Modulating Brain Circuits with Ultrasound

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Neuromodulation

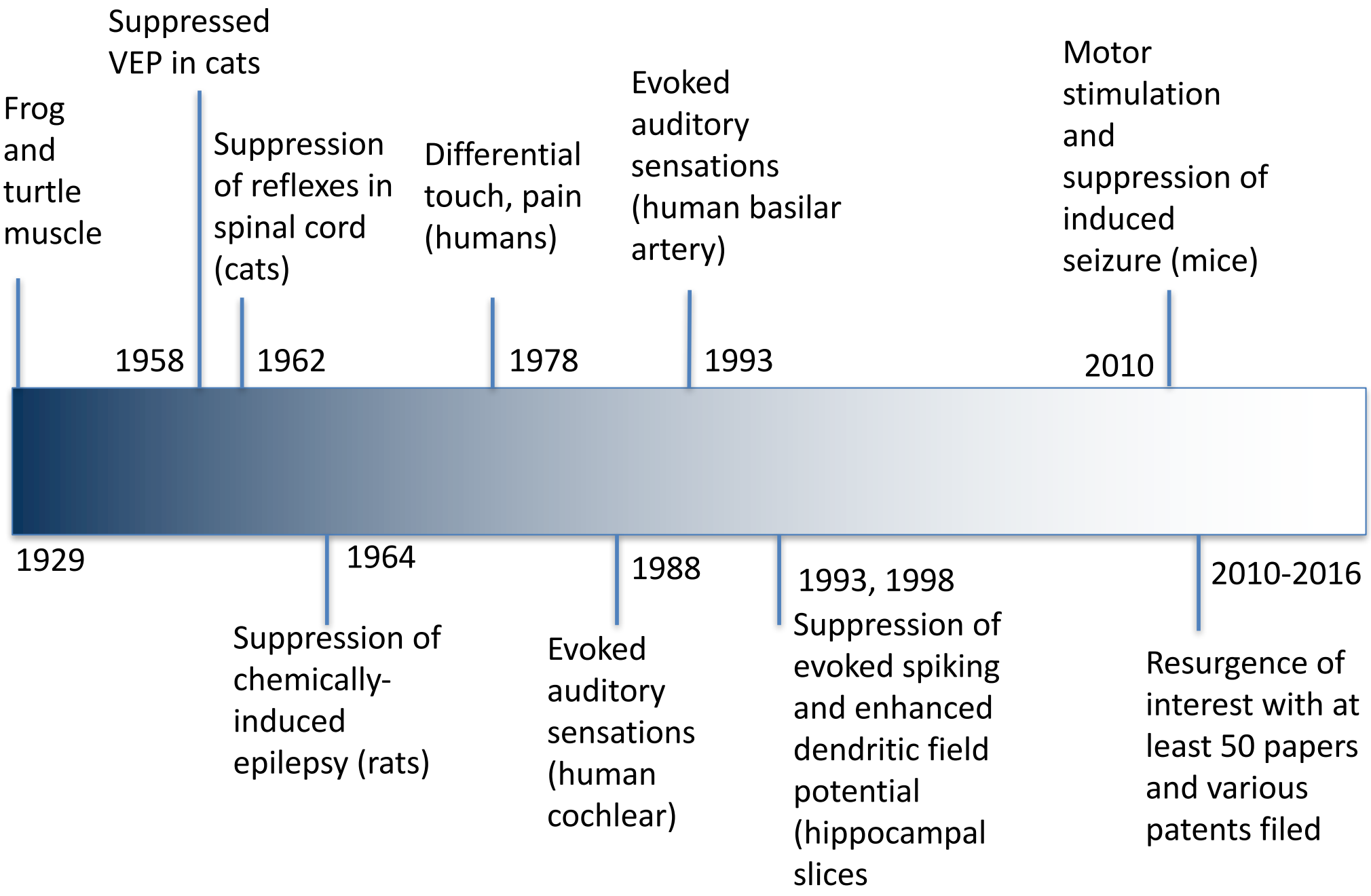
- Dysfunction of brain circuitries are a responsible for many neurological diseases [1]
- Identifying how different regions of the brain interact remains a difficult research goal
  - Casual relationships between circuits
- Method of investigating circuits
  - Manipulate circuitry (in excitatory or inhibitory directions) and correlate changes in behavior or other readouts

[1] A. A. Fingelkurts and S. Kahkonen, "Functional connectivity in the brain--is it an elusive concept?," *Neurosci Biobehav Rev,* vol. 28, pp. 827-36, Jan 2005.

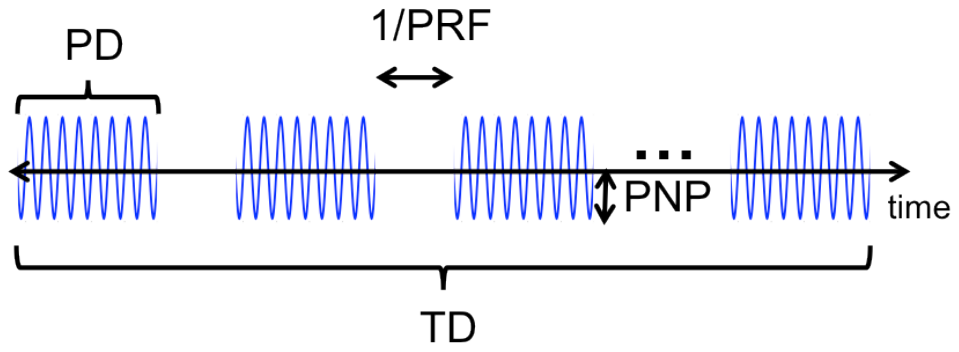
US overcomes limitations of other methods

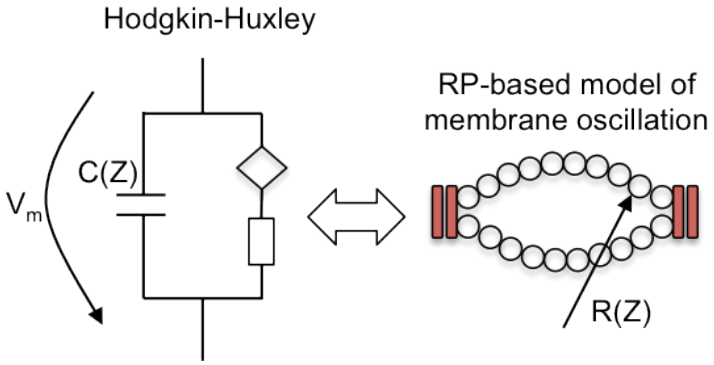
Method	Invasiveness	Spatial selectivity	Excite/Inhibit
Transcranial magnetic			
Transcranial electrode			
Direct electrode			
Deep brain stimulation			
Ultrasound			

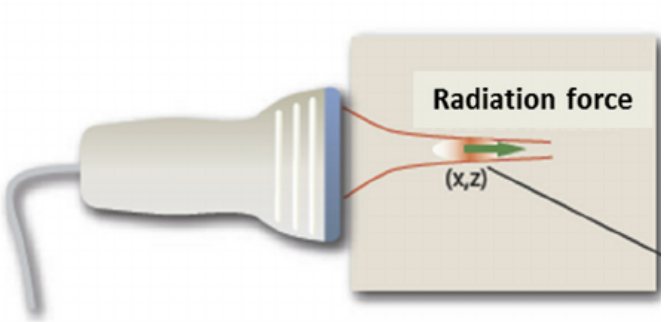
Timeline of FUS Neuromod.



Possible underlying mechanisms

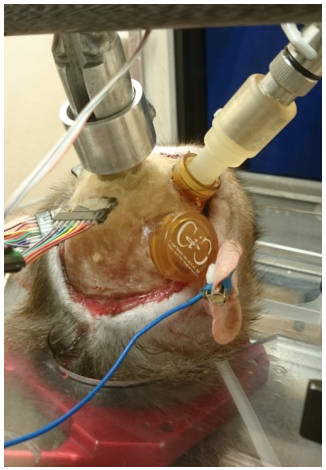


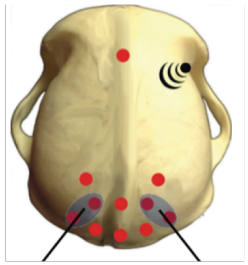


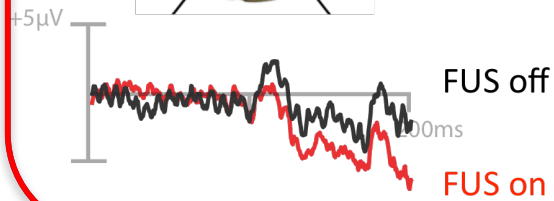


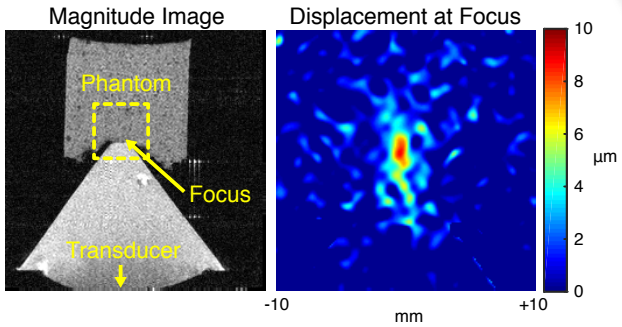
Combined neuromodulation and imaging

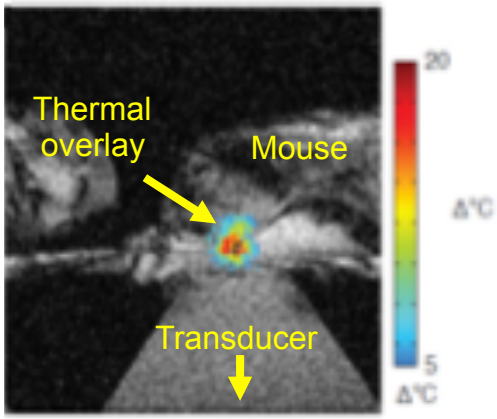
Ultrasound neuromodulation → Perform under MR guidance → Couple to functional MRI

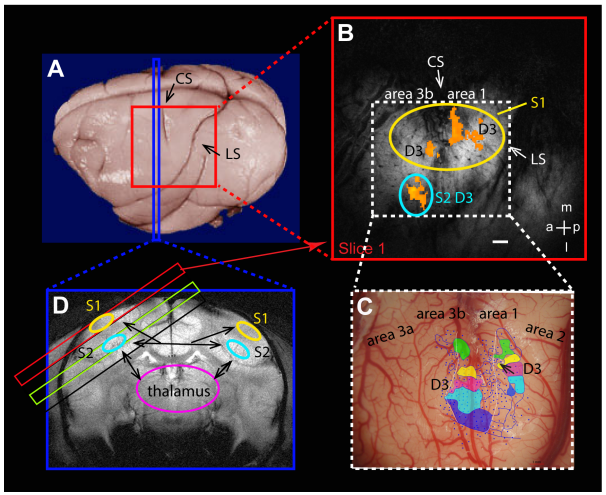








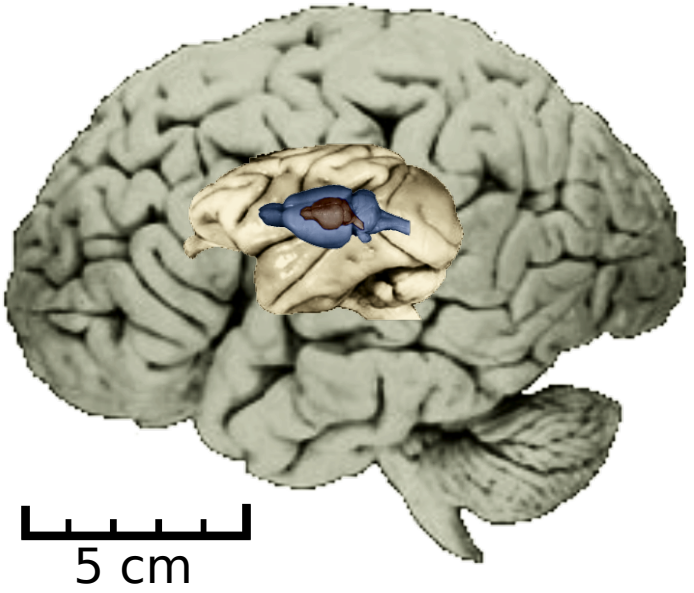




Network-level imaging with focal neuromodulation

Scale: size and complexity

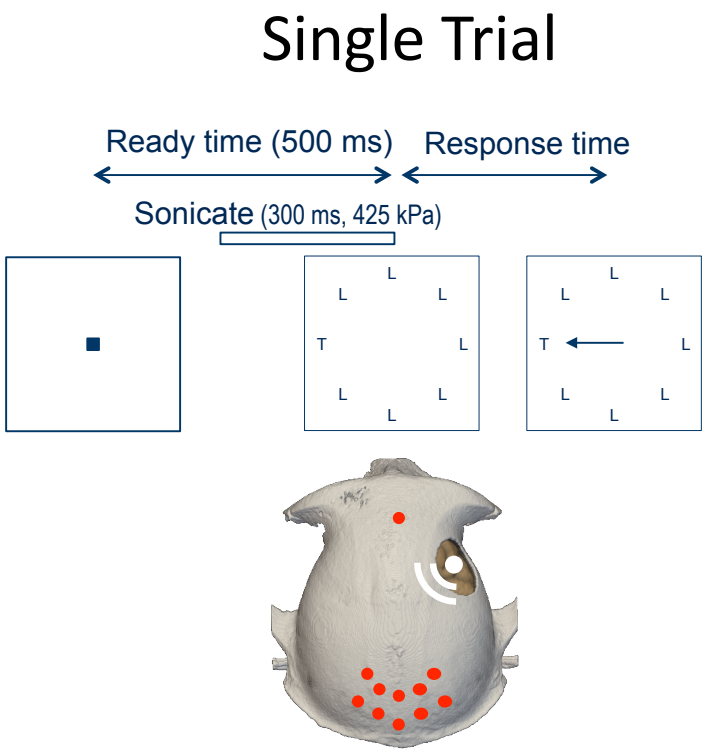
- Brain size
  - Wavelengths on the order of 1 mm with 100s of cycles
  - Standing waves increase pressure [1,2]
- Circuits increase in complexity



[1] Younan, Youliana, et al. Medical physics 40.8 (2013): 082902.
[2] O'Reilly, Meaghan A., et al. Physics in medicine and biology 55.18 (2010): 5251.

Modulating FEF with FUS

- Apply ultrasound to frontal eye field (FEF) during task
  - Measure gaze behavior, event-related potentials
    - Saccade response time (SRT), accuracy, EEG
    - Slowing of saccades has been observed previously [1]
  - Expectations stimulating FEF
    - Eliciting saccadic eye movement

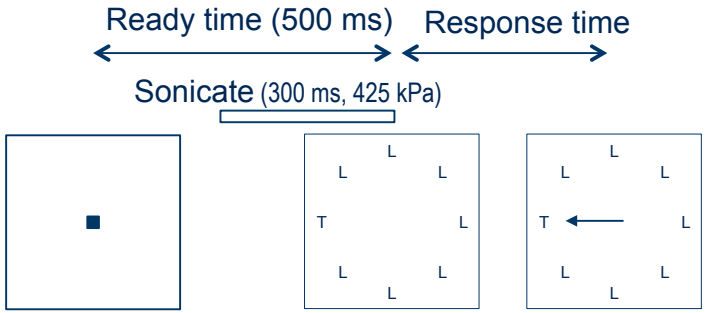


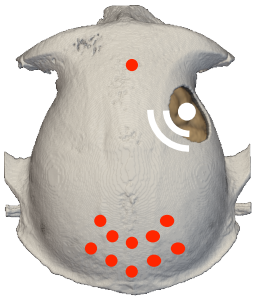
[1] Deffieux, Thomas, et al. Current Biology 23.23 (2013): 2430-2433.

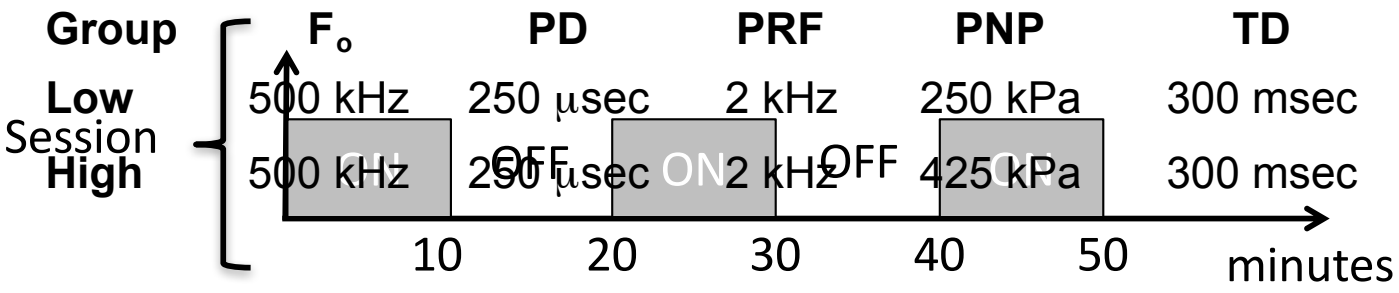
Modulating FEF with FUS

- Study design
  - Two monkeys studied (H and G)
    - 7 sessions with 10-minute blocks alternating between US on and off
    - ~125 trials in block and 800 in session

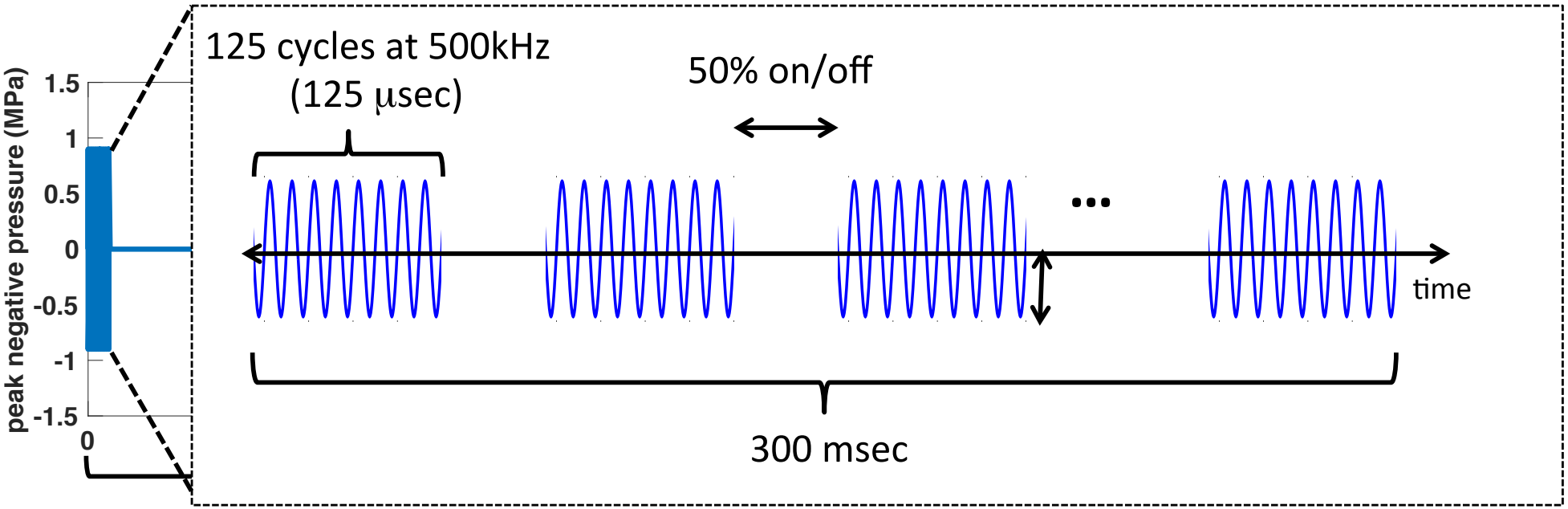
Single Trial







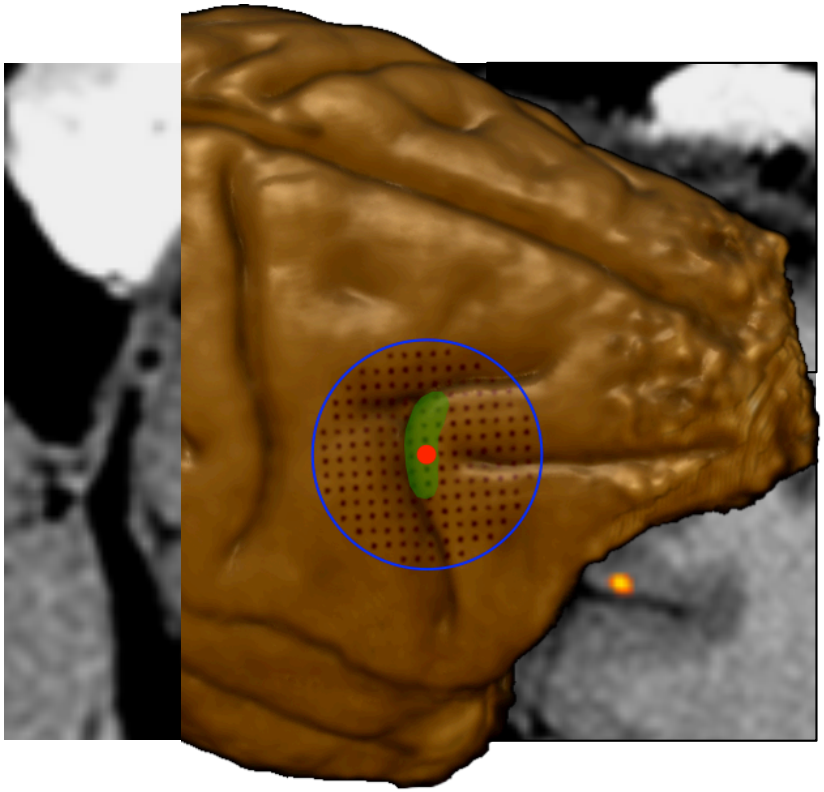
Pulses are within diagnostic limits



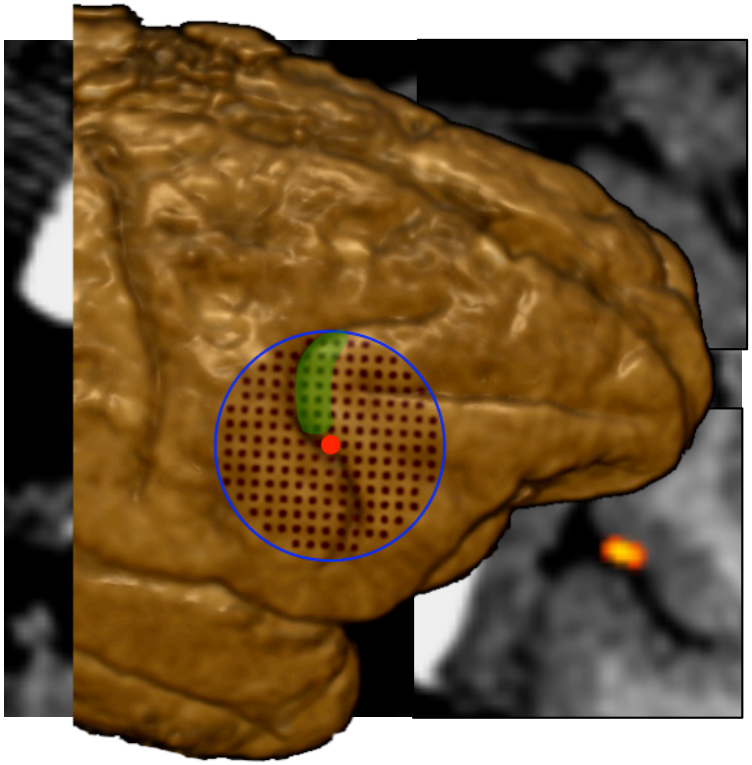
Minimum inter-pulse time allowed was 2 sec => Maximum duty factor possible 7.5%

	Neuromod	FDA Guidelines [1]
Ispta.3 [mW/cm^2]	530	720
MI	0.6	1.9
Isppa.3 [W/cm^2]	7	190

Beam localization

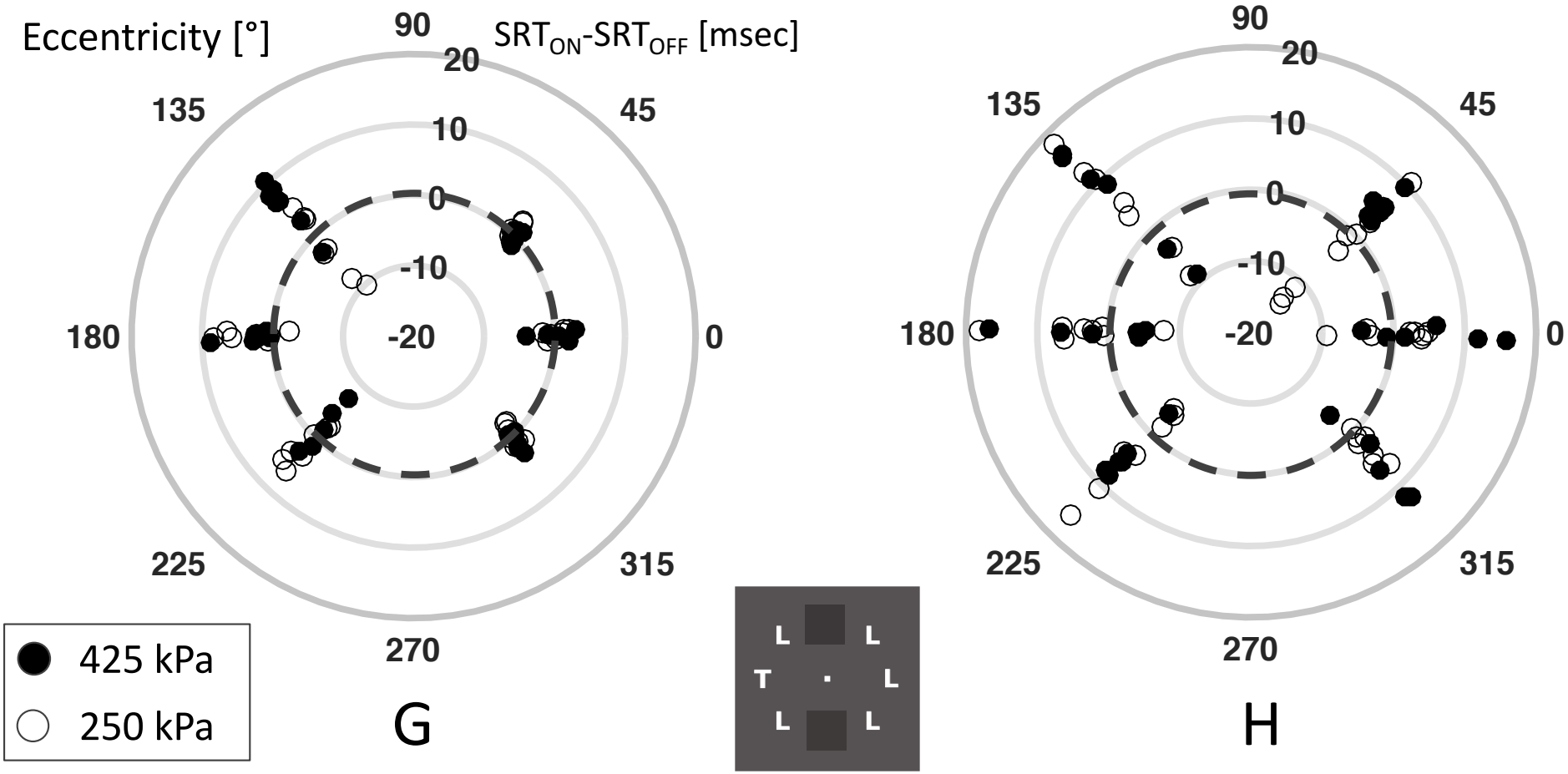


G

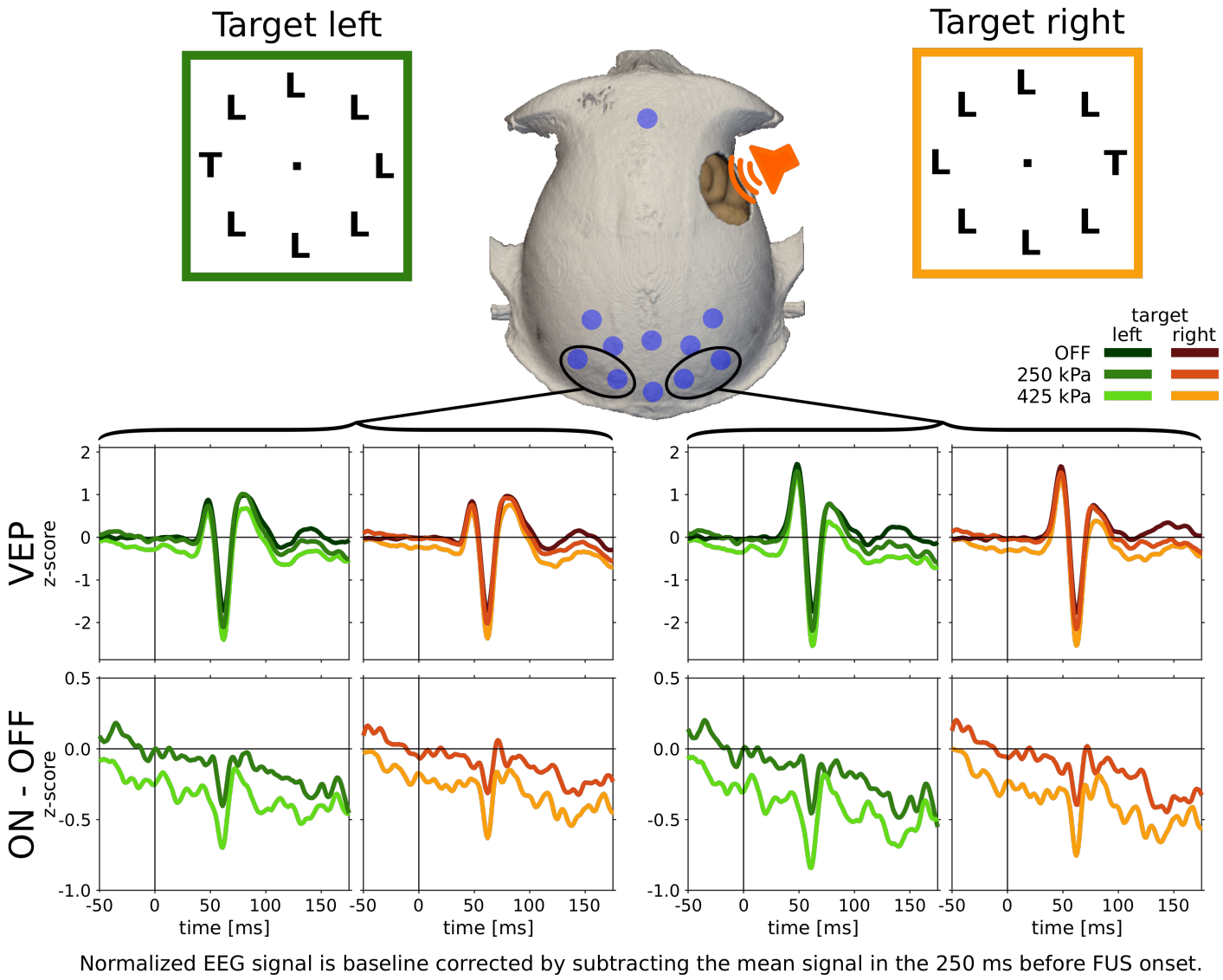


H

Spatially selective modulation



Intensity dependent modulation of ERP



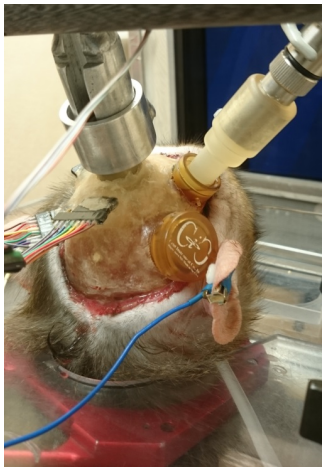
Zinke et al. SfN 2016

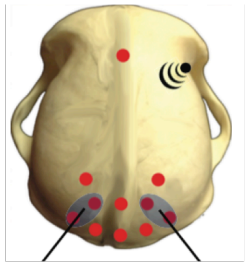
Combined neuromodulation and imaging

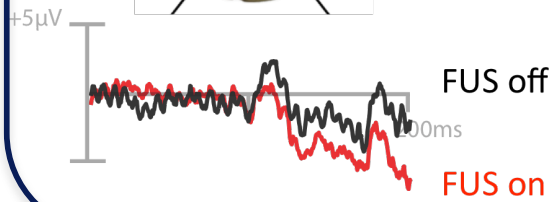
Ultrasound neuromodulation

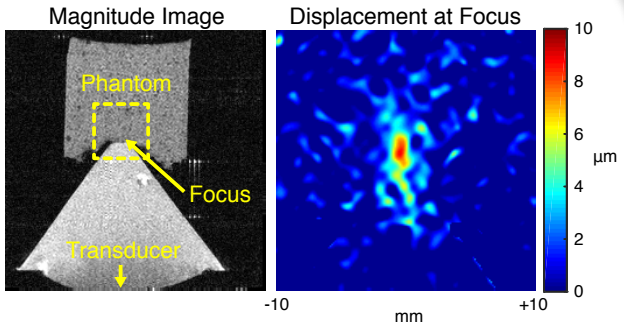
Perform under MR guidance

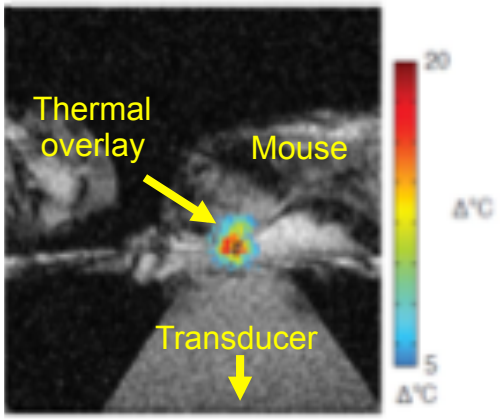
Couple to functional MRI

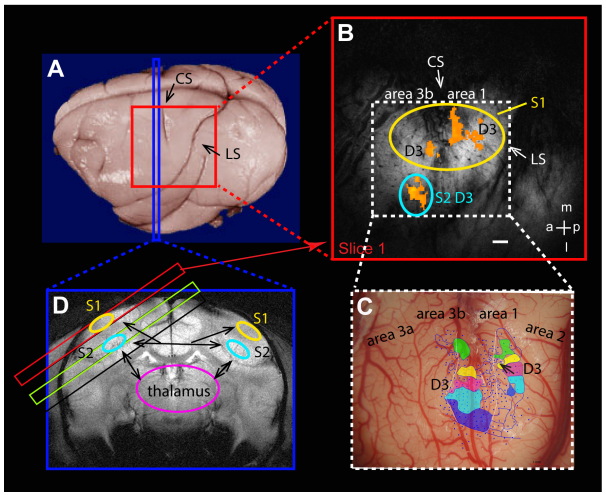






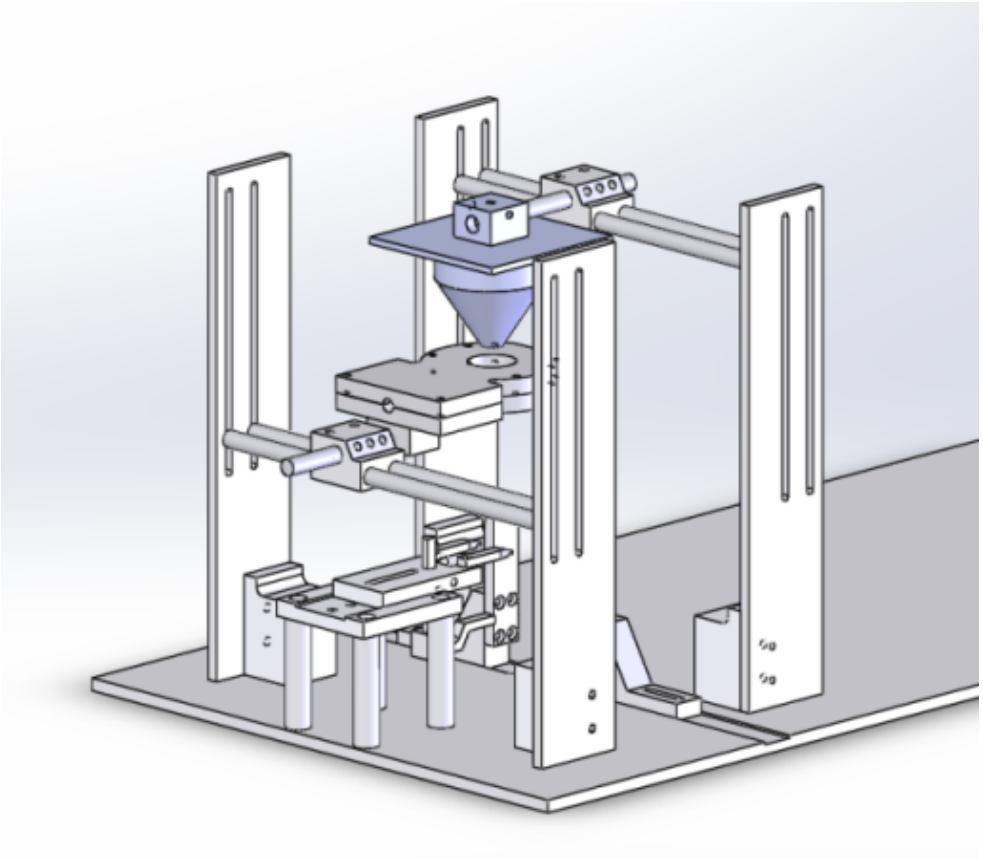


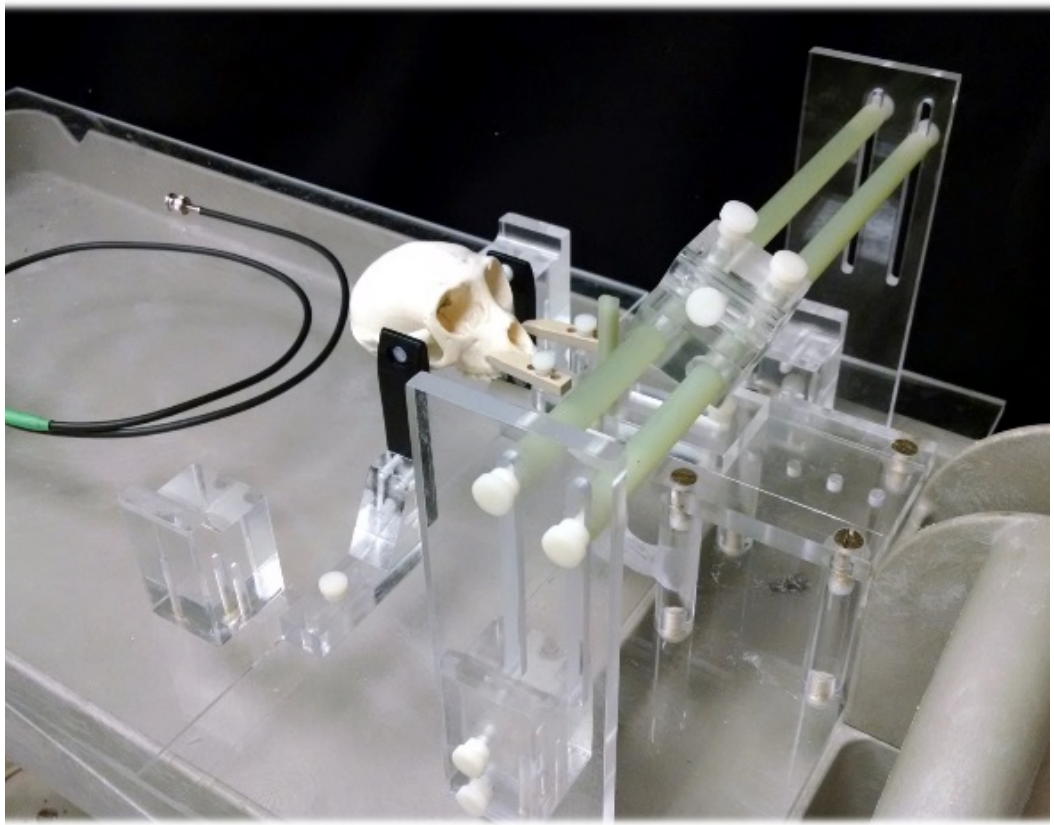




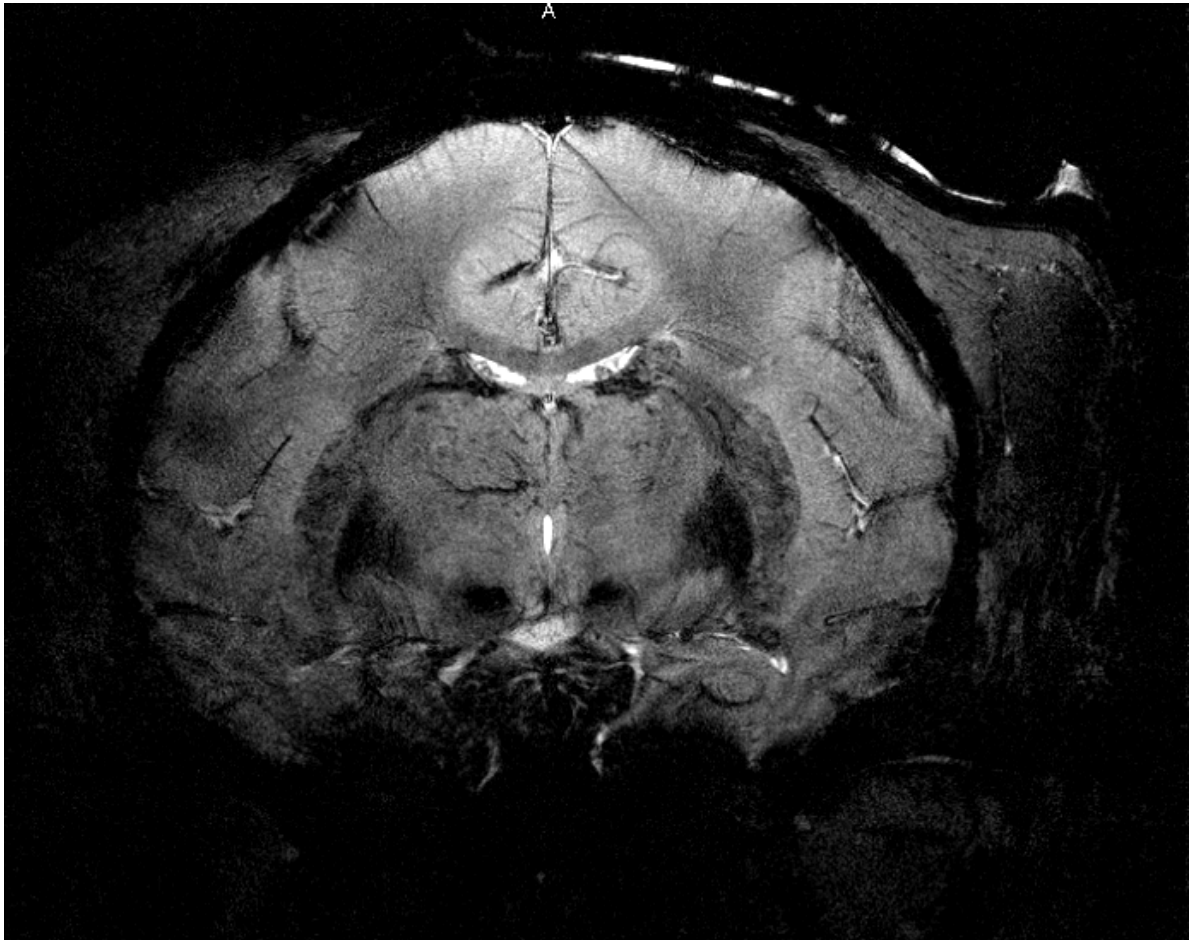
Network-level imaging with focal neuromodulation

Integrating into MRI





High quality images



Surface coil

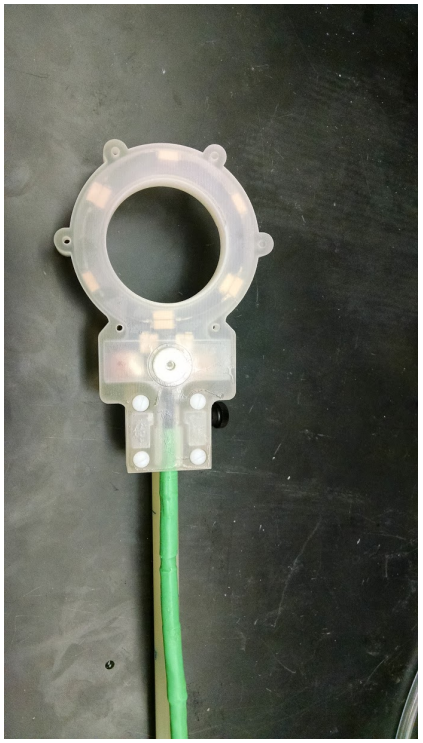
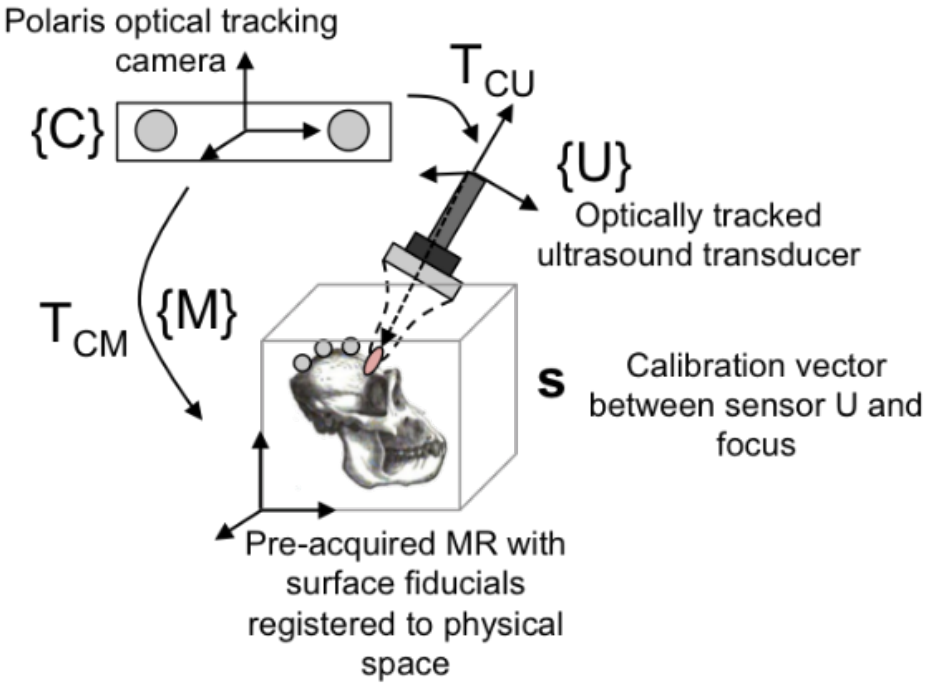
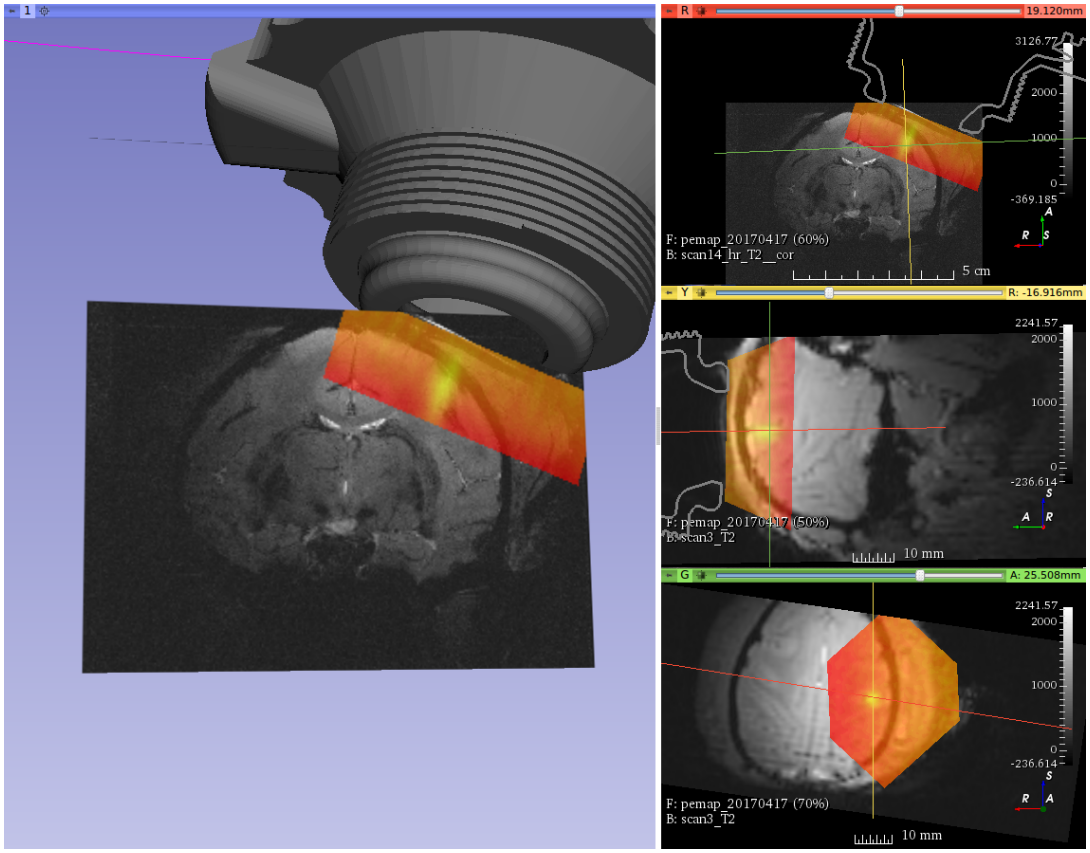


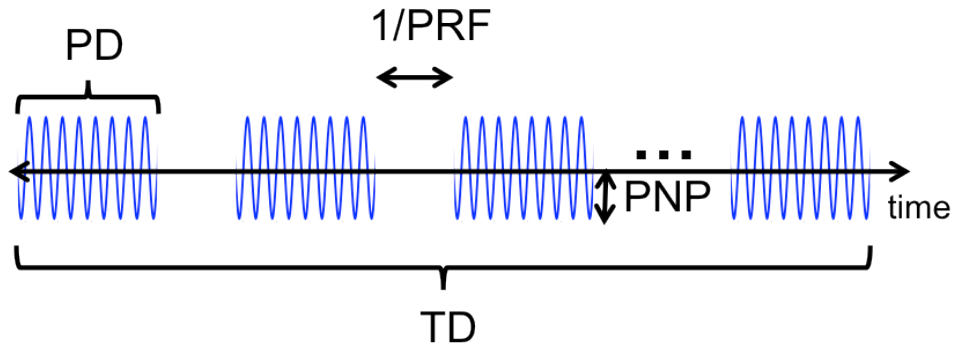
Image-guidance for placing probe

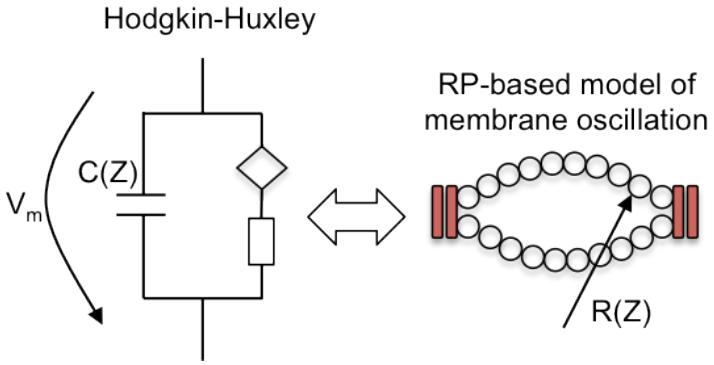


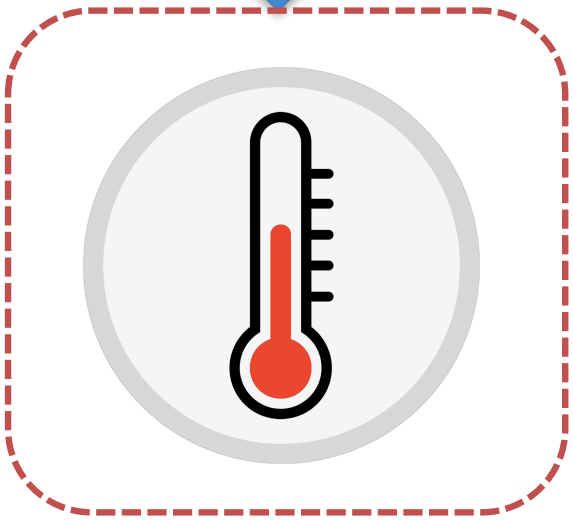


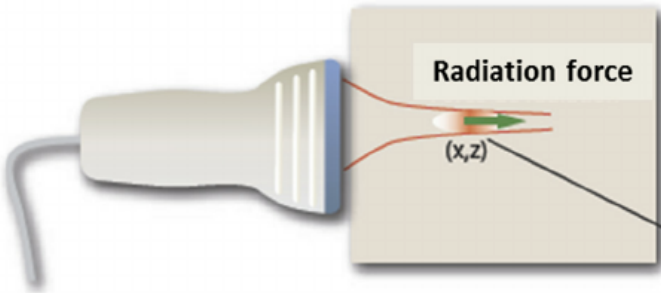
Chaplin, V, et al. "Development of an Optically-guided System for Transcranial Ultrasound Neuromodulation." **FUS Foundation 2016**

Mechanisms visible with MRI

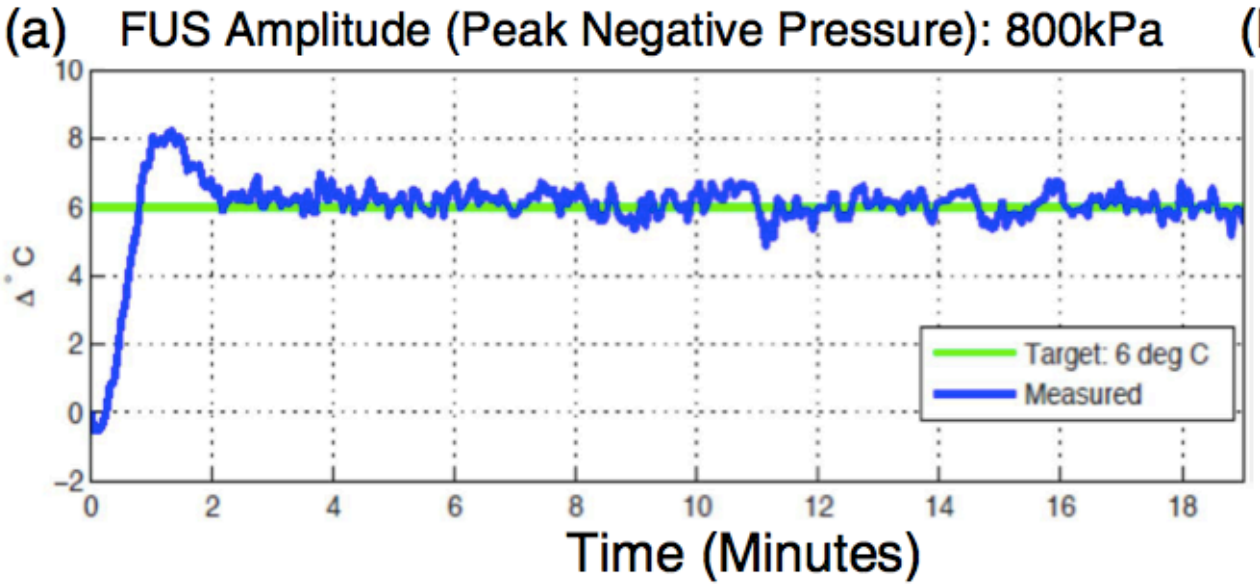


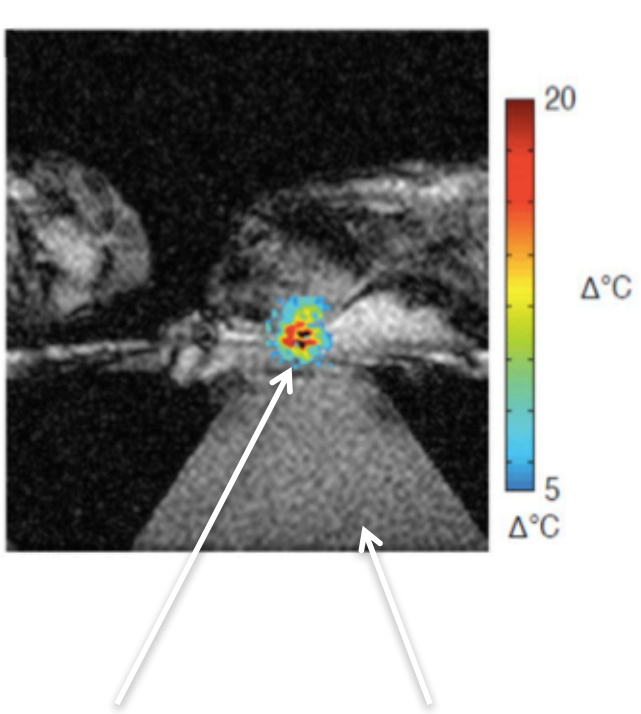






Tracking heat with MRI



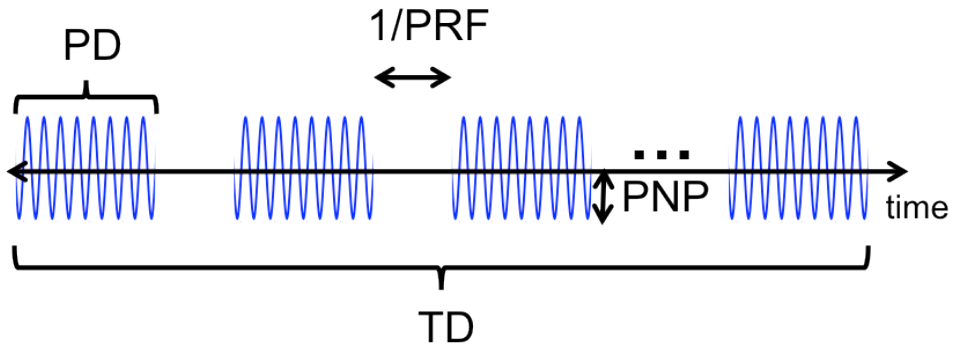


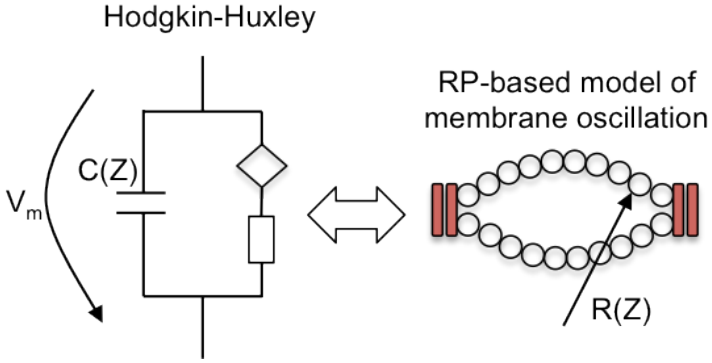
Focal heating

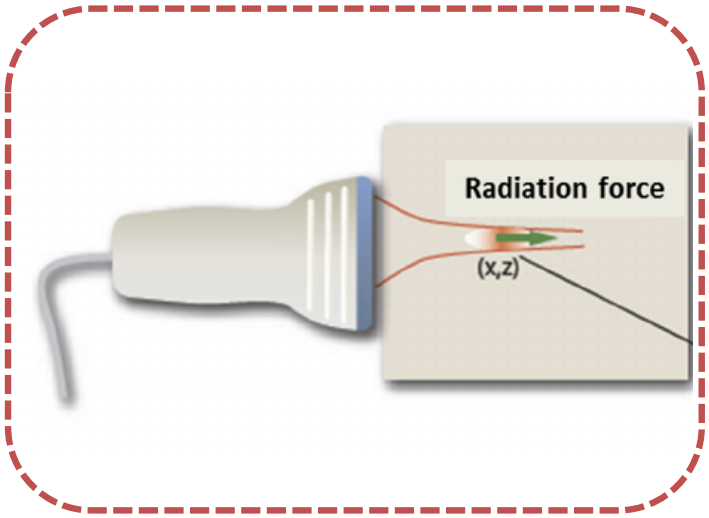
Transducer with coupling cone

Poorman, et al. “Open-source, small-animal magnetic resonance-guided focused ultrasound system,” Journal of Therapeutic Ultrasound (2016) 4:22

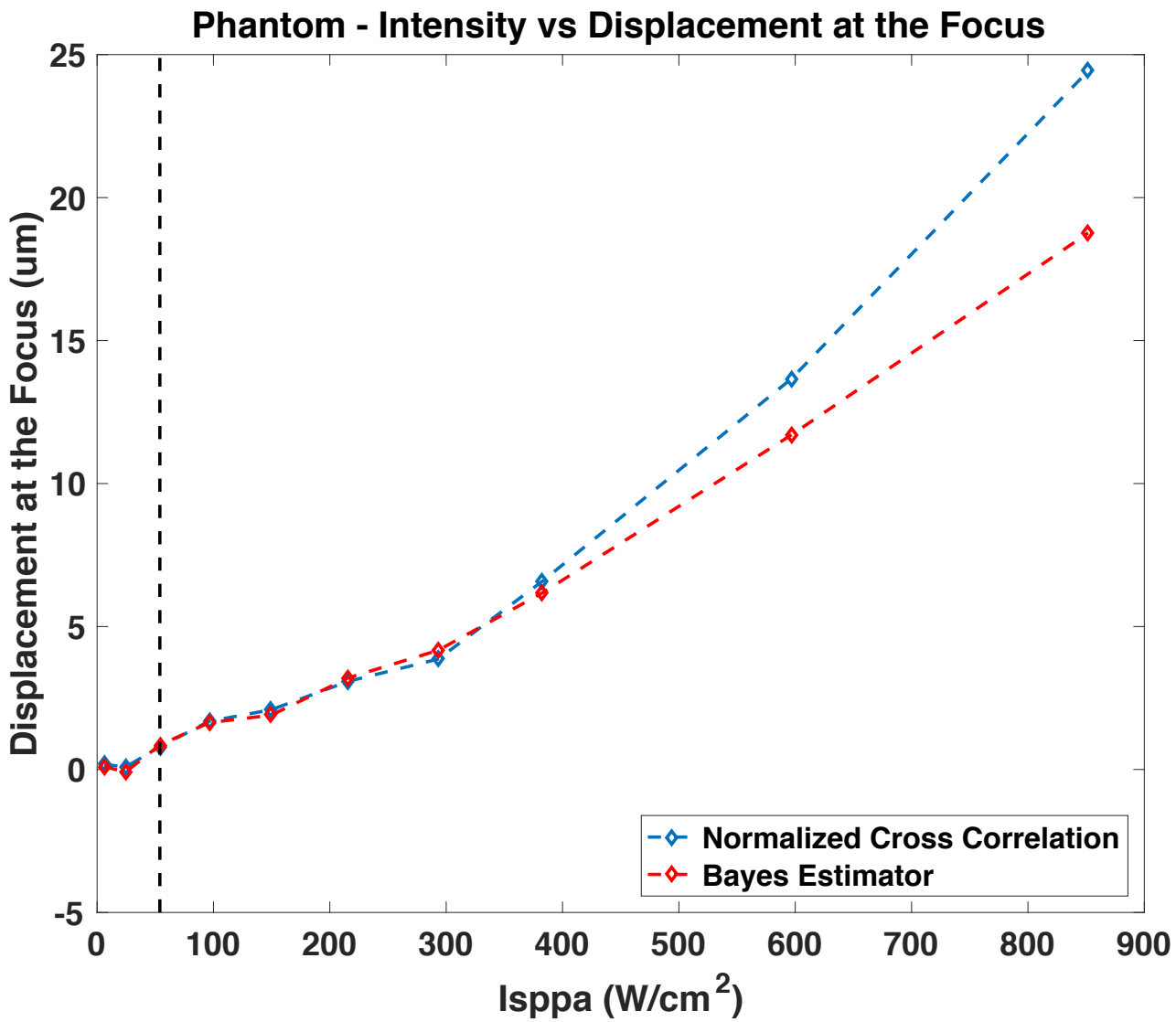
Mechanisms visible with MRI



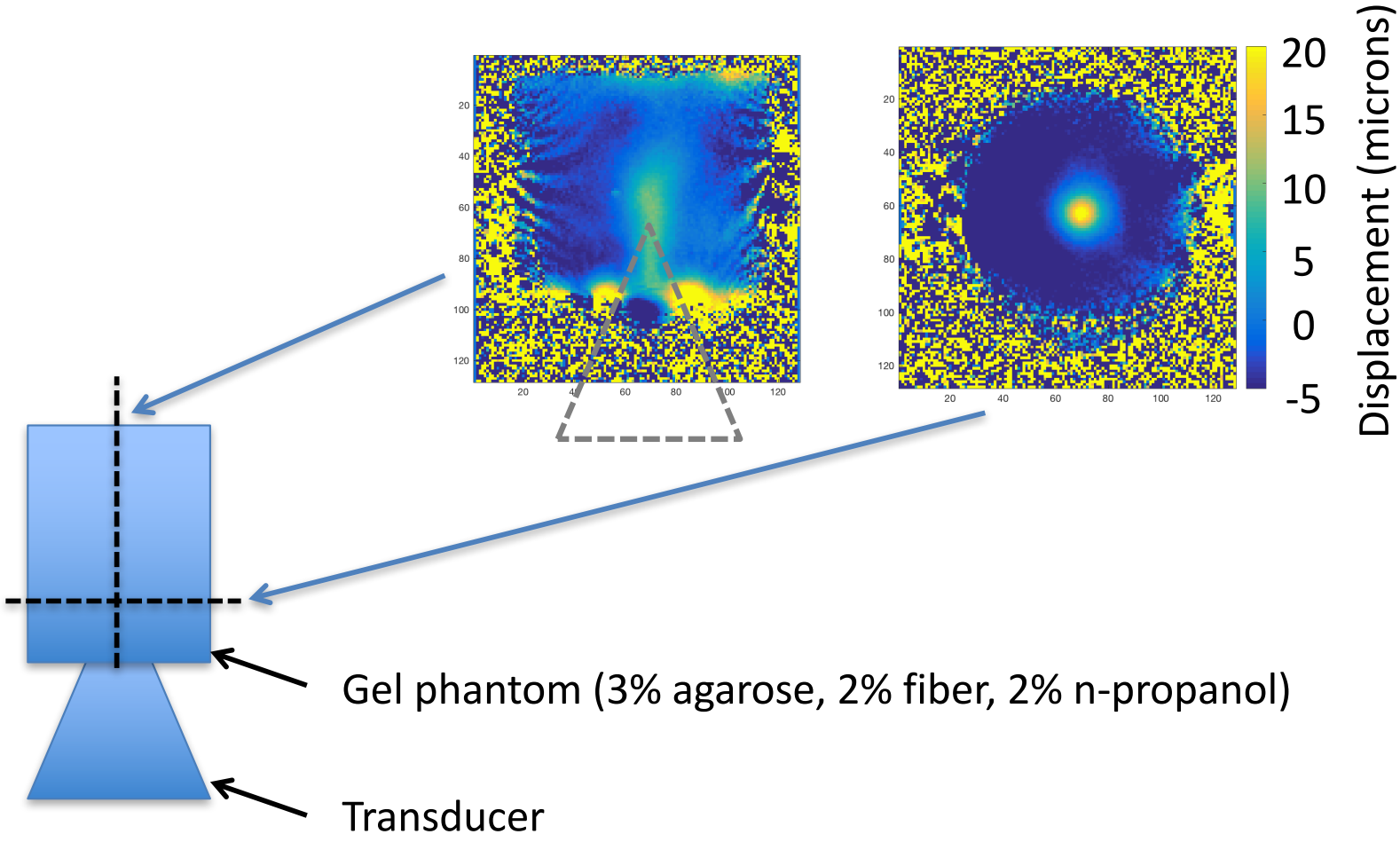




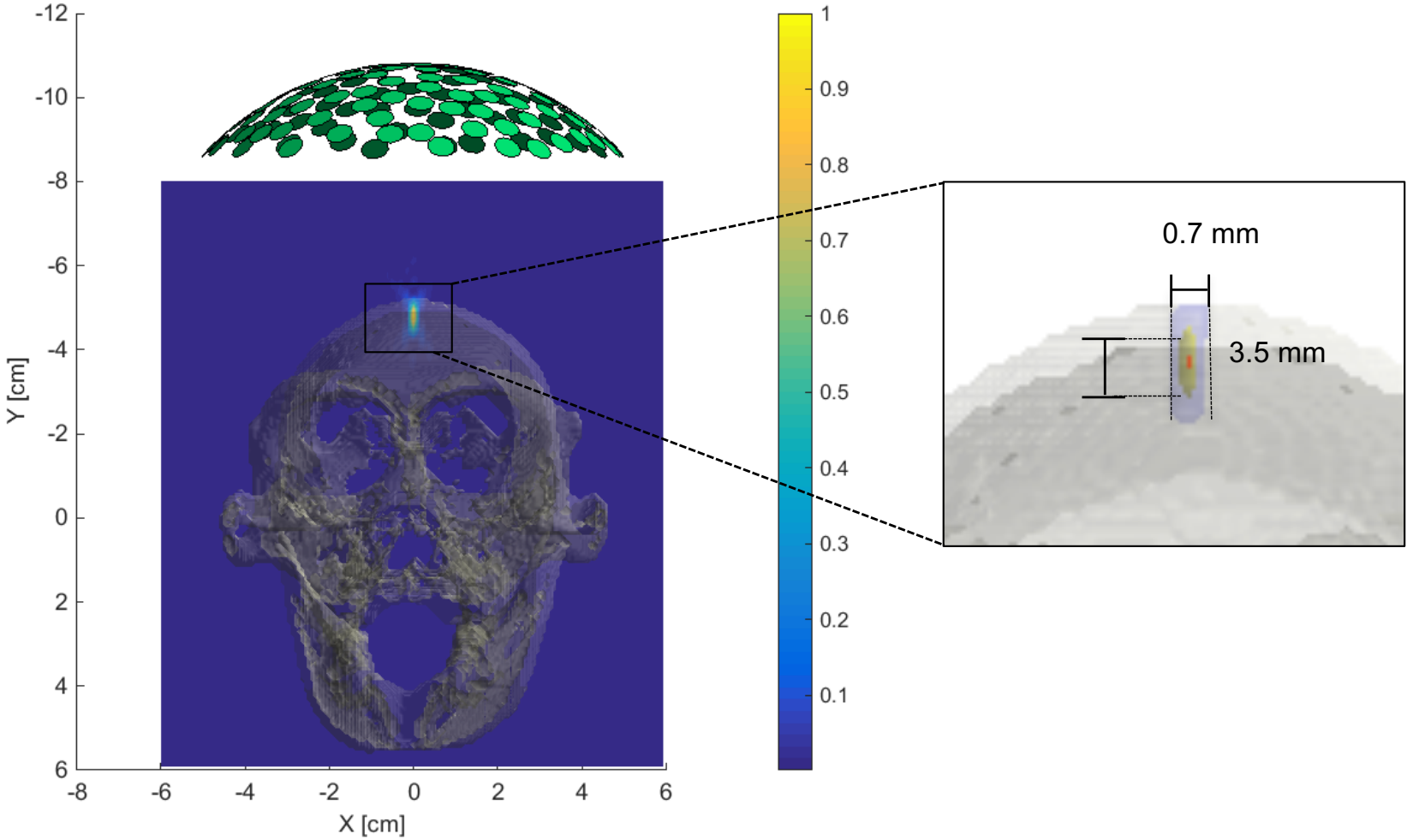
Displacement at safe pressures



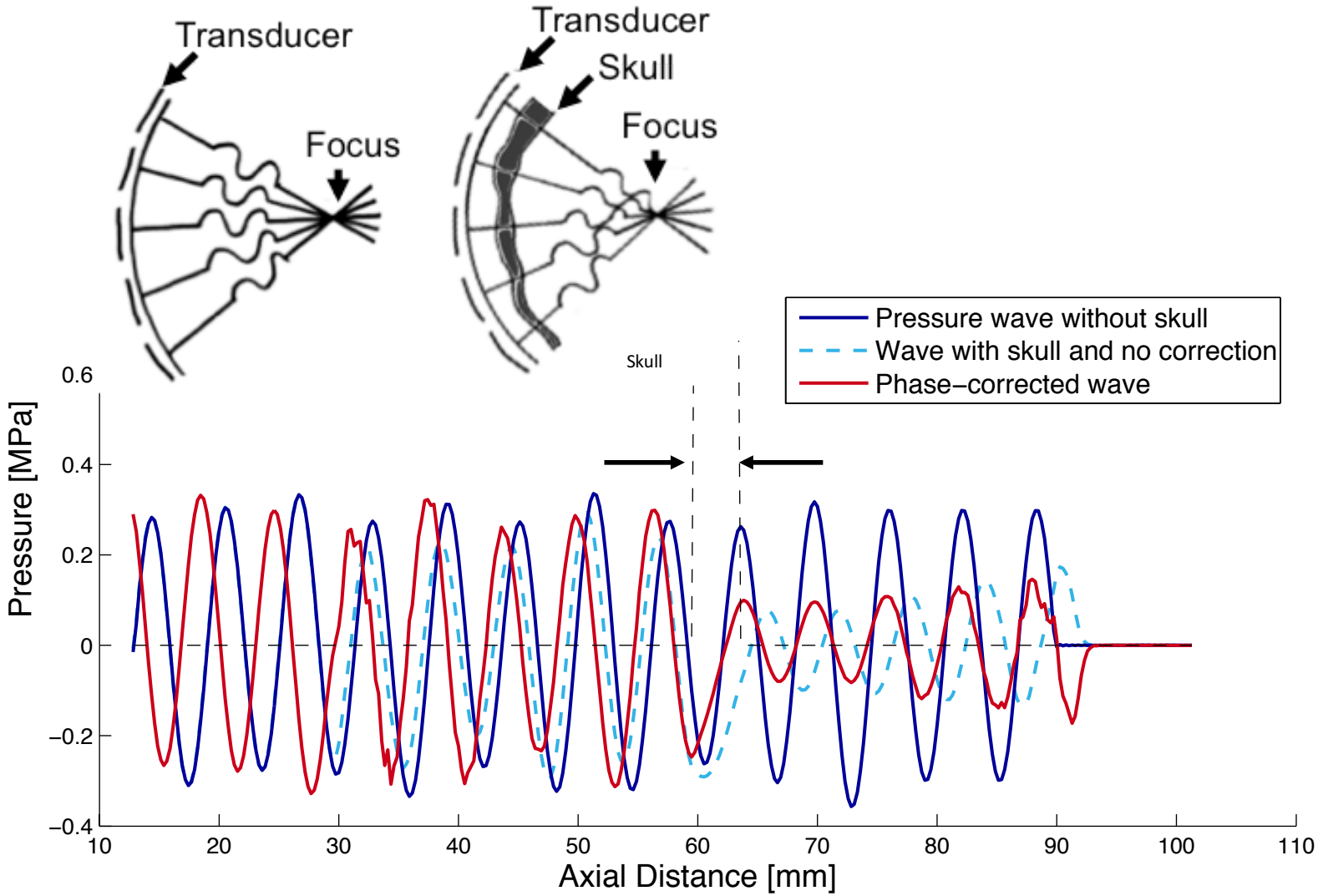
Imaging radiation force in phantom



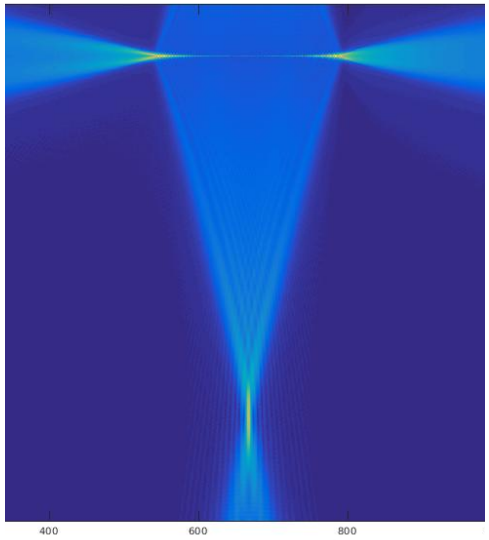
Array-based ultrasound



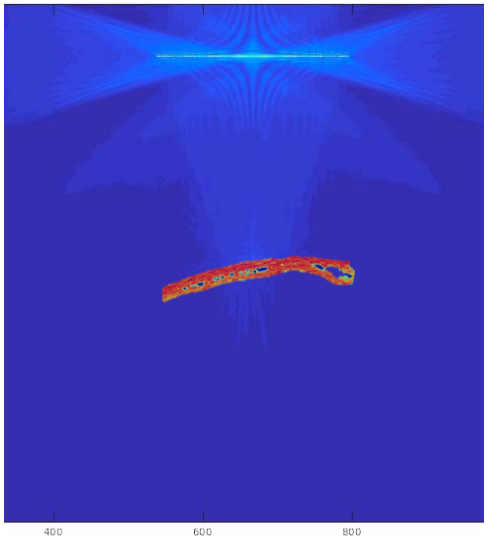
Aberration Correction



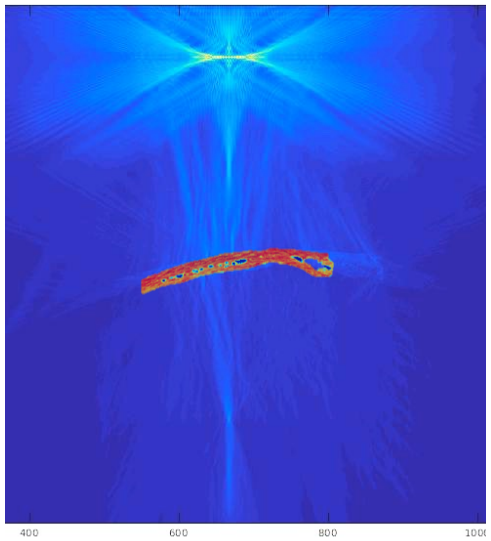
Time reversal implemented in simulations



Native focus



Skull present, no applied delays



Skull present, time reversal delays applied

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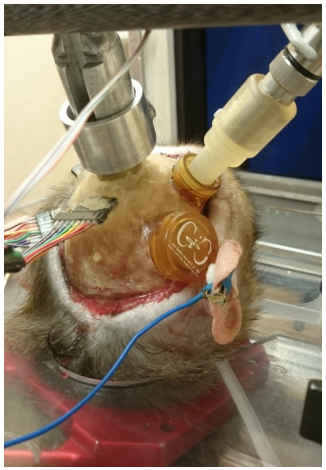
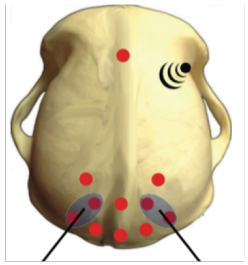
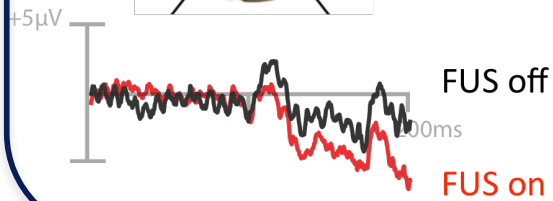
Ultrasound neuromodulation

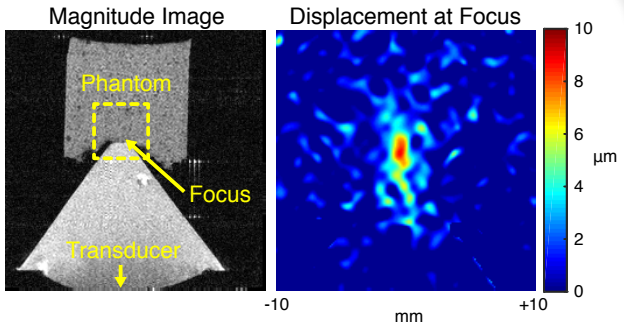
Perform under MR guidance

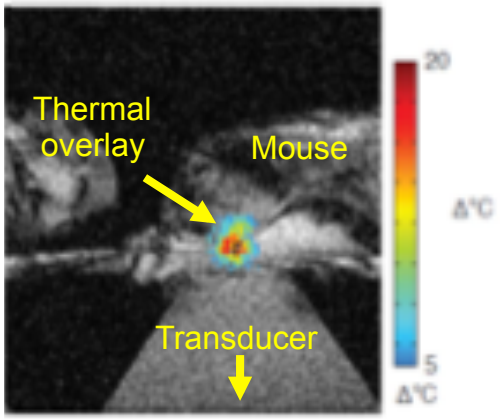
Couple to functional MRI

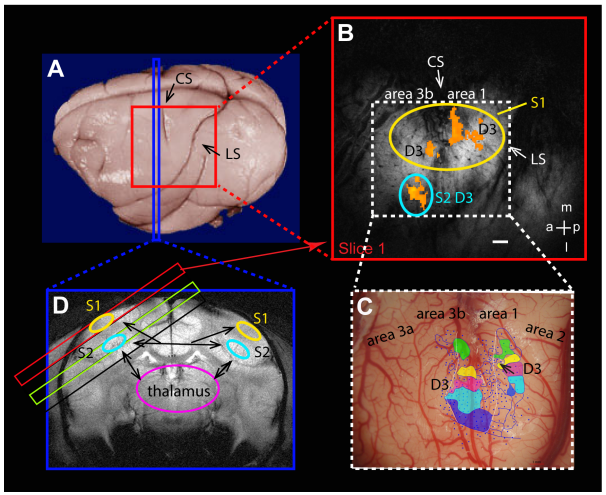








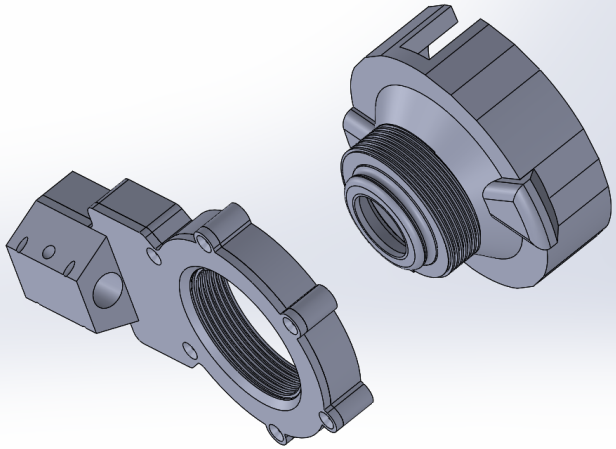




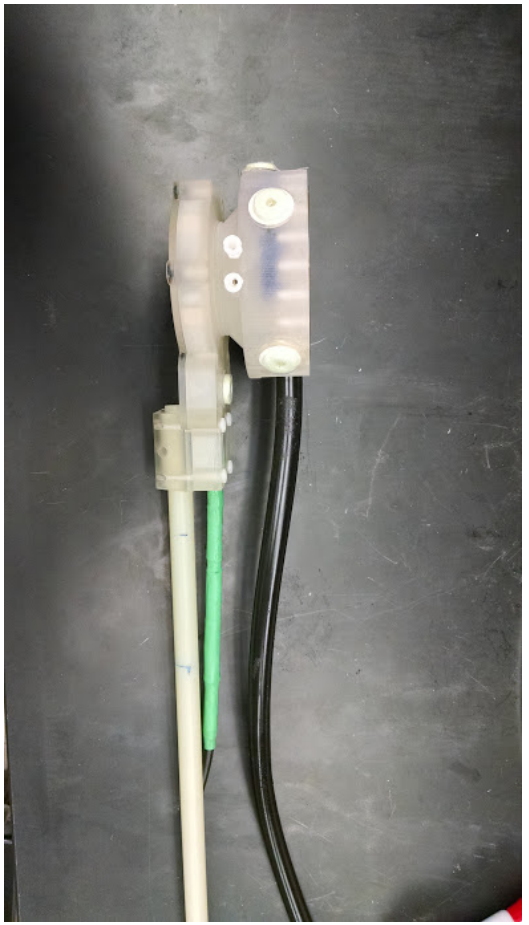
Network-level imaging with focal neuromodulation

Acoustic coupling + shimming

Transducer coupling cone

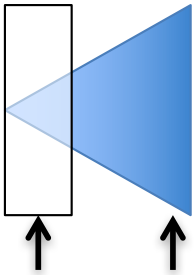


Surface coil



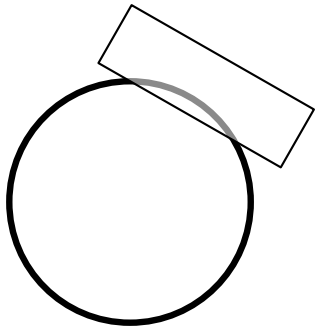
Parts adjoined for combined imaging and neuromodulation

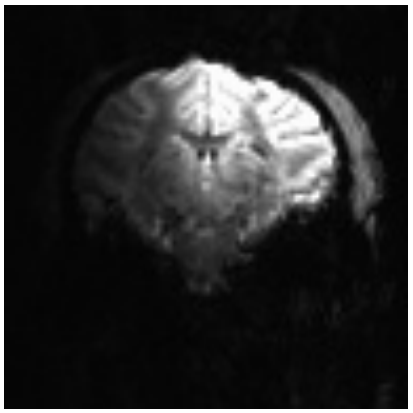
Schematic representation



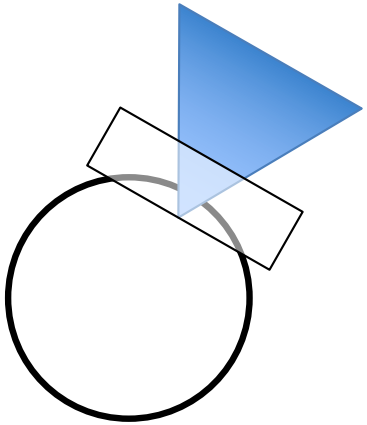
EPI in presence of ultrasound

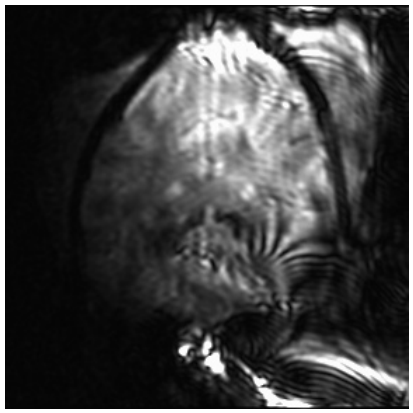
No ultrasound



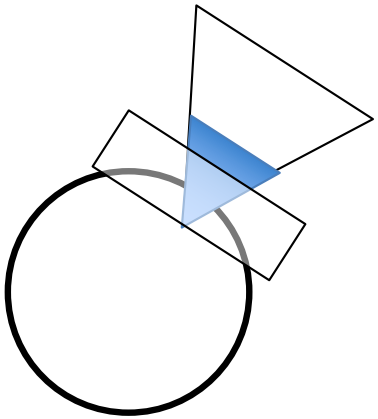


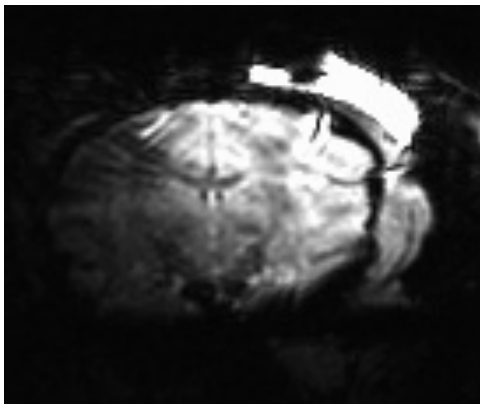
Water-filled



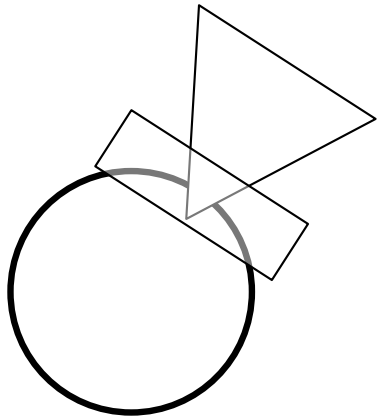


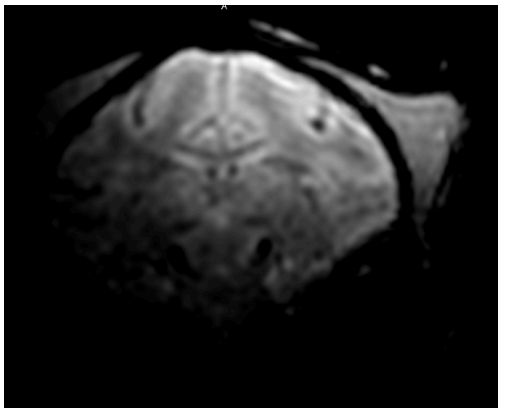
Gd-doped cone





Fomblin-filled

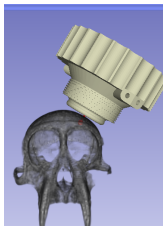




FUS Stimulation

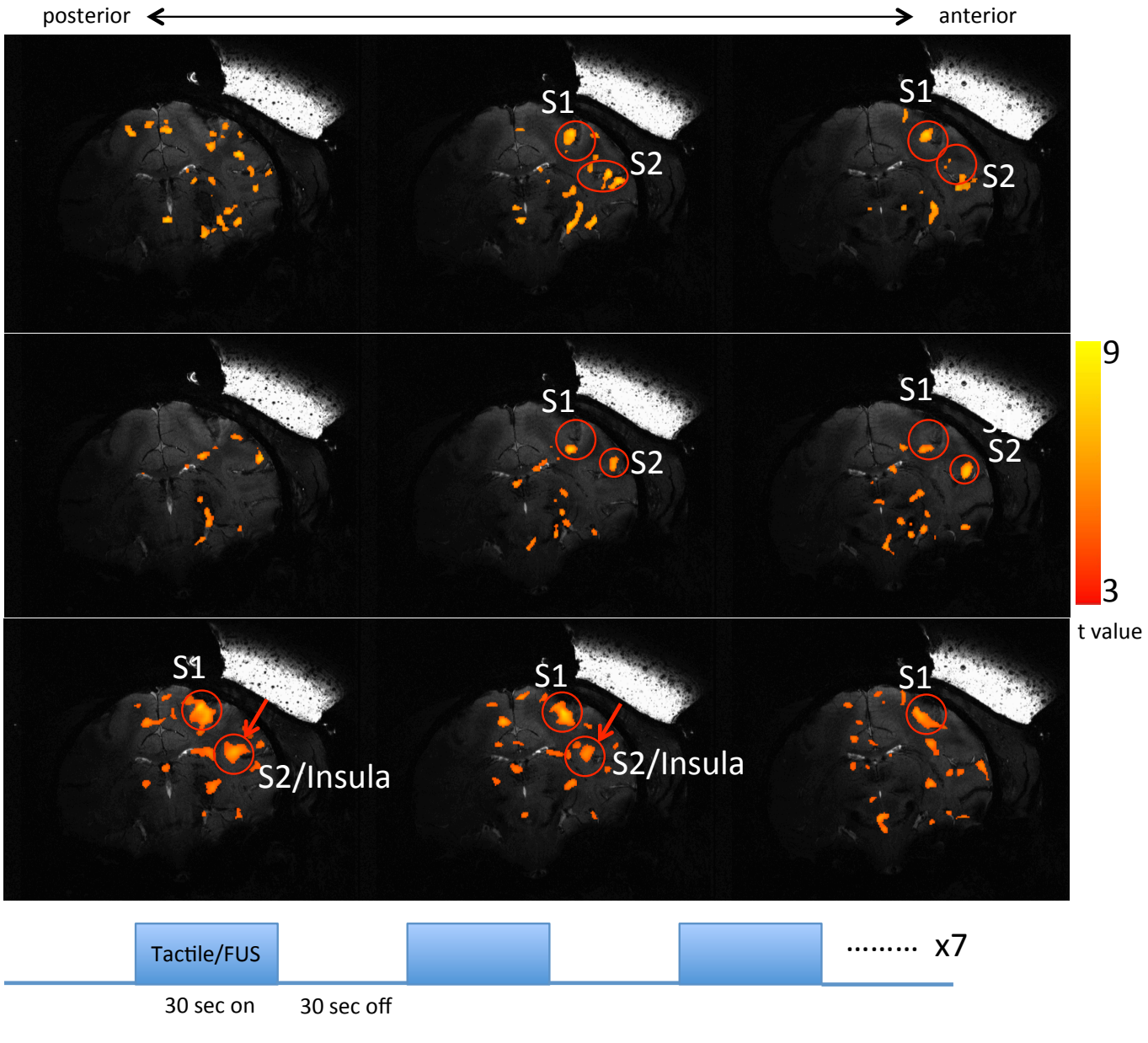
Tactile stimulation (D2&D3) Run 1

Tactile stimulation (D2&D3) Run 2



FUS

P<0.001 (corrected)

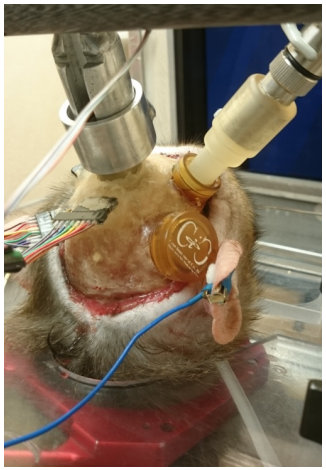


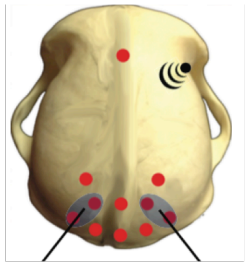
Combined neuromodulation and imaging

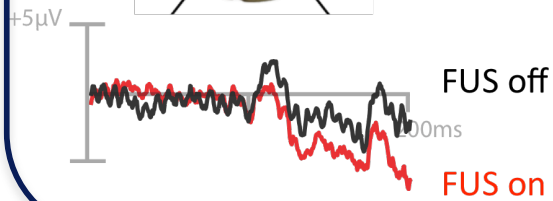
Ultrasound neuromodulation

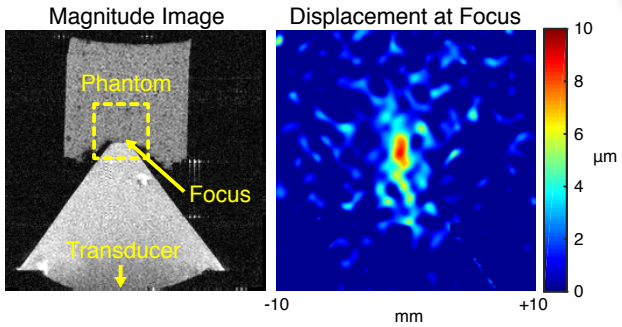
Perform under MR guidance

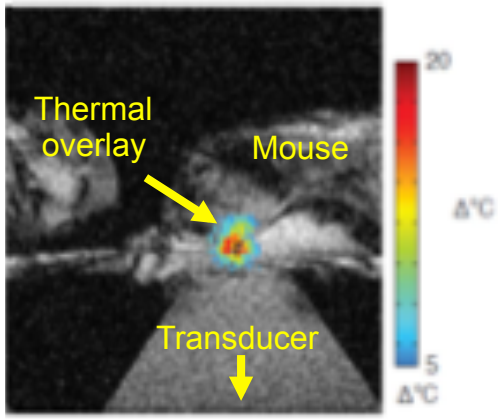
Couple to functional MRI

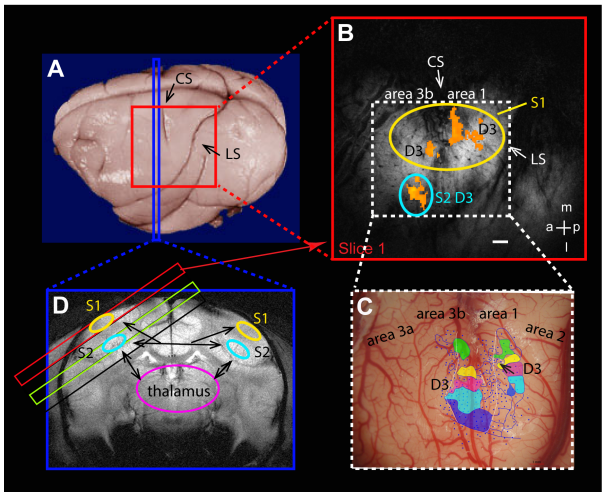












Network-level imaging with focal neuromodulation

Acknowledgments

Vanderbilt / VUMC

– John Gore
– Limin Chen
– Jeffrey Schall
– VUIIS

Acoustics lab

– Vandiver Chaplin
– Tony Phipps
– Jiro Kusunose
– Patricia Twilley

This study was funded by **the Focused Ultrasound Foundation** and **NIH R24 MH109105.**