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STANFORD MEDICINE

Tissue safety study of non-ablative focused ultrasound in large animals

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SCIT seminar

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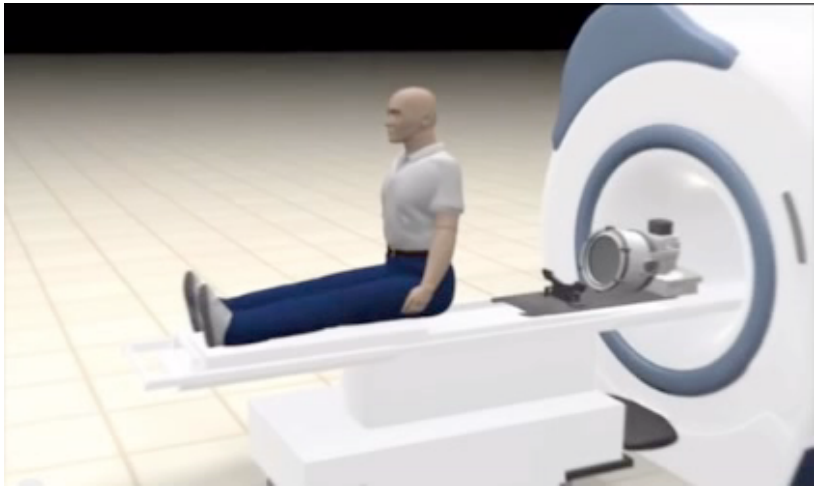
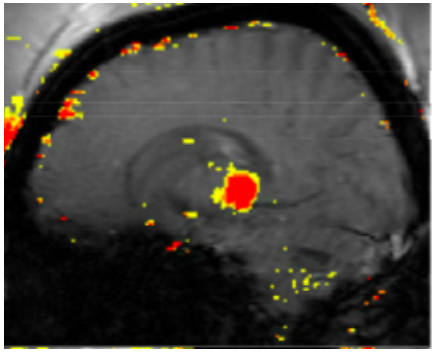
July 31, 2019

MRI-guided focused ultrasound (FUS)



www.insightec.com

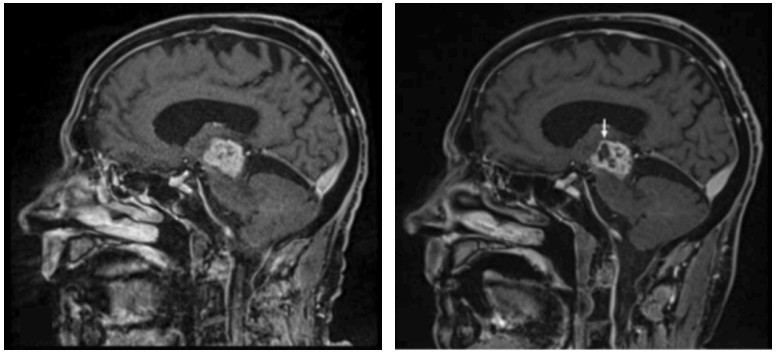
MRI treatment monitoring



Rieke et al., JMRI 2013

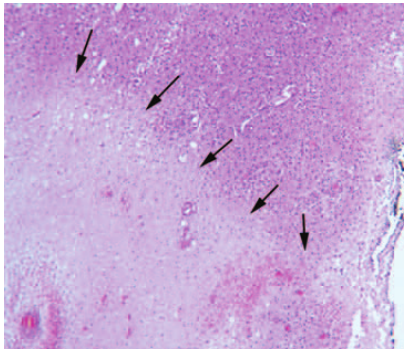
Before treatment

After treatment



Coluccia et al., J Ther Ultrasound 2014

Resected tumor shows necrosis



Ram et al., Neurosurgery 2006

Blood-brain barrier opening enables delivery of large drug molecules to brain

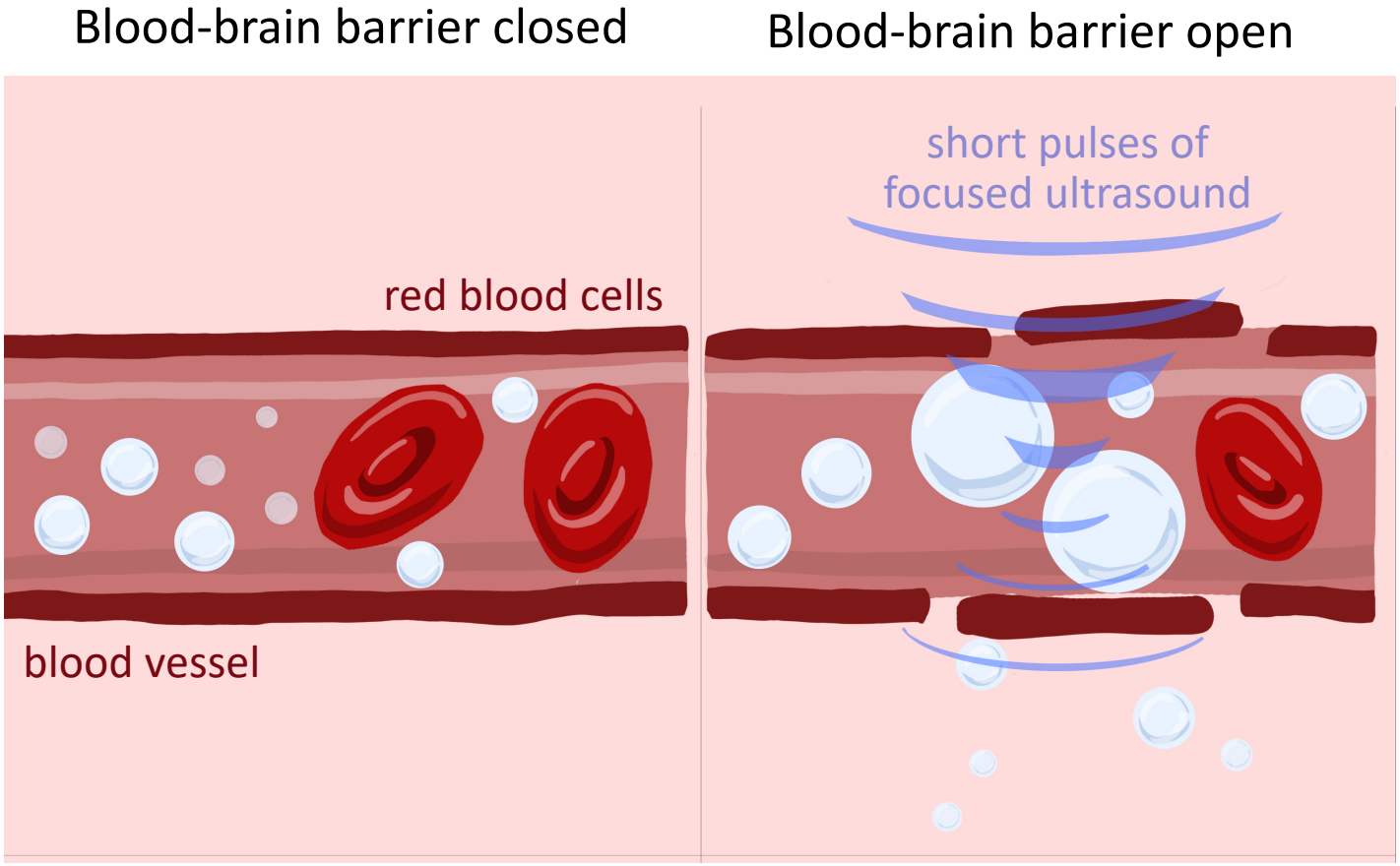


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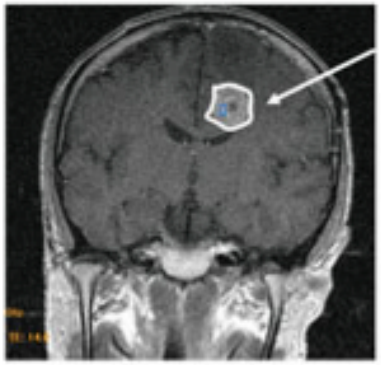
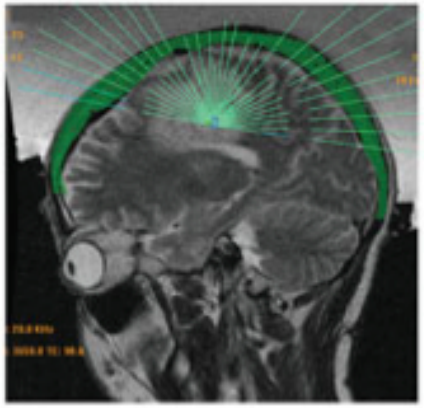
Illustration credit: Sarah Hwang

Ablative and non-ablative FUS can be combined

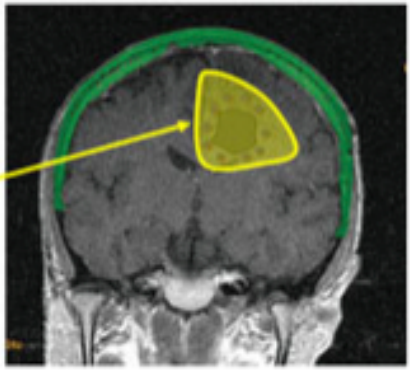
Tumor volume



Noninvasive tumor ablation



Blood-brain barrier opening for adjuvant chemotherapy



Mar 2014 First noninvasive thermal ablation of a brain tumor with MR-guided focused ultrasound

Nov 2015 World first: blood-brain barrier opened non-invasively to deliver chemotherapy

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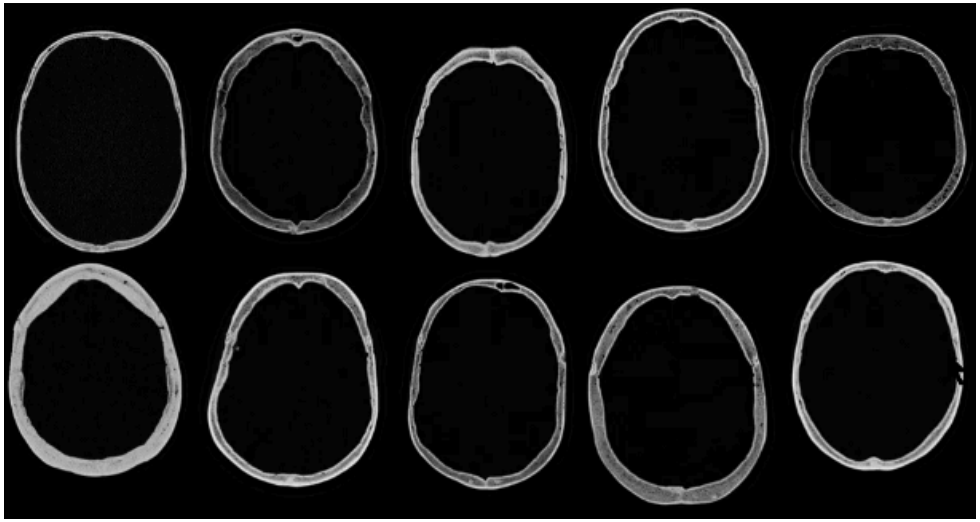
Figure adapted from Martin et al., Curr Radiol Rep 2013

Challenges with applying FUS through the skull

Skull characteristics vary from person to person



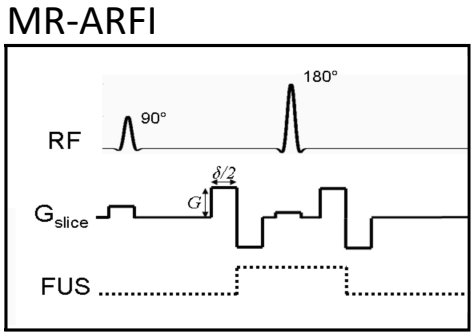
Leung et al., Scientific Reports 2019

Skull varies in shape, thickness, composition, and can distort ultrasound beam

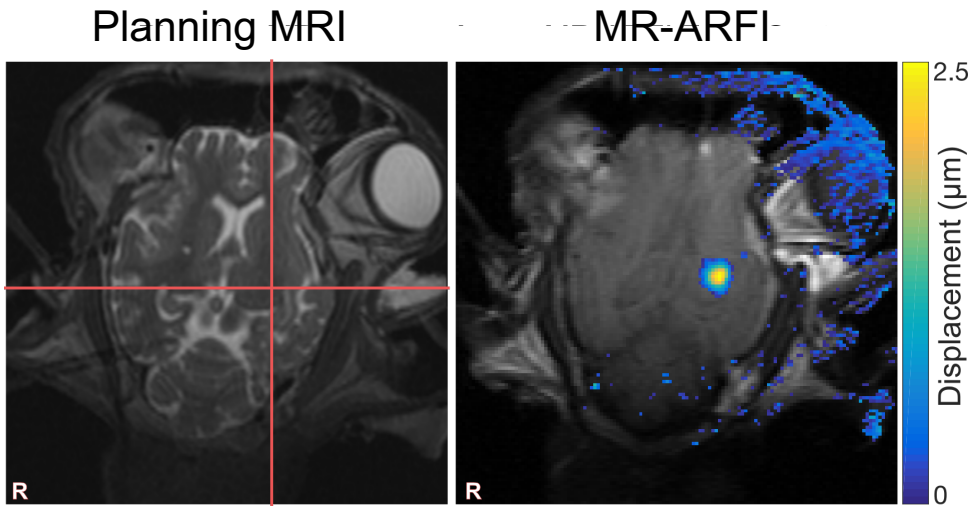
→ errors in focal spot position and intensity

Visualize focal spot in brain using MR acoustic radiation force imaging (ARFI)

We can image tissue displacement at the focal spot by synchronizing MRI motion encoding gradients with focused ultrasound



Kaye et al., ISMRM 2010



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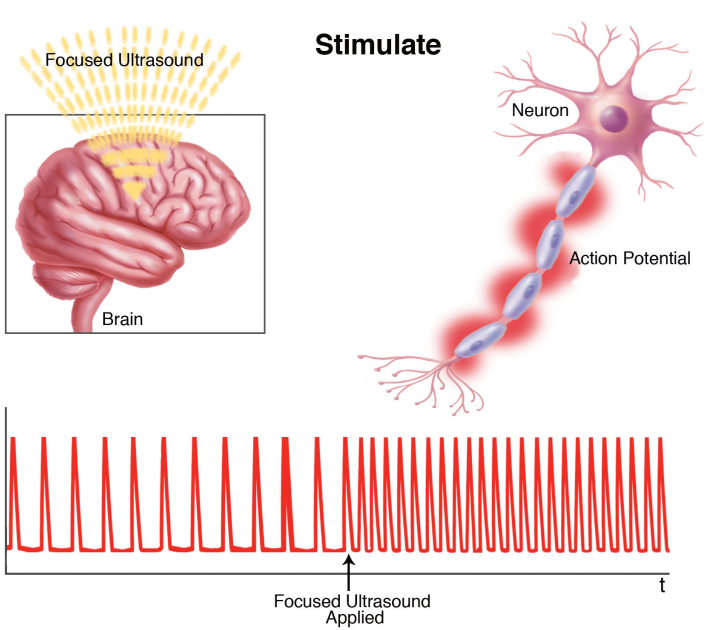
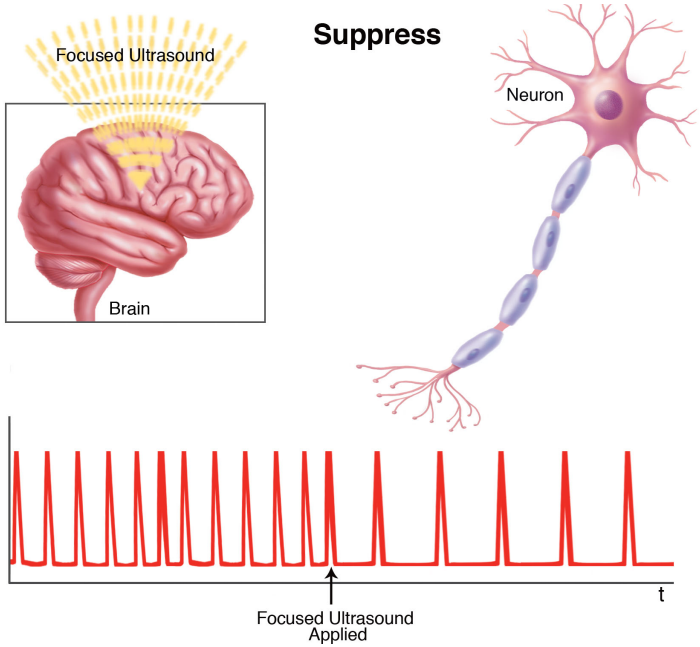
Neuromodulation can excite/inhibit neural circuits





Emerging applications: are they safe?

Magnetic Resonance Acoustic Radiation Force Imaging (MR-ARFI)

- Has not been used clinically
- Almost no reports of tissue safety

Neuromodulation

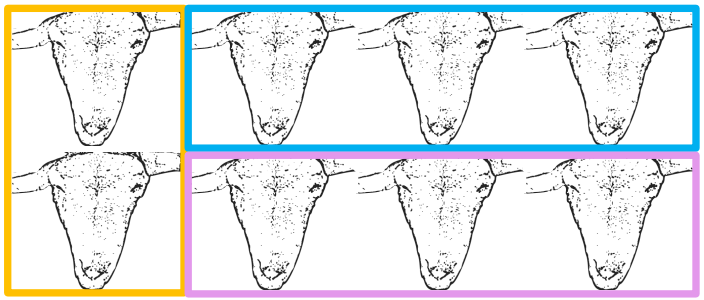
- Use in humans is growing
- Inconsistent reports of tissue safety

Both are thought to be reversible (non tissue damaging)

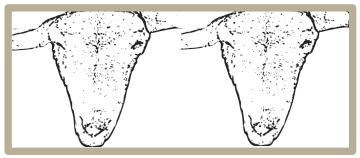
To study this, we evaluate histological findings in sheep with MR-ARFI and neuromodulation, and in controls without FUS.

Safety study: methods

FUS



Control



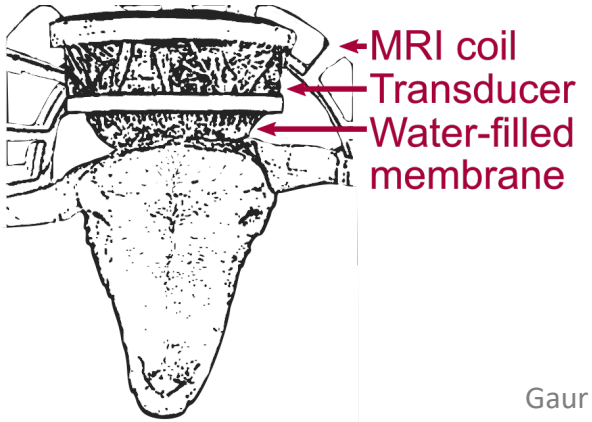
- **acute** (euthanized 0 days after FUS),
- **delayed** (euthanized 4-7 days after FUS),
- **repeated** (treated again 3-6 days after the previous FUS session, and euthanized 4 days later)

- **control** (MRI and anesthesia, no FUS)

Transducer array

550 kHz
1024 elements

Setup



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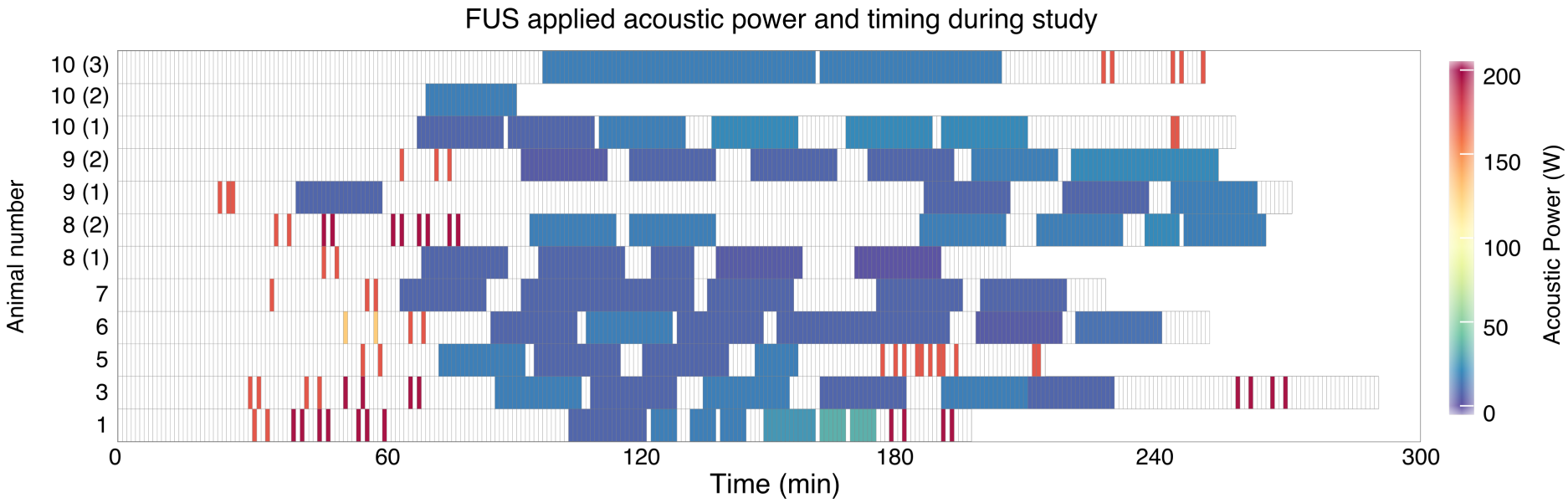
Gaur et al., in revision

We tested repeated applications of focused ultrasound



Both MR-ARFI and neuromodulation use a series of short FUS pulses. Neuromodulation typically has a higher number of pulses at lower intensity.

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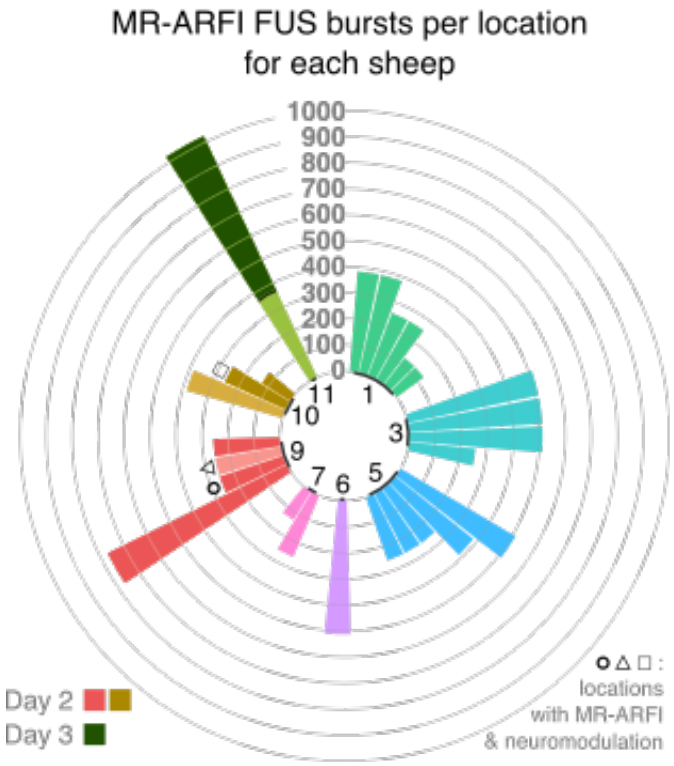
Gaur et al., in revision

We applied varying numbers of FUS pulses at targeted locations



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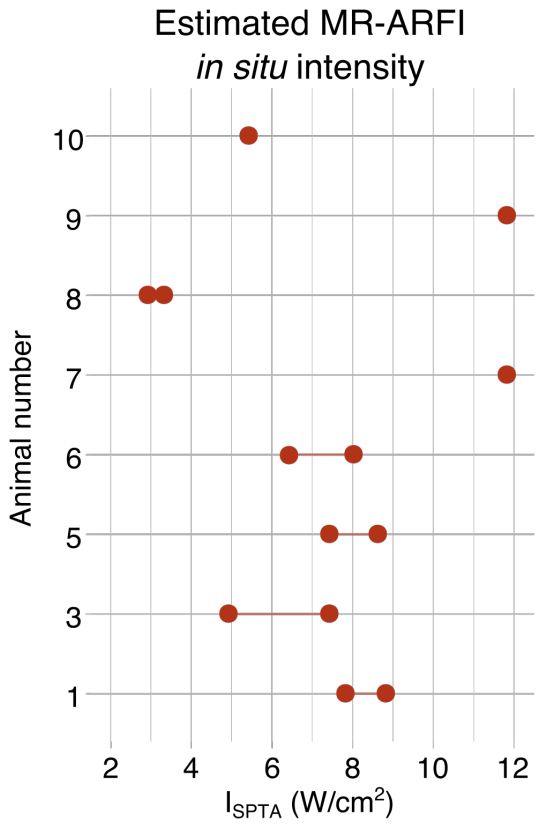
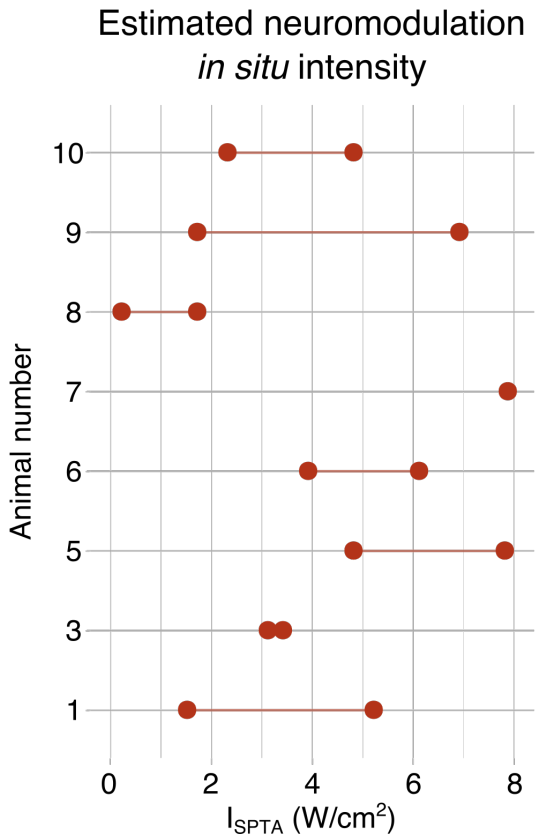
Gaur et al., in revision

We tested a range of FUS intensity levels across animals





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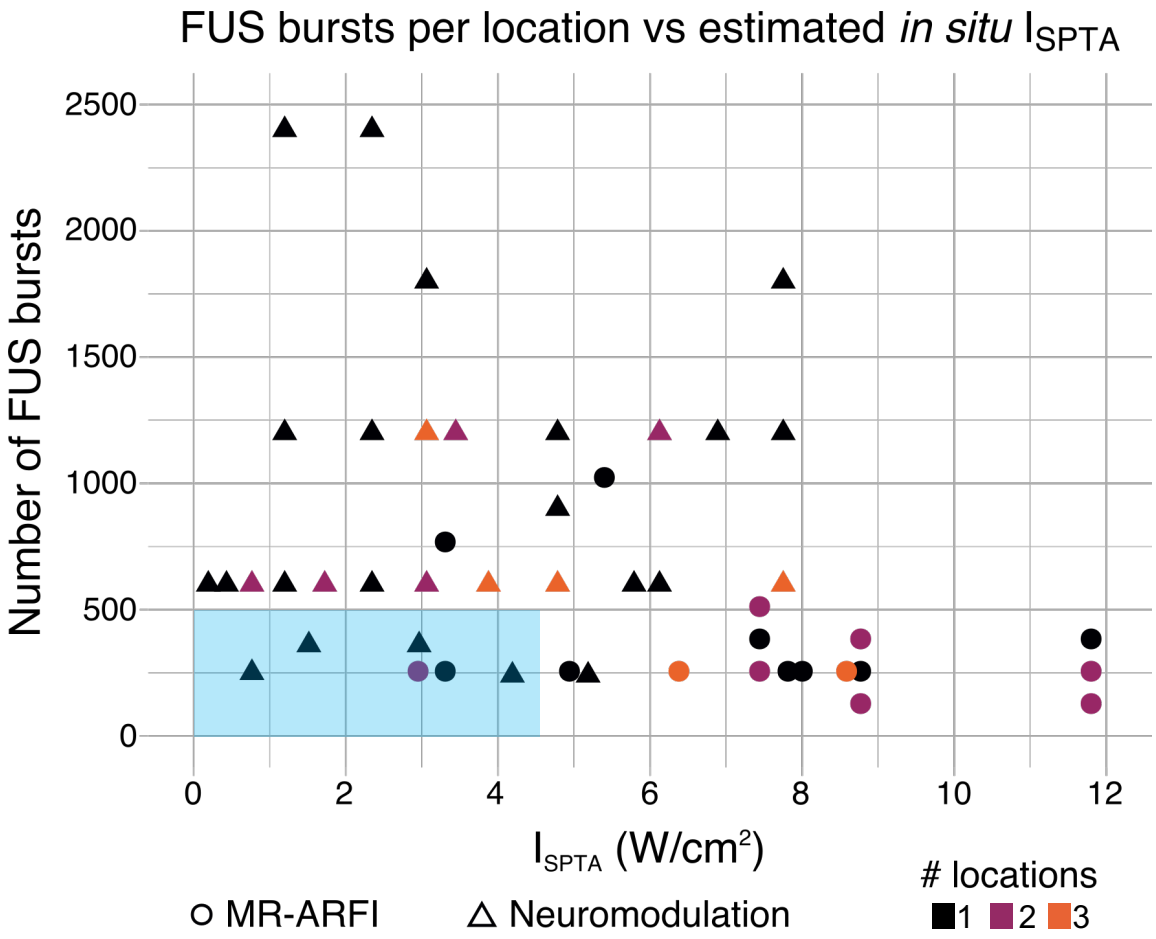
Gaur et al., in revision

We tested a range of FUS intensity levels across targeted locations



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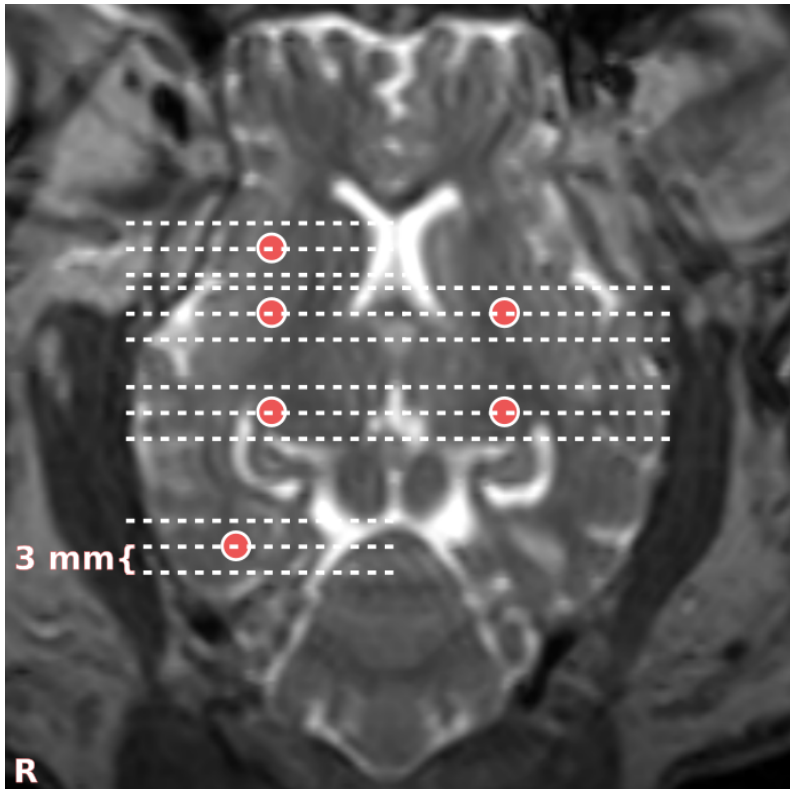
Gaur et al., in revision

We evaluated histology at targeted locations in FUS groups, and similar locations in control groups

Subcortical FUS targets



H&E stained sections (dashed lines) at

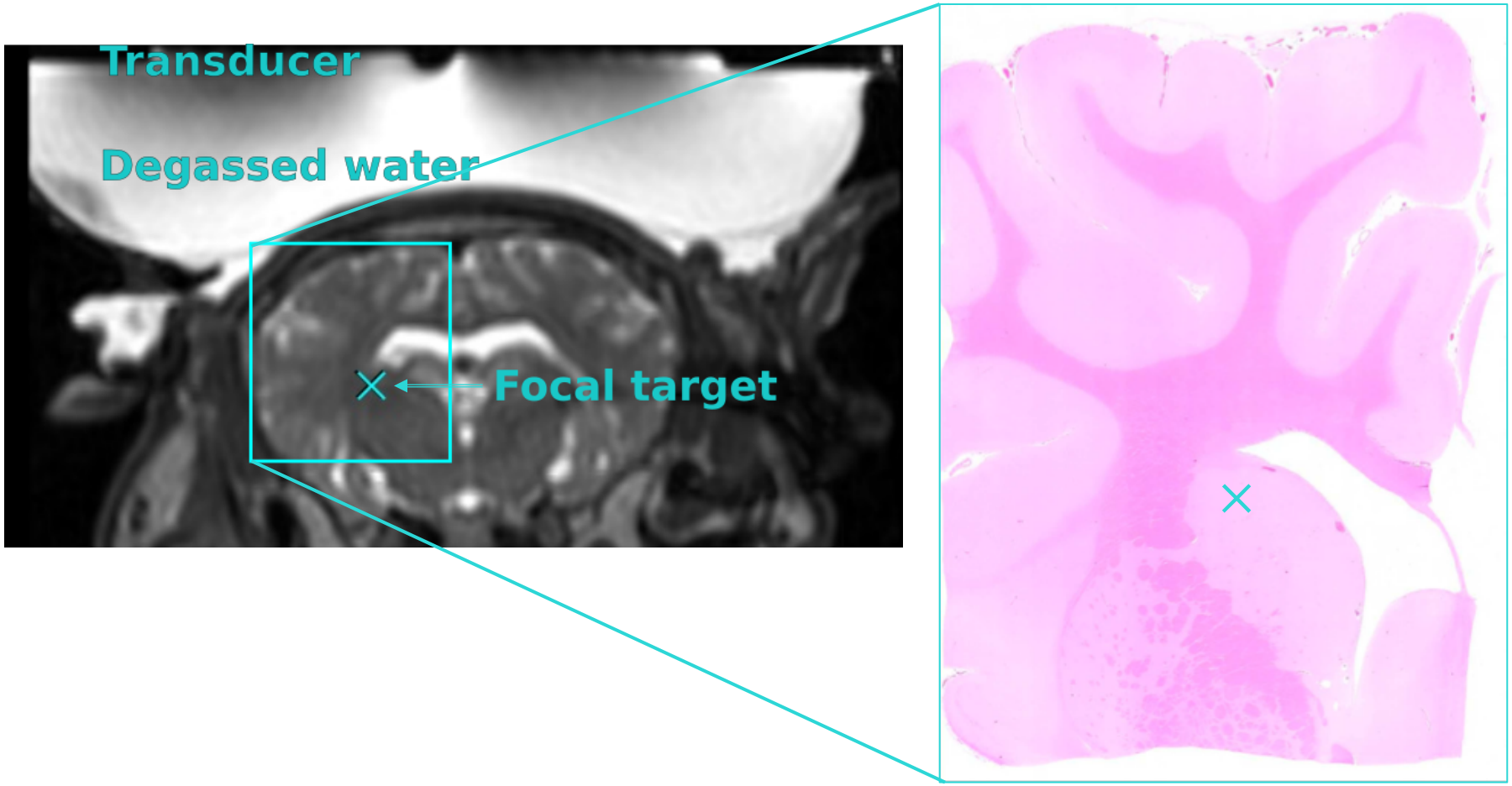
- FUS target (red circles)
- 3 mm rostral
- 3 mm caudal

We looked for signs of tissue reactivity:

- red blood cells beginning <24 hours,
- necrosis beginning <24 hours,
- macrophages >24 hours,
- red blood cell engulfment >48 hours,
- hemosiderin 72-96 hours

Gaur et al., in revision

No abnormal findings in tissue at any focal targets



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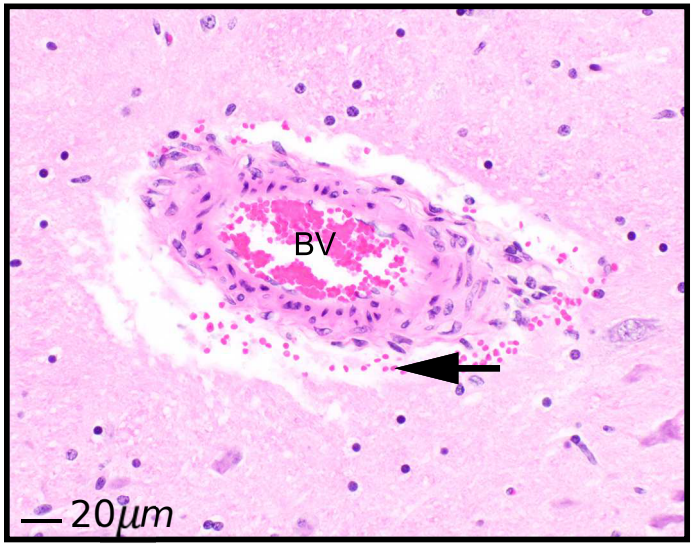
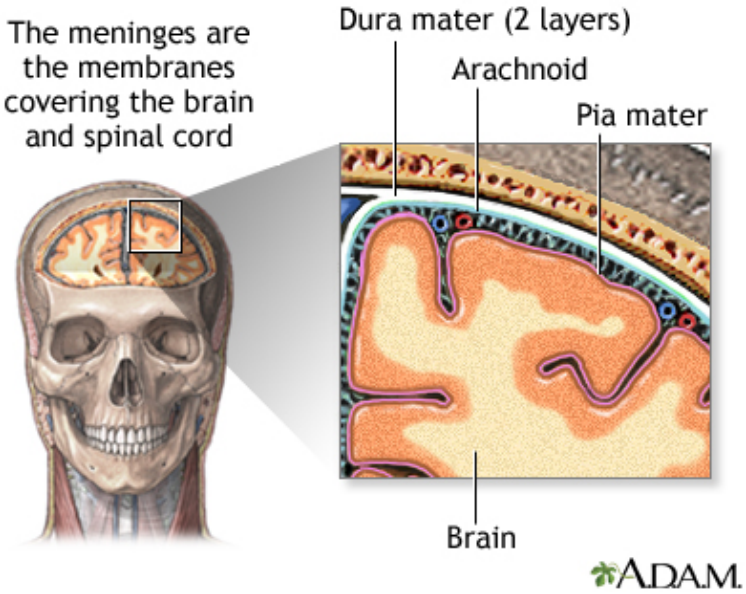
Gaur et al., in revision

Some red blood cell extravasation in tissue locations away from the focal target

Cortical tissue



Meninges

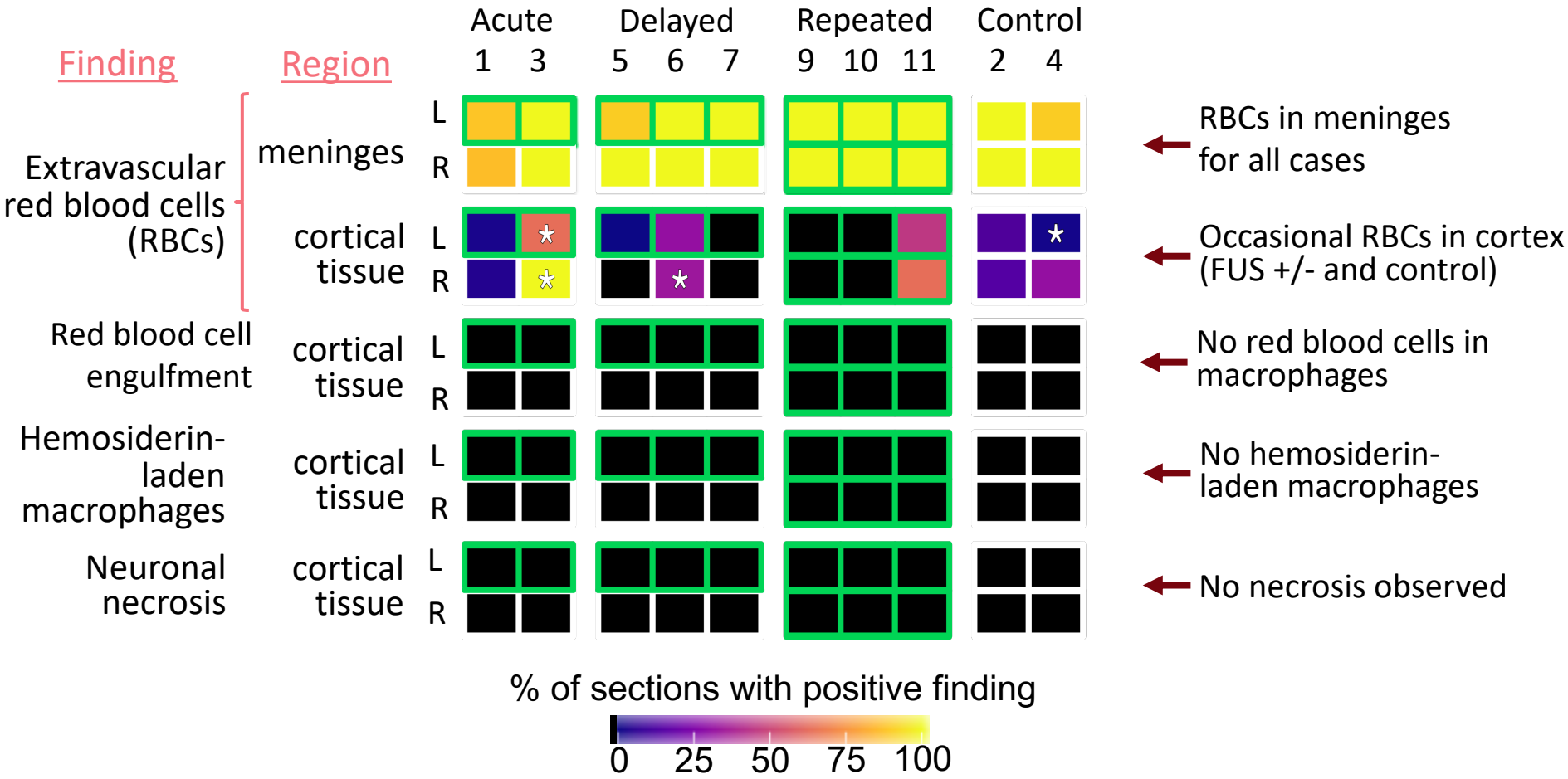


Gaur et al., in revision

Results summary

Summary of histologic findings in tissue sections

No histologic findings observed at sites of FUS targets



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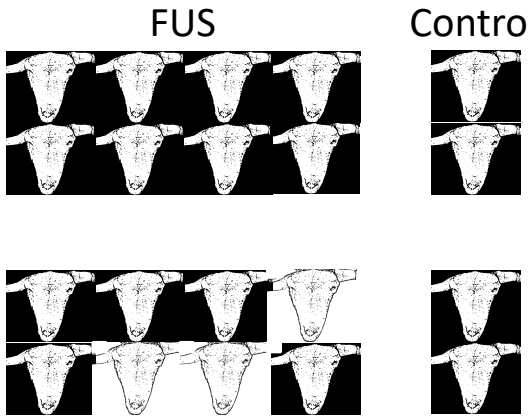
Gaur et al., in revision

Discussion



- **All sheep** had RBC extravasation in the meninges, regardless of FUS application, treated hemisphere, or survival time.
- **Both FUS and control groups** had occasional RBC extravasation in cortical tissue.

Evidence of tissue reactivity in areas of RBC extravasation would distinguish hemorrhage that occurred when the animal was alive from post-mortem artifact.

The absence of concurrent histological lesions, and similarity of findings regardless of FUS application suggests that extravasated red blood cells may be post-mortem artifacts of the brain extraction process.

Our findings suggest MR-ARFI and neuromodulation did not cause tissue damage.

Gaur et al., in revision

Acknowledgements

We thank Gary Glover and Jan Kubanek for help with FUS protocols, Kevin and Karla Epperson for help with MRI, Rachelle Bitton for help with MR-ARFI, Yamil Saenz and Ben Franco for help with experiments, and Elias Godoy for tissue harvesting.

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