Diffusion-weighted Magnetic Resonance Imaging Guidance for Transcranial Focused Ultrasound

The Tractography Workshop

Meeting Summary

12–13 August 2019

University of Virginia Darden School of Business
Charlottesville, VA

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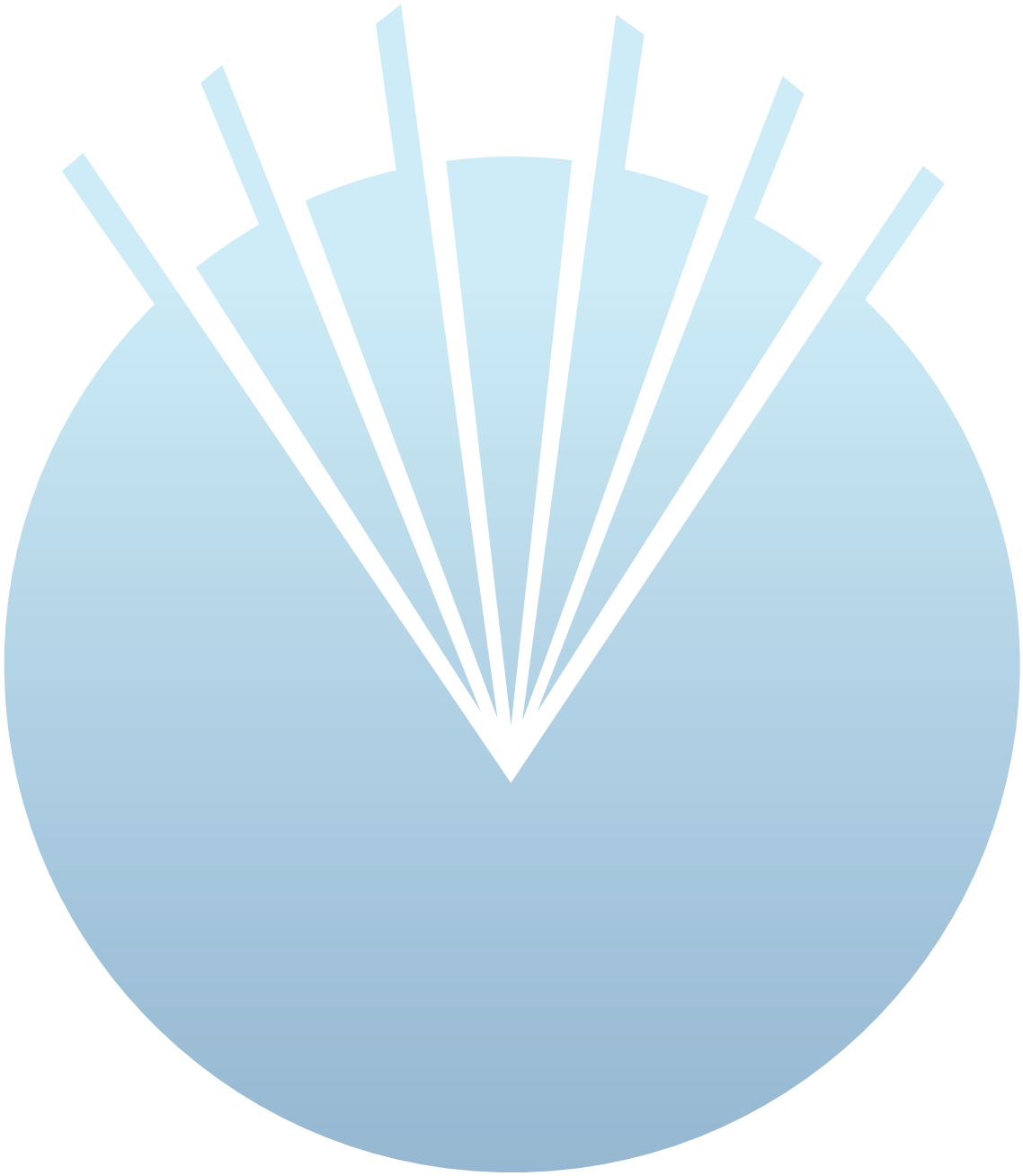

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Focused Ultrasound is an emerging technology that has begun to improve the lives of patients through incisionless, transcranial ablative treatments (or focused ultrasound ablation (FUSA)). Tractography, based on the diffusion magnetic resonance imaging (dMRI), non-invasively estimates the trajectory of white matter pathways or "tracts" within the brain. The resulting tract visualization has led physicians to term this type of imaging as "tractography." Clinicians recognize the utility of tractography for improving localization of the therapeutic target and ultimately improving the outcomes after FUSA. On August 12–13, 2019, the Foundation hosted a workshop to establish consensus among critical stakeholders surrounding the usage of and future directions for tractography guidance in transcranial focused ultrasound procedures.

The Foundation is thankful for Vibhor Krishna and Francesco Sammartino, who organized and led the workshop. Attendees included experts in neurosurgery, neuroradiology, neurology, and biomedical engineering. The workshop's overarching goal was to share knowledge and create a framework to develop best practices for acquisition, post-processing, and target visualization for tractography guidance during focused ultrasound ablation. Also, we hoped to inspire participants to identify meaningful research projects or initiatives that could move this field forward.

The workshop began with presentations on the rationale for tractography-based targeting and detailed descriptions of different methods for target localization for focused ultrasound treatments. Because essential tremor (ET) treatment is the most advanced application of focused ultrasound, much of the discussion was in the context of ventral intermediate (VIM) thalamic nucleus ablation. On the second day, the discussion involved investigational indications and a presentation about the role of tractography in optimizing deep brain stimulation (DBS) surgery for the treatment of depression. Following the presentations, expert panelists led a discussion to generate ideas, answer questions, and identify if and how tractography should be integrated into the transcranial focused ultrasound space. Specifically, the workshop attendees came to the following conclusions:

1. dMRI should be integrated into the transcranial focused ultrasound ablation workflow. There is emerging data that tractography-based targeting can improve the safety of focused ultrasound. Future investigations are required to develop a standardized technique for tractography based focused ultrasound procedures. The advances in target identification and optimizing ablation parameters will be critical for improving the safety and efficacy of FUSA.
2. In order to promote the use of tractography, the best practices of acquisition, post-processing, and analysis that were developed from this meeting should be shared broadly.

The group was thoroughly engaged in discussions throughout the workshop. The attendees were open to sharing their work and were encouraged to continue collaborating in the future to facilitate the further advancement of tractography into the clinical environment.

Workshop Presentations

Workshop presentations provided background information on and the current state of the field for this technology as it relates to enhancing targeting and ablation effects.

The rationale for Tractography-based Targeting

Vibhor Krishna from Ohio State University described the rationale for tractography-based targeting using his experience treating patients with ET. ET is one of the most common movement disorders in clinical neurology.[1] Focused ultrasound has emerged as an exciting treatment option for ET. As an incisionless technique, it could change the landscape of movement disorder surgery with refinements in pretreatment planning and image guidance. The treatment goals for focused ultrasound ablation of the VIM are increasingly evident and create the need and rationale for tractography-based targeting.

The cerebellum, VIM, and their connections play an essential role in the pathophysiology of ET. The tremor network generally consists of two separate pathways: 1) the cerebello-thalamocortical loop and 2) the olivocerebellar pathway (also called the triangle of Guillain and Mollaret). Pathological changes in this network, including the loss of Purkinje cells in the cerebellum or abnormal GABAergic transmission, cause thalamic hyperactivity that produces an oscillation in the thalamocortical network.

The VIM nucleus of the thalamus is the cerebellar receiving nucleus and the target for stereotactic surgery in the treatment of ET. The challenge with stereotactic targeting of this nucleus, using structural MRI, is that it is difficult to visualize. Currently, a formulaic method, or the atlas-based method, is used to target the VIM nucleus for focused ultrasound treatments. Coordinates based on anatomical landmarks (such as the anterior commissure (AC), the posterior commissure (PC), and the lateral wall of the third ventricle) are used to estimate the VIM location. Most commonly, the VIM is identified using the following measurements: X coordinate 11 mm from the lateral wall of the third ventricle, Y coordinate 25% to 33% of the AC-PC distance, and Z coordinate at the AC-PC plane (corresponds to the bottom of the thalamus) (Figure 1).

The goals of neurophysiology guidance during tremor surgery are:

1. physiologic exploration of the ventral thalamus to identify VIM,
2. definition of the ventral VIM border for implantation/lesioning at this border,
3. determination of the threshold of electrical stimulation that causes motor contractions (i.e., the motor threshold),
4. determination of the threshold of electrical stimulation that causes persistent paresthesias (i.e., sensory threshold), and
5. obtaining tremor arrest prior to eliciting side effects (i.e., optimal therapeutic window).

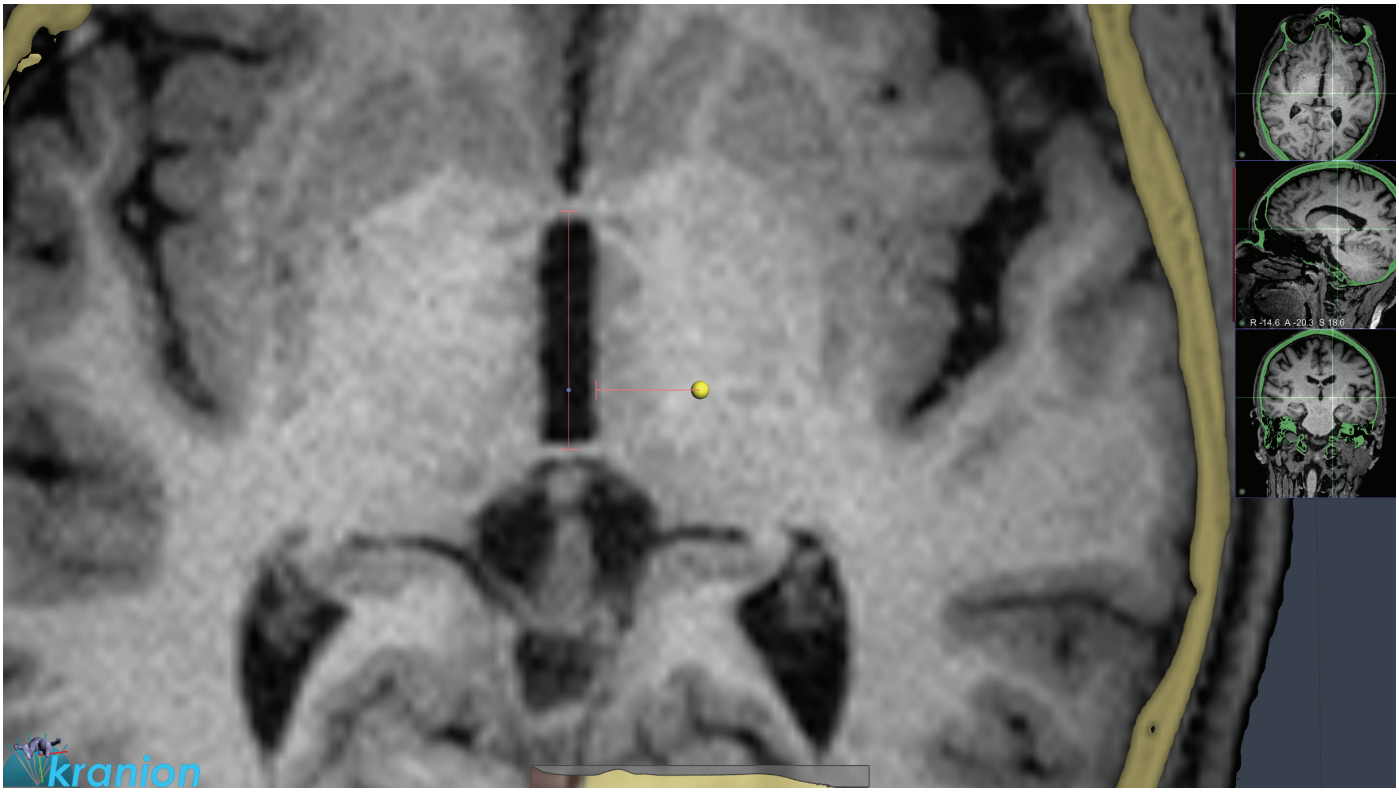

Figure 1
Indirect targeting of the VIM based on anterior and posterior commissures. X coordinate is 11mm from the lateral wall of the third ventricle, Y coordinate is 25% of the AC-PC distance, and Z coordinate is on the AC-PC plane. The yellow sphere is 2 mm in diameter and located at the target. This targeting is further refined with intra-operative physiology during conventional tremor surgery.

Although physiology guidance is not possible during focused ultrasound ablation, these goals provide a broader framework for understanding the operative goals for ablation, for standardizing techniques, and eventually, for improving patient outcomes.

The clinical outcomes with the current approach of tremor surgery are heterogeneous. Several groups reported excellent tremor control (70% to 80% tremor improvement in 70% to 80% of patients) in the initial 25 years after the first publication by Dr. Alim Benabid.[2] Subsequently, however, clinicians began reporting rates of non-responders or long-term failures and examining issues related to disease progression and treatment tolerance.[3-5] Although results were reasonably good, suggestions arose for further improving the success rate of the procedure. One crucial paper (that is useful for further discussion around focused ultrasound thalamotomy targeting) examined outcomes related to DBS lead location.[6] It found that a variation in the DBS location was significantly associated with outcomes. DBS implantation greater than 2 mm away from the optimal coordinates was more likely to be associated with poor tremor control than leads placed within 2 mm of the

optimal coordinates. Therefore, to achieve the best outcomes, focused ultrasound-based thalamotomies should also have the goal to ablate within 2 mm of the optimal location.

Among others, improving tremor efficacy and avoiding off-target side effects are two important goals. The multisite, randomized, sham-controlled clinical trial of focused ultrasound thalamotomy for ET showed less than 50% tremor reduction in 40% of patients at two years post-treatment.[7] In patients who experienced tremor control at one year, the outcomes were maintained at two and even as far out as four years. The proximity to the internal capsule and sensory nucleus to the therapeutic target creates a risk for off-target ablation during focused ultrasound VIM thalamotomy that can lead to adverse events such as paresthesia, taste disturbance, weakness, and gait disturbance. Although most of these deficits are reported to be mild, ideally, these side effects should be avoided.

Krishna and colleagues recently determined significant predictors of outcomes using multivariate analysis and found that age less than 70, shorter duration of disease, less than 20 sonications, and a maximum temperature of more than 55 degrees Celsius at the target portended a better outcome. Therefore, delivering therapeutic temperatures with the least number of sonications becomes another critical goal for focused ultrasound ablation.

Limited physiological exploration can be performed using focused ultrasound-induced thermal neuromodulation, e.g., subablative temperatures cause temporary clinical effects that can be detected with careful intraoperative testing. However, this process does not provide information about the proximity of critical neural structures because of the constraints of spot size. In general, the thermal spot varies with the focal temperature at the ablation site. When using subablative temperatures (40 to 50 degrees Celsius), the spot size remains relatively small, with an approximately 1-mm radius. Although the spot shape varies between treatments, focused ultrasound—induced thermal neuromodulation provides information only from a confined region roughly 2 mm in diameter. In contrast, the spot size increases to approximately a 5-mm radius during ablative temperatures (51 degrees Celsius and higher). Although a temperature gradient exists at the focal spot such that the central spot (radius roughly 1 mm) reaches ablative temperatures while the surrounding tissue receives sub-ablative temperatures. This variation in spot size has implications for intraoperative testing during focused ultrasound ablation. Side effects from off-target ablation may still appear during therapeutic ablations (wider spot size) despite no adverse effects during subablative testing (restricted spot size). This phenomenon also contributes to the overestimation of tremor control during focused ultrasound abltation (e.g., despite having a 70% to 80% tremor reduction immediately after surgery, the tremor reduction was reported to be 56% at the 3-month follow up). Overall, differences in spot size make intraoperative tremor testing during focused ultrasound ablation less reliable. Novel methods for pretreatment planning are required to visualize the target anatomy: both the VIM nucleus and the neighboring motor and sensory tract.

Wintermark and colleagues reported persistent changes in white matter microstructure within the cerebello-thalamocortical pathway after focused ultrasound ablation of the VIM.[8] These microstructural changes, defined by a decrease in the fractional anisotropy (FA),

correlated with long-term tremor control. Therefore, the role of dMRI may not be limited to pretreatment target planning for transcranial focused ultrasound treatments but potentially includes intraoperative and postoperative lesion assessment.

In summary, the emerging goals during transcranial focused ultrasound ablation are to avoid off-target ablation, to perform therapeutic ablations by reaching a temperature of 55°C or higher at the target, and to create a large enough lesion while avoiding excess sonications to prevent issues with skull heating. With these goals in mind, it is natural to see where tractography mapping of the VIM, medial lemniscus (ML), and pyramidal tract (PT) could potentially provide a more accurate target to help achieve these goals. In addition, intraoperative monitoring of the focused ultrasound lesion can be useful because relying on the loss of tremor alone during focused ultrasound ablation appears to be insufficient. Changes in microstructure—as monitored with dMRI—may lead to better long-term outcomes.

Introduction to Diffusion MRI Tractography

Frank Yeh from The University of Pittsburgh presented an introduction to diffusion-weighted imaging (DWI). He began with a brief history of the technology, saying that DWI was first described in the mid-1980s. The method used existing MRI technology and created specific contrasted images based on tissue water diffusion.[9] In 1994, Peter Basser introduced the diffusion tensor model, which enabled the indirect measurement of the directionality (anisotropy) of water diffusion and the structural orientation of axons within each picture element (voxel).[10] Basser and colleagues modeled the diffusion process using an ellipsoid, which can mathematically be represented by a 3×3 symmetric matrix, also known as a tensor. More simply, diffusion tensor imaging (DTI) is a three-dimensional (3D) Gaussian method to model water diffusion and determine local fiber orientation within each voxel. Ultimately, in 1999, Susumu Mori and colleagues[12] described the first 3D reconstruction of rat brain axonal projections using DTI in combination with a computer algorithm designed to trace an axonal pathway bidirectionally. This process is now termed "tractography." In its simplest form, tractography joins the orientation of all determined fibers and uses DTI to reconstruct axonal pathways.

Given the complexity and crossing of neural pathways within the brain, those working with tractography agree that calculations and modeling techniques that are more advanced than the currently used DTI model, are needed to advance the field. There are currently two separate "beyond-DTI" methodologies under investigation:

1. model-based, accounting for 80% of research, and
2. model-free, accounting for 20% of research.

New techniques are under exploration, but DTI is still the most common method of fiber tracking at this time. In the future, more of the "beyond DTI" methodologies should gain traction and increase the reliability of fiber tracking.

There are three main steps in fiber tracking. The first step is the determination of a starting point, otherwise known as **seeding**. The point that is chosen is a sub-voxel coordinate within the white matter. It is better to seed within the white matter because its diffusion signal is stronger than gray matter. After a seed is chosen, the second step is **propagation**, which is performed in both directions until the third step, **termination**. There are two different values that define where a tract terminates:

1. the angular threshold and
2. the anisotropy threshold.

With the angular threshold, if the propagation of a tract makes a sudden sharp turn, the pathway is terminated. With the anisotropy threshold, the tract is stopped when the FA gets too low because this most likely means that it has reached gray matter (i.e., diffusion in white matter is restricted along the axon and tends to be anisotropic whereas in gray matter diffusion is usually less anisotropic).

There are two types of fiber tracking algorithms: deterministic and probabilistic. These methods differ based on their propagation. With deterministic fiber tracking, the propagation of a tract is always based on the DTI or beyond-DTI modeling and will give the *single most likely pathway* and endpoint. Because the computer algorithms making these assumptions can contain errors and can never be entirely accurate, probabilistic fiber tracking is an option to determine more than the single best pathway. Probabilistic tractography estimates the "most likely" fiber orientations. The other possible orientations are also computed using a distribution representing the likelihood of other orientations along a fiber. The set of all these different paths are then collectively a measure of the connection likelihood or probability. Clinically, deterministic fiber tracking is commonly used for pre-surgical planning. In contrast, probabilistic fiber tracking is often used in the connectivity-related study in psychology or general neuroscience.

To close, Dr. Yeh shared the standard protocol for MRI acquisition for tractography at his institution. He explained that b-value is a factor that reflects the strength and timing of the gradients used to generate diffusion-weighted images. It reflects the strength of sensitization to diffusion. The higher the b-value, the stronger the diffusion effects, and therefore, the more sensitive the image is to the effects of restricted diffusion. The user chooses this value before image acquisition and usually ranges from 0 to 4000 s/mm2. Historically, the trend in the field was to use high angular resolution diffusion imaging (HARDI), which acquires hundreds of sampling at one b-value (typically 3000). HARDI was gradually replaced by a "multishell" acquisition, which acquired diffusion MRI using at least two different b-values/shells (typically three b-values). This trend was motivated by studies confirming the benefit of combining data from multiple b-values.[13] Dr. Yeh recommended 10-minute, 258-grid sampling with a maximum b-value of 4000 to acquire 23 different b-values over 258 directions. A similar scan using 101 directions usually takes 5 minutes.

Tractography-based VIM Targeting

Francesco Sammartino from Ohio State University described his experience with tractography-based VIM targeting. He and his colleagues incorporated tractography into their neurosurgery practice to improve the safety and effectiveness of focused ultrasound treatments for ET. As previously mentioned, off-target lesioning and loss of efficacy were reported to be complications for patients enrolled in a clinical trial.[7] Visualizing the VIM and the surrounding white matter pathways, such as the PT and ML, might improve the safety profile when using focused ultrasound. Improving the treatment outcomes was the impetus for Sammartino and colleagues to develop a tractography-based methodology for the stereotactic targeting of the VIM.

In 2012, a landmark paper by Klein et al.[14] described the use of tractography to define the structural tremor network in patients undergoing VIM DBS. They used the efficacious DBS electrode locations as a seeding point for probabilistic tractography and identified the fiber pathway crucial for tremor reduction: the dentatorubrothalamic tract (DRT). Similarly, Wintermark et al. reported microstructural changes in the cerebello-thalamocortical fibers after focused ultrasound ablation treatment for ET.[8]

With the results of the above studies as a background, Dr. Sammartino and colleagues began using tractography to aid VIM targeting for focused ultrasound ET treatments. This method determines the VIM location based upon the location of its neighboring tracts: the PT and ML.

He described their acquisition and preprocessing protocol, in which they use a voxel size of 2x2x2 mm with 60 or more diffusion directions for acquisition. They then perform precise co-registration between anatomic T1 and B0 images and calculate a streamline tensor calculation using an algorithm based on fiber assessment by continuous tracking (FACT). This algorithm is integrated into the software Medtronic StealthViz, which is approved by the US Food and Drug Administration (FDA) for clinical use.

The DTI-based method is not an unreasonable choice, given that beyond-DTI methods come at the expense of increased false positive rates. To support the choice of a FACT-based DTI targeting method, Dr. Sammartino cited a 2014 study by Thomas and colleagues[15] that investigated the anatomical accuracy of different diffusion modeling approaches. They compared traditional DTI with three beyond DTI, HARDI-type methods. The study found that a traditional DTI based tractography technique shows high sensitivity (i.e., a high rate of true positives) and high specificity (i.e., a low rate of false positives).

The number of diffusion directions is another critical consideration. A study from 200616 analyzed the effect of diffusion directions (6, 21, or 31) on different DTI indices (FA, mean diffusivity, and individual eigenvalues $\lambda 1$, $\lambda 2$, and $\lambda 3$) using the regions of interest (ROI)-based and voxel-based analyses. In the ROI-based analysis, no statistically significant differences in the FA or the mean diffusivity values were observed between diffusion directions but the eigenvalues were significantly different. At the voxel level, there was a statistically significant difference between all indices calculated using the different diffusion directions with the higher diffusion directions having reliable results. Therefore, when voxel-based measurements are calculated, a higher number of diffusion directions should be used.

Given the challenges of proper co-registration, Sammartino, and colleagues created a checklist of structures to determine coregistration accuracy between the anatomic image and diffusion image (b0 image). These structures located within 3 cm of the intended target are: AC, PC, splenium, bilateral colliculi, bilateral superior cerebellar peduncle, and bilateral fornices. Because the dMRI voxel size was 2 mm, they reasoned that a 2-mm difference between the two images was optimal for accurate coregistration.

Dr. Sammartino tested the tractography-based VIM in a 2016 clinical study that enrolled 14 patients with ET and 15 healthy controls.[17] The group used tractography to map the PT and ML because, anatomically, PT, and ML represent the lateral and posterior ventral borders of the VIM. These tracts became a reference to place a VIM ROI with a center that was equidistant (3 mm) from the borders of the PT and ML. This ROI was used to perform tractography to explore the VIMs structural connections. The tracking parameters were a tracking angle of 60°, an FA stop value of 0.2, and a seed density of 1. After determining the VIM ROI using the process described above, the group exports this ROI as an object into the presurgical planning software for targeting purposes rather than using the traditional formulaic method.

In this same study, they compared the tractography-based and the formulaic methods for VIM targeting. They found the tractography-based method to be better for capturing the anatomic variability of patients (e.g., the varying size of the third ventricles). This study also found that the tractography-based target was more lateral and anterior to the PC compared with conventional targeting. During intraoperative verification, the locations of the sensory thalamus, lemniscus, and PTs were concordant within less than 2 mm, showing tractography-based VIM targeting to be accurate and useful.

Following the 2016 study, Sammartino and colleagues began a prospective study to assess the outcomes of focused ultrasound thalamotomy in 10 patients with refractory ET who underwent tractography-based VIM targeting.[18] The VIM was targeted based on PT and ML tracts. Intraoperatively, therapeutic sonications at the tractography target resulted in significant tremor improvement with no motor or sensory side effects. Three patients developed transient ataxia that resolved during the follow-up. Three-month outcomes were assessed independently and revealed significant improvement in tremor scores (56% for hand tremor score and 45% total tremor score). This study suggested that tractography-guided targeting was safe and produced satisfactory short-term clinical outcomes.

Tractography-based VIM targeting is an indirect method to visually identify the boundaries within which ablation can be safely performed while avoiding motor and sensory side effects. Sammartino's group performs a safety check to ensure that the target is within the VIM by confirming that the tractography-determined connections to the cortex and the cerebellum are consistent. This method can be used to improve safety during stereotactic targeting in functional neurosurgery procedures.

Targeting for GPi and VIM

Dheeraj Gandhi, from the University of Maryland, discussed his experience with GPi and VIM targeting using different MRI methodologies. Dr. Gandhi stated that DTI is essential for focused ultrasound ablation when used in conjunction with an advanced imaging algorithm that also incorporates high-resolution structural images. Together, the two modalities create the most accurate target.

A significant drawback of indirect GPi targeting for the focused ultrasound treatment of Parkinson's disease (PD) is the variability in the size, shape, and location of GPi. For example, in a cohort of 13 patients who participated in the PD trial, the GPi volume ranged from 150 mm^3 to 500 mm^3. Only 2 of 13 patients would have had a proper target based solely on traditional formulaic or atlas-based targeting methods. Therefore, Dr. Gandhi used fast gray matter acquisition T1 inversion recovery (FGATIR) imaging to optimize contrast between white and gray matter and aid in distinguishing the GPi.

Suboptimal targeting in PD patients has been a long-standing concern, as described in a 2008 retrospective DBS study by Okun and colleagues.[19] In this publication, 10 of 11 patients with DBS failure that required reoperation improved after repositioning of the DBS leads. The average vector distance of the location of the active DBS contact was adjusted by 5.5 mm, which is substantial and points to the difficulty in accurate targeting methodology.

Dr. Gandhi's preoperative MRI imaging protocol includes a 45- to 50-minute scan (3D volumetric magnetization-prepared rapid gradient echo with T2 images, a 3D 1x1 mm isotropic FGATIR, DWI/DTI, fluid-attenuated inversion recovery, resting-state functional MRI, and an arterial spin labeling perfusion scan). Most of the sequences are performed on a 3T Siemens MRI scanner. For fiber tracking, Dr. Gandhi uses deterministic tractography to track the PT. The position of the PT within the internal capsule is variable between patients; therefore, fiber tracking can help personalize targeting.

With regard to VIM targeting for focused ultrasound ablation, Dr. Gandhi's group uses a deterministic tractography technique described by Yamada and colleagues in 2013.[20] Because they are able to obtain well-defined images of the internal capsule and thalamus with FGATIR, his group only tracks the DRT for VIM targeting. They previously used freeware but today perform the DTI and then superimpose those images onto the FGATIR images and import them into the Insightec workstation. Maryland's outcome results with this protocol are similar to what has been published in the literature regarding focused ultrasound treatment of ET (approximately 60% reduction in hand tremor). There have been no significant long-term side effects, and this group has not witnessed any issues with gait disturbance or ataxia in their treatment cohort.

Dr. Gandhi closed his presentation by highlighting some of the pitfalls and difficulties faced when using tractography. One difficulty is how vendors differ in their tract-generation results. Another difficulty, especially in tremor-dominant PD, is that the seed can be too small to generate a tract. In these cases, he extends his seeding to the entire precentral motor cortex.

Finally, there are still treatment failures despite using advanced imaging techniques and re-treatment. To compensate for some of these pitfalls, Dr. Gandhi feels that more advanced imaging, in addition to tractography, would be useful.

Focused Ultrasound for ET

Technical Considerations and Advanced Imaging Guidance

J. Levi Chazen from Weill Cornell Medicine discussed the Weill Cornell experience with tractography and focused ultrasound procedures. As a neuroradiologist, Dr. Chazen works collaboratively with his neurosurgical colleagues for planning procedures. After preplanning the MRI and DTI scans, Dr. Chazen performs fiber tracking to determine the target and, in parallel, the neurosurgical team plans with the traditional methodology to determine the target. Both targets are then compared, and their proximity confirms the accuracy of the tractography methods.

Dr. Chazen shared Weill Cornell's MR imaging protocol and stated that most preoperative imaging is performed on a GE MRI system (See Appendix I).

Dr. Chazen uses Brainlab's postprocessing software. He emphasized the importance of good image fusion between the DTI (b0) and anatomic (T1 or T2) images to obtain accurate tract locations. He uses seed locations that have been established in other studies to map the corticospinal tract, the ML and DRT, and performs tract generation with an FA of 0.2 to 0.3 and a minimum fiber length of 90 mm. This technique allows him to generate a visual representation of these relevant fiber tracts, gain a sense of the tract borders, and decide where to place the focused ultrasound target safely.
In addition to performing pre-procedure tractography, Dr. Chazen also performs fiber tracking at immediate and 24-hours post-procedure follow-ups. His findings are similar to those published by Wintermark et al.8: reduced diffusion signal immediately postprocedure with DRT fiber tract disruption at the treatment side both immediately and 24 hours after the procedure.

With regard to intraoperative imaging, Dr. Chazen uses the 3T GE MRI with a body coil to acquire reasonably good resolution diffusion images during focused ultrasound procedures. This allows his group to visualize the lesion on diffusion imaging as they are treating the patient, and they use that information to decide whether further lesioning is necessary. The advantage of diffusion images over T2 images is that edema is distinguishable from ablated tissue, making it easier to determine whether a permanent lesion has been created.

Dr. Chazen closed his discussion by briefly sharing his experience with GPi targeting, something that has been somewhat of a challenge in his practice. In his experience, quantitative susceptibility mapping creates the best image definition of the GPi, and he shared several images to demonstrate these results.

Diffusion MR Tractography for Focused Ultrasound
Capabilities, Challenges, and Platforms

Sonia Pujol from Brigham and Women's Hospital reviewed various methods of tractography, discussed factors that influence tractography results, and shared challenges in tracking white matter fibers within the basal ganglia.

Although MR-guided focused ultrasound thalamotomy for the treatment of ET can achieve excellent results, challenges with clinical outcomes remain. Namely, the tremor can return, or the patient may have transient side effects, such as weakness or paresthesia. These challenges might arise from the fact that the VIM is located in a highly complex network of white matter fibers. Indirect VIM targeting using a formulaic method has limitations secondary to anatomic variations in head size and lack the contrast to visualize the white matter tracks in the vicinity of the target. The PT, DRT, and ML are among the critical tracts in the area. The trajectory of these three tracts can be visualized in each patient relative to the therapeutic target using diffusion MRI tractography.

Diffusion MRI enables noninvasive exploration of the structural features of neural tissues in the human brain.[21] The underlying principle relies on the measurement of the diffusion of water molecules in brain tissue using diffusion-sensitizing gradients. The technology can be used without adding additional hardware to the scanner. In white matter fibers, the diffusion is anisotropic due to the presence of myelin sheets and axonal membranes that act as barriers. In grey matter and cerebrospinal fluid, the displacement of water is identical in all directions, so the diffusion is isotropic. The diffusion tensor was the first mathematical framework that was introduced to model the direction of the diffusion of water molecules at each voxel.10 The tensor can be represented by an ellipsoid with the longest axis corresponding to the direction of principal direction of diffusion. The first tractography algorithms introduced in the late nineties reconstruct the trajectory of white matter fibers based on the assumption that the main eigenvector of the diffusion tensor is parallel to the principal fiber orientation at each voxel.[12]

The final step of tractography is reached after following a complex workflow that includes the acquisition of diffusion-weighted MR images, the correction of eddy-current distortion and patient motion artifacts, the computation of the diffusion model, and the segmentation of the anatomical regions of interest.

Numerous deterministic, probabilistic and global tractography algorithms have been developed by the medical imaging community in the past two decades. Deterministic tractography algorithms propagate a streamline by following the orientation of the main eigenvector of the diffusion tensor until a termination criteria based on an anisotropy threshold or a local tract curvature is reached.[22] A drawback of deterministic tractography is that it does not incorporate the uncertainty of the reconstructed pathway, which led to the development of probabilistic tractography. Probabilistic tractography algorithms propagate a large number of streamlines chosen from the distribution of possible fiber orientations from a given seed point.[23] While probabilistic tractography maps provide useful information on the reproducibility of the tracking process, a highly reproducible

tract could be anatomically inaccurate. Global tractography methods aim at reconstructing the full-brain fiber configuration that best explains the measured diffusion-weighted imaging data.[24]

Tractography is gaining increasing interest in the neurosurgical community due to the availability of diffusion MRI sequences on clinical scanners, and the dissemination of fiber tracking tools integrated to commercial neuronavigation systems or available as open-source tools. The 3D Slicer software is an example of open-source platform that provides tools for the analysis and 3D visualization of diffusion MRI data. There are advantages and limitations to both commercial software and open-source platforms, and users can choose their platform based on the goals of tractography. Different post-processing tools can be combined to reconstruct the tracts.

Focusing on the challenges within the basal ganglia reveals additional layers of complexity. First, the clinical targets belong to complex motor circuits in which information is carried via white matter tracts. The white matter tracts are an intricate network of fibers with multiple fiber crossings in a restricted space. Some of the tracts of interest that can be reconstructed in the basal ganglia include the thalamic fasciculus, the DRT, the subthalamic fasciculus, and the nigrostriatal tract. Additional challenges associated with intraoperative MRI imaging must be considered if intraoperative guidance with dMRI is going to become the future.

Tractography reconstructions are generated using mathematical models that rely on several assumptions; therefore, interpreting tractography results can be difficult. A diffusion MRI voxel contains thousands of axons with different orientation, and the single tensor model may be inadequate for the tractography of complex white matter configuration such as the decussation of the DRT. Finally, the variability of tractography results when using different tractography methods presents another challenge.

The overall goal of dMRI research for focused ultrasound intervention is to develop methods for improving patient outcomes. Several tool-dependent or user-dependent factors influence tractography results. These factors include:

1. the diffusion model (single tensor versus multi-tensor);
2. the type of fiber tracking algorithm (deterministic versus probabilistic);
3. the placement of ROIs (including seed points and end points) and
4. tract-tracing parameters (FA and angular threshold stopping criteria).

Besides the user-dependent factors listed above, non-user-dependent factors also affect tractography results. Low-quality data quality can produce incorrect tractography reconstructions, and the diffusion properties of edema, necrosis, and tumor tissue or neurodegeneration can affect results.

Two types of tractography errors result from these influencing factors. The first error is when tractography fails to recognize an anatomic pathway, resulting in a false negative tract. The second error is when tractography creates an artefactual, or “false positive,” tract that does not represent an anatomic tract. Both false negative and false positive tracts display the current limitations of tractography as a tool for neurosurgical decision making, but this does not mean that tractography is useless. Instead, this information needs to be taken into consideration when analyzing fiber tracking results, especially for clinical decision making.

In 2009, Pujol and colleagues performed a study to compare tractography results in healthy subjects using different algorithms. The evaluation of tractography reconstructions showed a large inter-algorithm variability. These results, being one of the first projects to analyze this question, were presented at the 2009 International Society for Magnetic Resonance in Medicine (ISMRM) meeting. After studying healthy subjects, Pujol and colleagues investigated tractography results using various algorithms in brain tumor patients. The reconstruction of the PT using eight tractography techniques showed a large variability among different tractography approaches.

Validation of tractography reconstructions must be performed to ensure that tractography results are reliable for clinical decision making during surgery. Pujol and colleagues[25] used multi-fiber reconstruction to examine the PT in five different subjects. The team evaluated the anatomic accuracy of the tracts using knowledge from experts in neuroanatomy, neurosurgery, and neuroimaging, which is one way to validate the anatomic correctness of results. An additional approach to verifying data is by evaluating patient outcomes in functional neurosurgery.

Dr. Pujol closed by sharing some of her recent tractography work in mapping the PT, hyperdirect pathway, rubro-thalamic tract and subthalamic fasciculus. She shared results presented at the 23rd Congress of the European Society for Stereotactic and Functional Neurosurgery that included a study of hyperdirect pathway tractography results among five subjects. The consistent results among all subjects were encouraging.

In summary, personalized connectivity maps of the VIM may enable neurosurgeons to refine clinical targets and better understand the origin of side effects. Planning focused ultrasound ablation using tractography mapping may help determine the effect of lesioning in that exact area (e.g., improved tremor control, weakness, and paresthesia). Correlation with clinical outcomes may help optimize treatment and promote understanding of functional neuroanatomy and connectivity of thalamic structures, including the VIM.

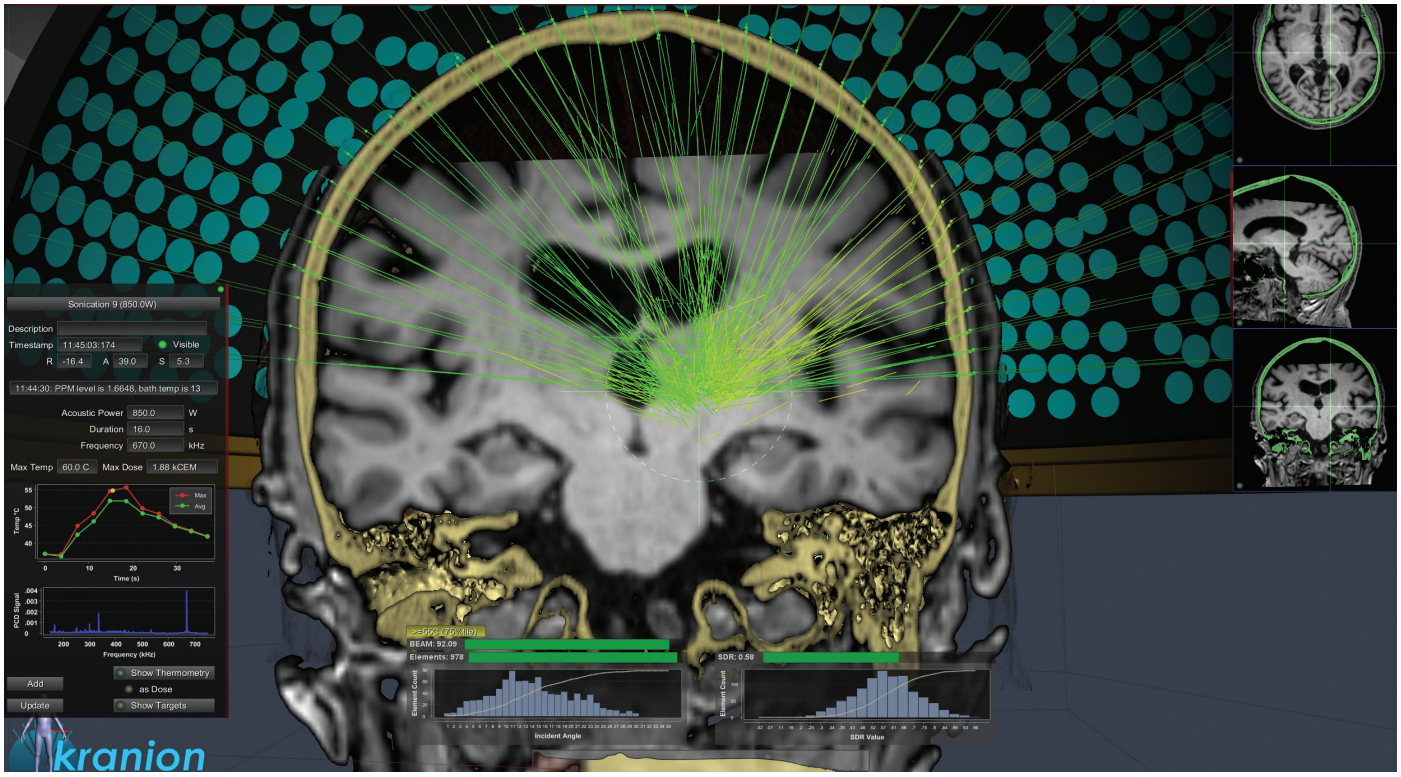

Figure 2
An example of the Kranion user interface, which allows the user to visualize the treatment.

Kranion

John Snell from the Focused Ultrasound Foundation, presented Kranion, a visual computing platform for planning, rehearsing, and reviewing transcranial focused ultrasound treatments. This software combines MR, CT, and transducer geometry to visualize the interaction of planned treatment targets with patient-specific skull geometry (Figure 2). Kranion is open source and freely available to the community for research purposes. Visualization of tractography data will soon be incorporated.

MRI Temperature Monitoring

Dennis Parker from the University of Utah presented a brief overview of MRI thermography, which is used during focused ultrasound procedures to map the target temperature and its surrounding tissue accurately. Thermography ensures the safety and efficacy of the treatment.

MRI thermography is based on the proton resonance frequency (PRF), which has been shown to be reliable for quantifying temperature rises in aqueous tissue. As the water heats, the hydrogen bonding between adjacent oxygen and hydrogen atoms decreases, which increases the electron cloud around the proton and results in a decrease in PRF. Frequency is a linear function of temperature, and this is currently how MRI thermography is commonly performed.

Most focused ultrasound procedures use multi-slice, two-dimensional imaging for temperature monitoring. However, the disadvantage of this technique is that it does not cover the entire ultrasound beam path. Therefore, it does not monitor skull heating. Instead, optimal temperature monitoring for focused ultrasound requires 3D temperature maps with an extensive volume coverage and high spatiotemporal resolution to rapidly track the changes in temperature—not only at the target but also at the bone-tissue interface.[26]

There are some challenges with 3D coverage, and one such challenge is the long acquisition time, which limits "real-time" temperature monitoring. Due to this issue, Parker and colleagues[26] developed a technique called "model predictive filtering" that predicts temperature based on the current temperature and knowledge of other properties. This technique is faster, reporting fully volumetric temperature measurements within seconds.

A current barrierr to the mainstream adoption of 3D MRI thermometry is FDA approval. Furthermore, vendors need to adopt the technology to make it widely available to focused ultrasound users.

Connectomic Targeting in Clinical Practice

Dr. Robert Gross from Emory University discussed his experience using tractography for DBS of the subcallosal cingulate gyrus (SCG) for the treatment of patients with depression. Neuromodulation has been used for depression treatment for a number of years, and researchers have explored several different targets—from the cortex to the thalamus to the striatum and the white matter tracts in between.

Dr. Gross described his experience with neuromodulation of the SCG, which became a target for the treatment of depression after a 2005 pilot study by Mayberg and colleagues[27] demonstrated that chronic stimulation of the white matter tracts adjacent to the SCG was associated with a substantial and sustained remission of depression in 4 out of 6 patients (67%). In 2008, Gross and colleagues[28] replicated this study to find only a 41% response rate at six months. They wondered why all patients did not improve and why all patients did not respond at the same time course. When Harmani and colleagues[29] investigated whether the DBS lead location played a role, they found no relationship between the location of the

DBS lead and the outcome if the lead was placed within the SCG. This discovery led them to believe that MRI localization might be inadequate for the procedure.

Background information gathered when assessing the mechanism of DBS within the subthalamic nucleus showed white matter tract stimulation rather than grey matter stimulation. Therefore, Gross and colleagues sought to assess DBS at the subgenual cingulate to determine whether it had a similar mechanism of engaging white matter tracts. Using dMRI and probabilistic tractography, they found significant differences between responders and non-responders in the white matter pathways that were engaged.[30] Specifically, they identified four pathways that were within stimulation volume in responders. When they attempted to engage these pathways by changing contact position and volume of tissue stimulated in non-responders, they were successful, suggesting a novel method for patient-specific targeting and stimulation parameter selection.

This led Gross and colleagues to take a prospective, connectomic approach to SCG targeting for DBS.[31] During presurgical targeting, patients received high-resolution T2 MRI, DTI, distortion and movement correction, registration, normalization, segmentation, and local DTI fitting. The team then performed deterministic tractography using TrackVis software (http://trackvis.org), and they identified a target using a four-bundle blueprint. The surgical procedure was then performed, and the lead was implanted into the target region with TrackVis assistance. The surgeon selected the contacts for chronic stimulation based on matching the postoperative probabilistic tractography map to the presurgical deterministic tractography map for each subject. The prospective targeting method resulted in 72% of patients showing improvement in their depression scores at the 6-month mark as compared to 41% improvement at six months with retrospective methodology. At the one-year follow-up, 9 of 11 subjects were responders, and 6 of the responders were in remission.

Tractography is also being used for DBS targeting of the medial forebrain bundle (MFB) for the treatment of the obsessive-compulsive disorder (OCD) and depression.[32,33] In fact, physicians were unable to visualize the MFB prior to the application of tractography. One study mapped MFBs using deterministic tractography and transferred the fiber tracking results to the stereotactic planning software. Physicians placed the DBS leads at the center of the MFB fiber tract. Preliminary results were positive, showing an 80% response rate at six months and sustained response rates up to 50 months post-DBS placement.[34]

Dr. Gross concluded his talk by describing his technique for tractography-guided DBS targeting of the subgenual cingulate, which begins with whole-brain probabilistic tractography and then uses a connectomic blueprint or template to model the four patient-specific tracts of interest. The team identifies patient-specific targets in the TrackVis system and then burns a mark on the T1 image. Next, the team imports the T1 images with the burn marks into the stereotactic planning software (StealthStation, Medtronic, Inc). The surgeon implants the DBS leads using stereotactic coordinates that are specific to each patient. Finally, the stimulation volume is modeled, follow-up CT scan images are acquired, and probabilistic tractography is performed to validate proper lead placement based on the predetermined target tracts.

Discussion throughout Workshop Presentations

The rationale for Tractography-based Targeting

- Dr. Cosgrove and Dr. Gross commented on the variability of the VIM location. They said that formulaic methods could be inaccurate.
- Dr. Cosgrove asked the group to consider how tractography could help focused ultrasound achieve the "five goals of tremor surgery." Dr. Krishna added that one technique would not be the answer to achieving all five goals; instead, the integration of several techniques would provide the best and most reliable information.
- Dr. Cosgrove mentioned ablating an optimal volume for durable outcomes after ET. Dr. Gandhi added that he would like to see data comparing the effect of lesion volume on adverse effects. He wondered whether tractography and other advanced techniques could help produce a small lesion with effective tremor suppression without side effects.
- Dr. Gross asked how the focused ultrasound ablation technique was different from radiofrequency (RF) ablation. He explained that during RF ablation, patient feedback and the temperature at the tip of the needle guide the determination of treatment endpoint. He commented that during focused ultrasound ablation, tractography and MRI mapping could provide intraoperative feedback and that refining thermal mapping or improving real-time imaging to see live treatment results was an advantage. Dr. Elias added that the advantage of focused ultrasound is that it can be image-guided, but most institutions do not use image guidance during the actual thermal lesioning. He asked whether there might be a better way to guide ultrasound sonications and said that treatment should be guided by intraoperative confirmation that the preplanned target was ablated.

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Introduction to MR Diffusion Tractography

- Dr. Krishna and Dr. Cosgrove said that DTI makes assumptions about microstructure/subvoxel structures at the voxel level. Dr. Cosgrove commented that a typical 2x2-mm voxel contains a large volume of brain tissue.
- Dr. Yeh commented that although diffusion MRI acquires images within the constraints of one voxel, tractography has the potential to analyze data at the subvoxel level.
- Dr. Krishna said that the tract termination point is usually determined by combining the angular and anisotropic thresholds.
- Dr. Gross asked how tractography could achieve 100% reliability and assist surgeons in deciding where to cut or ablate. Dr. Yeh said that he currently advises his neurosurgery colleagues to use tractography information as a tool and be aware of its limitations.

- Dr. Krishna asked whether specific disease pathologies in the brain affect tractography. Dr. Yeh responded yes, disease processes such as edema affect the reliability of tractography. Dr. Yeh stated that the longer the tract, the more suspicious he is of its reliability.
- Dr. Cosgrove asked how tracts that cross the midline are analyzed. Dr. Yeh said that crossing tracts are a significant challenge because it is difficult to determine whether two tracts actually cross, whether they kiss and separate again, or whether they even cross at all. A perfect example of this dilemma is the optic chiasm, where all three of these situations occur but appear the same on tractography. This challenge can be overcome with increased spatial resolution.
- Dr. Yeh commented that background knowledge in neuroanatomy is essential for confirming the location of the predicted tracts.
- Dr. Ghandi mentioned that he uses "waypoints" to direct the tract through specific structures through which the pathway is known to pass. Dr. Yeh agreed that this works well unless there are sharp turns within the pathway.
- Dr. Krishna asked whether the size of the fiber system changed the reliability of the tract. Dr. Yeh said yes, a larger fiber system is easier to map.
- Dr. Zhuo made the analogy of driving and that deterministic fiber tracking takes the most direct route from point A to B, whereas probabilistic tracking takes side roads and detours.
- Dr. Chazen commented that due to its large size, depicting the corticospinal tract could quickly be done using deterministic tractography with DTI. However, depicting a smaller tract, such as the corticobulbar fibers, would require advanced techniques such as probabilistic tractography.
- Dr. Gross asked about the reliability of the tract borders because his main goal is to avoid lesioning an area at the edge of the internal capsule. Dr. Yeh said that when the pathway is relatively straight, the border should be almost 100% accurate; however, the pathway is less reliable when it makes significant turns.
- Dr. Cosgrove said that T1 MRI images define the internal capsule well enough that tractography would not be needed. Dr. Gandhi commented that his group uses FGATIR T1 MRI images for ET cases so that they can reliably see the thalamo-capsular border. Combining T1 MRI and tractography allows the surgeon to avoid the internal capsule while targeting the tract reliably.
- Dr. Chazen commented that tractography is better at showing the epicenter of the tract, which is useful for targeting.

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Tractography-based VIM Targeting

- Dr. Krishna said that their 2016 VIM tractography study started with 18 patients, but only 14 could be tracked due to image quality issues and challenges with co-registration and signal strength.
- Dr. Cosgrove commented that the group did not discuss lesion depth. Dr. Sammartino replied that he usually targets one slice above the PC line and standardizes the height of the ROI to around 4 to 6 mm (similar to the actual size of the VIM).

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Diffusion MR Tractography for Focused Ultrasound

Limitations, Challenges, and Platforms

- Dr. Gross commented that the space between the VIM and the capsule appeared to be significant in Dr. Pujol's reconstruction of the PT. Dr. Cosgrove commented that the lateral medullary lamina measured 2 mm. Dr. Pujol commented that it is a cross-sectional color map, and the tracts are consistent with the DTI color map, signifying that they are in the right place. She acknowledged that although the gap may be a bit large, the tract location appears to be correct.
- Dr. D'Haese asked how the distance of the tract could be used. Dr. Pujol replied that the field is not yet at the point where it can use the quantitative results.
- Dr. D'Haese asked whether non-experts in DTI could effectively use open-source tractography programs. Dr. Pujol replied that scientists and clinicians who use these tools should know their limitations; otherwise, they should ask for help. She emphasized that open source tools should be used primarily for research because they are not FDA approved. Dr. D'Haese agreed that although high-level experts can perform this work, it is not ready to be adopted by those with little or no experience with tractography.
  There was lively discussion from multiple audience members surrounding the importance of educating scientists and clinicians who may use tractography on the uses and limitations of the technology.
- Dr. Cosgrove commented that Dr. Pujol's results were the most complex tractography results he had seen and that their anatomic correctness was striking.

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Connectomic Targeting in Clinical Practice

- Dr. LeBlang asked Dr. Gross for his opinion on how focused ultrasound could be used to treat refractory depression, citing some previous work. Dr. Gross replied that focused ultrasound targets could be defined using tractography. However, the challenge with using thermal ablation of brain tissue to treat psychiatric disorders is the bias that destroying brain tissue in patients with psychiatric disorders is contraindicated. He stated that this type of treatment might first be performed outside of the US.
- When Dr. Cosgrove asked Dr. Gross which tracts he would be interested in targeting with focused ultrasound if, given the opportunity, Dr. Gross replied that the tracts that go downstream to the striatum were significant, as were the tracts traveling to the medial frontal orbital region. He added that he would like to see the tracts traveling to the subgenual cingulate engaged, but this would require making multiple lesions. Dr. Gross said that focused ultrasound was much more economical than DBS, which might be an advantage that the focused ultrasound community could capitalize on

Roundtable Discussions

Topic 1
Acquisition

Expert Panel: Dr. J. Levi Chazen, Dr. Frank Yeh, Dr. Srinivasan Mukundan

Question 1
Scan time optimization: How many diffusion directions is enough?

- Dr. Mukundan: If we want to end up with something operational in the clinical space, 30-60 diffusion directions should be enough to keep the time of acquisition reasonable. In addition to diffusion directions, the b-values are essential. We should be exploiting high b-values.

  Dr. Mukundan then asked, "How do we increase the b-values to get better images?"
- Dr. Yeh: With DTI fitting, a higher b-value will not help because the software will take the data and make it fit into the tensor model. The optimal b-value depends on which method you are using for fiber tracking. While using DTI, a fixed b-value between 1000-2000 is the optimal setting. Higher b-values are useful for detecting subtle diffusion changes and necessary for identifying small, subtle changes.
- Dr. Chazen: A 33-direction b-value of 1000 works fine for ET tracking. A 60-direction scan did not seem to be better. Start with protocols that are publicly available (from the MRI platform). More advanced techniques, like multi-shell acquisition, can be challenging to process.

Question 2
What should the order of scan type be?

- Dr. Mukundan: Start with the anatomic/structural images (T1 and T2) and then move to the DTI.

Question 3
Is there an optimal signal to noise ratio (SNR)?

- Dr. Chazen: Rather than identifying an optimal SNR, I recommend a practical protocol that works well, has a reasonably good SNR and can be confidently used by less-experienced providers.

Question 4
What recommendations do you have for minimizing head motion?

- Dr. Yeh: My group uses head padding and nose alignment.
- Dr. Mukundan: My group also uses head padding, but there are many devices on the horizon for motion registration and rejection of transients based on set tolerances that are camera-based. This problem may be solved within the next few years.

Summary recommendations on the acquisition

1. Use a 3T scanner with a head coil with at least 32 channels, multi-band acquisition
2. 2 mm Isovoxel
3. 30-60 directions
4. b-value of 1000-2000
5. The optimal scan time of between 5 to 10 minutes
6. Begin with the anatomic images and end with the diffusion images
7. Use head padding to minimize head motion and stay tuned for new technology that will track motion and automatically reject transients based on set thresholds.

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Topic 2

Processing

Expert Panel: Dr. Frank Yeh, Dr. Sonia Pujol, Dr. Jiachen Zhuo

Question 1

What FA and angular thresholds should be used?

- Dr. Yeh: The FA is more important than the angular threshold. Dr. Yeh uses an FA of 0.2 to 0.3 and an angular threshold between 40 to 70 degrees.
- Dr. Pujol: FA 0.2 to 0.3, angular threshold 40 to 50 degrees with 5 to 10 degree changes.
- Dr. Zhuo uses FA of 0.1 to 0.2 and an angular threshold of 35 to 60 degrees. Deterministic tractography algorithms have built-in FA and angular thresholds (i.e., FACT).

Question 2

How do you measure the accuracy of co-registration?

- Dr. Pujol: I use the 3D slicer and co-register the b0 and T2 images. Different modules in the 3D slicer check the accuracy of co-registration. Dr. Yeh: I used a platform similar to the 3D slicer.
- Dr. Zhuo: I use a few different platforms, including the Siemens workstation and the NordicNeuro workstation. Siemens does the co-registration on its own. NordicNeuro registers first and then allows the user to visually confirm how well the images overlay and then make any desired changes.
- Dr. Krishna: In StealthViz, I place a crosshair on an anatomically visible landmark, such as the splenium, and then toggle over to the DTI image; if the difference is greater than 2 mm, my level of confidence in the system's co-registration is low, and I attempt to manually co-register the images.
- Elizabeth Vasconcellos: Brainlab has been working on something called elastic registration, which can take two images (i.e., a T1 and a b0 image) and run a distortion correction, which then corrects subsequent scans that are connected to the b0 images. This method has been validated.

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Topic 3

Software and Clinical integration

Expert panel: Bruce Leggett, Elizabeth Vasconcellos, Ryan Clanton

Question 1

What capabilities exist today (i.e. number of diffusion directions, number of b0 images) and where do you see this heading in the future?

- Bruce Leggett: Even with the current version of SteathVis, this software can incorporate as many b0's and as many directions as the user would like as long as the gradient directions are included in the dicom editors. All of the standard vendors are getting better at including this information. In the next generation, I don't see huge changes besides keeping up with the scanning manufacturers.
- Elizabeth Vasconcellos: Brainlab has had stereotactic fiber tracking packages for quite some time, but the adoption rate has been low. Its latest generation updates were mostly focused on the graphical user interface. However, the next-generation update will include templating options based on atlas landmarks and updates to the fiber tracking algorithms (i.e., a two tensor model).

Question 2

Are there ways where the imaging can be automatically uploaded into the server and automatically checked for accuracy, and the neurosurgeons are notified of these results?

- Elizabeth Vasconcellos: This quality control capability is best accomplished by the individual MRI scanner companies. One caveat is that this type of workflow can be quite challenging in a hospital setting due to information technology security and patient privacy issues.
- Bruce Leggett: Synaptive medical has a product called "The Bridge," which acts as a quality control check for data sets that are acquired and intended for navigation. However, it is more of a check against the recommended protocol, not of the data quality itself.

Question 3

From an industry perspective, how do you feel about tractography for FUSA? What is your vision for the development of a planning system that incorporates tractography into the workflow?

- Ryan Clanton: The stereotactic target defined by atlas-based measurements is often accurate enough, but there are cases that are difficult to treat where tractography could be beneficial. Using tractography in cases of treatment failure & re-treatment is where I see it fitting in right now. My company is conservative in recommending tractography because it is still a developing technology that requires expert knowledge to interpret. I do not foresee our company creating a third-party tool.

Question 4

Dr. Cosgrove: Should we be performing tractography on our focused ultrasound patients, and how should we be using these data?

- Dr. Krishna: Tractography can enhance targeting for transcranial focused ultrasound procedures and allow treatment providers to improve the reliability of the treatment in a larger number of centers. Dr. Gandhi: There is nothing to lose in gathering this information, so the first step should be to acquire the information and make it is available if needed. After providers begin to use this technology, they will become more reliant on it. Ryan Clanton: Combining tractography data with something like a cranial cloud to create density maps of adverse events would be helpful and highly likely to be used by my company.

Appendix

Summary of Imaging Protocols from Expert Institutions

Stanford[35]

	Diffusion-weighted	T2-weighted	T1-weighted
Sequence	2D single-refocused DW-SE-EPI	3D FSE	MPRAGE
TE/TR (ms)	81.6/8500	83.5/2500	3.73/8.3/1100 (T1)/3000 (TS)
Flip angle (°)	90	90	9
Field-of-view (mm^2)	240 x 240	240 x 240	180 x 180
Matirx	128 x 128	320 x320	180 x 180
In-plane res. (mm^2)	1.875 x 1.875	0.75 x 0.75	1 x 1
Slice thickness (mm)	2	1	1
Slice spacing (mm)	0	0.5	0.5
Number of slices	69 axial	180 sagittal	220 coronal
Parallel imaging	ASSET factor = 2	ARC factor = 2	ARC factor = 2
Acq. time (min)	10	7	3.5
DIffusion encoding	6 x b = 0 60 directions x b = 2500 s/mm^3		

Key

MRI data acquisition sequences and parameters:

DW-SE-EPI = diffusion-weighted spin-echo echo-planar imaging
FSE = fast spin echo
MPRAGE = magnetization-prepared rapic gradient-echo
TE = echo time
TR = repetition time
TI = inversion time
TS = short interval time
ASSET = array coil spatial sensitivity encoding
ARC = autocalibrating reconstruction for Cartesian imaging

Weill Cornell[36]

Sequence	Matrix	TR (ms)	TE (ms)	TI (ms)	FOV (cm)	Slice Thickness (mm)	Imaging Options	Acquisition Time (min)
3D Sagittal T2 CUBE	256 x 256	3000	70	None	25.6	1	NPW, EDT, Fast, ZIP512, ZIP2, FR, ARC	4:45
3D Sagittal T1 BRAVO	256 x 256	10	Min	450	25.6	1	EDR, Fast, IrP, ZIP2, ARC	4:25
Axial T2 FSE	384 x 256	2700	110	None	24.0	2	FC, EDR, TRF, Fast, FR	3:45
Axial QSM/SWI	416 x 320	30	Min Full	None	24.0	3	FC, Fast, ASSET	3:30
Axial DTI (33-Direction)	128 x 128	7500	Min	None	24.0	2.5	EDR, EPI, DIFF, ASSET	5:00

Ohio State University[37]

Sequence	Diffusion-weighted Axial Single-shot Spin Echo EPI	T1-weighted Axial Fast Gradient Echo	T2-weighted Axial
TE/TR (ms)	68/8100	3.7/8.2	80/6650
Flip angle (°)	90	8	90
Field-of-view (mm^2)	240 x 240	240 x 240	—
Voxel size	2 mm isotropic	1 mm isotropic	0.83 x 0.83 x 1.2 mm
Number of slices	60	160	—
Gradient directions	59	—	—
b values (s/mm2)	0, 1000	—	—

Brigham and Women's Hospital

Sequence	Diffusion-weighted EPI simultaneous multi-slice (SMS) sequence	T1-weighted Axial	T2-weighted Axial FSE	T2-weighted 3D Sagittal SPACE
TE/TR (ms)	69/2900	2.54/1900	95/6040	411/2900
Flip angle (°)	90	9	138	120
Voxel size	2 mm isotropic	0.97 x 0.97 x 1.0 mm	0.23 x 0.23 x 2.5 mm	0.66 x 0.66 x 0.9 mm
Gradient directions	30	—	—	—
b values (s/mm2)	1000	—	—	—

Next Steps

The Focused Ultrasound Foundation encouraged participants to submit research ideas and project proposals in this area. The Foundation will continue engagement with the community to move this research forward.

Abbreviations

AC	anterior commissure
b-value	a factor that reflects the strength and timing of the gradients used to generate diffusion-weighted images
DBS	deep brain stimulation
DTI	diffusion tensor imaging
DRT	dentatorubrothalamic tracth
DWI	diffusion-weighted imaging
ET	essential tremor
FA	fractional anisotropy
FACT	fiber assessment by continuous tracking
FDA	US Food and Drug Administration
FGATIR	fast gray matter acquisition T1 inversion recovery
GPi	internal globus pallidus
HARDI	high-intensity focused ultrasound
MFB	medial forebrain bundle
ML	medial lemniscus
MRI	magnetic resonance imaging
PC	posterior commissure
PD	Parkinson's disease
PRF	proton resonance frequency
PT	pyramidal tract
ROI	regions of interest
SCG	subcallosal cingulate gyrus
VIM	ventral intermediate nucleus

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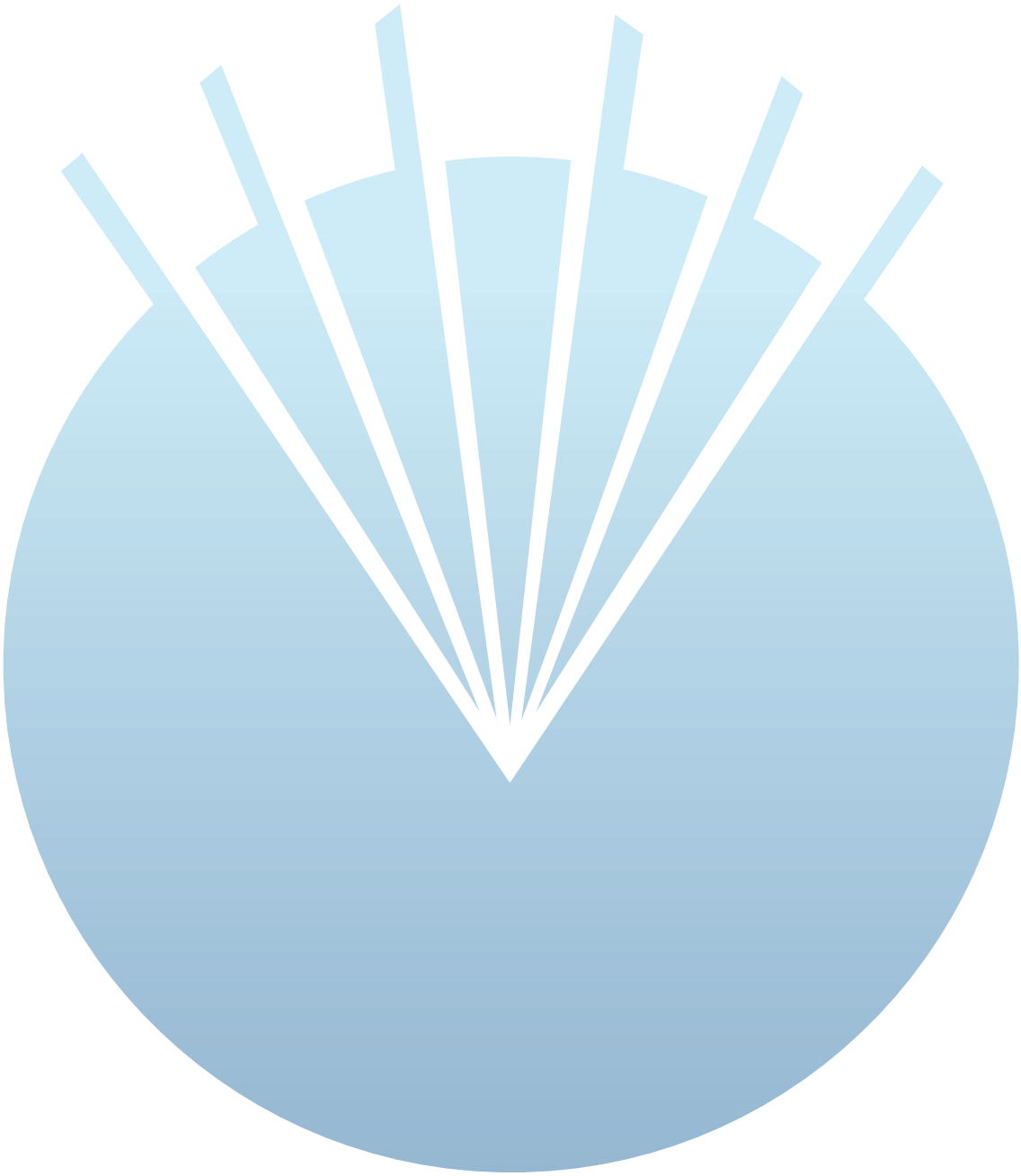

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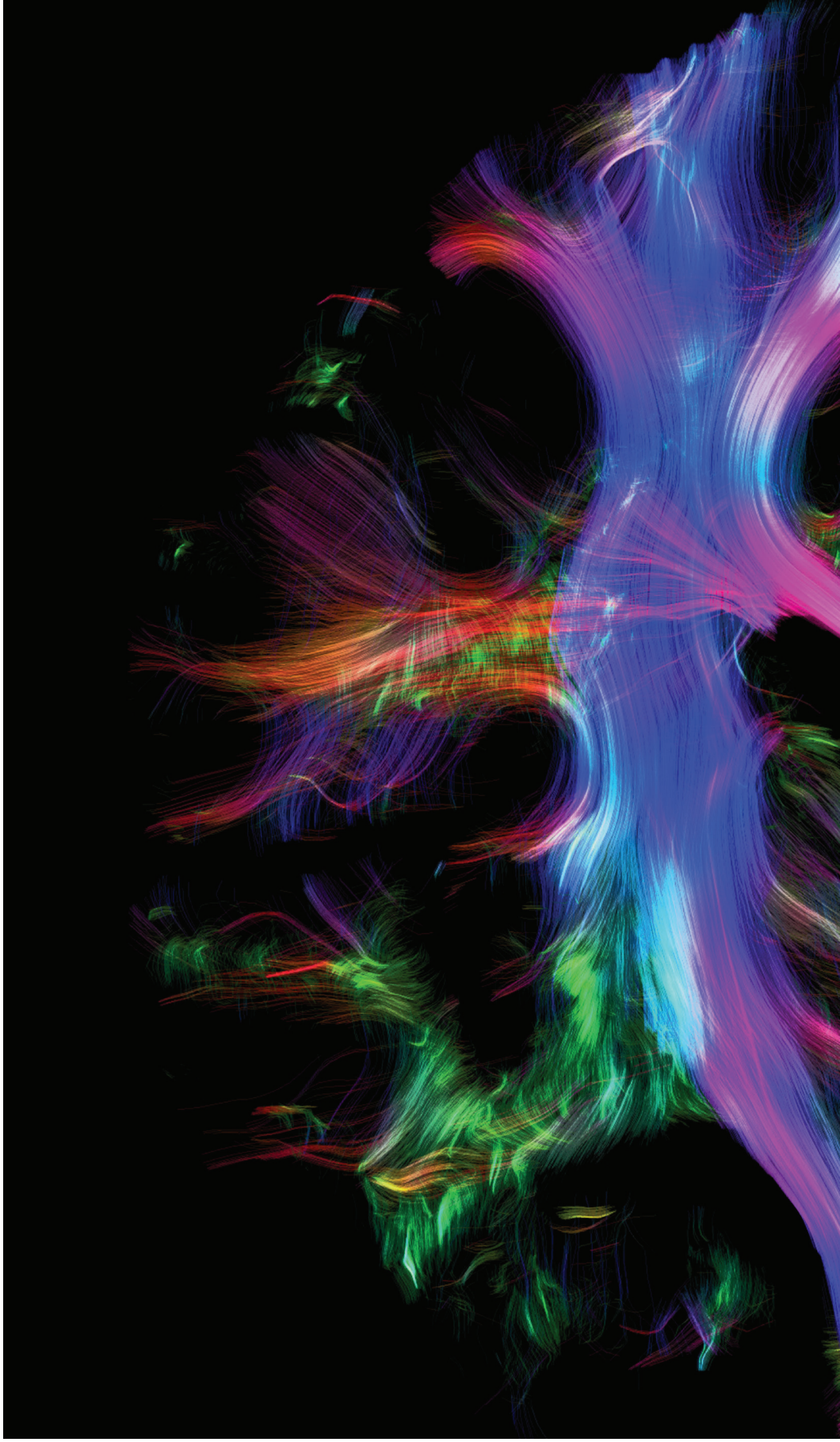

Healthy human brain from a young adult, tractography. Credit: Wellcome Collection