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The Nuts, Bolts and History of Focused Ultrasound for Tremor

Travis Tierney MD PhD

APDA – Iowa Chapter "*Living **Boldly** with PD!*"

West Des Moines - 16th June 2023

“The Nuts” & “The Bolts”

1. 3 Brief theoretical concepts & 3 practical principles
2. Thalamotomy Essential Lessons: The Vim
3. Tremor Dominant Parkinson Disease: The Vim+
4. Pallidotomy LID Dyskinesia: The GPi

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Disclosure & Conflicts

1. No commercial ties with ANY device manufacturer
2. NIH and FUSF funding (CT.gov ID NCT03028246)
3. 501(c)(3) US public charity (Watch All Night)
4. Use of the ExAblate4000® 650 kHz array

(Insightec Exablate Neuro®)

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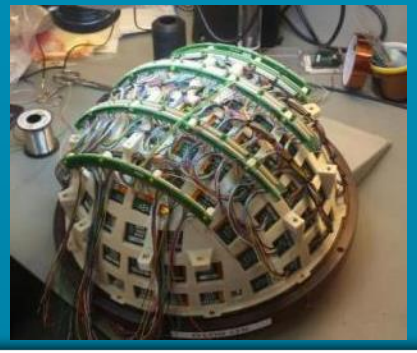
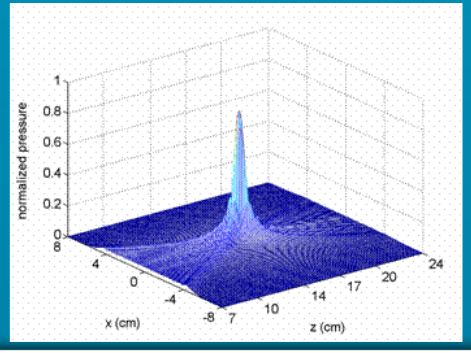
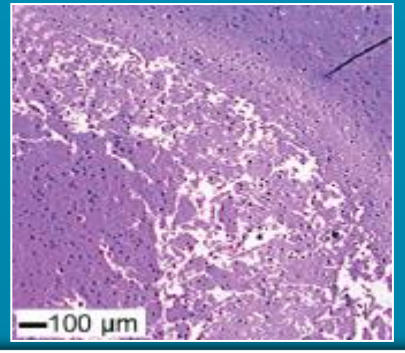
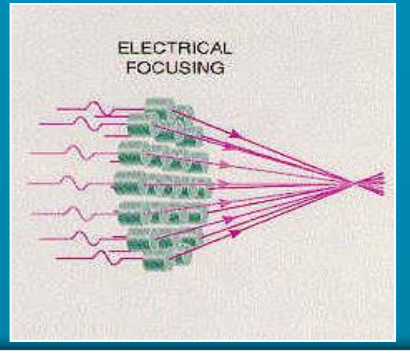
Tc Thermoablation: The Insightec Array









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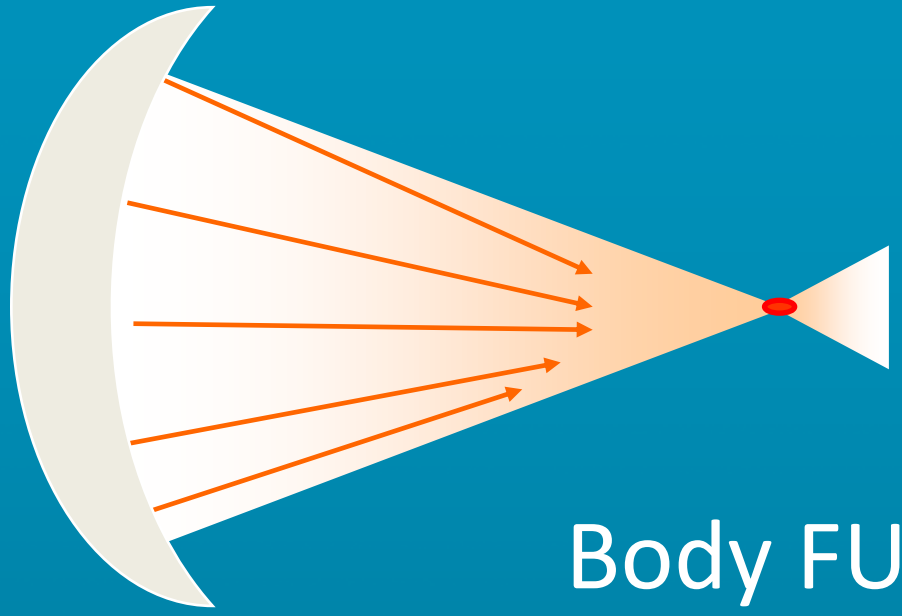
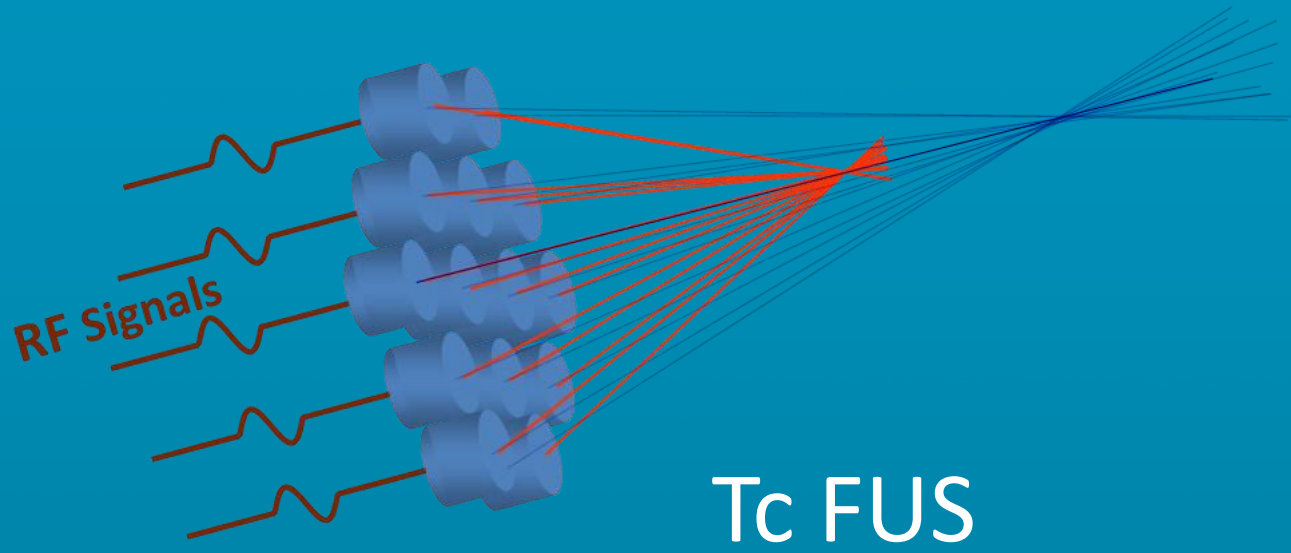
Three Basic FUS Transducer Concepts

Fixed Arc Reflector Vs. "Steerable" Phased Array

3. 2. 1.



Body FUS



Tc FUS

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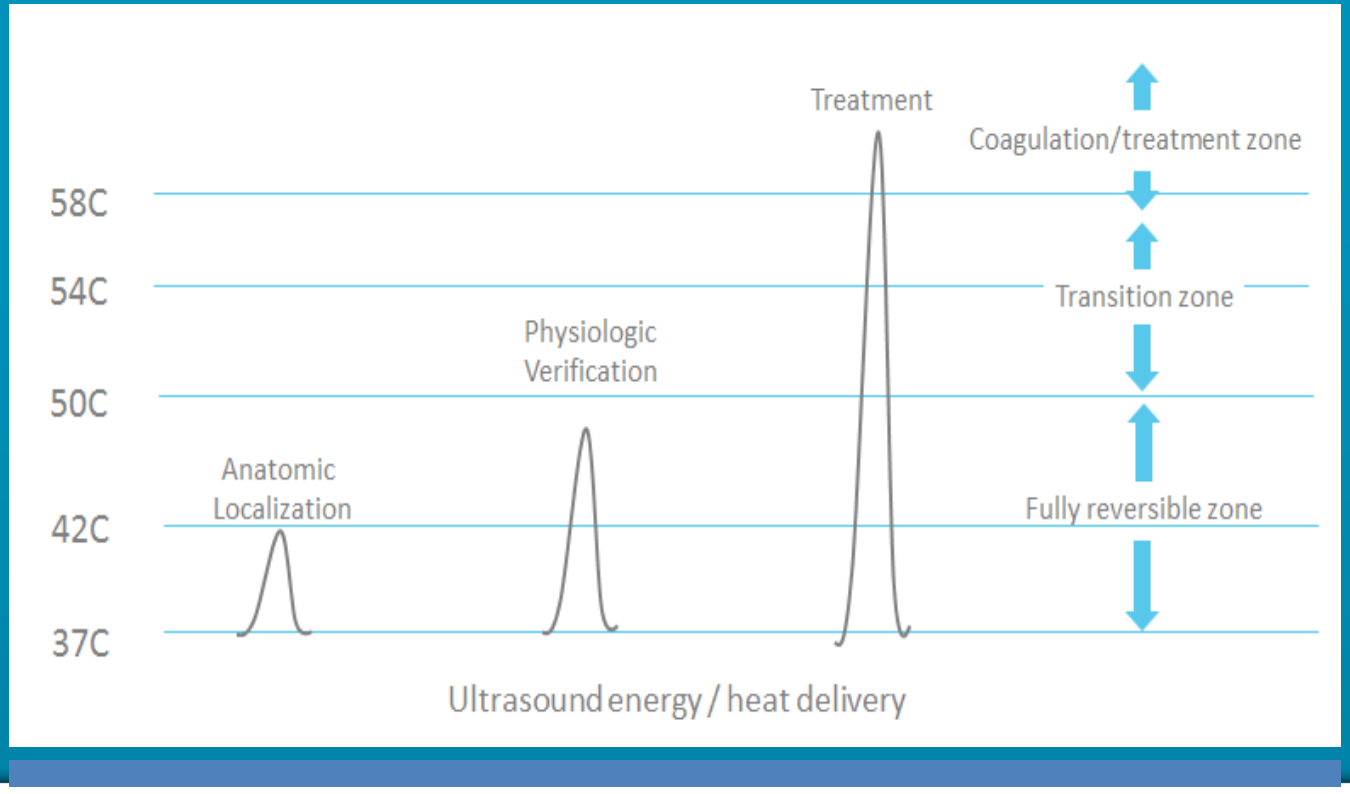
1. Practical Principle: **Thermocoagulation**

- 42° Neurons stop firing
- 43° Proteins begin to denature
- 43°-54° Time-dependent coagulation
- 54° Instant coagulative necrosis
- >60° Cavitation - boiling

TREATMENT EVALUATION AND CONTROL



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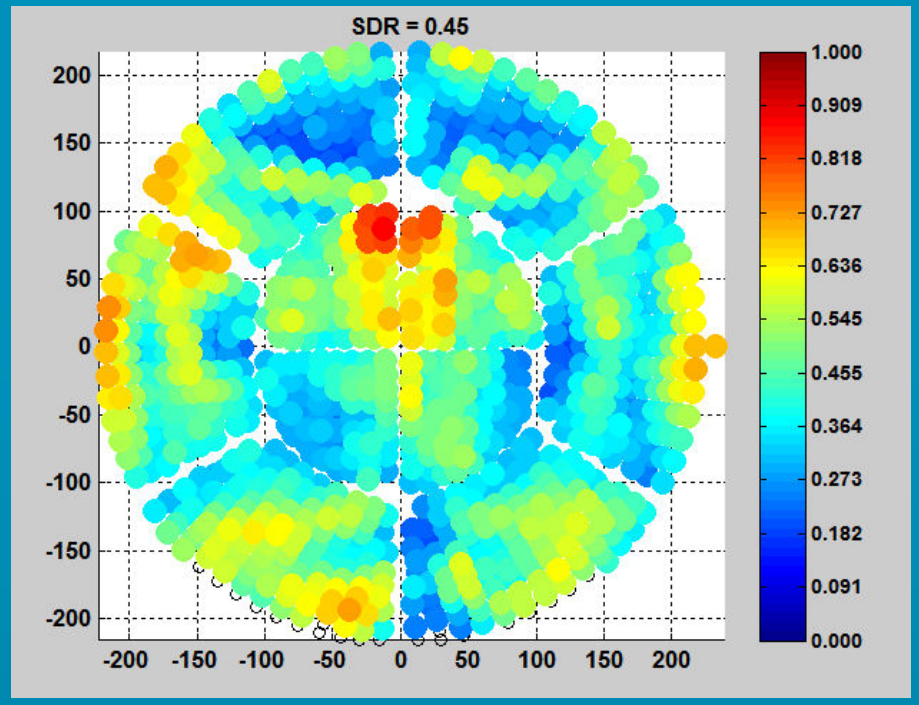
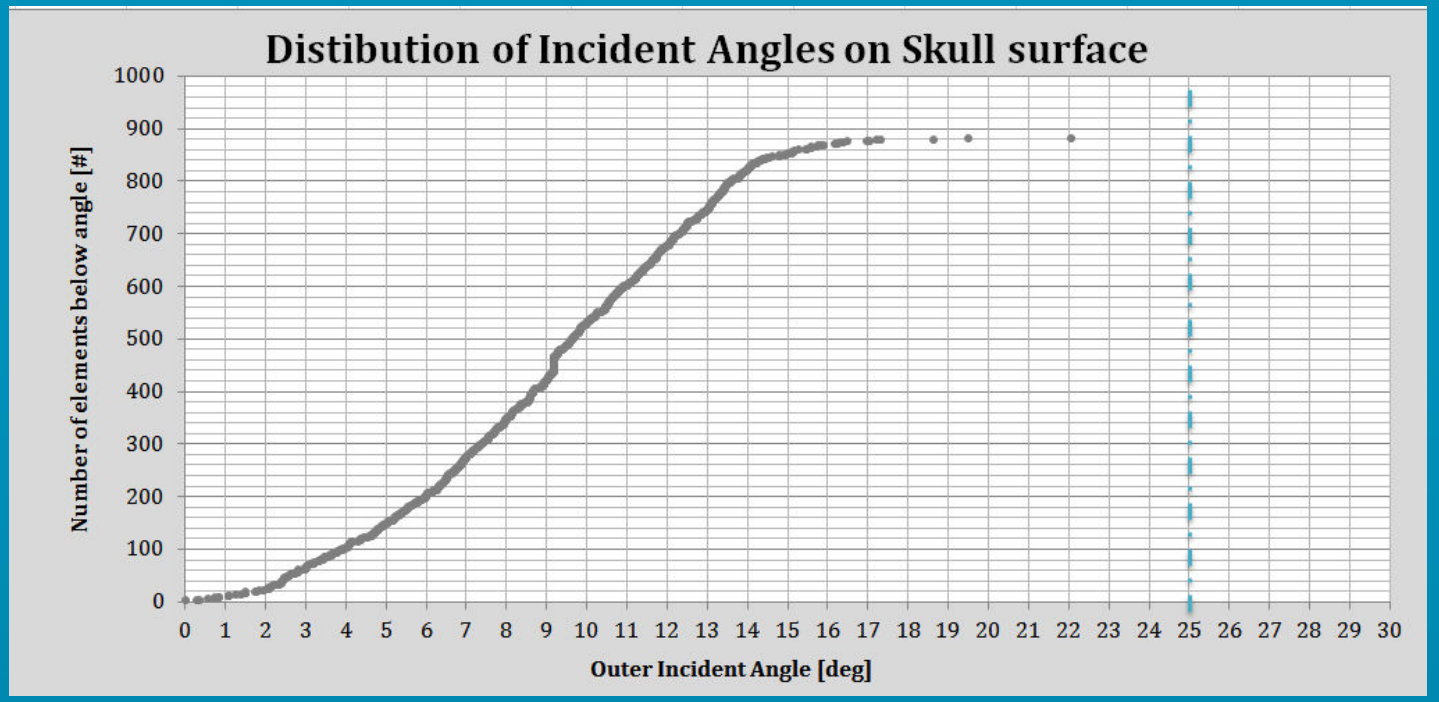
2. Practical Principle: **Skull Geometry**





High Skull Density Ratio: > 0.40 (SDR)
Avoids sound scattering/absorption

Low Incident Angle: < 25 degrees transmits
Avoids total external reflectance of sound

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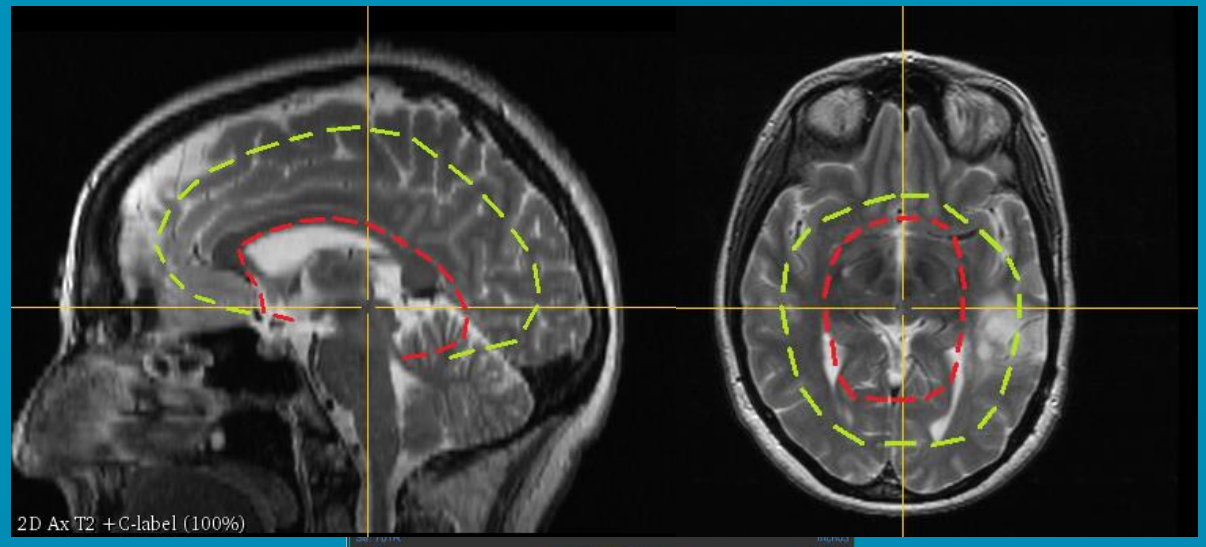
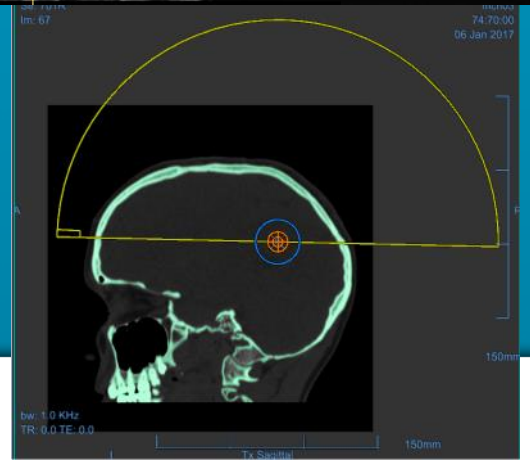
3. Practical Principle: **Acoustic Envelope**

650 kHz device limited to deep brain

220 kHz device wider envelope
- mostly due to higher *i* angle tolerances
- but also lower bony absorption at 220

LoFU BBB reaches cortex
- does not depend on thermal energy
- concept of micro-bubble cavitation





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Bringing All Those Nuts & Bolts Together

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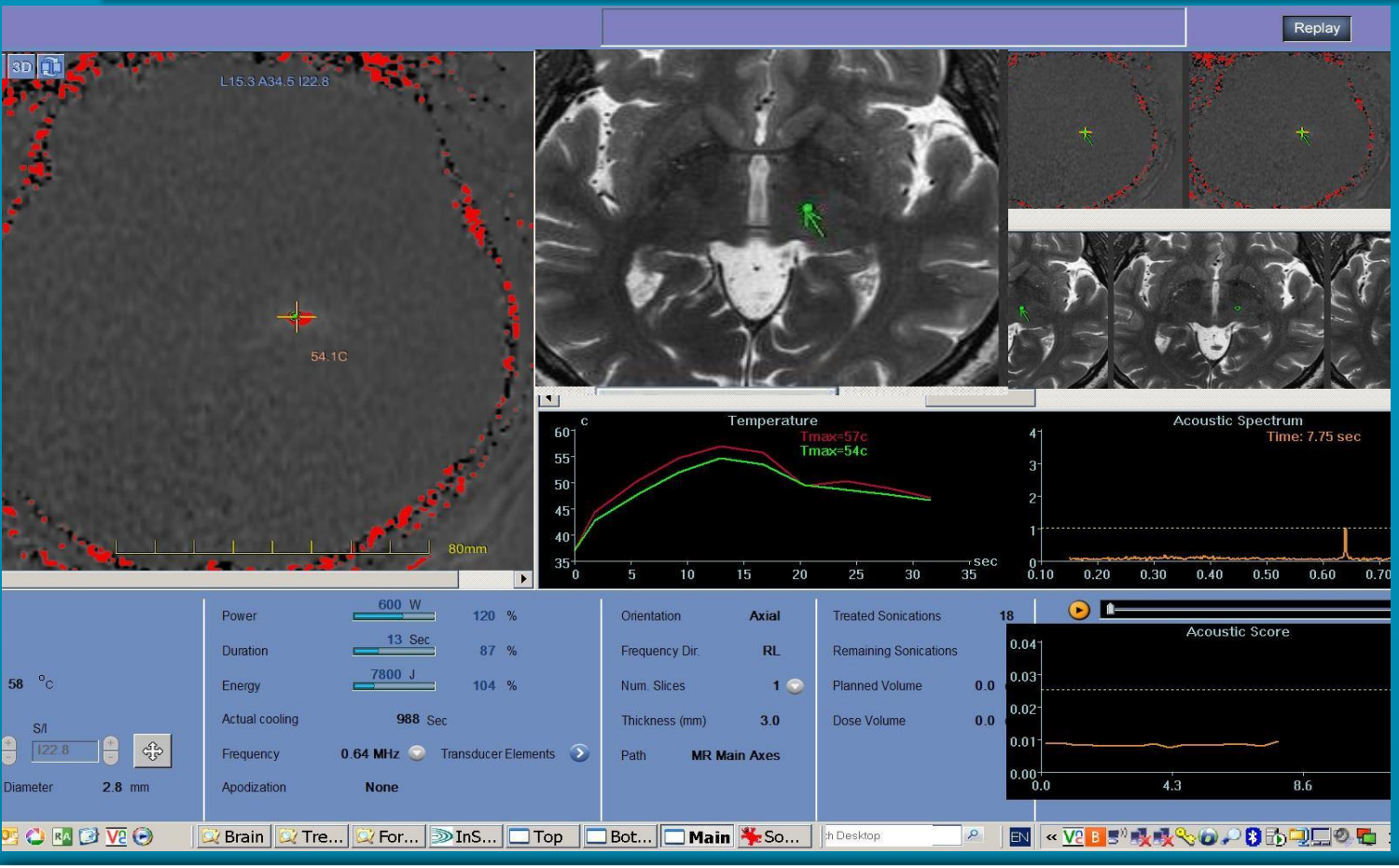
Tc FUS Proof-of-Principle: **Essential Tremor**



- **1st Ever Tc FUS FDA approval:** July 2016
  2nd side (contralateral): December 2022
- **<u>Initial</u> Indirect targeting Vim with FUS**:
  X: Between 16 ML & 11.5mm from 3rd
  Y: 25% PC>AC distance (6mm stop)
  Z: 2-4 above HIC plane
- **<u>Direct</u>**: DTI(?), Giulia's sequence
- Couples near real-time MR phased thermography to Tc FUS sonication
- Electronically steerable centroid

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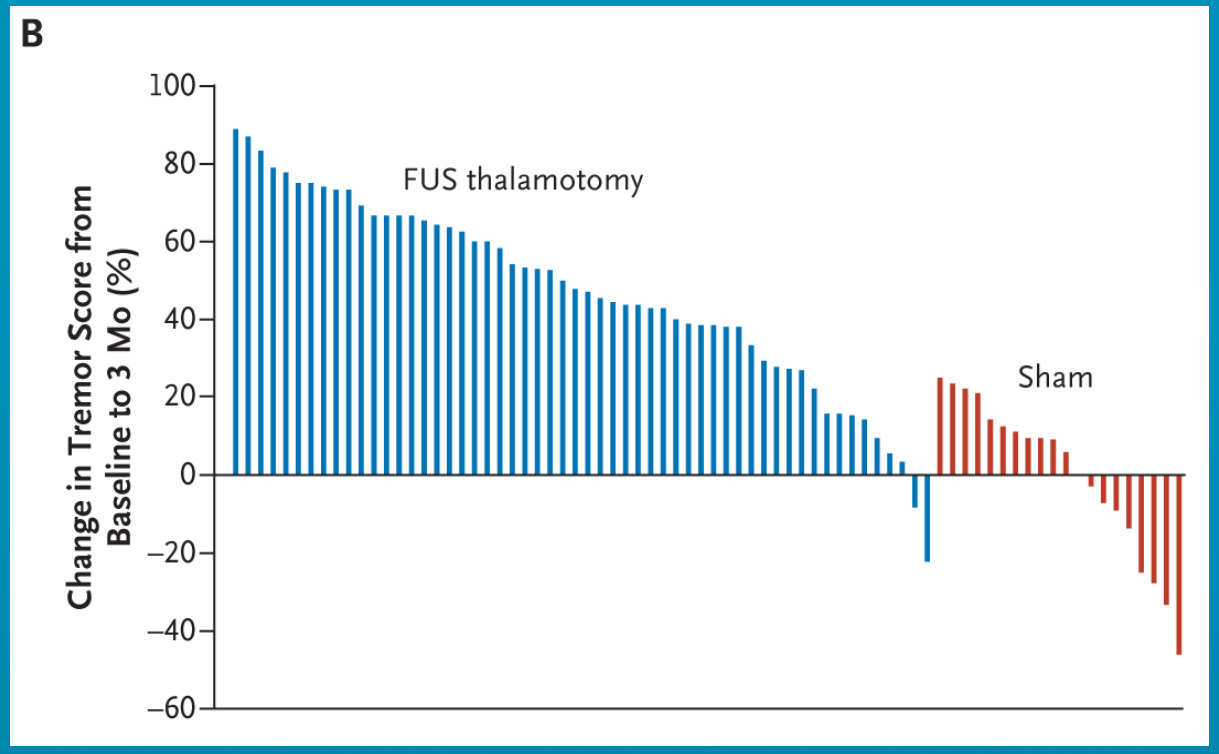
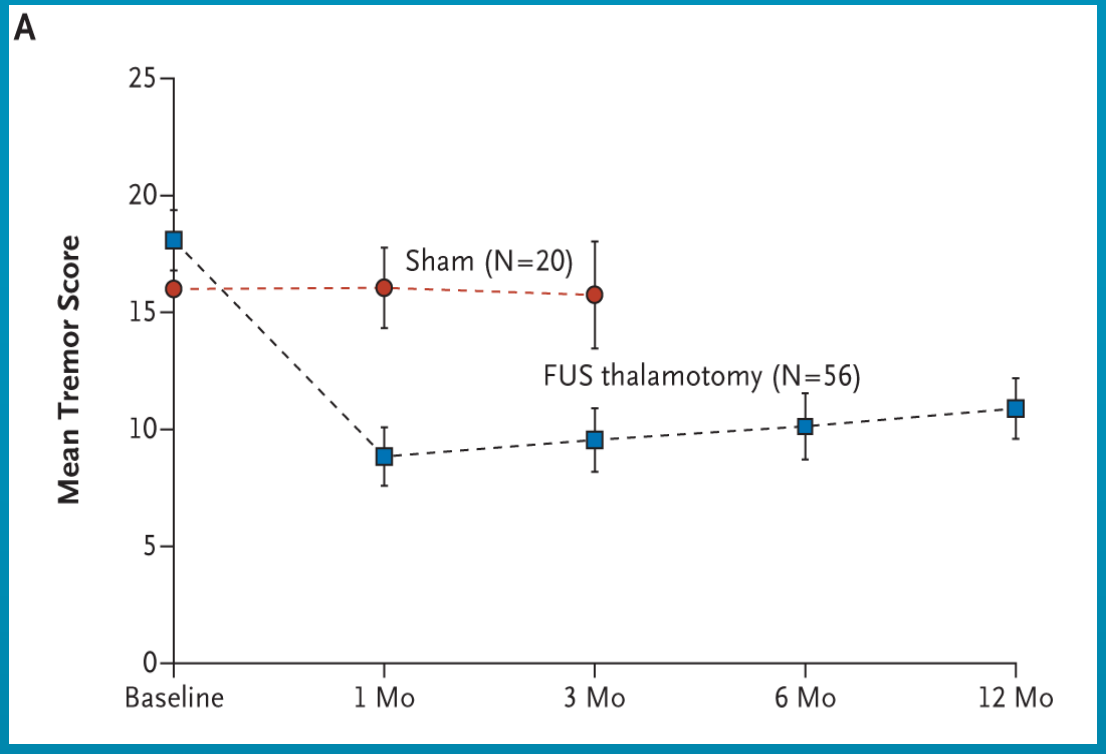
Primary Efficacy – Tremor Control





Data from **Figure 1** Elias et al. (2016) A randomized trial of focused ultrasound thalamotomy for ET. **NEJM 375:734**.

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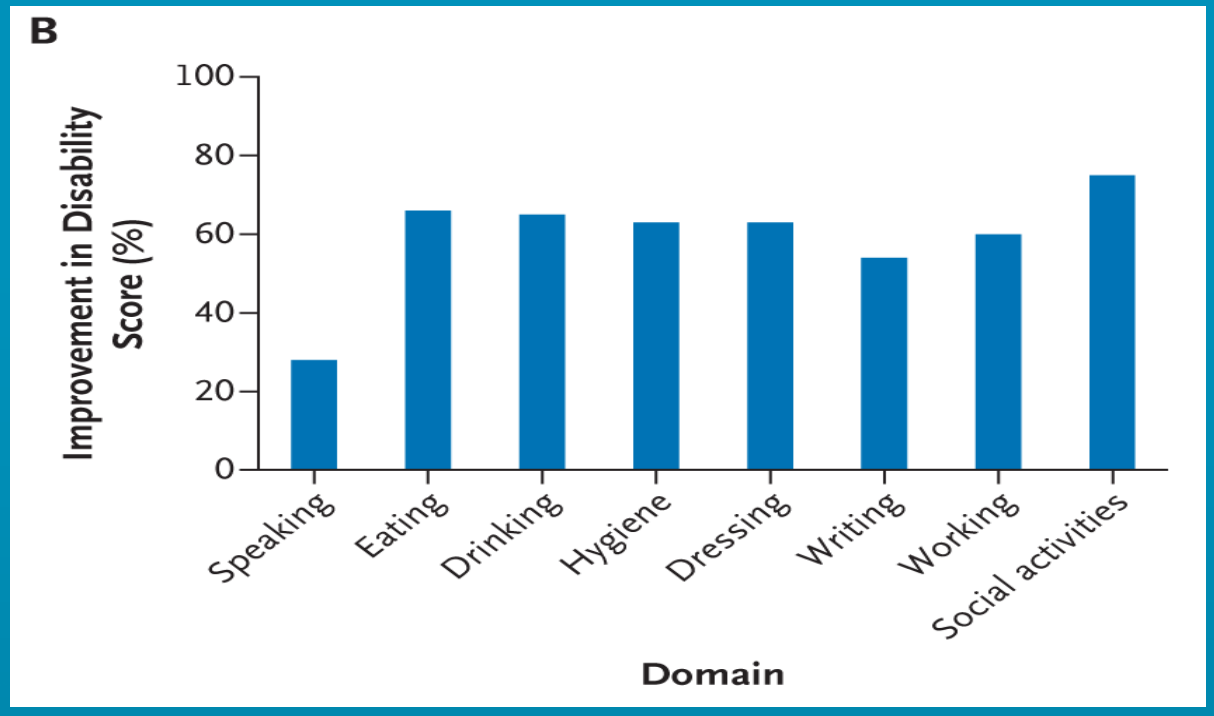
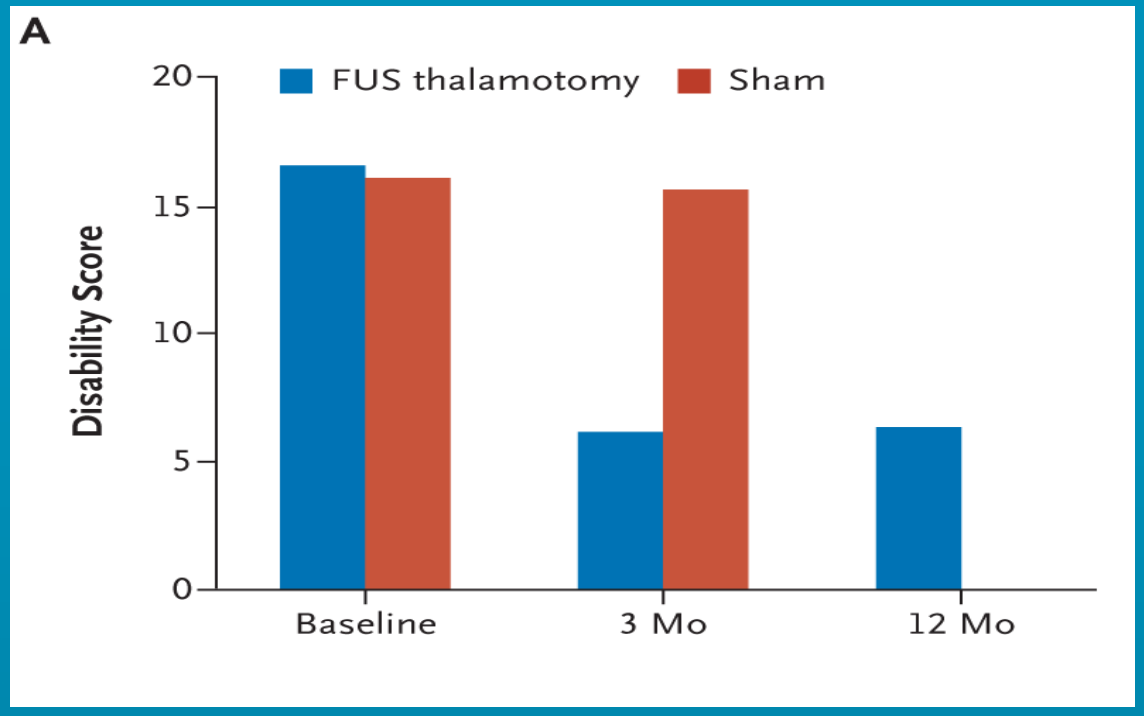
Secondary Efficacy – Disability of Life





Data from **Figure 2** Elias et al. (2016) A randomized trial of focused ultrasound thalamotomy for essential tremor. **NEJM 375:735**.

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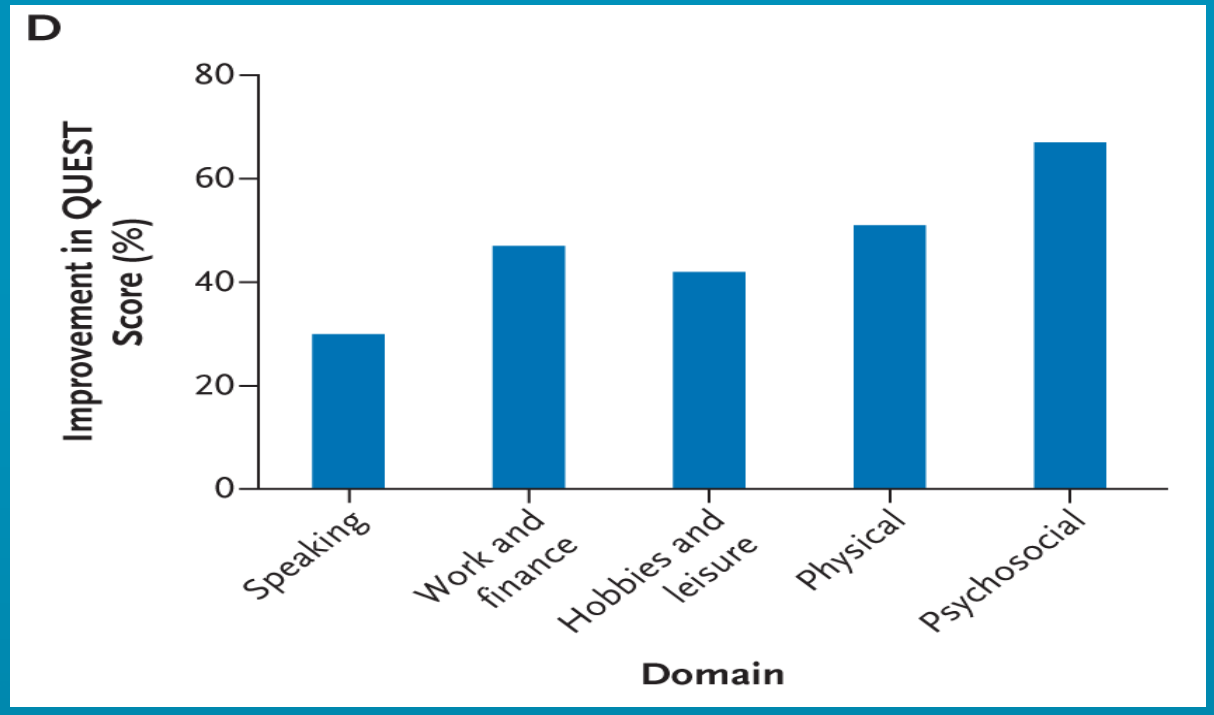
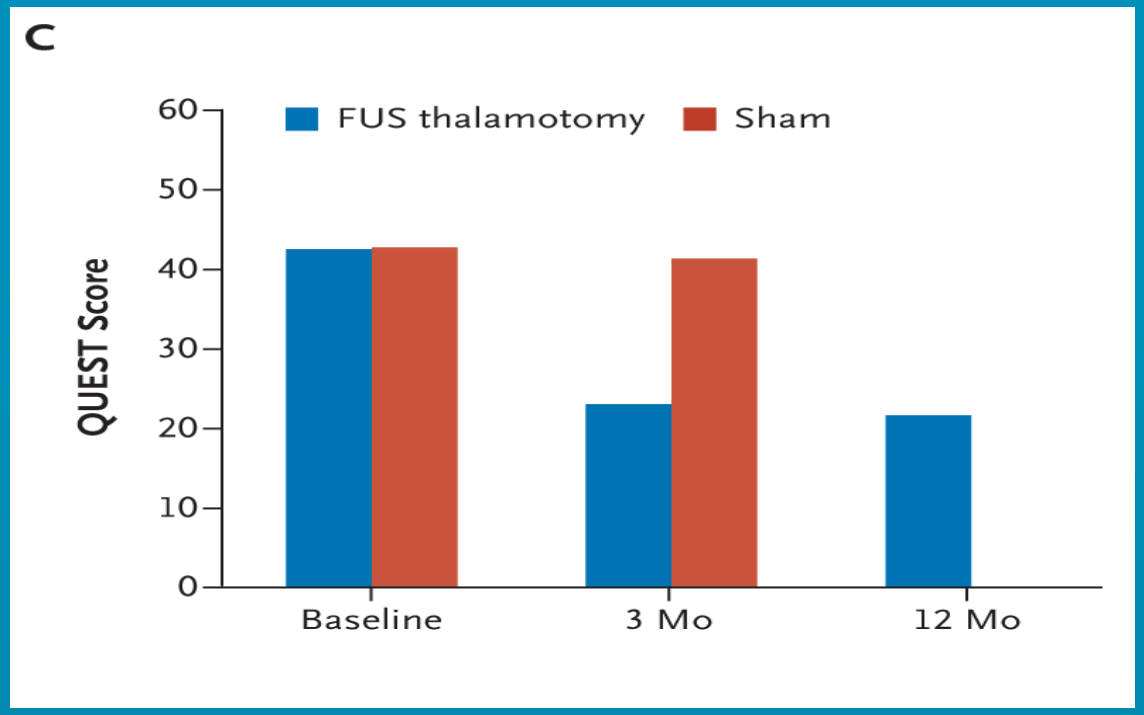
Secondary Efficacy – QUEST for Life





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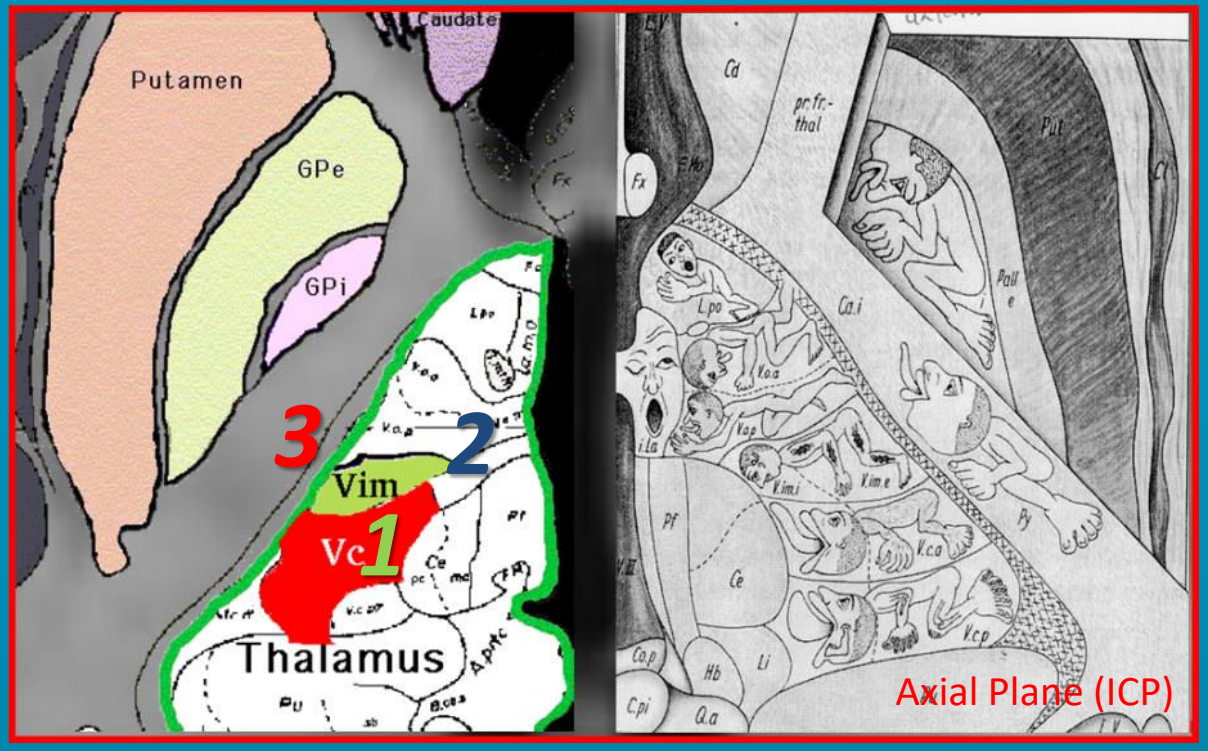
Mistakes & Essential Lessons from the ET pivotal

	Adverse Event	% → 1 year	PROBLEM	Anatomy
1	Parasthesias	38 → 14	Too posterior	Vc
2	Dysarthria	2 → 0	Too medial	Vop/Vc
3	Paresis	4 → 2	Too lateral	PLIC (CST)
4	**Ataxia**	36 → 9	**Too deep**	**RST**

SOLUTION

Aim FUS **superiorly** & **anteriorly** to the "classic" Vim target by 1.5-2 mm



Modified after Hassler et al. (1979) Stereotaxis in Parkinson Syndrome. Springer-Verlag:Berlin. (Fig. 29, p. 39)

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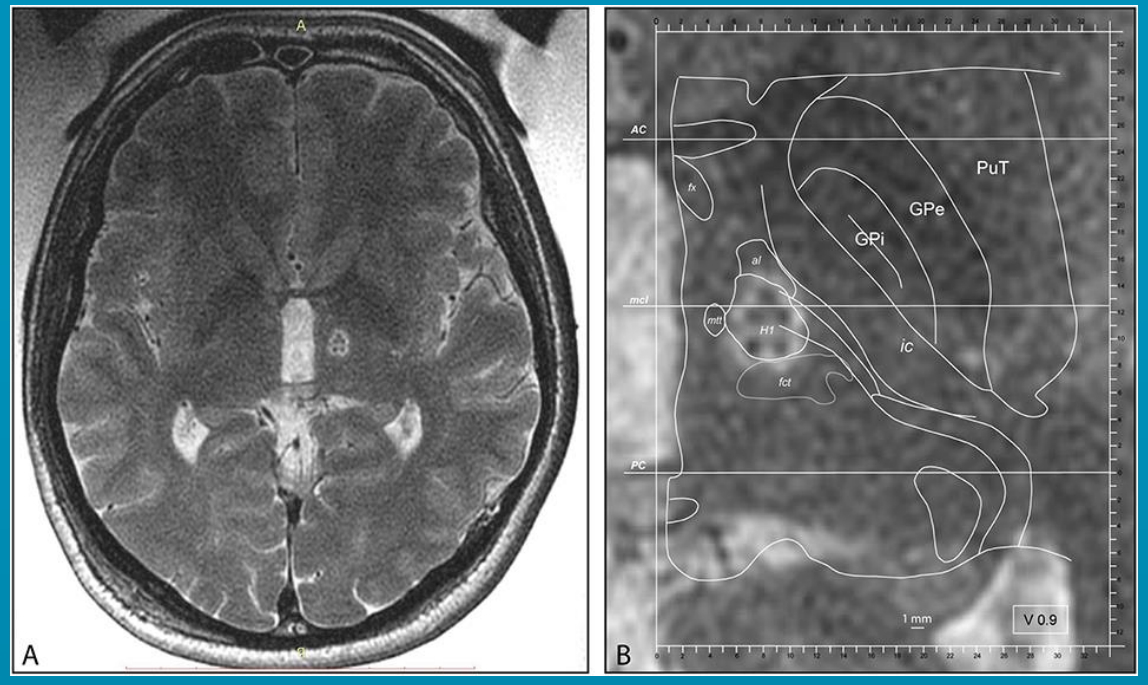
TDPD & Vim Plus Thalamotomy



- **Indications**: 2+tremor, UPDRSm↓30% & >800mg LED (8 pill rule)
- **FDA approval**: December 2018

- **Initial Indirect targeting of Vim**:
  X=M/L: Between 16 ML & 11.5 from 3rd
  Y=A/P: 25% PC>AC distance (6mm stop)
  Z=S/I: 2-4mm above HIC plane
- **Extended:** Forward to Voa

- **2-3 hours** round trip

Figure 1 Gallay et al. (2019) MRgFUS Pallidothalamic Tractotomy for Chronic Therapy-Resistant Parkinson's Disease. **Front. Surg. 6:76**.

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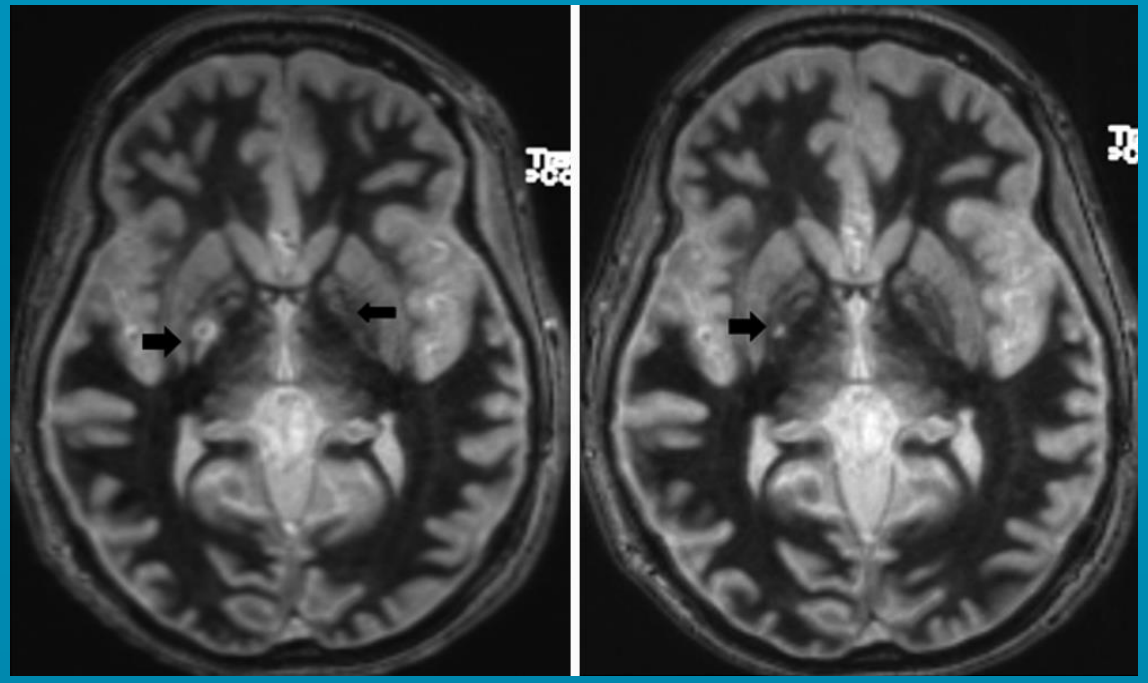
LID Dyskinesia & GPi Pallidotomy



- **Indications**: PD with peak-dose dyskinesia & end-dose freezing (motor flux)
- **FDA approval**: November 2021

- **Pallidotomy: Targeting the GPi**
  X=M/L: 20-22mm lateral & above OT
  Y=A/P: 50% PC>AC (@the MCP)
  Z=D/V: -5mm below HIC plane

- **1.5 hours** round trip

Figure 2 Krishna et al. (2023) Trial of Globus Pallidus Focused Ultrasound Ablation in Parkinson's Disease. **NEJM 388:683-93.**

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Some Take Home Messages

- FUS uses sound to create “holes” in the brain.
- An awake, immediate outpatient procedure.
- No incision, No radiation, No hemorrhage, No infection.
- FDA approved for ET, TDPD and Dyskinesia.

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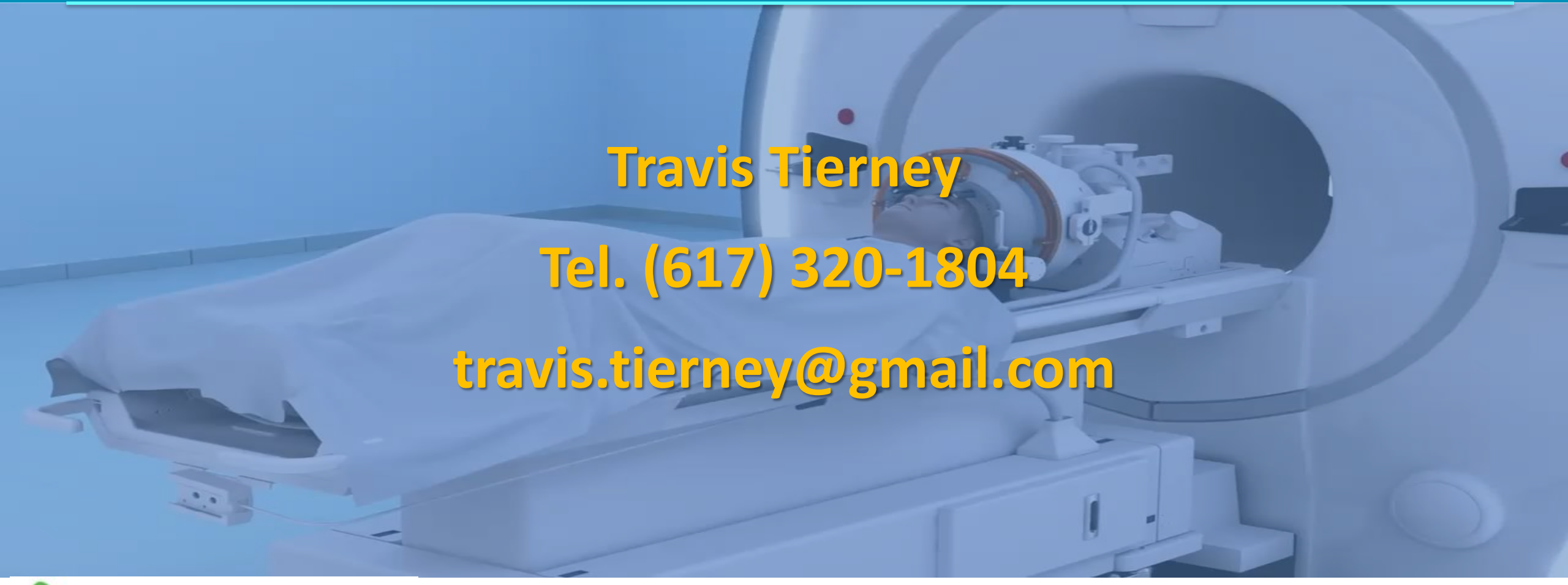
¿Questions?



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Rationale for Pediatric FUS

- No statistically safe dose of ionizing radiation
- Incisionless, non-ionizing tumor ablation
- Safer alternative or adjuvant to:
  - Conventional Surgery (open, endo, embo)
  - LITT
  - Conventional Radiotherapy (ExBRT, SRS, BT)

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FUS for Pediatric Neurosurgery: Safety Trial

"A Feasibility Safety Study Using the ExAblate 4000 System in the Management of Benign Centrally-Located Intracranial Tumors Which Require Clinical Intervention in Pediatric and Young Adult Subjects."

(FDA IDE no: G160189)

Tierney et al. (2022) Initial Experience with Magnetic Resonance-Guided Focused Ultrasound Stereotactic Surgery for Central Brain Lesion in Young Adults. **JNS 14:1-8**

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FUS for Pediatric Neurosurgery: Inclusions

- 10 pts 8-22yrs (3 cohorts: 18+, 12+, 8+ with DSMB pause)
- WHO grade 1, sub-cortical, relatively hypovascular
- Ideally, asymptomatic with some growth velocity
- A child *currently* being considered for surgery
- Tech inclusions: SDR>0.40, OFC >52cm, prior crani OK!

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FUS for Pediatric Neurosurgery: Exclusions

- Bleed risk: VPA, Avastin, prior ICH, DVA, flow voids
- HCP risk: large tumor, prior shunt/ETV, Hx HA
- Onc risk: Need histopathology, prior biopsy, HG MRI
- Any child that *should* be followed in clinic, e.g. sirolimus
- Tech exclusions: Surg & GA, VNS, RNS, AX1, no IQ limit!

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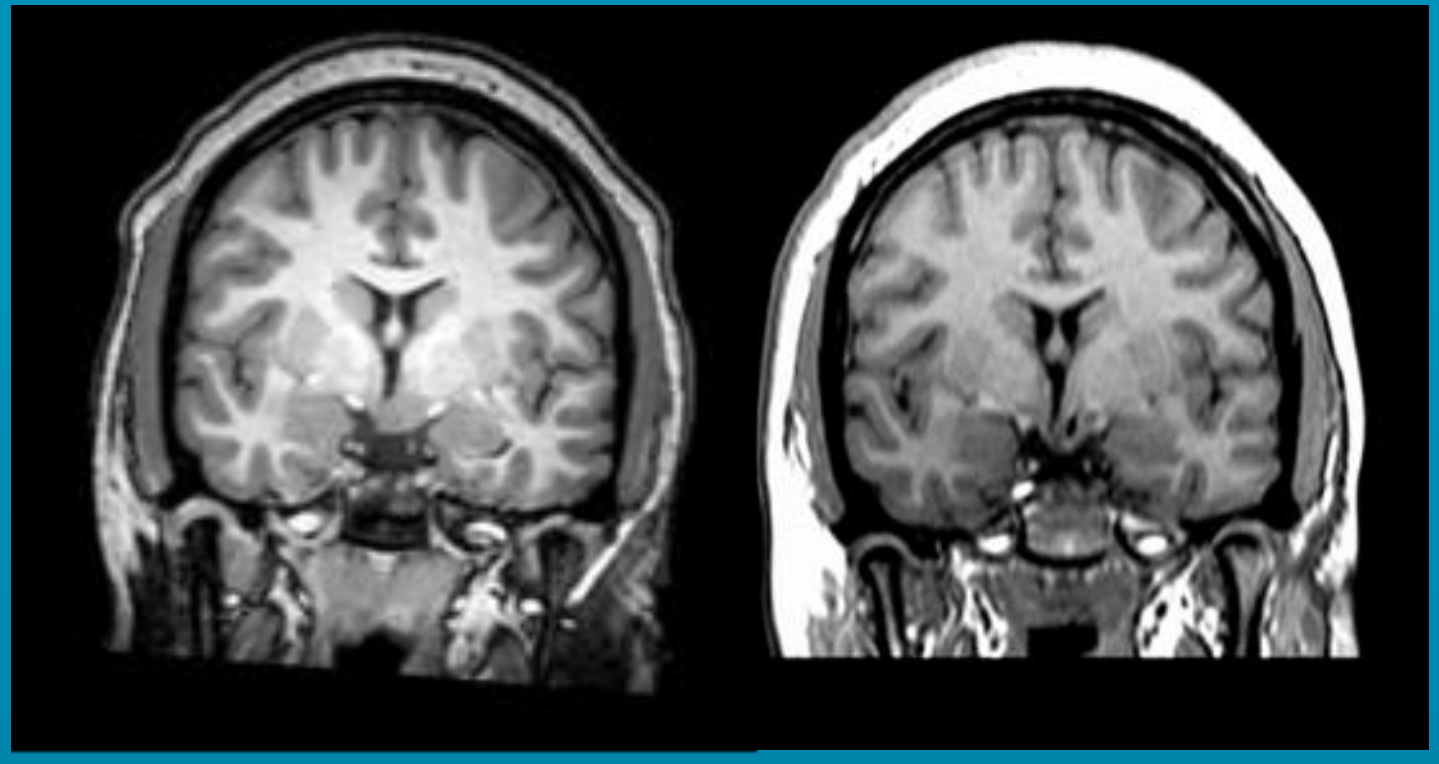
Case 1. Home run > FUS for Epilepsy

22 yo RHF with history of GZ

Left transcortical LITT two years prior at 19 to 1.3 cm HH

No metabolic, endocrine or cognitive complications, but no remission of sz either

Clear residual HH, and gliosis



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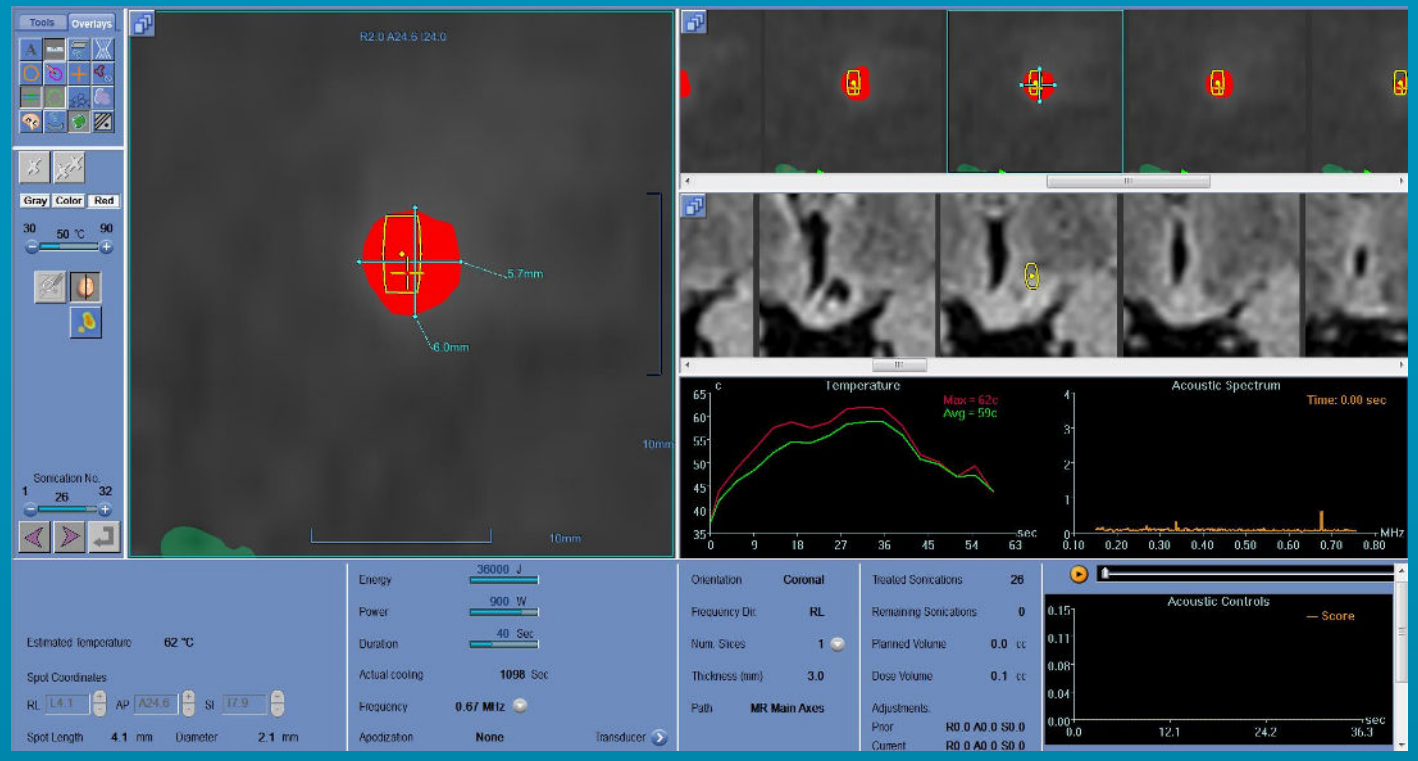

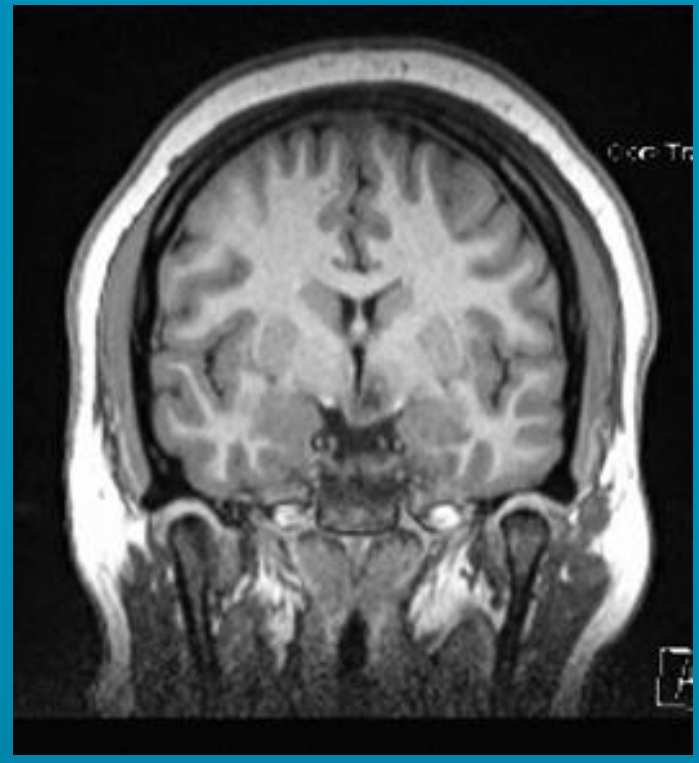

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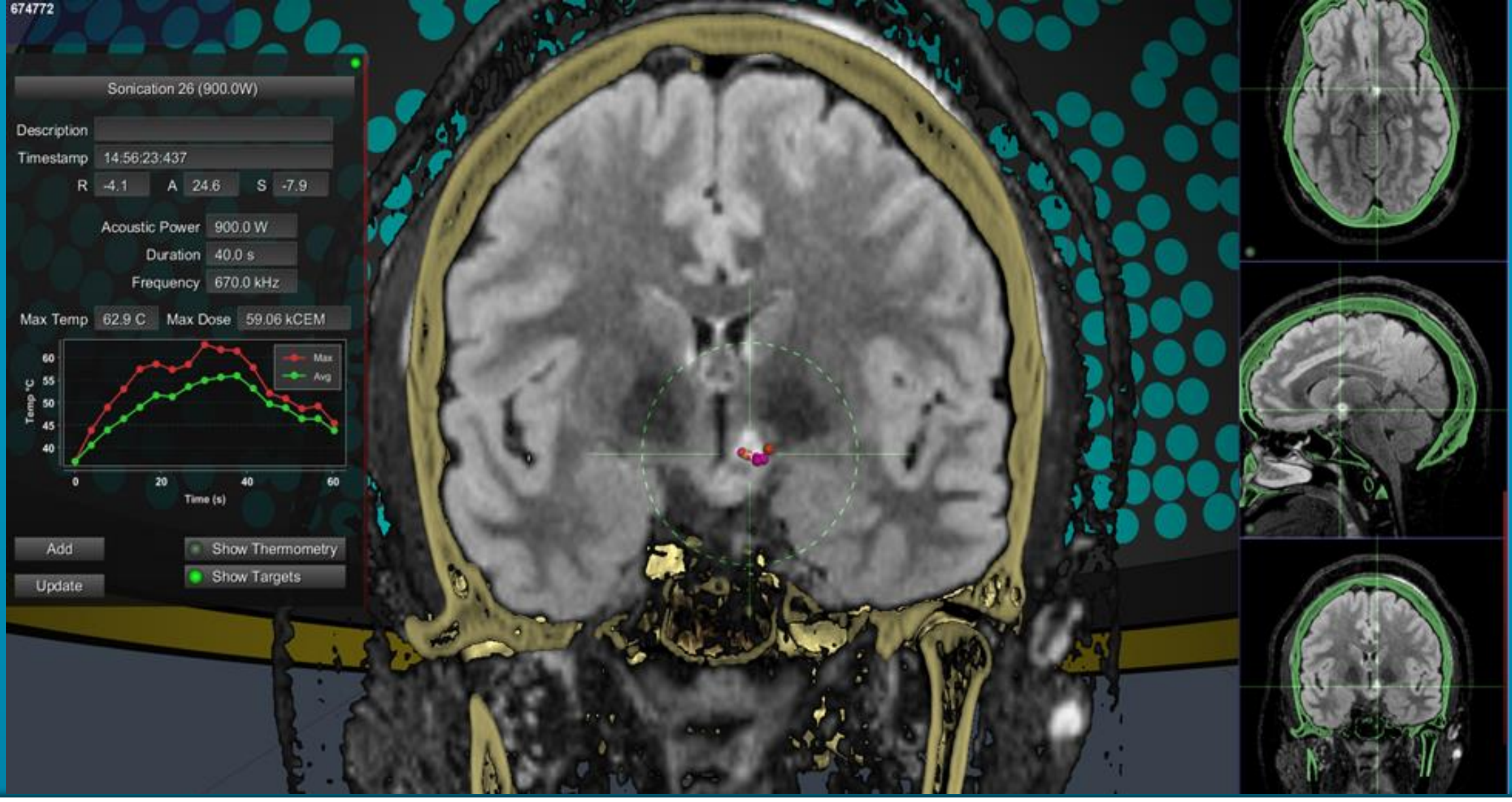

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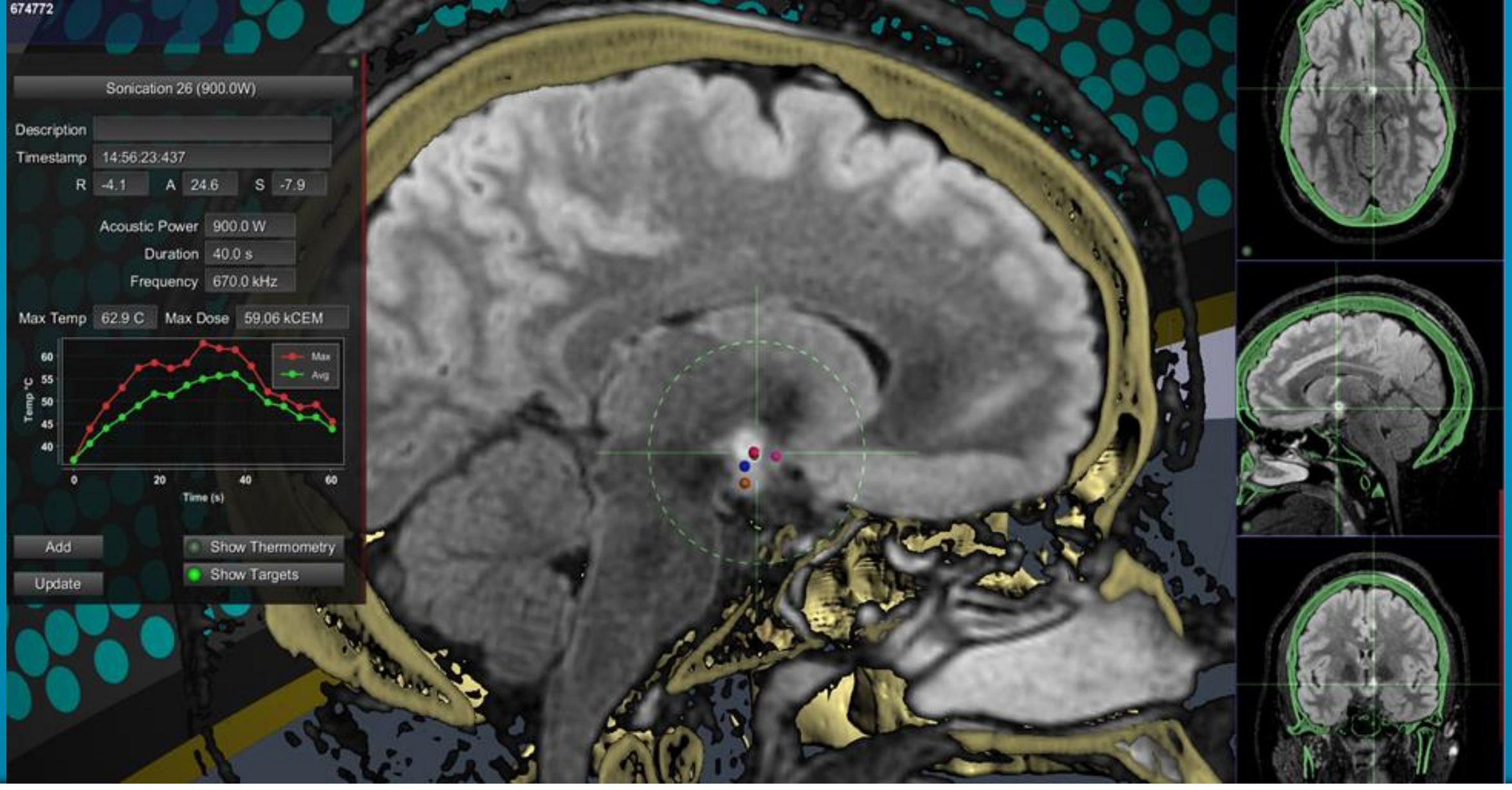
Courtesy of John Snell, PhD Focused Ultrasound Foundation of Virginia



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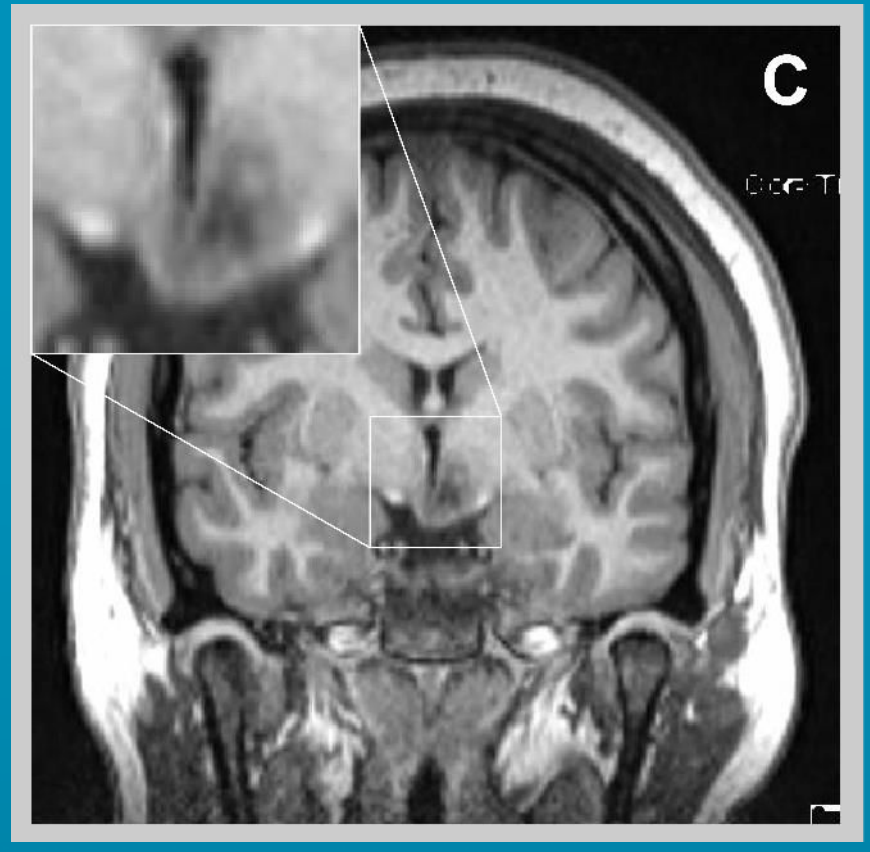
Case 1. Home run > FUS for Epilepsy

RESULT:

1. Radiographic thermodiscconection
2. DC'ed POD 2 on short steroid taper
3. No endocrine, metabolic or cognitive abnl
4. ILAE class 1a control >5 years.



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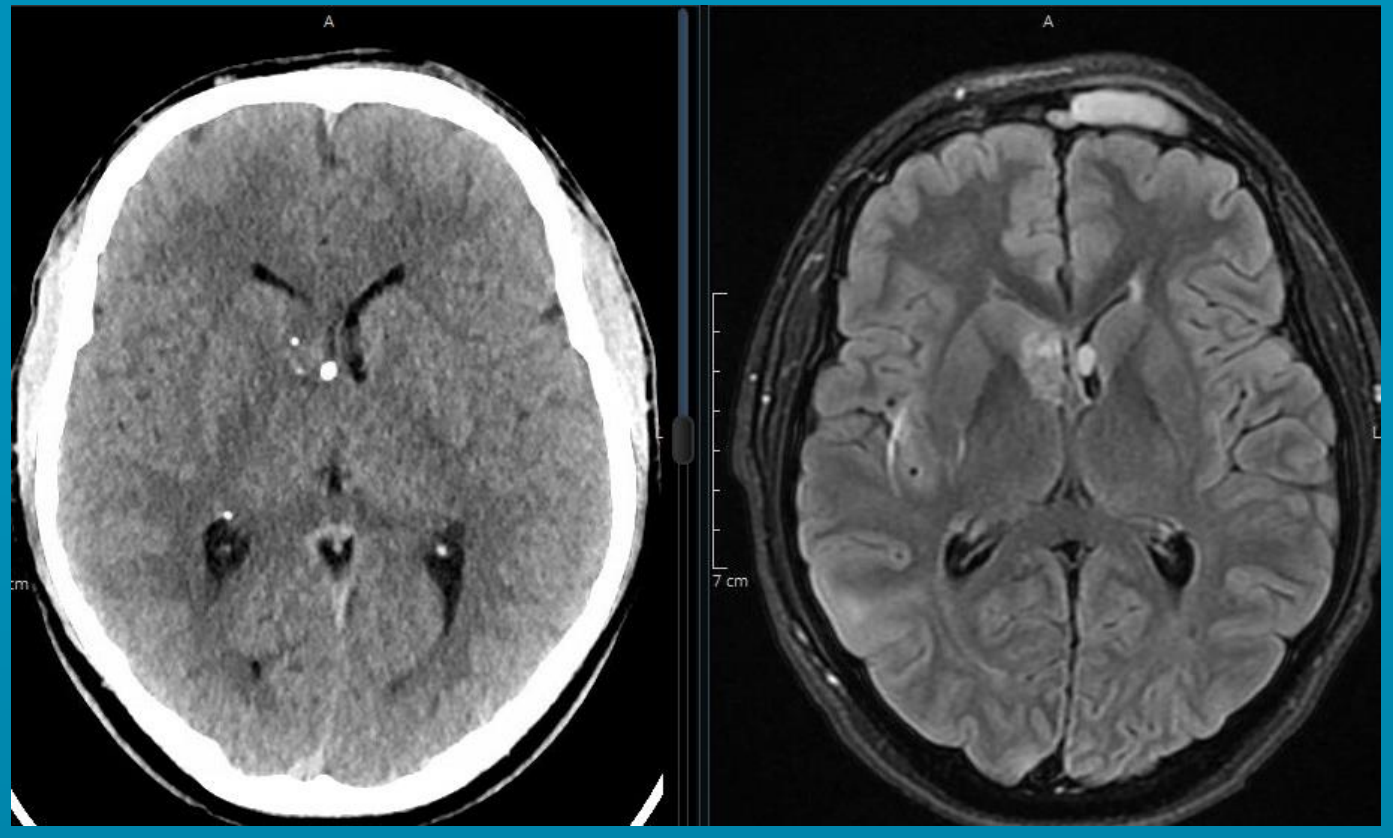
Case 2. Strike out > FUS for Tumor

19 year old male with history of TSC

On the mTOR inhibitor, everolimus

No HCP, no current sz, no previous surg



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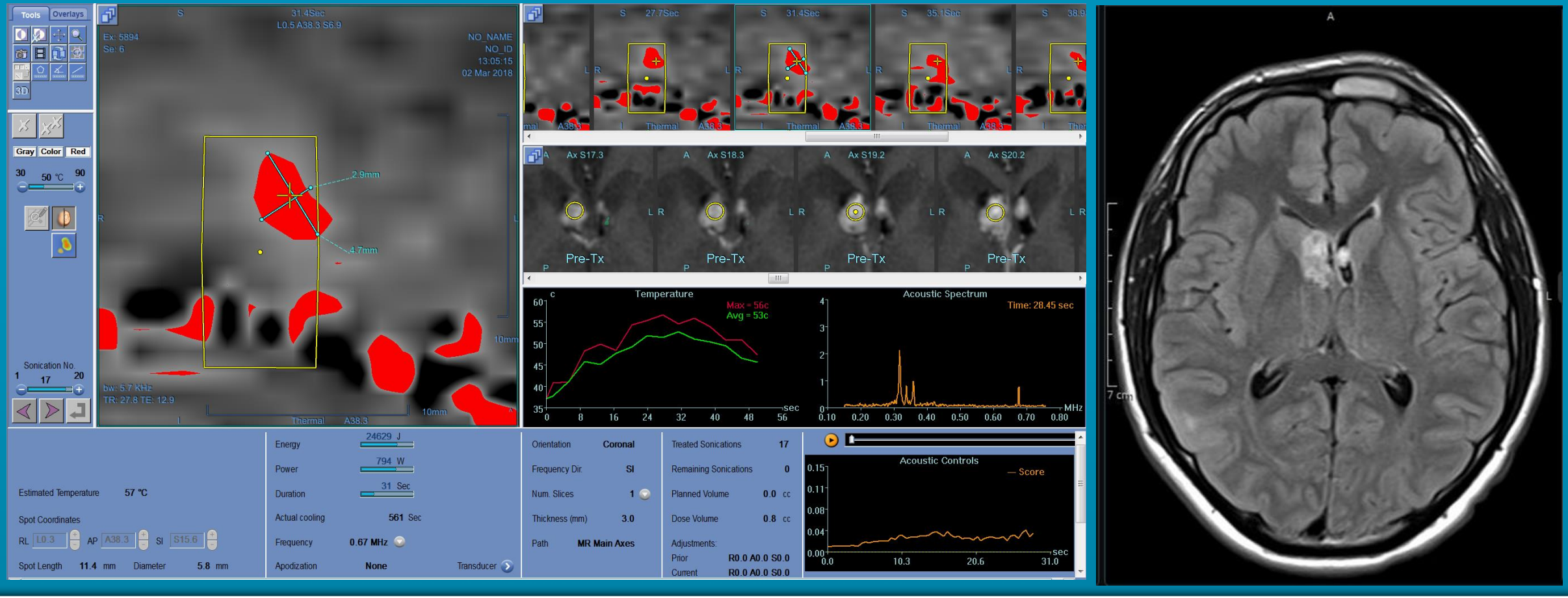
Case 2. Strike out > FUS for Tumor



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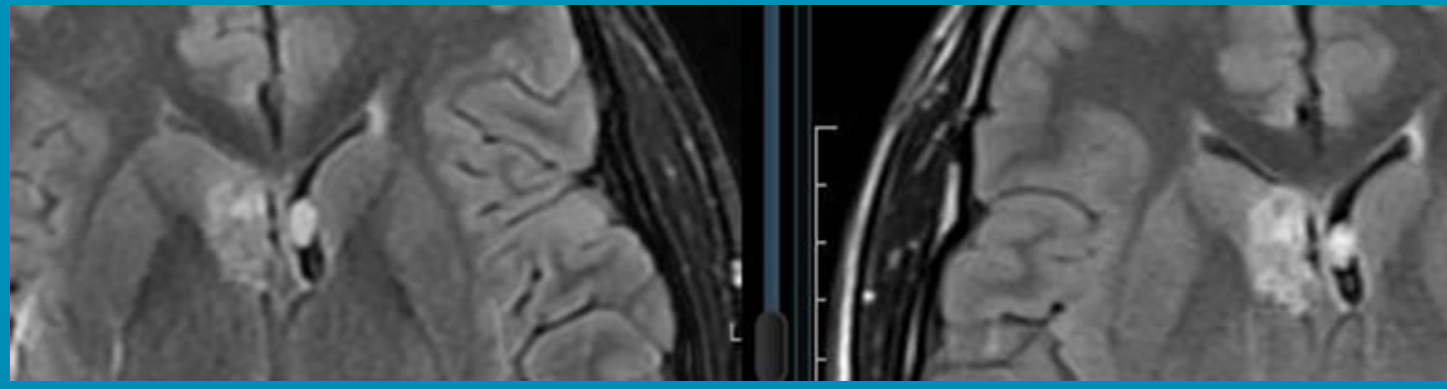
Case 2. Strike out > FUS for Tumor

RESULT:



1. Subtotal thermoablation
2. Ca^{2+} in near field limited power
3. Inertial cavitation events limited courage
4. No endocrine, metabolic or cognitive abnl

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PEDS FUS: The Field's Horizon

- Multicenter RCT: Tumor vs. Epilepsy? 220kHz
- Pallidotomy: **Secondary** > Primary dystonias 650kHz
- BBB disruption for DIPG (LoFU + IV chemo) 220kHz
- **Epilepsy**: diagnostic (LoFU neuromodulation) 220kHz

  therapeutic (HiFU ablation, LoFU NM) 650 & 220

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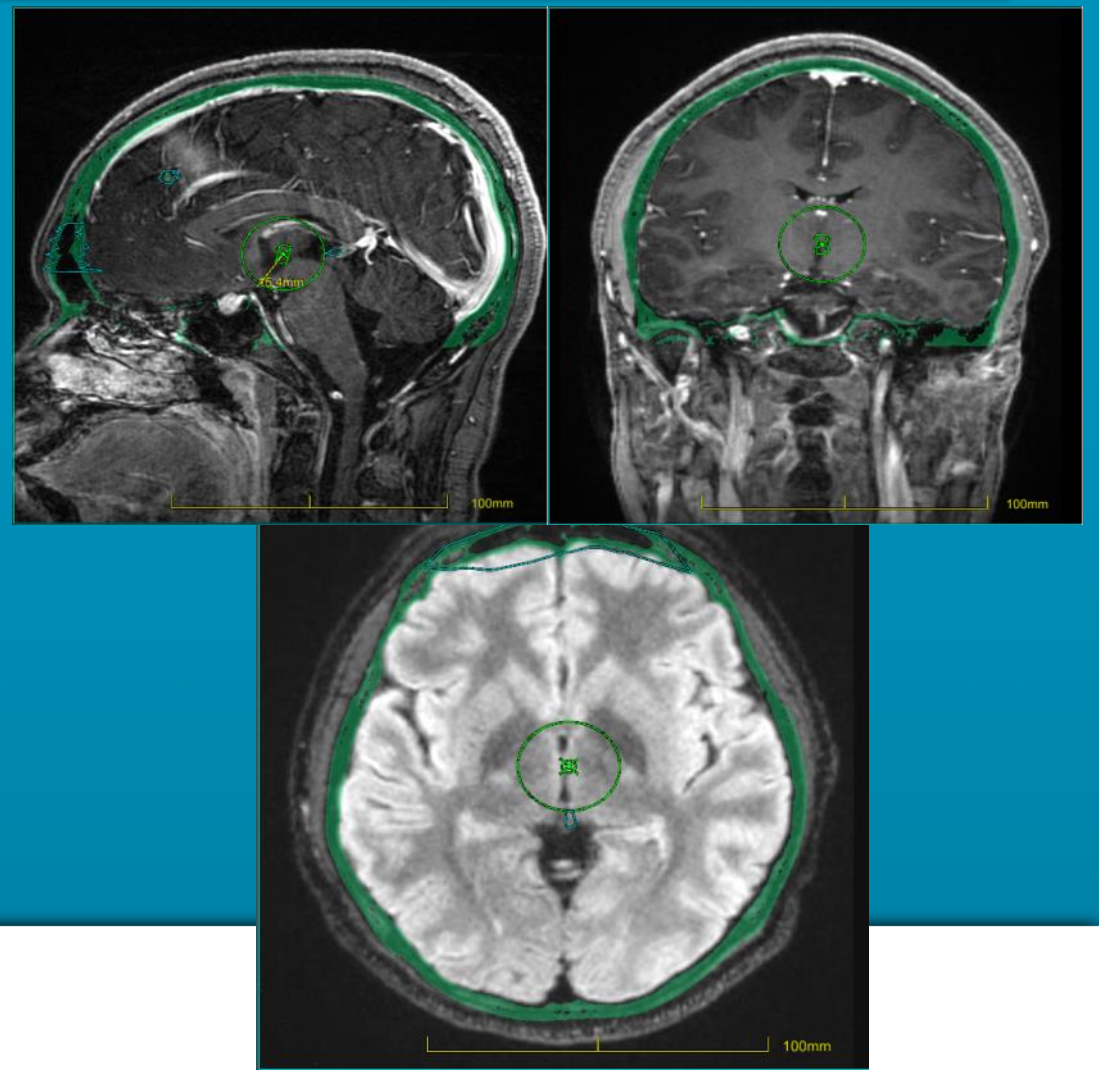
FUS for Hamartoma: First case

21 year old female with history of gelastic sz

Operated on by right transcoritcal transventricular endoscopic approach 5 years prior at age 16

Resulted in 100 lb weight gain and sz freedom for 18 months, but recurred having daily events

Known left parahypothalamic residual



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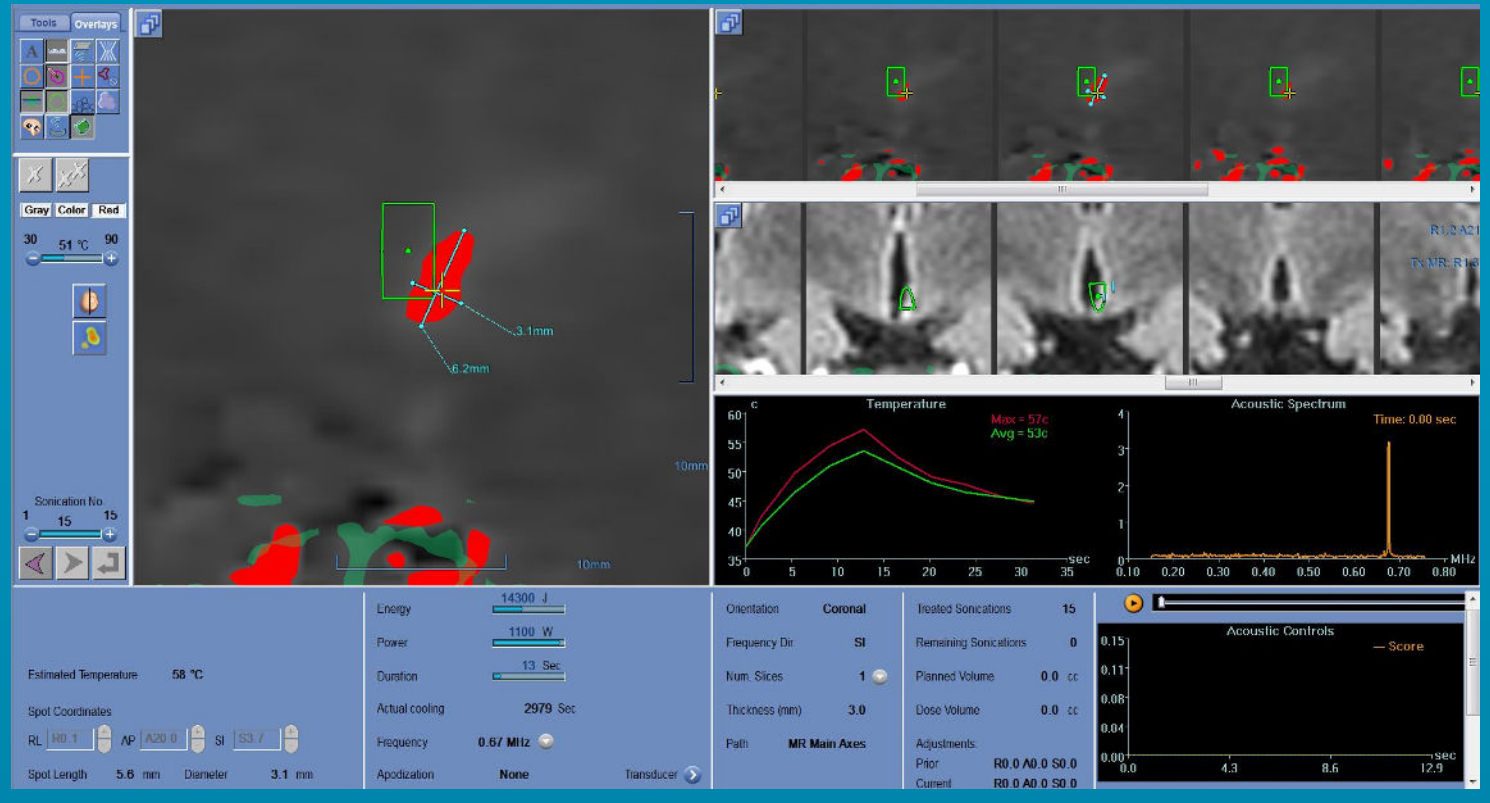
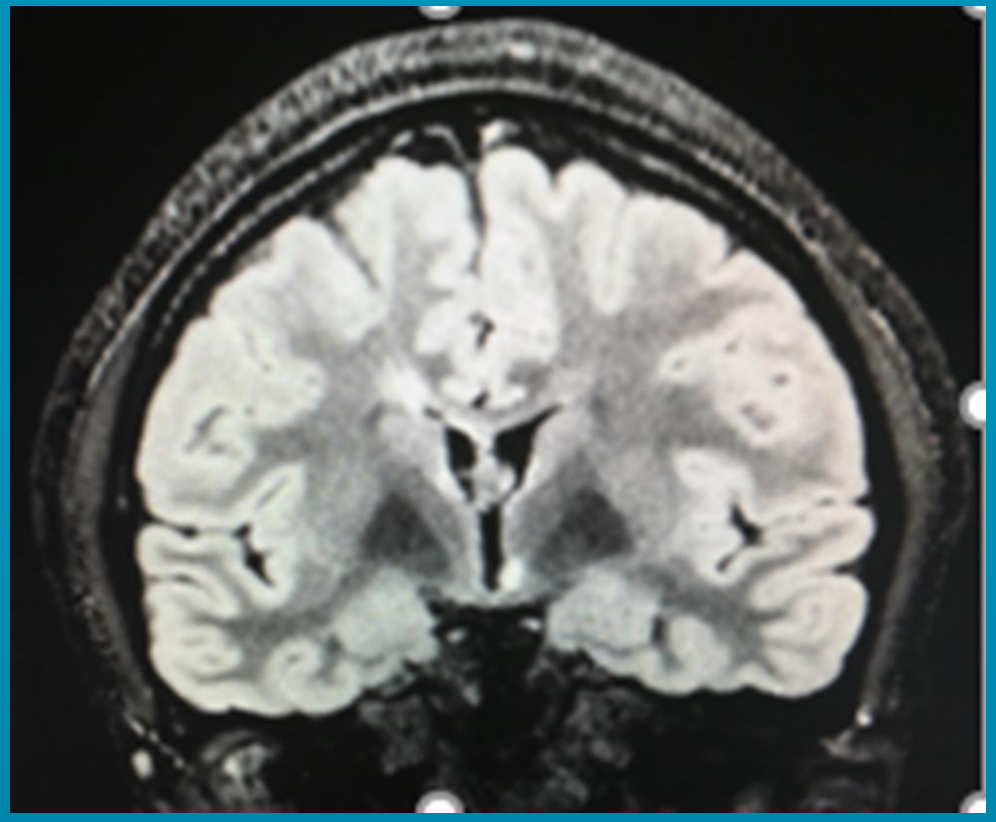
FUS for Hamartoma: First case





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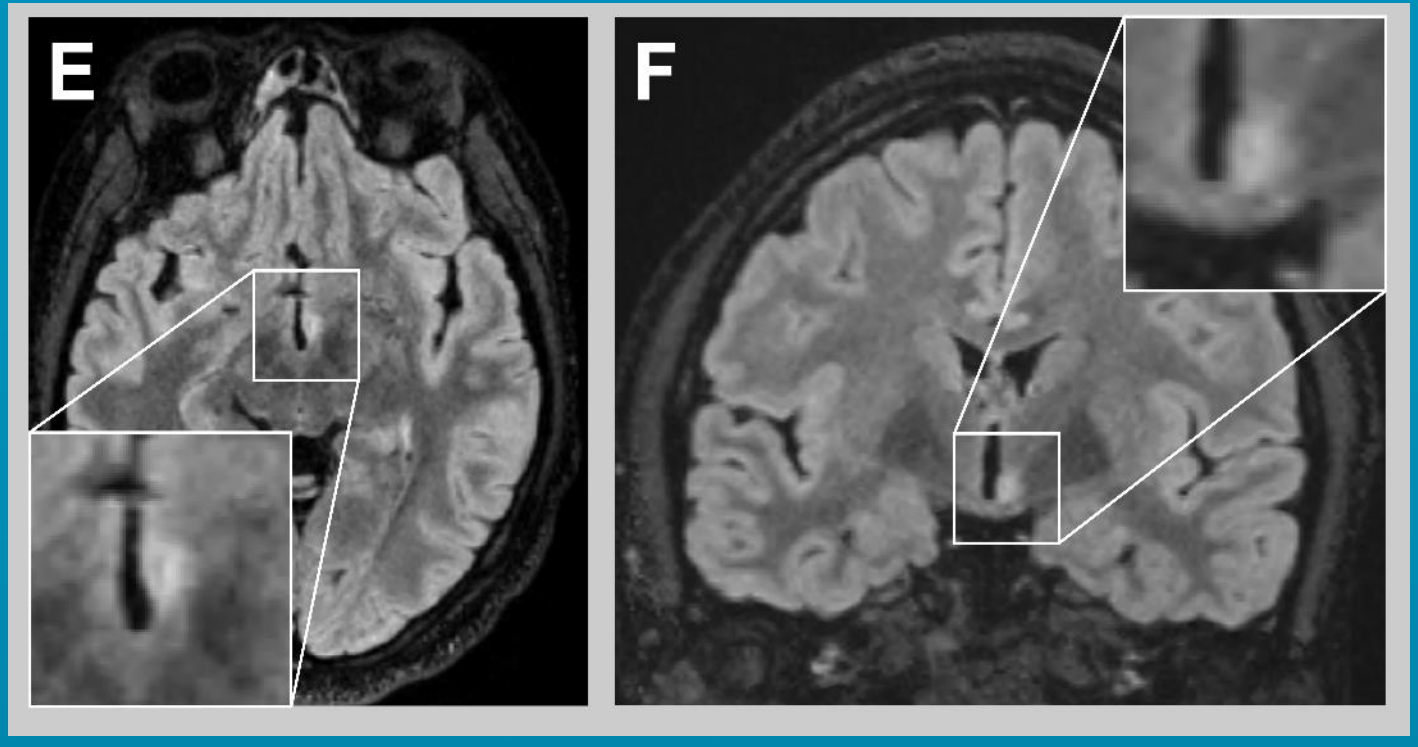
FUS for Hamartoma: First case

RESULT:

1. Radiographic thermoablation
2. POD 2 dc on short steroid taper
3. Remains sz free at 17 months
4. No endo, metabolic or cog abnl



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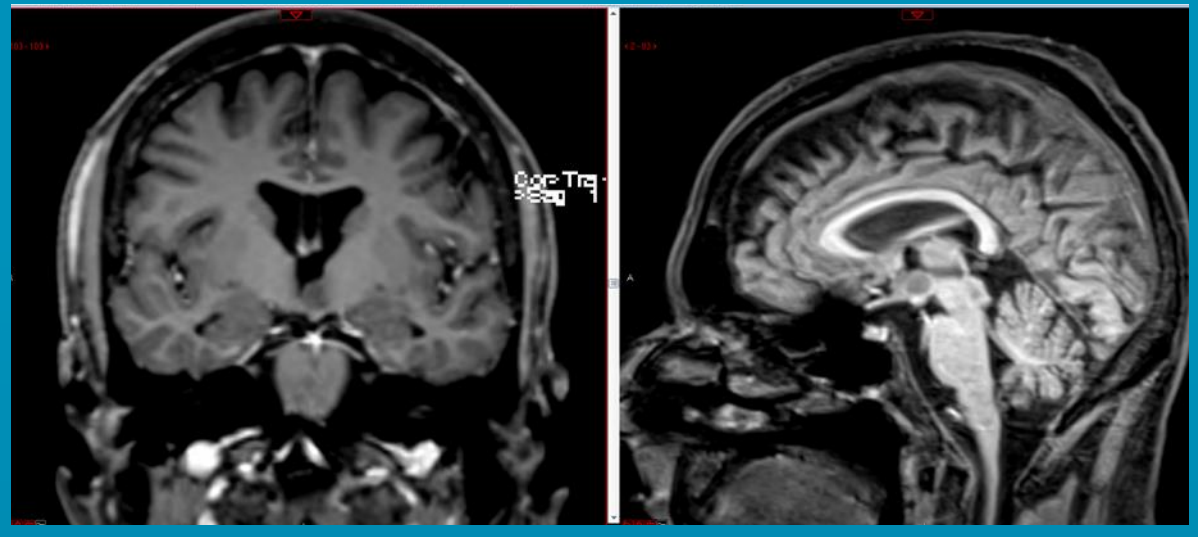
Peds FUS: Examples

Hypothalamic hamartoma

Ideally with vertical disconnection plane (D&F Type 2 and 3a)

<15mm

Intention to treat would be gelastics



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Peds FUS: Examples

TSC – SEGA

Ideally, away from the foramen

Again, <15mm

Intent to treat is growth velocity

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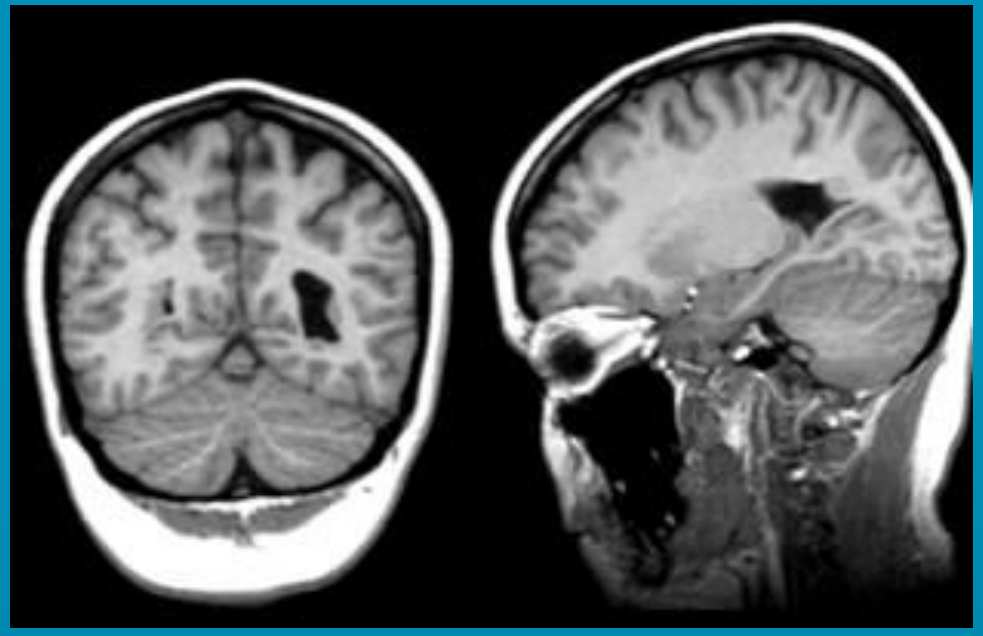
Peds FUS: Examples

Periventricular nodular heterotopias or deep tubers

Maximum volume is 8 cm^3

Intent to treat is seizures



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