brain areas. The rs-fMRI can be scanned in under 8 minutes, and the images processed in under one hour. In the anomaly view, brain areas are highlighted that have anomalous connections. Anomalous connections fall 3 standard deviations outside of the expected values based on a sample of average brain connection patterns. The highlighted areas can be further investigated for the number of anomalous connections, and whether those connections are correlated or not related. For example, different brain areas are active, under-active, or overactive in relation to a brain tumor. Future work will look at a larger sample size to refine how to view the brain. A registry that defines both symptoms and outcomes linked to images, along with outcomes of different treatments could be a useful tool.

Probabilistic Target Selection for MRgFUS Thalamotomy with Convolutional Neural Networks

Tom Gilbertson, PhD, discussed using artificial intelligence (AI) and computational methods to analyze MRI data from FUS thalamotomy procedures for ET. AI can combine information from normalized group level statistics with native space planning. A convolutional neural network (CNN) can predict clinical outcomes from post-operative imaging. CNN was trained on T2-FLAIR images, all scans were normalized into MNI space, and a volume of interest was defined. CNN performs a feature extraction on the images. A CNN sweetspot analysis is done by determining specific voxels that degrade the CNNs prediction with occlusion sensitivity analysis and local interpretable model-agnostic explanations (LIME). This builds a heatmap, and the researchers look at whether this overlaps with probabilistic heatmaps from manually masked lesions. The CNN was able to predict clinical outcomes with 90% accuracy from post-operative imaging in an initial proof-of-concept test. The next step is to test whether CNN can predict outcomes across different surgical sites. Lastly, they will test to see if they can plan a treatment in native space using a CNN trained on group data.

Question

Q. There was a question on what follow-up time points were used to train the CNN?

- Dr. Gilbertson replied that all follow-up data was included to add power. Future research will also look at comparing different time points to see what is optimal for prediction. There was some discussion that 3-month follow-up images might be better predictors of outcome than 12-month follow-up images.

Probabilistic Lesion Symptom Mapping
Findings and Challenges

Charles Guttmann, MD, stated that there is a need to share methods and data to explore how to optimize the procedure. Dr. Guttmann described a virtual laboratory platform that can collect data and methods from MRgFUS procedures and allow analytics and exploration. Using lesion volume analysis, there were some associations with sonication parameters such as number of sonications, thermal dose, max power, max temperature, and max duration.[18] Probabilistic lesion symptom mapping compares anatomical lesion coverage between groups of patients with different symptom profiles (e.g., dysarthria versus no dysarthria). This method can be used to look at lesion areas that correlate with side effects and ones that correlate with efficacy.

Using Non-Thermal Neuromodulation for Optimal FUS Targeting

Jean Francois Aubry, PhD, presented on non-thermal neuromodulation for optimal targeting prior to tremor treatment with MRgFUS. Tremor assessment was done using MR compatible accelerometers. Transcranial ultrasound stimulation (power <10 W) was used for neuromodulation with the Insightec system.[19] Low-power targeting of the VIM and DRT tract showed that targeting in the DRT tract led to a dramatic reduction in tremor for up to 30 minutes. With high-intensity FUS (power between 500–1,000 W), there was also a dramatic reduction in tremor of more than 90%.

Questions

Q. There was a question on whether this was a special Insightec system that was capable of very low power?

- Any Insightec machine is capable of this, but Insightec must enable the modified pulse sequences that were used here, which requires a research agreement with the company.

Q. What is the proposed mechanism and why did the VIM not respond?

- Dr. Aubry replied that they are not sure what the mechanisms might be nor why the VIM did not respond.

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Targeting Company Presentations

RebrAIn

Targeting is an issue for neurosurgeons. RebrAIn is AI software to improve targeting. For VIM targeting, the company has produced a VIM metamodel using a selected cohort of patients with good outcomes. The clinical target was identified, 18 landmarks were placed per side, and this was used to create the metamodel of prediction. The company is in the process of validating the AI solution for ET.

Omniscient Neurotechnology

Quicktome is an FDA-cleared platform for a variety of brain networks. Resting-state processing and interpretation tools were recently added to the platform. They have a structural connectome workflow and a functional connectome workflow, both aided by AI. The structural connectome was designed to show spatial connections and abnormalities from what is expected. The functional connectome is meant to show functional correlations obtained with resting-state fMRI changes in blood oxygenation level dependent (BOLD) signal. A user can select a seed region to look at connections correlated with that region or those that are not correlated with that region. There is also an anomaly view that can look at the degree of anomalous connections as well as the areas of anomalous connection (under-or over-connection).

Upstream Vision

There are diverse avenues to targeting. Some of the challenges in advanced imaging analytics include the need for specialized expertise, risk of variability, technological demands, and importance of clinical trust. There is also a burden on radiologists including consistency in imaging sequences, skill gap for imaging analytics, replicating research-level quality, quality control, and time and resource constraints.

Upstream Vision can ‘democratize’ advanced imaging. The software includes automated imaging workflows, accessible to all centers, streamlined clinical processes, and image analytics expertise in a box. Upstream Vision integrates with electronic health records (EHR), can perform automated image fetching, and has advanced analytics and processing (automated standard tractography, optimal map of efficacy, automated segmentation, and customizable options).

How Does the Clinician Know When to Stop—When is the Treatment Finished?

Roundtable Discussion

Moderators

Tom Gilbertson, PhD and Frantz Poulsen, MD

Panelists

Vivek Buch, MD, Paul Fishman, MD, PhD, Kristen Leeman, MD

- Participants discussed various parameters of the MRgFUS procedure, noting that each surgeon modifies the details, including the number of lesions, temperature dose, and volume treated. There was also discussion on when and how to assess the patient's tremor and the improvement in tremor. Patient tolerance for the procedure can also be a factor.
- Other important factors include the follow-up schedule. Some participants follow patients for up to 5 years.
- Key factors to analyze include clinical outcomes (tremor improvement, side effects), imaging, and details of the targeting approach used. Standardizing these factors for collaborative analysis is important.
- Overall, the group highlighted the importance of 3 main categories that influence when to stop the procedures: clinical factors, temperature, and volume/shape of the lesion.

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Once Determined and Standardized, What Percentage Reduction of Side Effects Could be Realized?

Roundtable Discussion

Moderator

Frantz Poulsen, MD

Panelists

Rees Cosgrove, MD, Howard Eisenberg, MD, Shayan Moosa, MD, and Daniel Roque, MD

- The group discussed side effects and how these impact on quality of life. Transient ataxia and imbalance are common post procedure but there is a risk of permanent ataxia which can be associated with a worse quality of life compared with tremor. The group agreed that ataxia risk needs to be very low, ideally under 5%.
- There was a discussion on ataxia and gait imbalances and that more research to understand this in general is needed, as well as how MRgFUS can affect it.
- Dysarthria, ataxia, and impaired balance are the most frequent side effects and are often mild.
- Participants mentioned that side effects are expected as the entire system has been perturbed by lesioning, and 6-12 weeks of mild side effects, such as imbalance, are to be expected.
- The group also discussed the use of physical therapy and/or pre-conditioning prior to MRgFUS and the fact that there is some published evidence for fall prevention following treatment for ET.
- Concern over the amount of potential side effects related to the MRgFUS procedure is a barrier to expanded use. A reduction in side effect risk would increase patient access to the procedure.
- Acceptable side effects may need to be personalized by individual patient considerations, such as age, tremor type, comorbidities, goals of therapy, etc.
- Motor deficits, and hemiparesis in particular, need to be very low at around less than 2% as these are unacceptable side effects. To reach this goal, technological improvements in beam shaping by the FUS device are needed.

Once Determined and Standardized, What Percentage Increase in Efficacy Could be Realized?

Roundtable Discussion

Moderator

Frantz Poulsen, MD

Panelists

Rees Cosgrove, MD, Howard Eisenberg, MD, Shayan Moosa, MD, and Daniel Roque, MD

- Attendees agreed that technological improvements with regards to the Insightec system would improve efficacy. The group wanted greater control of the lesion shape and predictability.
- Participants debated the optimal timeline for improvements and expectations to share with patients. Although some report that tremor improvement can continue to improve from 6 to 12 months following treatment, others have only seen partial recurrence during that time.
- There was some discussion on the use of MRgFUS for mixed tremors or tremors not caused by ET. Anecdotal evidence suggested that MRgFUS could treat other kinds of tremors, but the exact location for treatment is not clear and more research on these tremors is needed to treat with MRgFUS.

What Outcome Measures Should be Standardized Practice in Assessing the Thermal Lesion?

Roundtable Discussion

Moderator
Charles Guttmann, MD

Panelists
Howard Eisenberg, MD, Paul Fishman, MD, PhD, Daniel Roque, MD, and Niels Sunde, MD, PhD

- Participants discussed the variation in follow-up timing, and that timing and frequency of visits vary between centers and based on the individual patient. Each MRgFUS center has their own follow-up procedures. Some of the timepoints and types of follow-ups included:
    - Day 1 and 10 in-person visits to assess ataxia, fall risk, and need for physical therapy.
    - Imaging at 24 hours, 1 week and 1 month phone call, then 3, 6, and 12 months in person (or via virtual visit), and annually thereafter for up to 5 years.
- Immediately following the procedure, phone call at 24 hours and 1 week, efforts for in person follow up at 1 month struggled because patients did not live near the center, video follow up at 3, 6, and 12 months. Followed by yearly follow-up.
- Now that the procedure has been established, shorter and less frequent follow-up times could be possible as long as the side effect profile remains unchanged.
- There is also a need to make a distinction between regular care and research-oriented follow up. Participants suggested that they do not want to require a patient to follow up with two different physicians nor want to appear to be 'taking over' the patient from the referring neurologist.
- Video follow up can be challenging for older patients, and results in only around 40% participation with the remaining follow-up being done via phone.
- Patient perception of efficacy is an important consideration. This could be assessed with already existing questionnaires or tools (apps to allow a virtual visit, accelerometer, AI spiral scoring tool, etc.), perhaps at 3 months and 1-year post-treatment.
- There was agreement that MRI should be collected pre-procedure, during the procedure, and post-procedure. MRI at 1-year post-procedure is only done if the patient wants the second side treated.
    - Some collect MRI images 2 to 3 hours after the procedure (FGATIR, WMn-MPRAGE sequences), which allows visualization of the shape of the lesion and early edema.

- The group discussed MRI sequences for day 1 scans.
    - Some use FLAIR and T2 to assess edema.
    - Diffusion, possibly T1, and susceptibility-weighted imaging SWI could be collected for research purposes.
    - 240 cumulative number of equivalent minutes (240 CEM) correlates to lesion size on day 0.[20]
    - SWI preoperatively and post-operatively at 3 months to provide better detail of the VIM within the thalamus.
- The optimal MRI sequences and timing are yet to be determined and more research is needed. Participants recommended creating a working group to consider recommending a standardized imaging protocol to inform future decision making.
    - There was a suggestion to use natural language processing to mine a database.
    - Imaging may be useful for the surgeon to know what they have done for control purposes.

Participants discussed clinical outcome measures that should be standard practice.

- Ataxia
    - The Scale for the Assessment and Rating of Ataxia (SARA) was recommended as it is quick and designed for clinical use.
    - The International Cooperative Ataxia Rating Scale (ICARS) takes longer and would require a dedicated effort.
- Tremor
    - Drawing of spirals are useful but does not always correlate with patient perception.
- Basic sensory and motor assessment.
- The risk of falls should be assessed at 1 week.
- In terms of timing, all clinical follow up should be captured at 3 months and 1 year.
- Patient rating scales.

Roadmap Discussion

Moderator
Suzanne LeBlang, MD

1. What is the best ET ablation target?

- There was agreement regarding uncertainty about what location is the best target with ample discussion about which locations in and around the VIM should be included. Research analyzing clinical outcome data with imaging of target locations is essential.
- There is still uncertainty around the optimal target. Several targeting methods were discussed throughout the meeting including atlas-based, tractography, WMn anatomic imaging, neuromodulation, and connectomics.
- Participants noted that there remains a need to validate clinical outcomes and compare different targeting approaches (e.g., VIM or DRT tract). Efficacy versus side effects should also be evaluated on this same data set. A randomized controlled trial comparing different targets/approaches would be ideal, but this would be challenging and needs to be discussed in further detail.
- The group proposed collaborating to analyze retrospective data from different centers to gain insights, with the goal of informing future prospective studies. This could involve sharing data, methods, or both as well as the creation of a registry.
- Participants also discussed options like federated learning where methods are shared but data stays local. A registry could also help standardize prospective data collection.
- There was a suggestion to work with Insightec on obtaining treatment day data and note the 240 CEM contour correlates with quantitative DWI and treatment volume. Individual sites could provide clinical outcome data to correlate with treatment data from Insightec.
- Next steps will be to form a working group on the best ET ablation target.
    - To carry out data analysis from multiple sites there will need to be standardized imaging protocols (timing, sequences) and clinical outcomes (timing, measures) across participating sites.
    - Several participants agreed to meet monthly to get this project started.

2. How is the target identified and can these methods be standardized?

- There are three main methods to targeting: atlas-based, direct targeting (WMn), and indirect targeting (tractography, connectomics). Quality control is needed before using DTI.
- The participants agreed that the error (in mm) around various methods of identifying targets should be determined.
- DTI can be difficult for radiologists and may not be accessible to small clinics.

- Participants discussed exchange of expertise with experts in each of the targeting methods teaching those interested in learning that method. Sites could potentially trial methods and reach agreement on standardized methods to use in coordinated data collection efforts.

3. When is the treatment finished/when to stop?

- Participants suggested the following for defining the end of treatment:
    - Clinical testing for efficacy (70–80%).
    - 6-8 mm lesion size via thermal dose (240 CEM), but smaller in older patients with baseline ataxia.
    - Some of the lesion is below AC/PC plane.
    - Patient tolerance.

4. Once determined/standardized, how much might side effects be reduced?

- Participants suggested the following for long-term side effects:
    - Moderate to severe sensory, <5%
    - Moderate to severe motor <2%
    - Moderate to severe ataxia <5%
    - Mild ataxia, 5%–10%

5. Once determined/standardized, what increase in efficacy may be realized?

- The group had varying responses to improvement, the responses ranged from 60% to 85% improvement 3 months after the procedure. However, they caution that there may be a loss of efficacy after 1 year, but around 80% of patients have sustained efficacy.
- The group cautioned that increasing improvement to 90% to 100% would increase side effects.

6. What outcome measures should be standardized practice?

- Measures for follow up: activities of daily living (ADL), QoL, and patient impressions.
    - Subjective measures: Treds ADL and patient global impression of change (PGIC) at baseline, 3 months, and 12 months
    - Objective measures: TETRAS, CSRT, scores on standardized metrics at baseline, 3 months, and 12 months.
- Participants mentioned that these need to be simple in design that can be collected via letter/phone.
- It was also suggested to work with the ET Foundation to ensure buy-in from the patient community.

7. What Outcome Measures Should Be Standard Practice?

- Measures: patient phone call at 1 week (sensory: face, tongue, hand, taste), weakness, falls and balance issues. Ataxia at 3 and 12 months, patient reported imbalance/gait difficulty, PGIC.
- A simple way to do this is to ask the patient "better/same/worse; if you said, 'same or worse,' then why?"
- Participants also discussed how to recruit more neurologists to refer patients for MRgFUS for ET, there was a suggestion to send the referring physician a note via electronic health record before (what to expect and potential side effects) and after (treatment success and when follow was scheduled) the procedure.
- It was also noted that safety and side effects need more research, perhaps a small number of sites could research this at a deeper level.
- There was also a suggestion to form standardized training.

The group discussed the benefits and challenges of data sharing. Having a repository of case data could enable "digital twin" simulations. These simulations could predict patient outcomes based on their specific characteristics.

References

1 Elias WJ, Lipsman N, Ondo WG, et al. A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. *N Engl J Med*. 2016;375(8):730–739. doi:10.1056/NEJMoa1600159

2 Chang JW, Park CK, Lipsman N, et al. A prospective trial of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: Results at the 2-year follow-up. *Ann Neurol*. 2018;83(1):107–114. doi:10.1002/ana.25126

3 Cosgrove GR, Lipsman N, Lozano AM, et al. Magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor: 5-year follow-up results. *J Neurosurg*. 2023;138(4):1028–1033. doi:10.3171/2022.6.Jns212483

4 Fishman PS, Elias WJ, Ghanouni P, et al. Neurological adverse event profile of magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor. *Mov Disord*. 2018;33(5):843–847. doi:10.1002/mds.27401

5 Agrawal M, Garg K, Samala R, Rajan R, Naik V, Singh M. Outcome and Complications of MR Guided Focused Ultrasound for Essential Tremor: A Systematic Review and Meta-Analysis. *Front Neurol*. 2021;12:654711. doi:10.3389/fneur.2021.654711

6 Sammartino F, Yeh FC, Krishna V. Intraoperative lesion characterization after focused ultrasound thalamotomy. *J Neurosurg*. 2021:1–9. doi:10.3171/2021.10.Jns211651

7 Holcomb JM, Chopra R, Feltrin FS, et al. Improving tremor response to focused ultrasound thalamotomy. *Brain Commun*. 2023;5(4):fcad165. doi:10.1093/braincomms/fcad165

8 Saranathan M, Tourdias T, Bayram E, Ghanouni P, Rutt BK. Optimization of white-matter-nulled magnetization prepared rapid gradient echo (MP-RAGE) imaging. *Magn Reson Med*. 2015;73(5):1786–1794. doi:10.1002/mrm.25298

9 Su JH, Thomas FT, Kasoff WS, et al. Thalamus Optimized Multi Atlas Segmentation (THOMAS): fast, fully automated segmentation of thalamic nuclei from structural MRI. *Neuroimage*. 2019;194:272–282. doi:10.1016/j.neuroimage.2019.03.021

10 Datta R, Bacchus MK, Kumar D, et al. Fast automatic segmentation of thalamic nuclei from MP2RAGE acquisition at 7 Tesla. *Magn Reson Med*. 2021;85(5):2781–2790. doi:10.1002/mrm.28608

11 Umapathy L, Keerthivasan MB, Zahr NM, Bilgin A, Saranathan M. Convolutional Neural Network Based Frameworks for Fast Automatic Segmentation of Thalamic Nuclei from Native and Synthesized Contrast Structural MRI. *Neuroinformatics*. 2022;20(3):651–664. doi:10.1007/s12021-021-09544-5

12 Su JH, Choi EY, Tourdias T, et al. Improved Vim targeting for focused ultrasound ablation treatment of essential tremor: A probabilistic and patient-specific approach. *Hum Brain Mapp*. 2020;41(17):4769–4788. doi:10.1002/hbm.25157

13 McDannold N, Jason White P, Rees Cosgrove G. MRI-based thermal dosimetry based on single-slice imaging during focused ultrasound thalamotomy. *Phys Med Biol*. 2020;65(23):235018. doi:10.1088/1361-6560/abb7c4

14 Lehman VT, Lee KH, Klassen BT, et al. MRI and tractography techniques to localize the ventral intermediate nucleus and dentatorubrothalamic tract for deep brain stimulation and MR-guided focused ultrasound: a narrative review and update. *Neurosurg Focus*. 2020;49(1):E8. doi:10.3171/2020.4.Focus20170

15 Chazen JL, Sarva H, Stieg PE, et al. Clinical improvement associated with targeted interruption of the cerebellothalamic tract following MR-guided focused ultrasound for essential tremor. *J Neurosurg*. 2018;129(2):315–323. doi:10.3171/2017.4.Jns162803

16 Shah BR, Lehman VT, Kaufmann TJ, et al. Advanced MRI techniques for transcranial high intensity focused ultrasound targeting. *Brain*. 2020;143(9):2664–2672. doi:10.1093/brain/awaa107

17 Feltrin FS, Chopra R, Pouratian N, et al. Focused ultrasound using a novel targeting method four-tract tractography for magnetic resonance-guided high-intensity focused ultrasound targeting. *Brain Commun*. 2022;4(6):fcac273. doi:10.1093/braincomms/fcac273

18 Segar DJ, Lak AM, Lee S, et al. Lesion location and lesion creation affect outcomes after focused ultrasound thalamotomy. *Brain*. 2021;144(10):3089–3100. doi:10.1093/brain/awab176

19 Yoo SS, Bystritsky A, Lee JH, et al. Focused ultrasound modulates region-specific brain activity. *Neuroimage*. 2011;56(3):1267–1275. doi:10.1016/j.neuroimage.2011.02.058

20 Huang Y, Lipsman N, Schwartz ML, et al. Predicting lesion size by accumulated thermal dose in MR-guided focused ultrasound for essential tremor. *Med Phys.* 2018;45(10):4704–4710. doi:10.1002/mp.13126

Abbreviations

ADL	Activities of daily living
AI	Artificial intelligence
CNN	Convolutional neural network
DBS	Deep-brain stimulation
DRT	Dentato-rubro-thalamic
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted images
EHR	Electronic health records
ET	Essential treatment
FLAIR	Fluid-attenuated inversion recovery
FDA	U.S. Food and Drug Administration
FUS	focused ultrasound
IC	Internal capsule
ICARS	International Cooperative Ataxia Rating Scale
LIME	Local interpretable model-agnostic explanations
ML	Medial lemniscus
PGIC	Patient global impression of change
PSA	Posterior subthalamic area
SWI	Susceptibility weighted imaging
TETRAS	The Essential Tremor Rating Assessment Scale
THOMAS	Thalamus optimized multi-atlas segmentation
VC	Ventral caudalis

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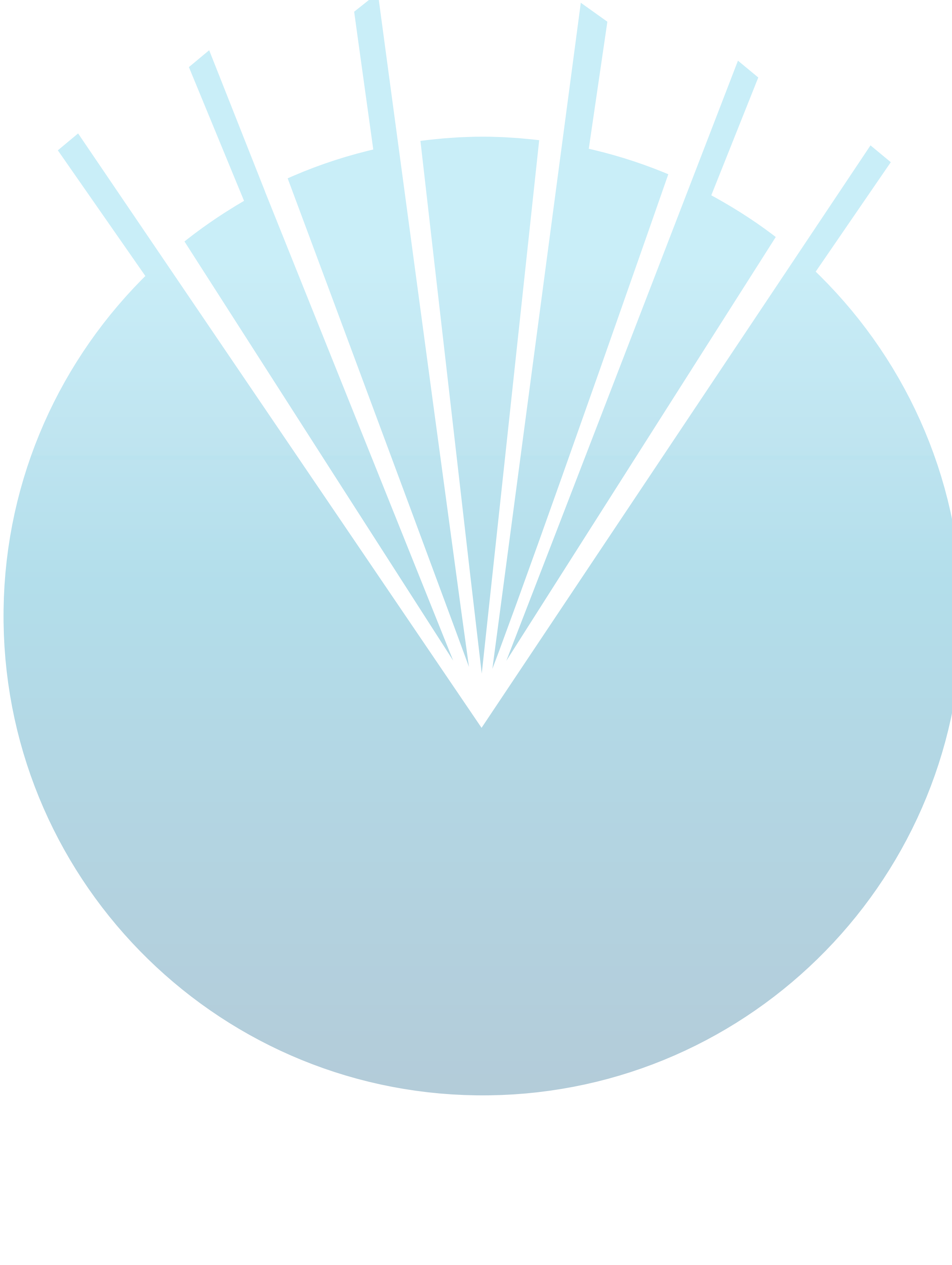
Acknowledgements

The Focused Ultrasound Ablation for Essential Tremor Brain Targeting Workshop was planned and sponsored jointly by The Focused Ultrasound Foundation in collaboration with Insightec. This summary was written by Heather Gorby, PhD. Each speaker reviewed and approved the content from their presentation and their discussion comments. Matt Eames, PhD, Suzanne LeBlang, MD, and the members of the steering committee provided final approval of the white paper.

Published by Focused Ultrasound Foundation



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