

MR Guided High Intensity Focused Ultrasound for tremor

Padraig O'Suilleabhain MD, Department of Neurology

Bhavya R. Shah MD, Department of Radiology & Neurological Surgery

UT Southwestern and O'Donnell Brain Institute

Tremor

- Involuntary movement with rhythmic displacement of body part
- Degrades skilled movements and functions, and looks bad
- Distribution: arm, hand, head, voice, face, leg, trunk
- Context: rest, posture, action

Causes of tremor

- Essential tremor
- Parkinson disease
- Drug induced tremor
- Functional tremor
- Enhanced physiologic tremor
- Cerebellar degeneration
- Structural brain diseases eg MS, strokes, TBI
- Hyperthyroidism
- CIDP

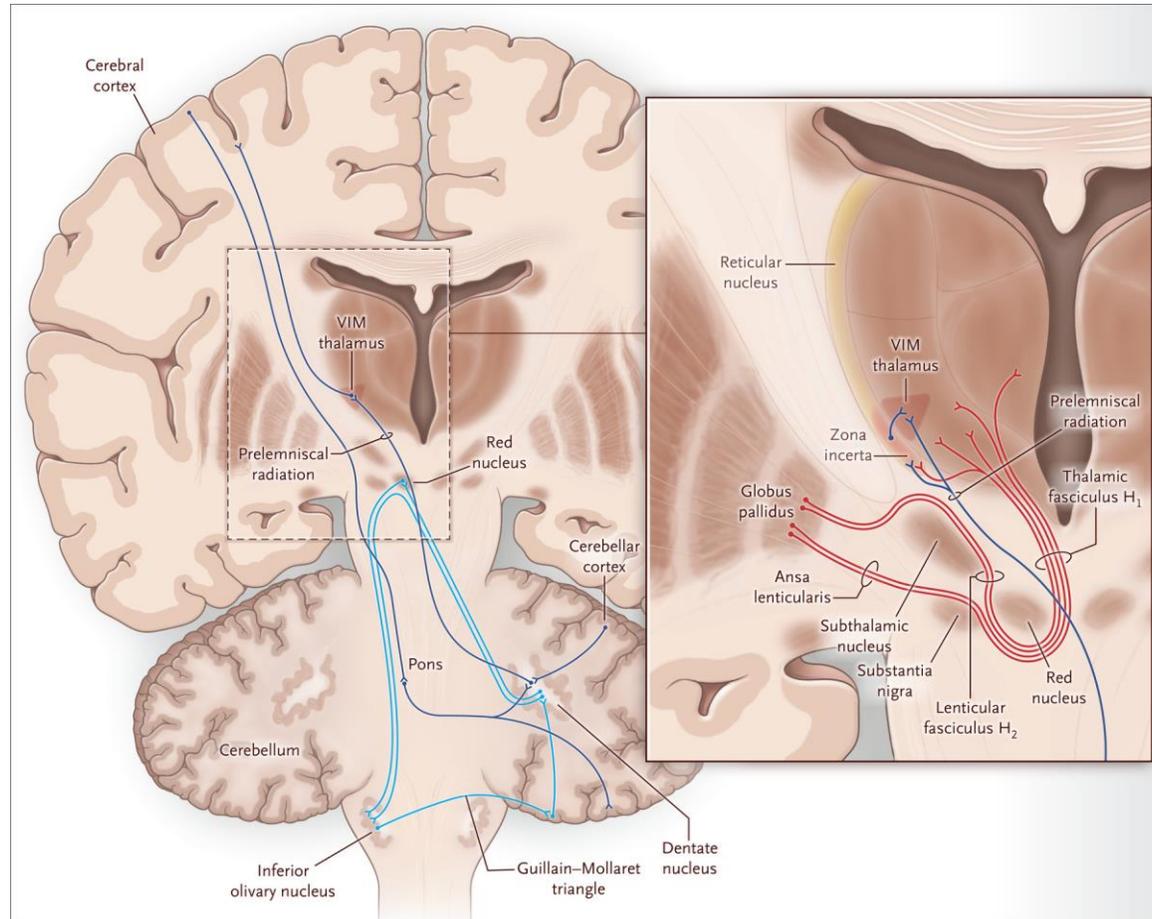
Overview Essential Tremor

- A common neurologic condition (1% all adults, 6% of people > 65 yrs)
- Involuntary rhythmic displacement of body parts in posture and action
- Arms and hands commonly affected, also head, voice, face, legs trunk
- Often bilateral can be symmetric or asymmetric
- Commonly interferes with writing, feeding, dressing, phone, hobbies,
- Exacerbated by stress, fatigue, beta agonists
- Rest tremor can co-exist if action tremor has become large
- “essential” implies unknown cause and usually isolated; else “ET-plus”
- Worsens over time

Overview Parkinson disease

- Second most common CNS degeneration
- Rest tremor, bradykinesia, rigidity
- Asymmetric onset gradual progression
- Advanced PD can develop dementia, postural instability
- Motor symptoms respond to dopaminergic meds
- Motor and non-motor fluctuations
- Lewy body neuronal inclusions contain synuclein
- Spreading pathology, early involvement of substantia nigra

Pathophysiology of tremor



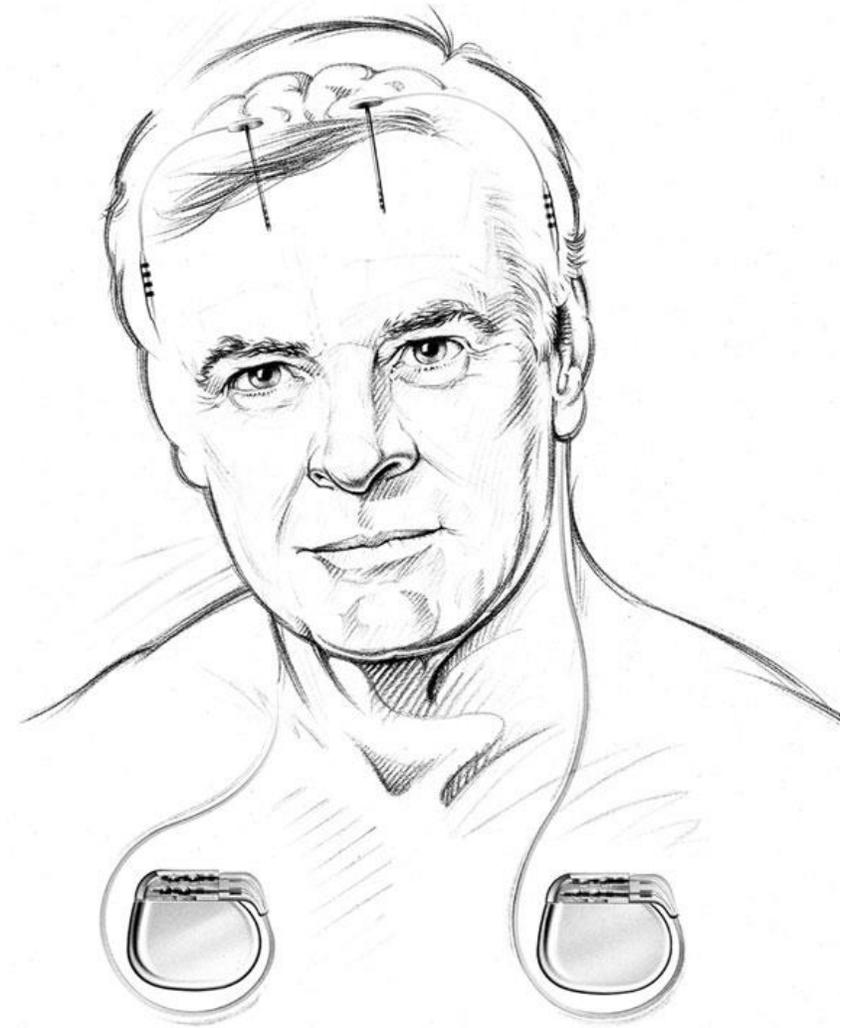
- Motor control via multiple servo-mechanism feedback loops
- Relevant circuits
 - cortex-pons-cerebellum-thalamus-cortex (dark blue)
 - dentate-red nucleus – inf olive – dentate (light blue)
 - striatum-GPI-thalamus (red)
 - corticospinal tract – motor neuron – muscle, joint – sensory pathways – thalamus - cortex
- If there is excess automaticity or cross-talk, get pathologic phasic synchrony
- And/or if ill-tuned (e.g. if synapses “loose”), get delay or jitter, and cyclic correction overshoots <--> undershoots
- And if the active body part is in resonance with the phasic neural bursting
- ... you’ll get TREMOR

Pharmacologic therapy of tremor is symptomatic

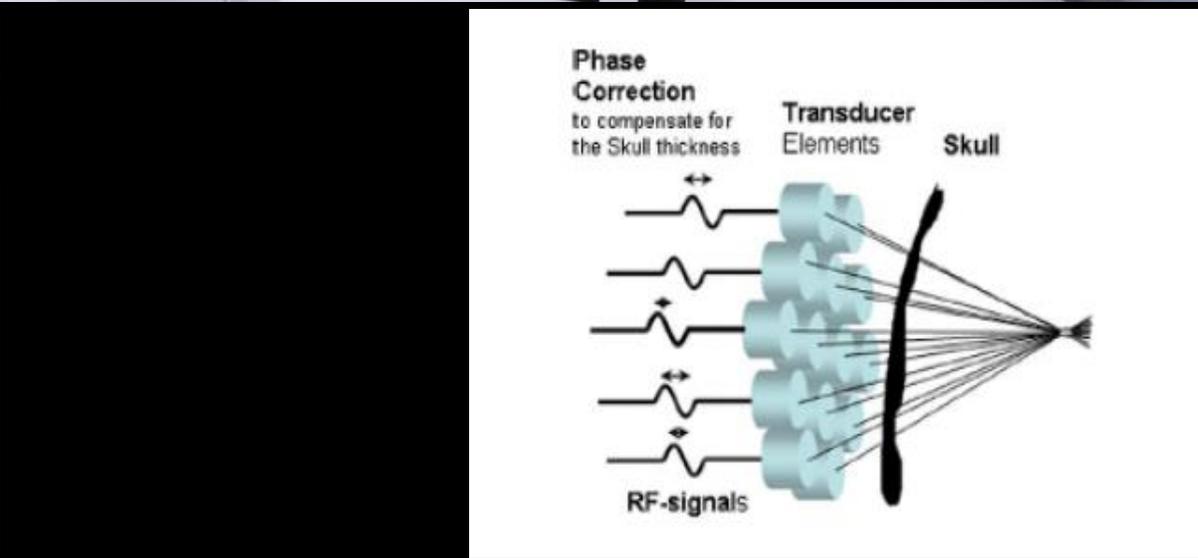
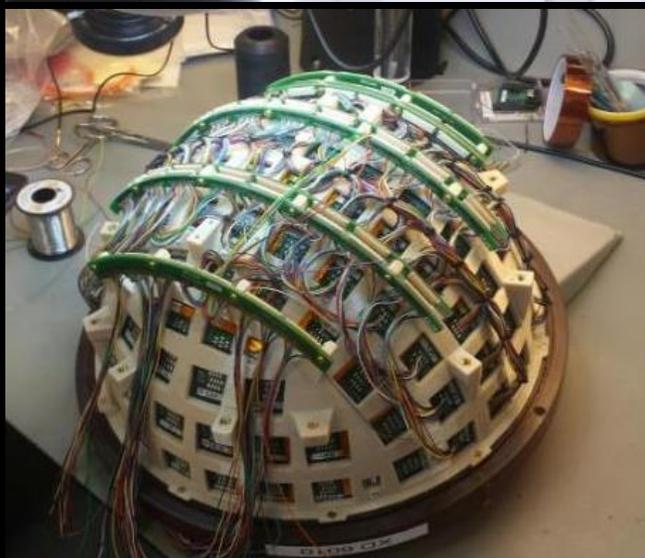
- Essential Tremor
 - Non-selective beta blockers
 - propranolol
 - nadolol
 - Anti-epileptic drugs
 - primidone
 - topiramate
 - gabapentin
- Parkinson disease
 - Levodopa
 - Dopamine agonists
 - (Anticholinergics)

DBS for treatment of refractory tremor

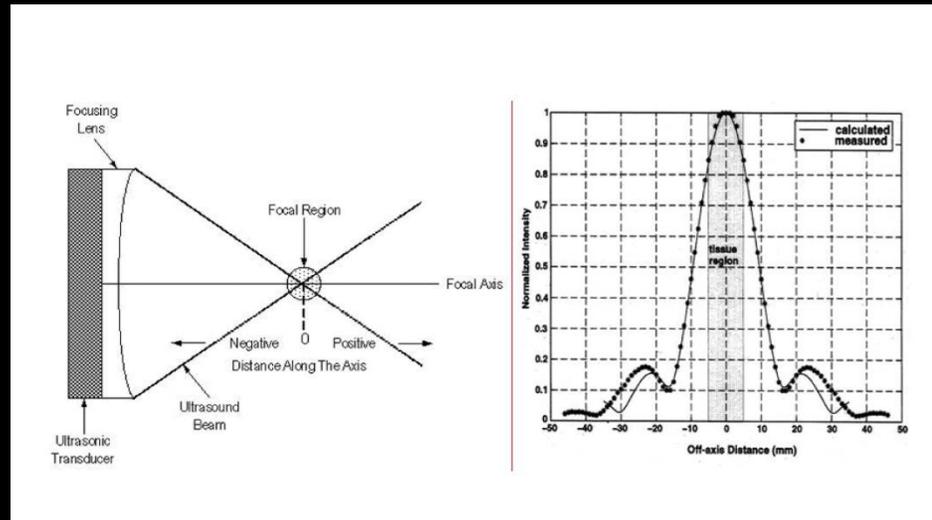
- An electrode can be stereotactically placed at or below thalamic VIM
- Electrical pulses e.g. 1 mA for 60 μ s at 130 hz co-opt tremor circuits (make refractory)
- Highly effective and lasting
- Invasive, carries surgical risks
- Expenses incl surgery & programming & battery change,



MR guided Focused Ultrasound (MRgFUS) Overview

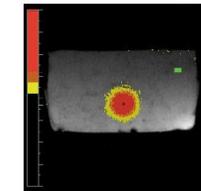
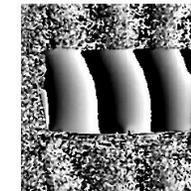
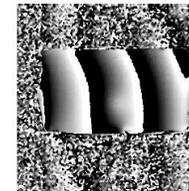


MR guided Focused Ultrasound (MRgFUS) Overview

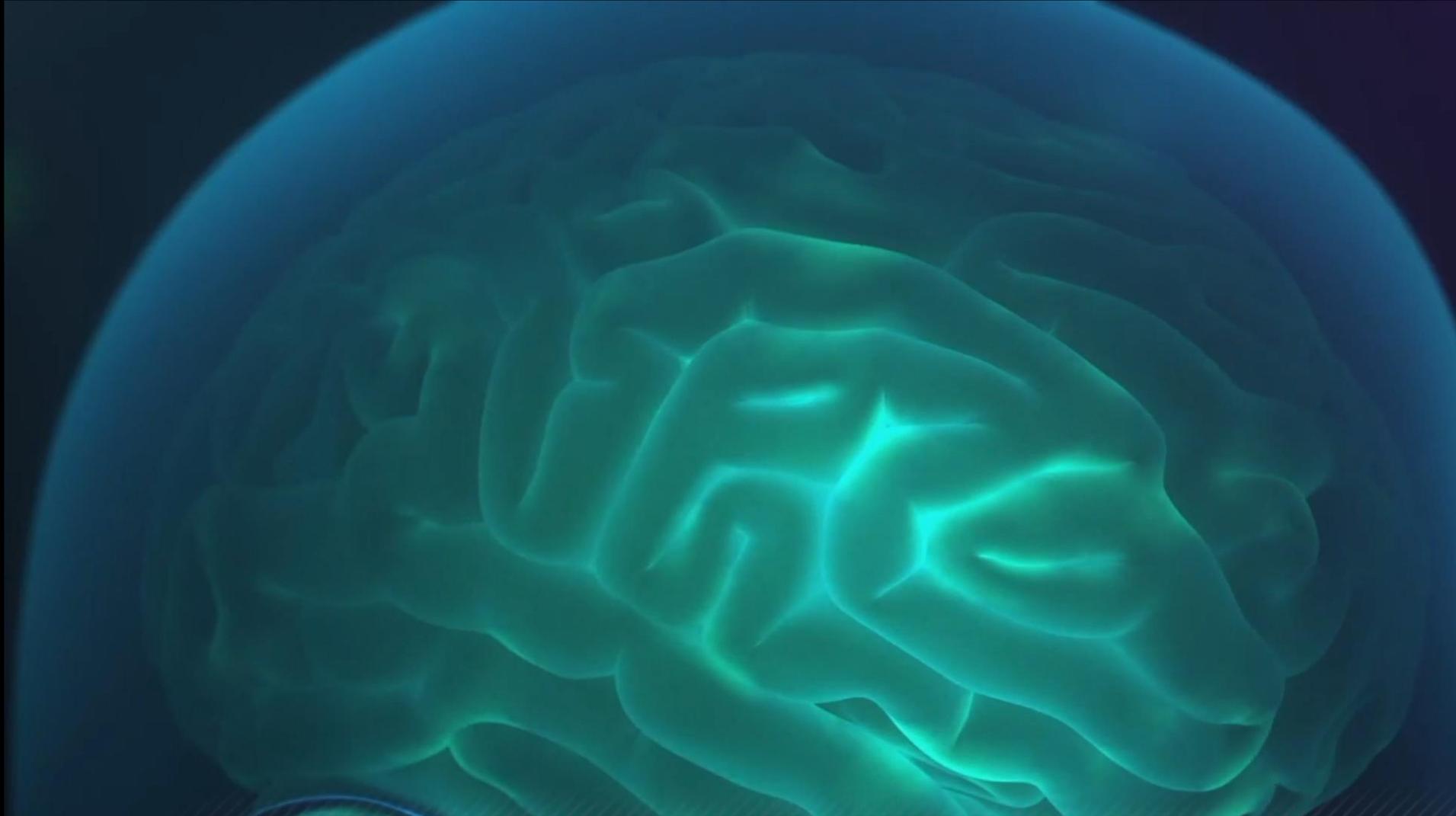


$$\Delta\Phi = \alpha \Delta T 2\pi \gamma B_0 TE$$

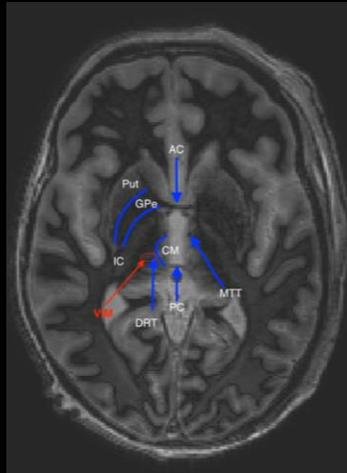
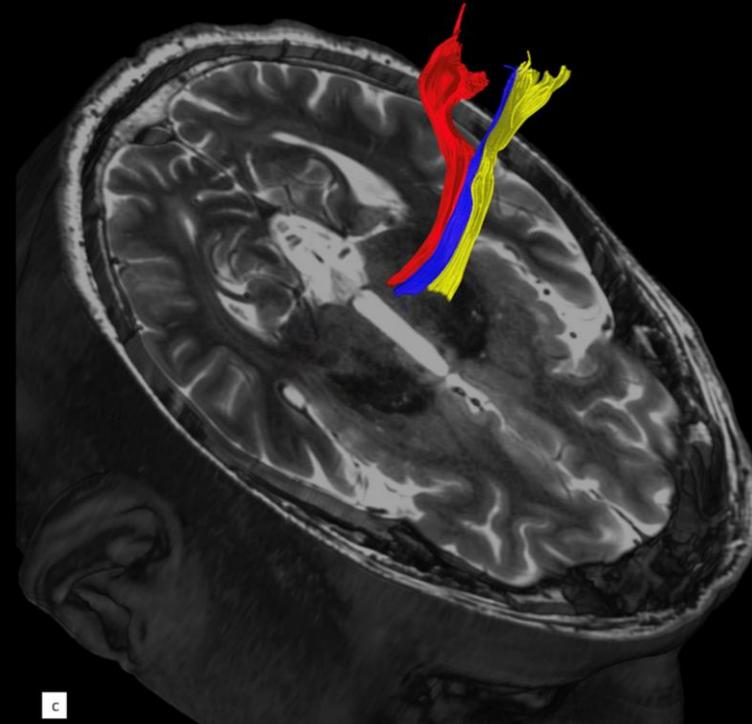
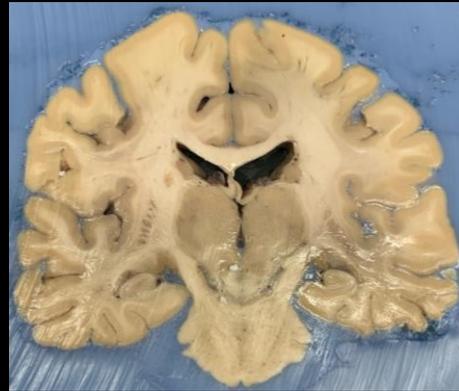
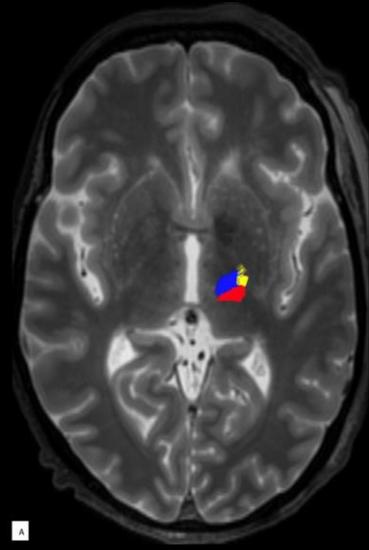
$$\alpha = -0.01 \text{ ppm}/^\circ\text{C}$$



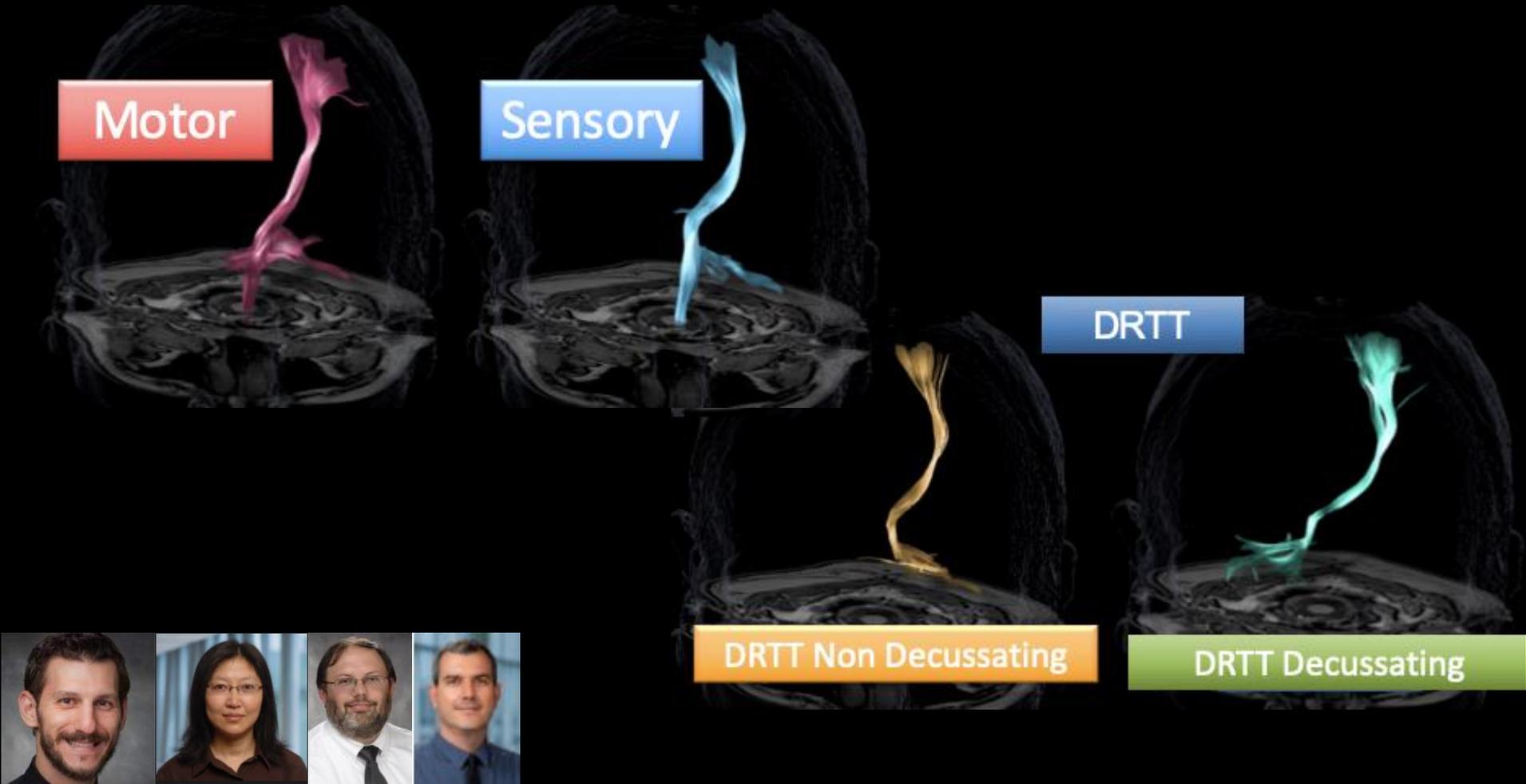
Tremor: Targeting The Ventral Intermediate Nucleus



Anatomic Validation of Advanced Imaging Techniques for DRTT Targeting

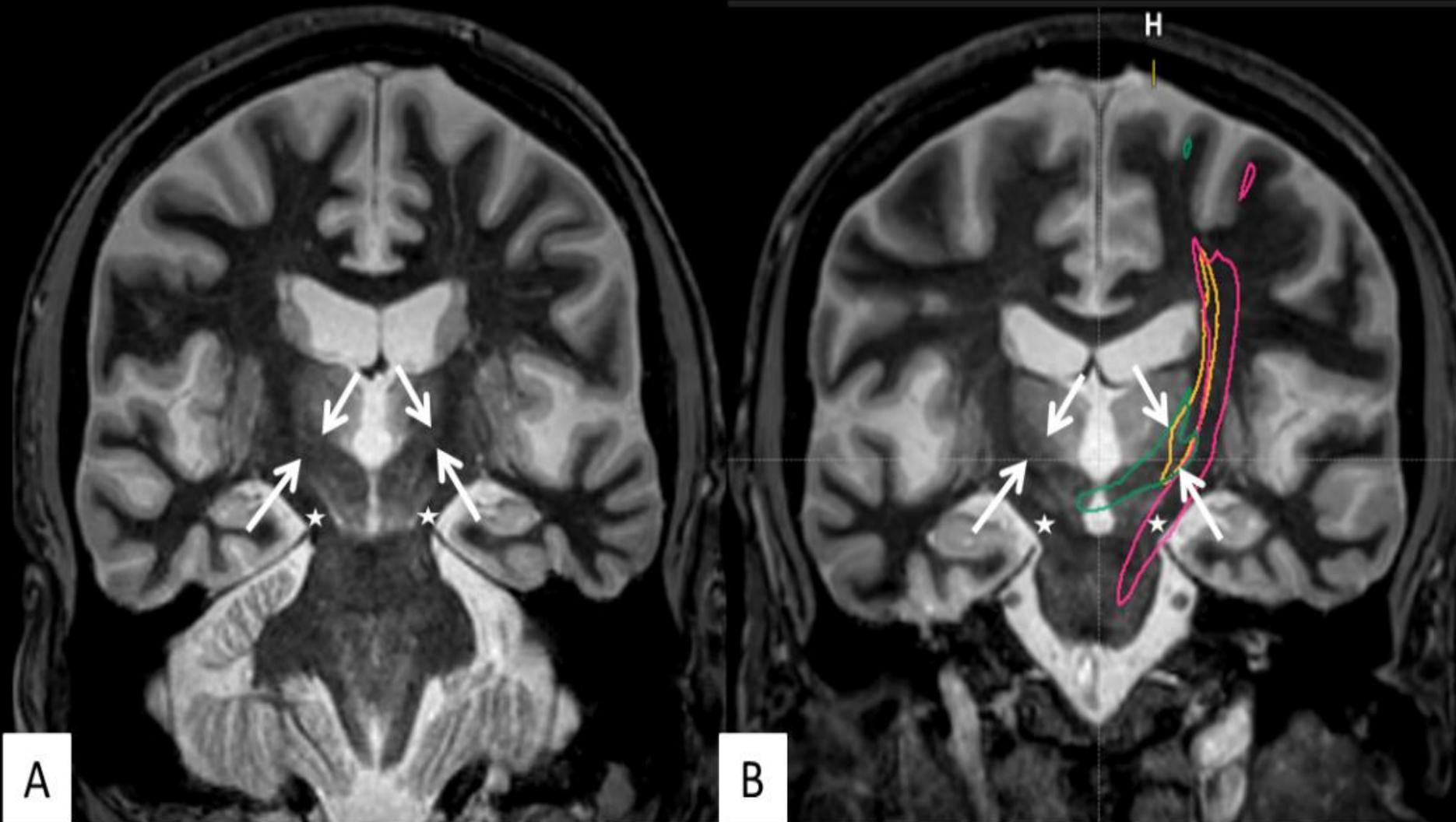


Four Tract Tractography

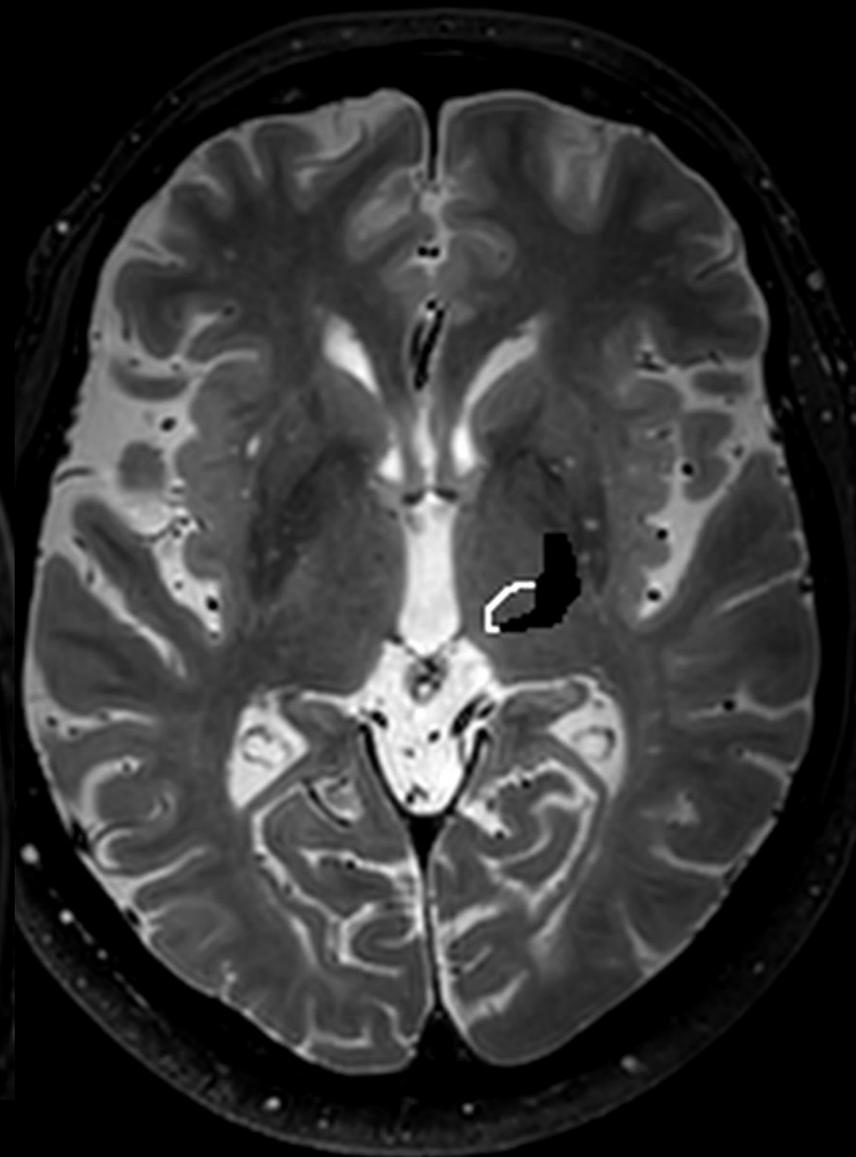
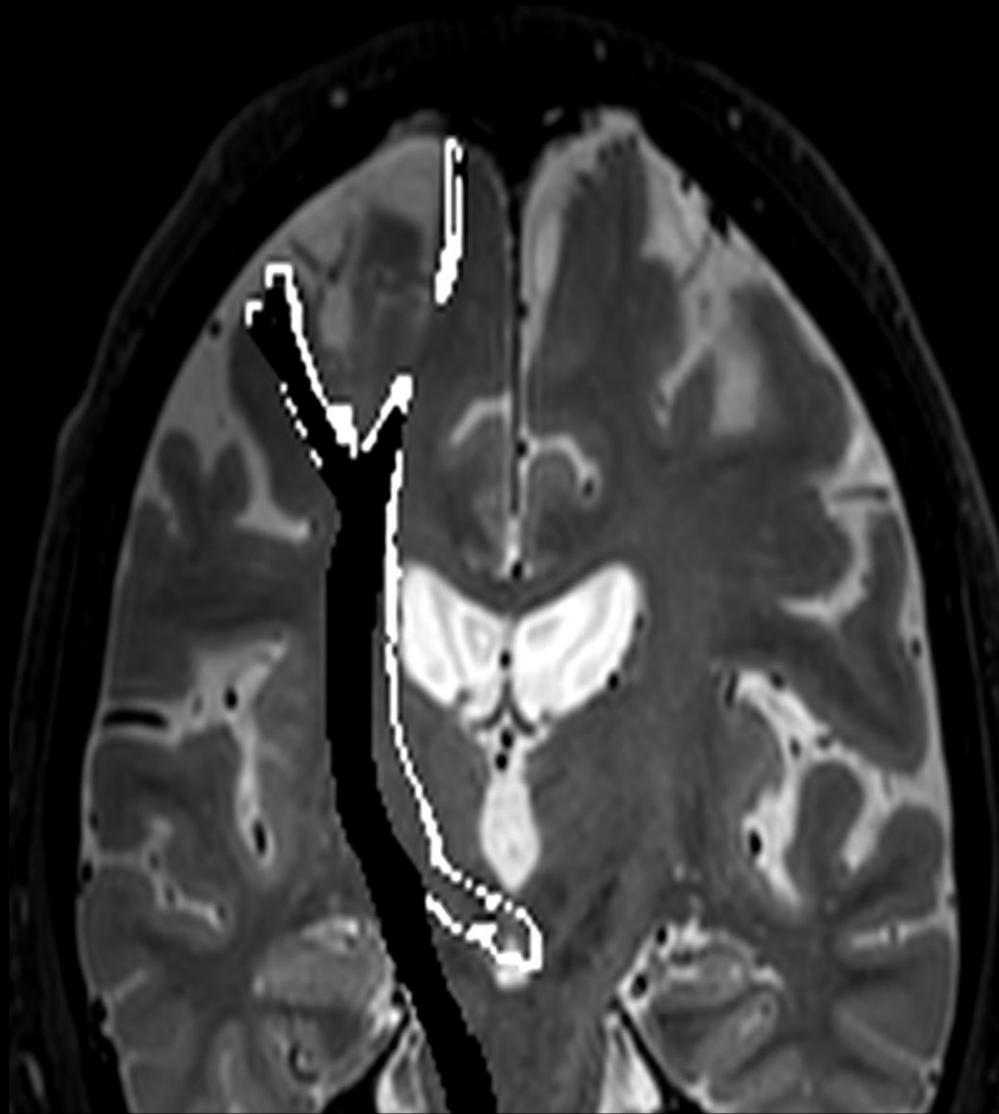


Four-Tract Tractography for Magnetic Resonance Guided High Intensity Focused Ultrasound Targeting
Brain Communications 2022

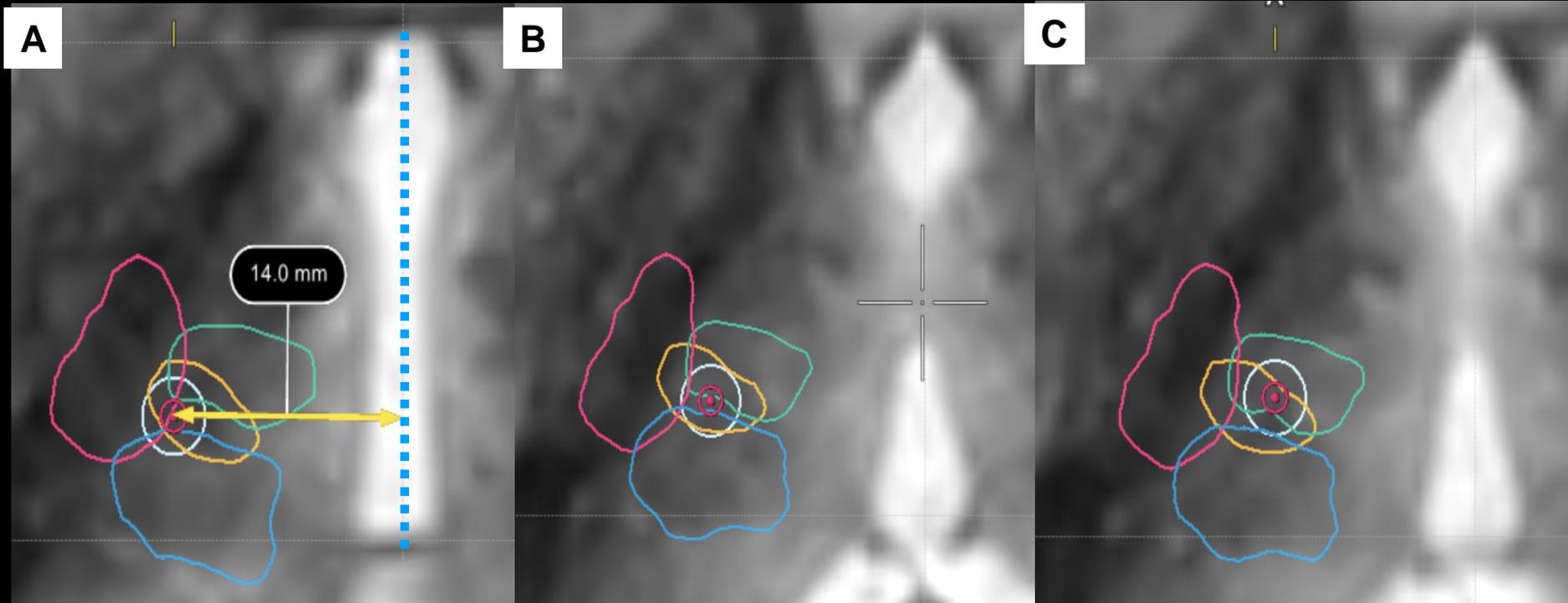
FGATIR CONFIRMATION



Advanced MRI Techniques for Transcranial Focused Ultrasound Targeting
Shah et al. Brain 2020



Indirect vs. Tractography Based Targeting for



| Coordinate | Indirect Targeting | Tractography based Targeting | P value |
|------------|--------------------|------------------------------|------------|
| Anterior | 6.8±0.5mm | 7.4±0.9mm | P* < 0.005 |
| Lateral | 14.1±0.49mm | 13.0±1.2mm | P* < 0.05 |
| Superior | 0 mm | S=2.0±0.6mm | |

* paired student T-test

Tract Based is more anterior and more medial.

Four-Tract Tractography for Magnetic Resonance Guided High Intensity Focused Ultrasound Targeting
Brain Communications 2022

The screenshot displays the Sonicate software interface for treatment planning. The main window shows a brain MRI with a treatment spot highlighted in purple. The interface includes a top navigation bar with 'Planning' and 'Treatment' tabs, a left sidebar with tool icons, and a bottom control panel with various parameters like Energy, Power, Duration, and Spot Coordinates. The bottom right corner shows a status bar with '17:20'.

Planning / Treatment

Task / Overlay

Spot Coordinates

| | | | |
|-------|----|----|----|
| RAS | RL | AP | IS |
| AC-PC | ML | AP | IS |

Spot Length: 3.9 mm Diameter: 2.1 mm

Energy 9000 J

Power 800 W

Duration 60 Sec

Time Extension 3 Sec

Cooling 270 Sec

Frequency 0.67 MHz

Application None

Orientation Axial

Frequency Dir AP

Thickness (mm) 3.0

Path M2 Main Axis

Treated Sonications 11

Remaining Sonications 1

Planned Volume 0.0 cc

Dose Volume 0.1 cc

Movement Detection On

Default Patient Movement

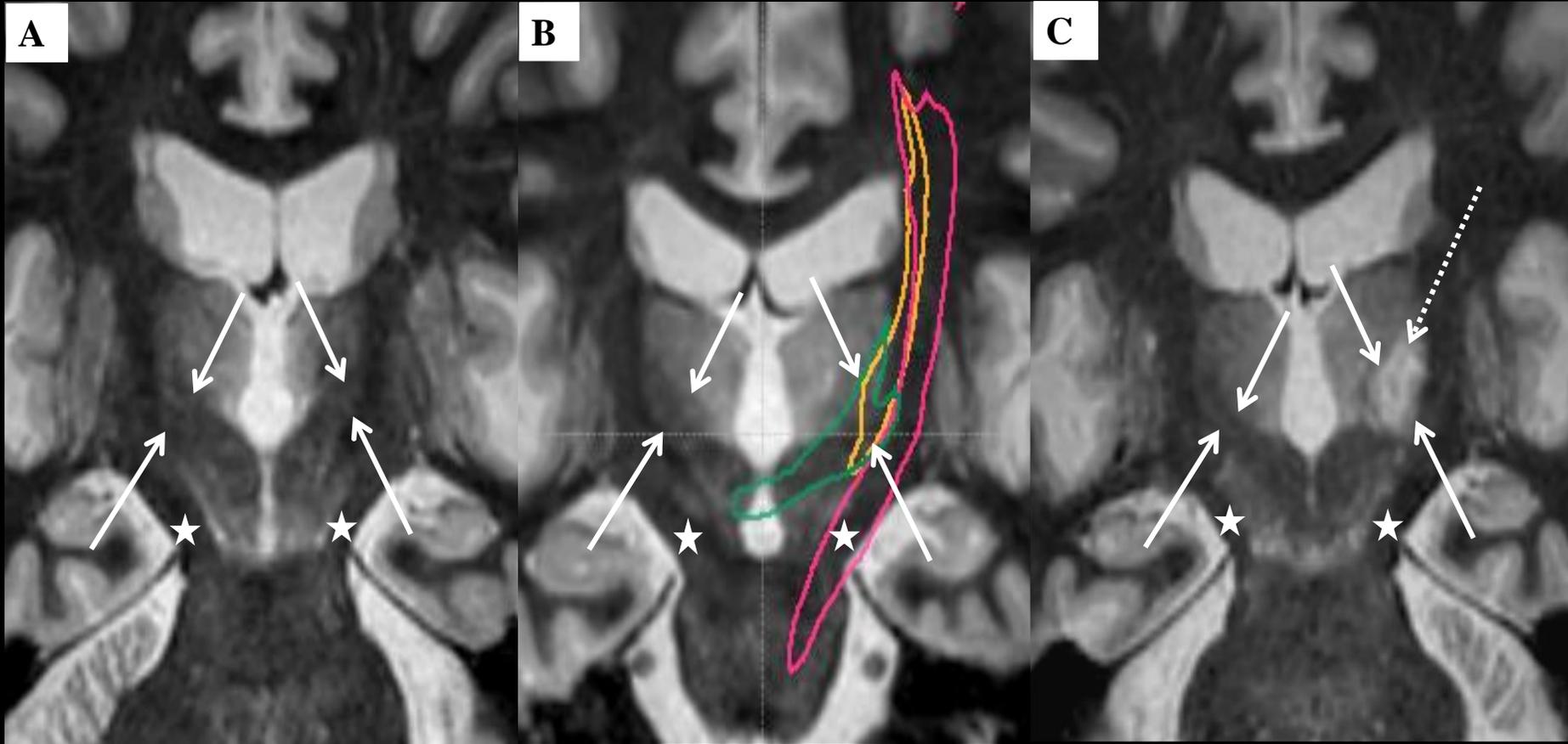
Movement 1.0 9 PD 1 10 5

Energy [Progress Bar]

Power [Progress Bar]

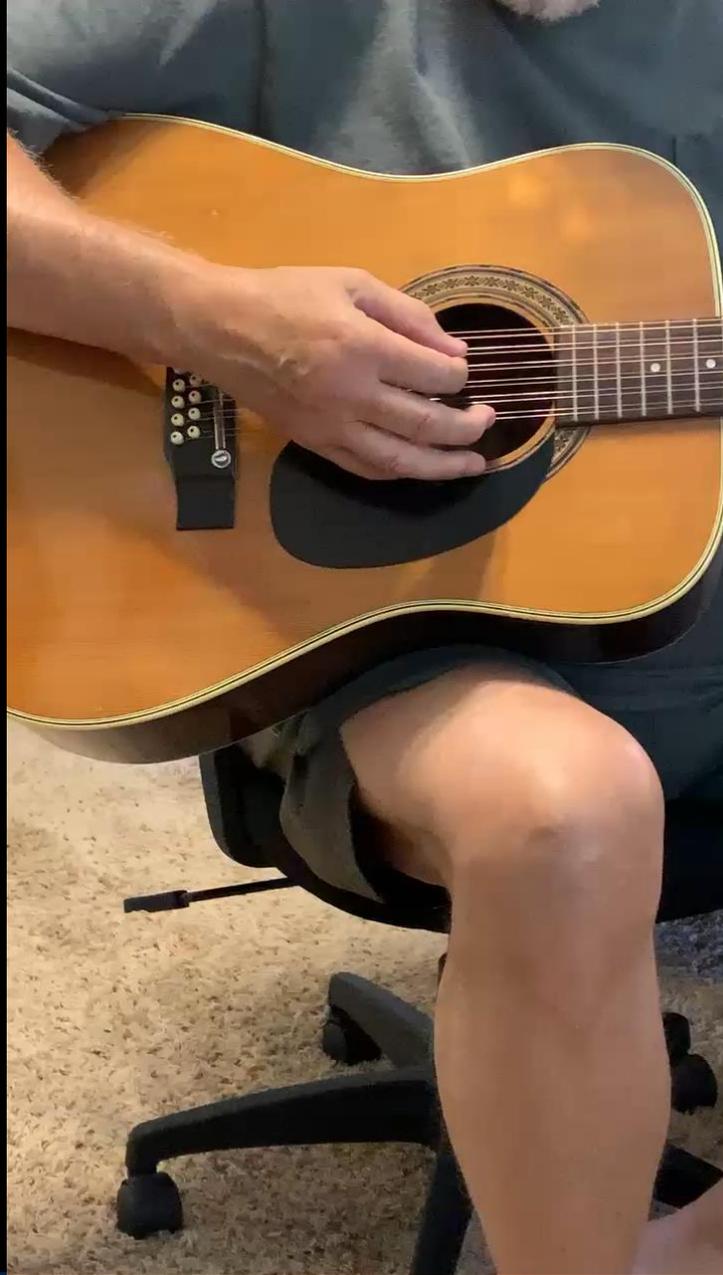
Device Ready (Cooling: (14 C), Error: (Insolved Dry: 0.95))

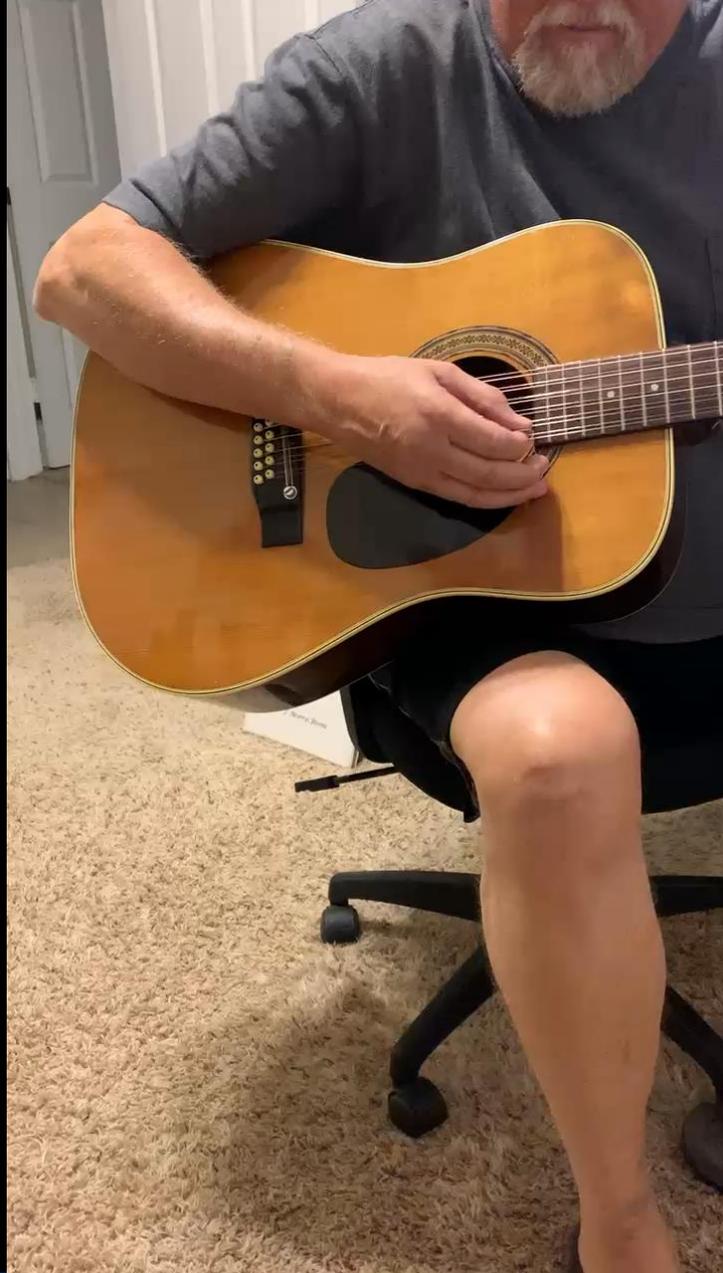
17:20



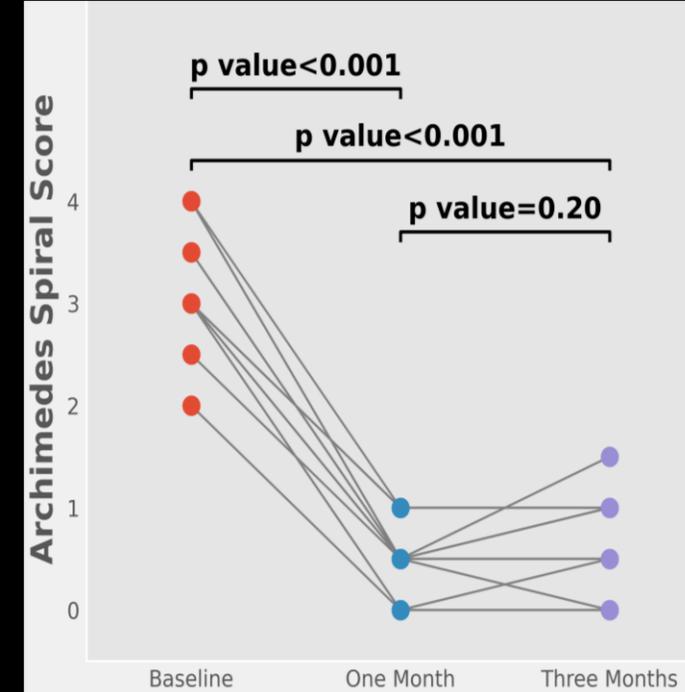
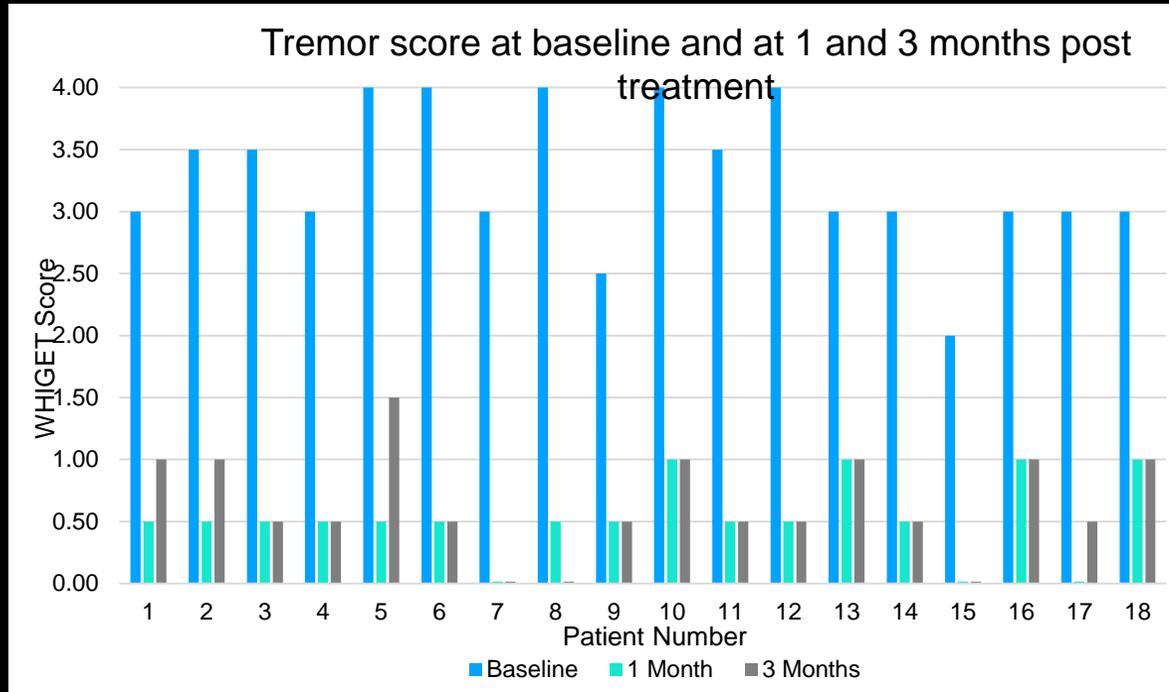
Four-Tract Tractography for Magnetic Resonance Guided High Intensity Focused Ultrasound Targeting
Brain Communications 2022







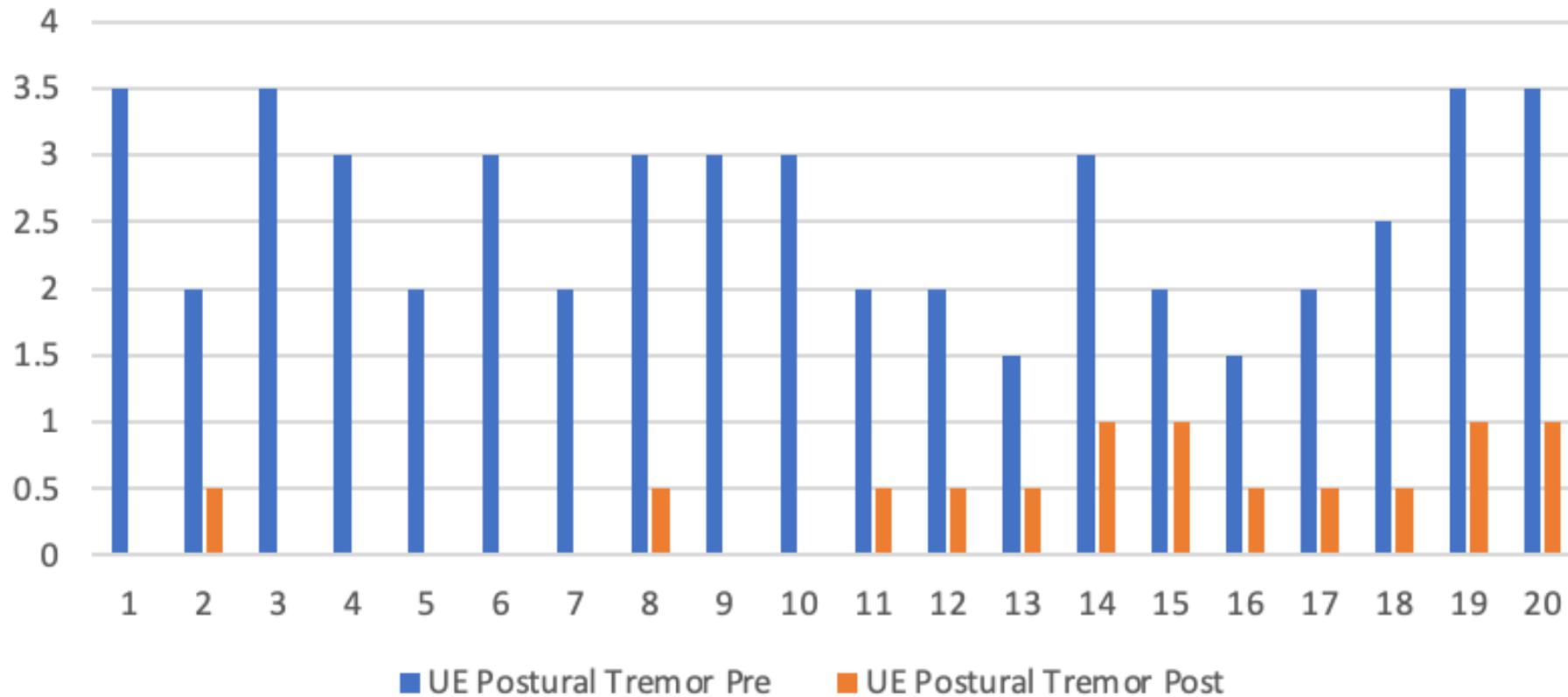
4 Tract Tractography Tremor Response



Tremor Response:
 ➤ **84% at 1 month**
 ➤ **81% at 1 year**

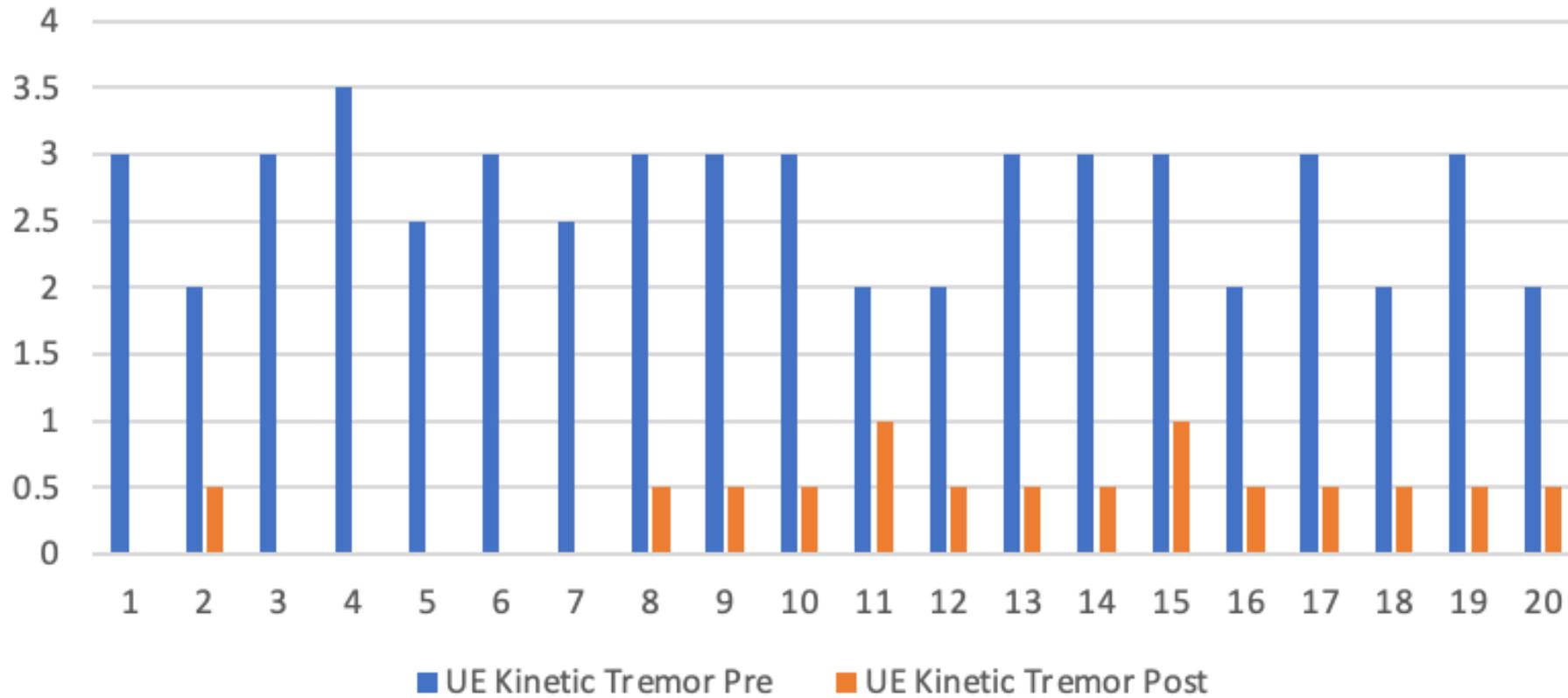
Elias et al. N Engl J Med 2016; 375:730-739. **Tremor Reduction at 3 months = 47% in blinded cohort and 55% in unblinded cohort; based on CRST tremor scale**

TETRAS Postural Tremor



1 year Average Postural Tremor Reduction ~ 83%

TETRAS Kinetic Tremor

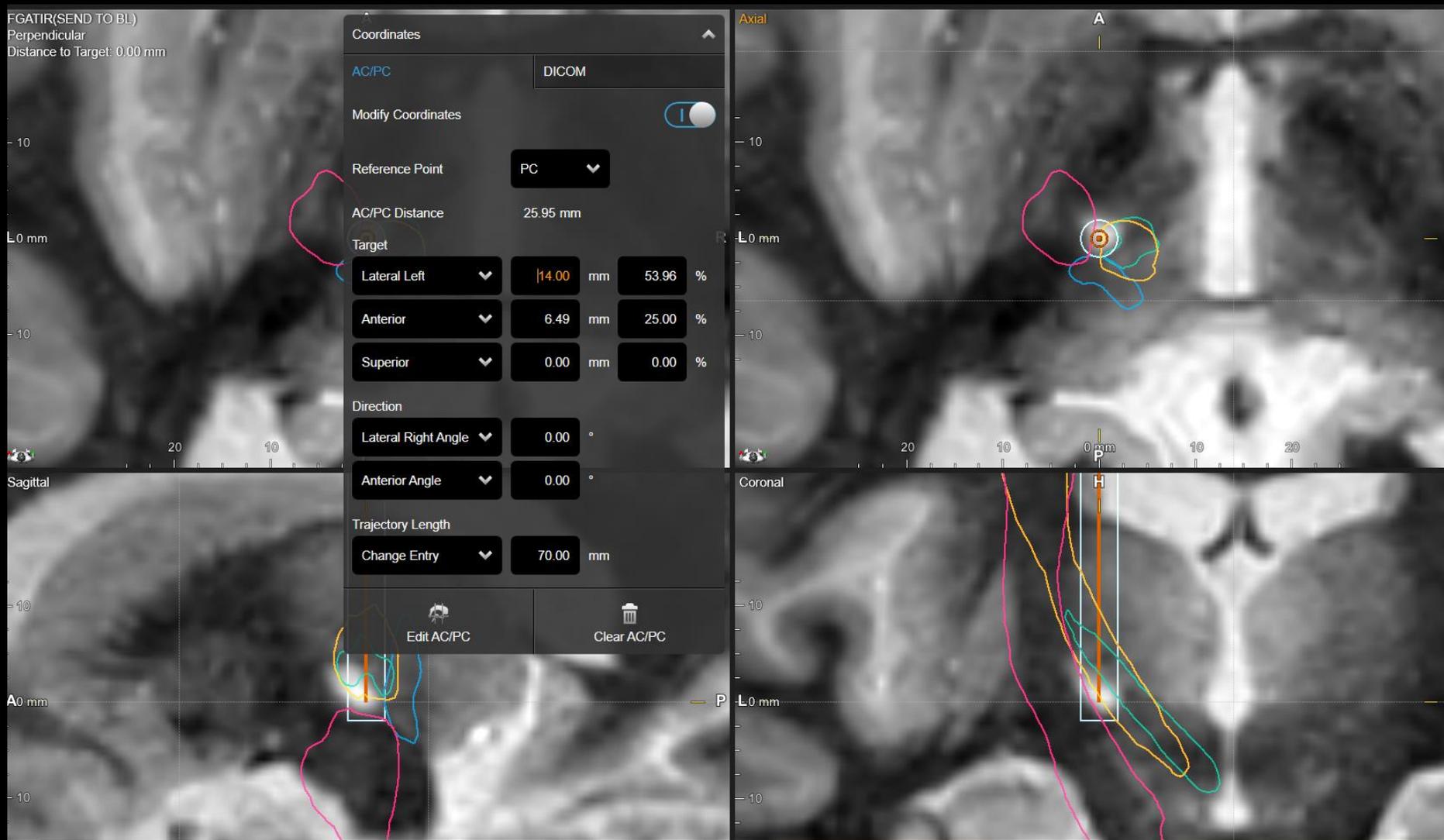


1 year Average Kinetic Tremor Reduction ~ 84%

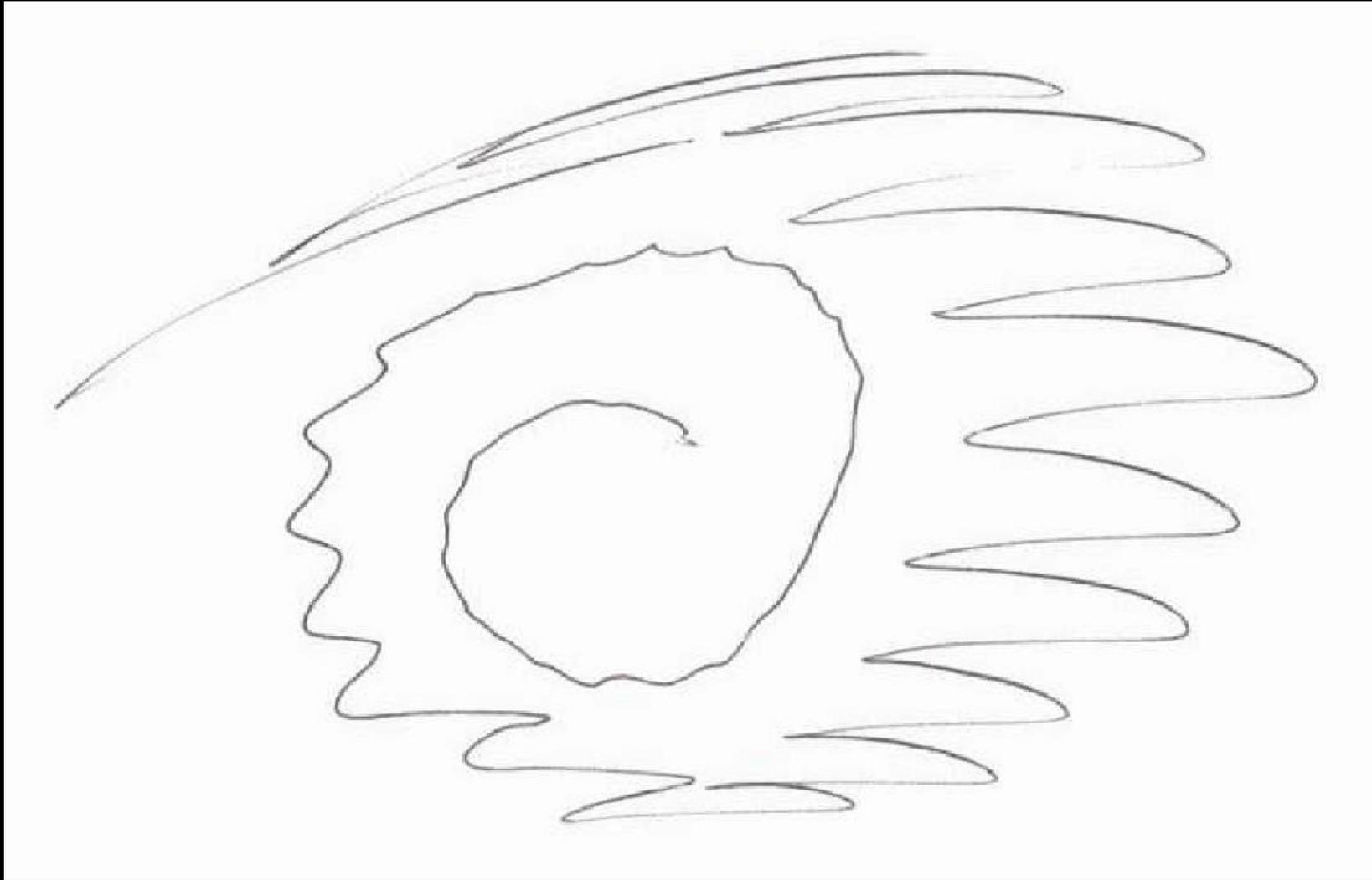
Adverse Effects Profile

| Side Effect | Elias et al. n=56 | | | Our Group n=89 | | | Segar et al. n= 123 | | |
|----------------|-------------------|-----------|-----------|----------------|---------|---------|---------------------|--------------|--------------|
| | 1 Day | 1 Month | 3 Month | 1 Day | 1 Month | 3 Month | 1 Day | 1 Month | 3 Month |
| Paresthesia | 8 (32%) | 16 (28%) | 14 (25%) | 6 (7%) | 0 | 0 | 32 (26%) | 26(33%) | 22(25%) |
| Gait Imbalance | 8 (16%) | 7 (12.5%) | 7 (12.5%) | 6 (7%) | 0 | 0 | 74 (60%) | 40 (46%) | 23(26%) |
| Ataxia | 11(20%) | 6 (11%) | 2 (3.6%) | 0 | 0 | 0 | Not reported | Not reported | Not reported |
| Weakness | 2 (3.5%) | 2 (3.6%) | 2 (3.6%) | 0 | 0 | 0 | 11 (9%) | 13 (15%) | 6 (7%) |
| Dysmetria | 7(12.5%) | 5 (9%) | 5 (9%) | 0 | 0 | 0 | 16 (13%) | 15 (17%) | 8 (9%) |
| Dysarthria | 1(1.8%) | 1(1.8%) | 1(1.8%) | 0 | 0 | 0 | 26 (21%) | 11 (13%) | 7 (8%) |
| Dysphagia | 1(1.8%) | 1(1.8%) | 1(1.8%) | 0 | 0 | 0 | Not reported | Not reported | Not reported |

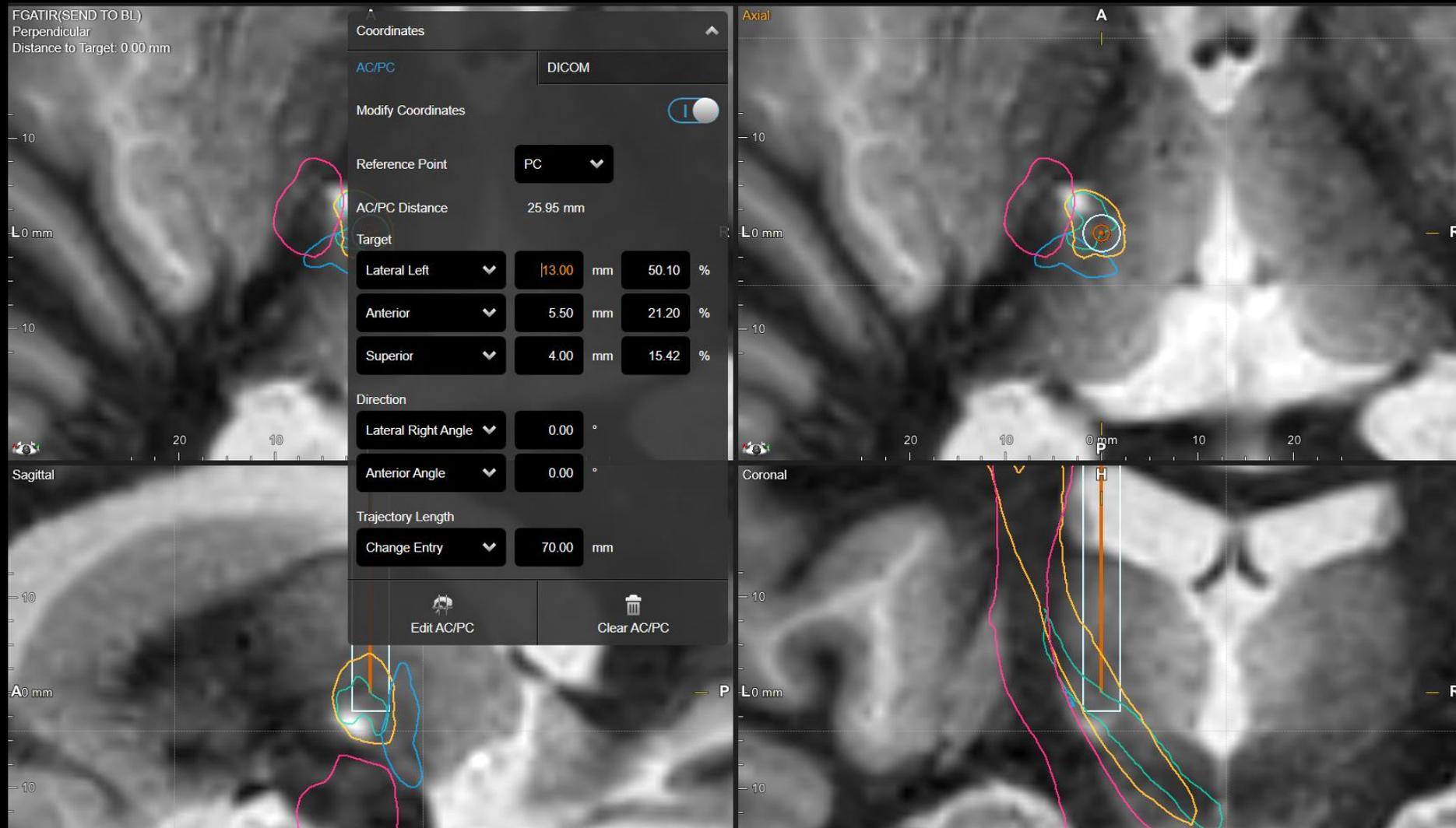
MRgHIFU Rescue after Failed RF Ablation



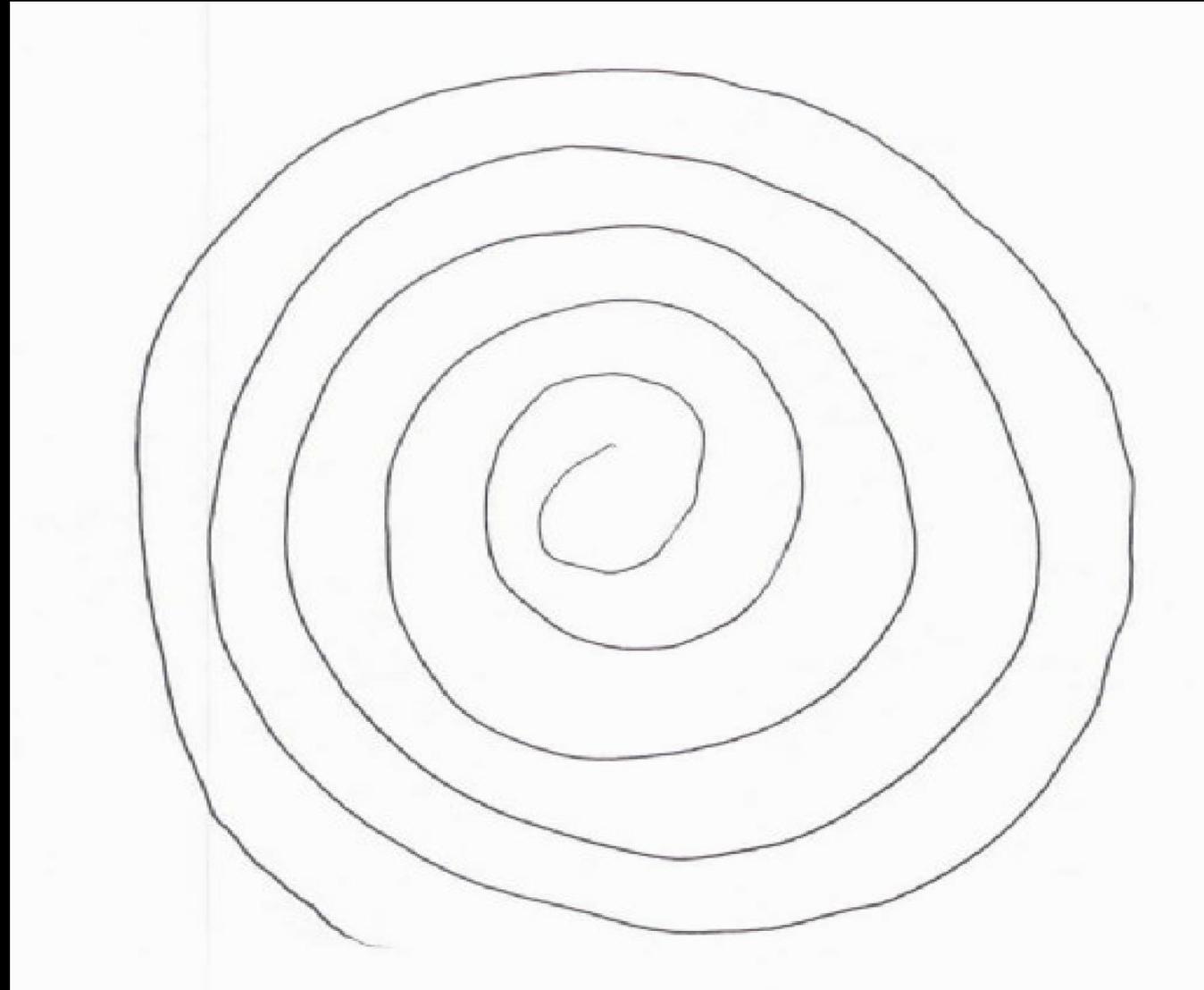
MRgHIFU Rescue after Failed RF Ablation



MRgHIFU Rescue after Failed RF Ablation



MRgHIFU Rescue after Failed RF Ablation



HIFU Work-up

- Movement disorder consultation
- Consultation with Dr. Shah
- Head CT for skull density ratio (SDR)
- MRI Scan with advanced imaging sequences for targeting
- Stop tremor and anti-coagulation medications 7 days prior to procedure (may require taper)
- Head Shave

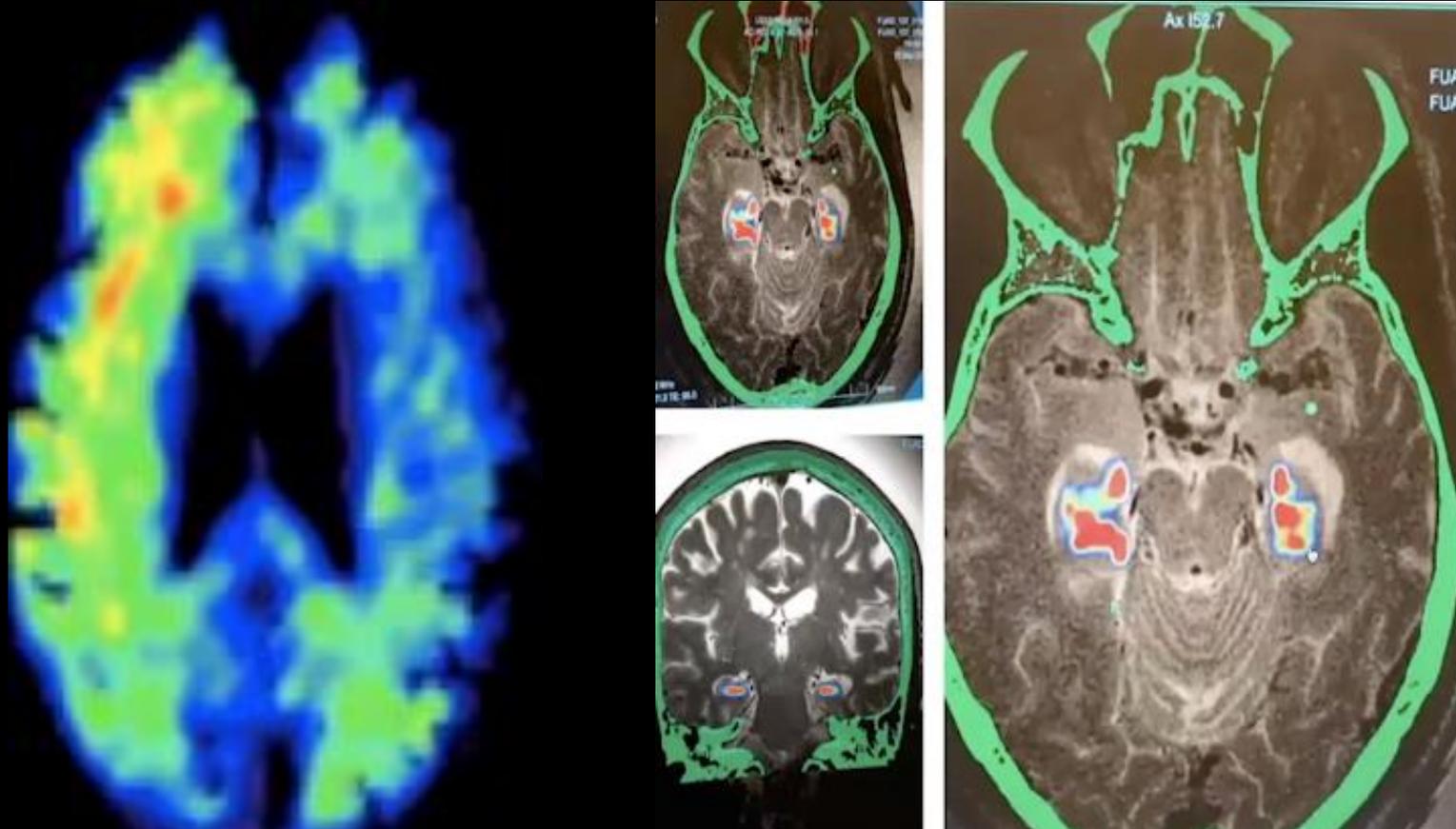
Who can benefit from HIFU

- Unilateral HIFU thalamotomy is approved for the treatment of
 - Refractory disabling essential tremor of the arm or hand
 - Refractory disabling rest-tremor predominant Parkinson disease
- Selection criteria
 - Severe enough (in terms of amplitude and function) to justify the intervention
 - If unilateral tremor control will improve QOL
 - If DBS is not desired or is not feasible e.g. cognitive impairment, debility
- HIFU contraindicated or relatively complicated
 - Low Skull Density Ratio (SDR <0.40)
 - Claustrophobia, incompatible implants

Future directions with HIFU

- Bilateral thalamotomy submitted to FDA
- Unilateral pallidotomy for select PD cases now approved
- Research on dystonia, OCD, tic disorders, mood disorders
- Targeted delivery of biologics via transient breakdown of BBB
- Stereotactic treatment of focal brain masses

Human BBB Opening: Alzheimer's Disease Clinical Trial



Human Brain Metastases Focused Ultrasound Clinical Trials

