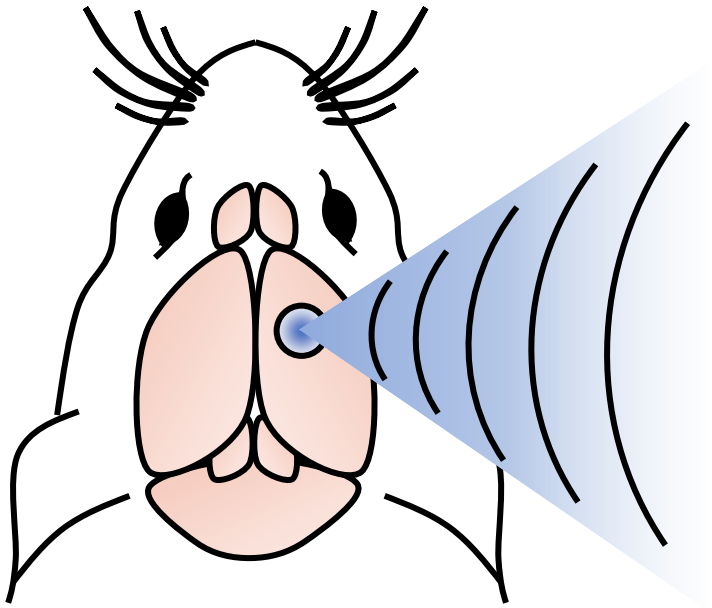
Ultrasound-responsive barbiturate nanodroplets for localized anesthesia across the blood-brain barrier

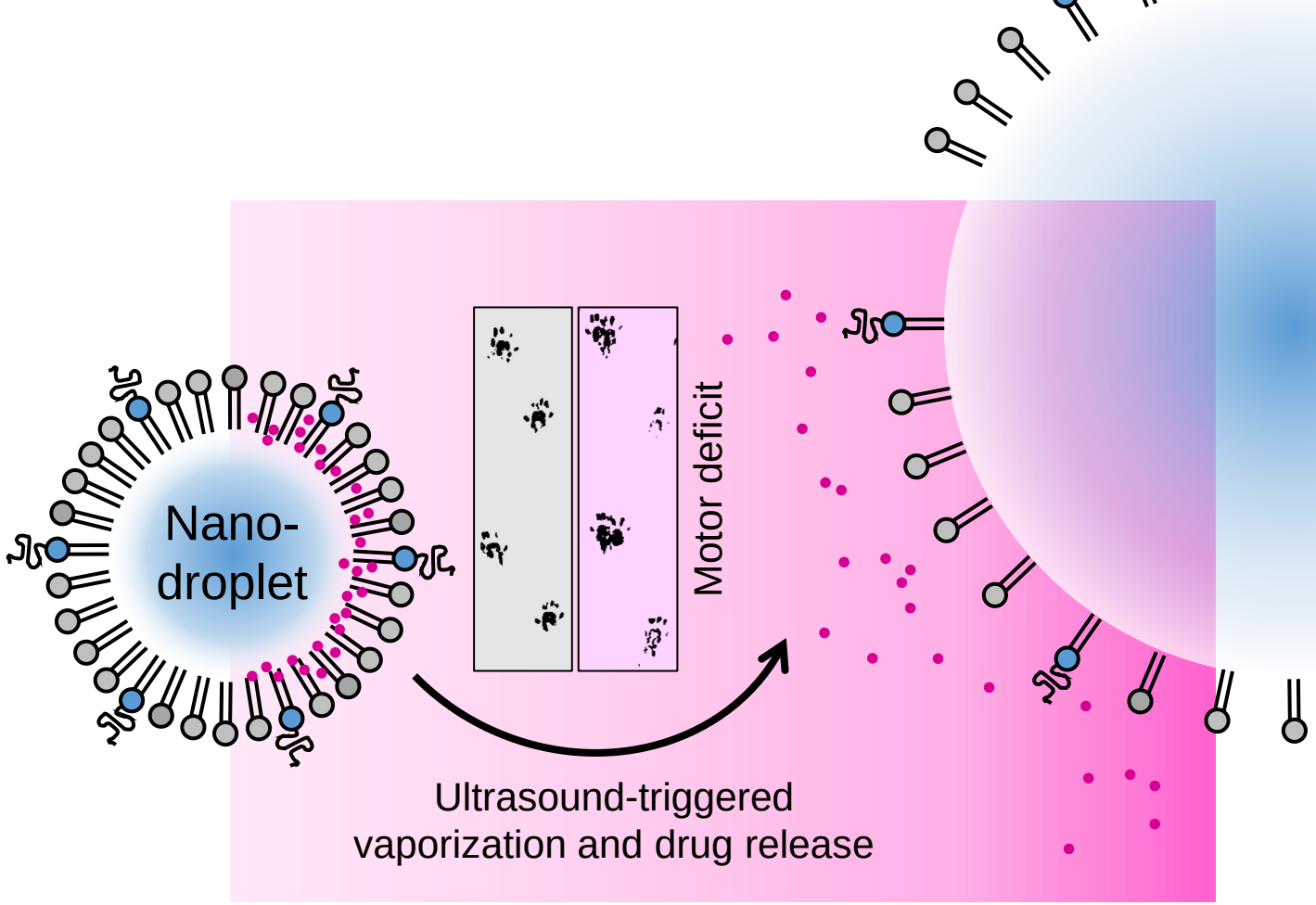
Harriet Lea-Banks[1], Ying Meng[1,2,3], Sheng-Kai Wu[1,2], Clement Hamani[3,4] and Kullervo Hynynen[1,2,5]

[1]Physical Sciences Platform, Sunnybrook Research Institute, Toronto, Canada
[2]Department of Medical Biophysics, University of Toronto, Toronto, Canada
[3]Harquail Centre for Neuromodulation, Sunnybrook Research Institute, University of Toronto, Toronto, Canada
[4]Division of Neurosurgery, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada
[5]Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Canada

CRS 2022 Annual Meeting & Expo
July 11 – 15, 2022 | Montreal Congress Center, Montreal Canada
Advanced Delivery Science

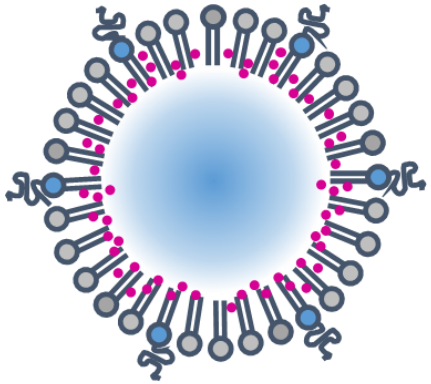
Introduction: Modulating neuronal activity with focused ultrasound (FUS) offers a minimally invasive approach to study and treat the brain.



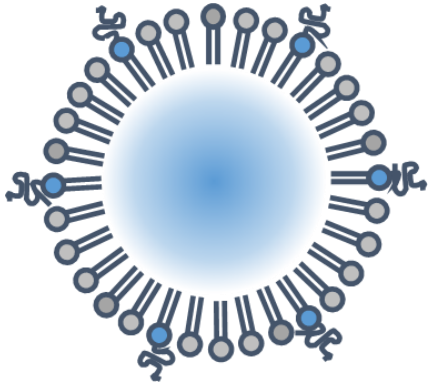


Previously we have reported how pentobarbital can be delivered non-invasively to specific brain regions in a rodent model using drug-loaded perfluorocarbon nanodroplets triggered with transcranial FUS.

Definity™ microbubbles

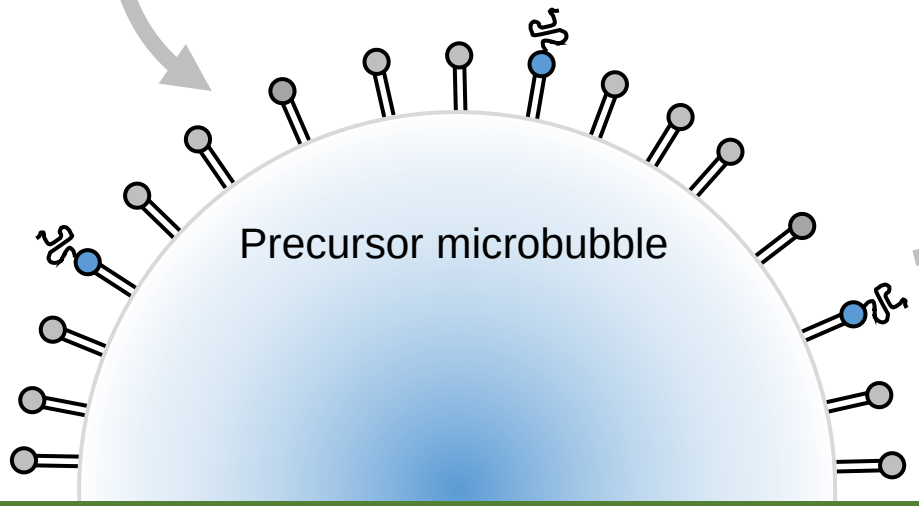


Pentobarbital-loaded nanodroplets



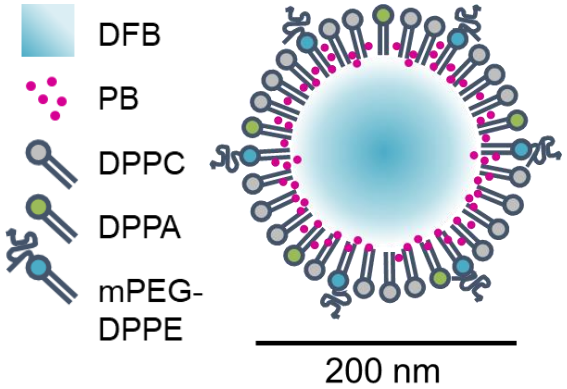
Sham nanodroplets

+ Decafluorobutane (C_4F_{10})

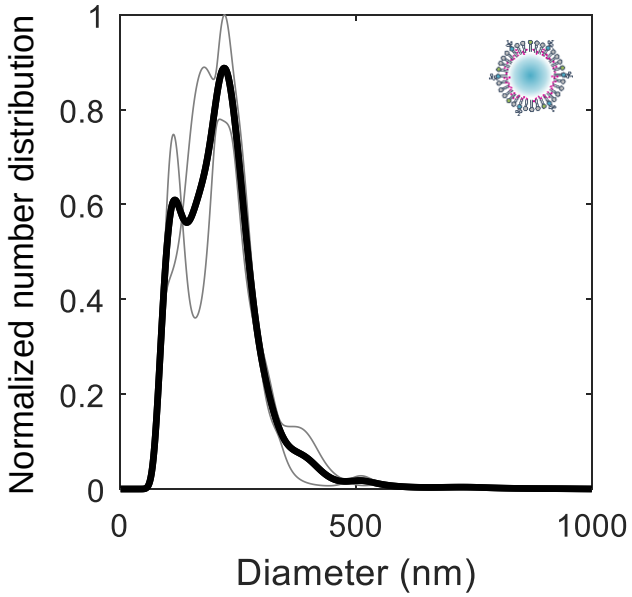


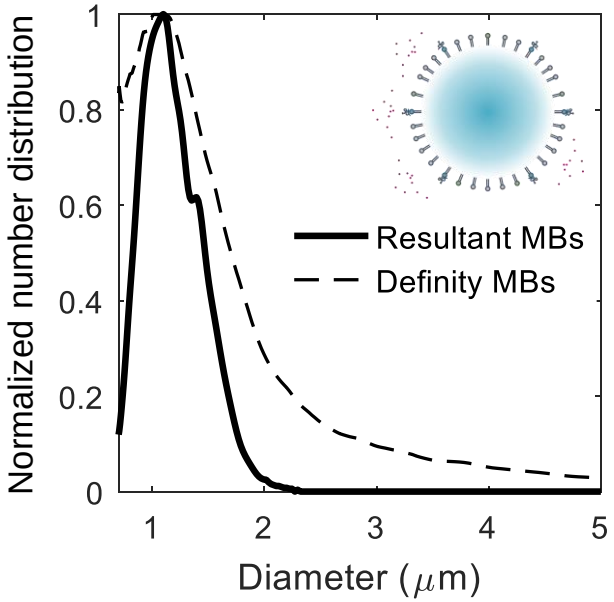
+ Cooling (-10°C)

Matsunaga *et al.* 2012. *Theranostics*, 2(12), pp.1185–1198.
Sheeran *et al.* 2017. *Ultrasound in medicine & biology*, *43*(2), pp.531-540.

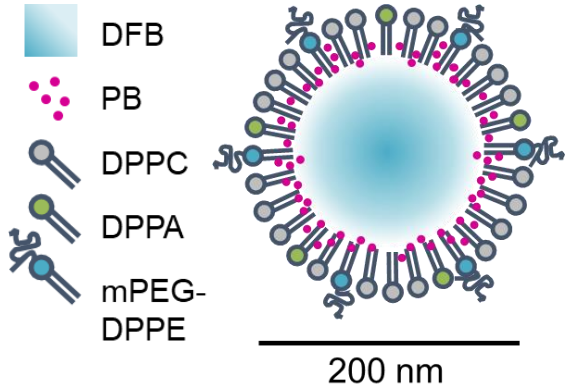


- Pentobarbital (PB)

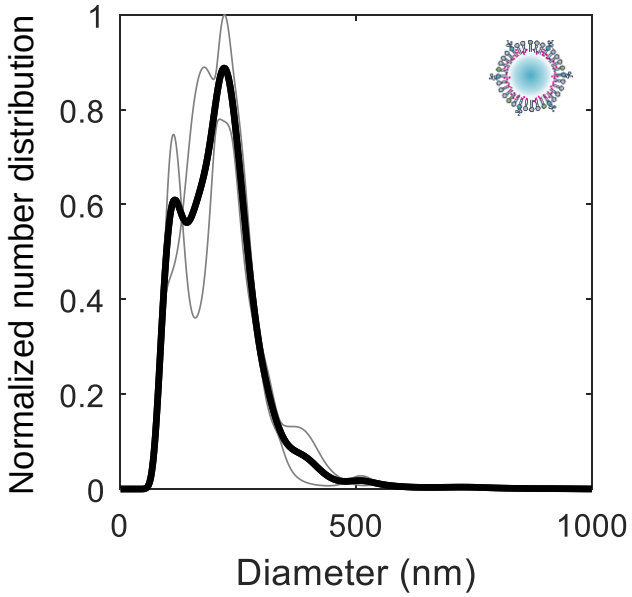


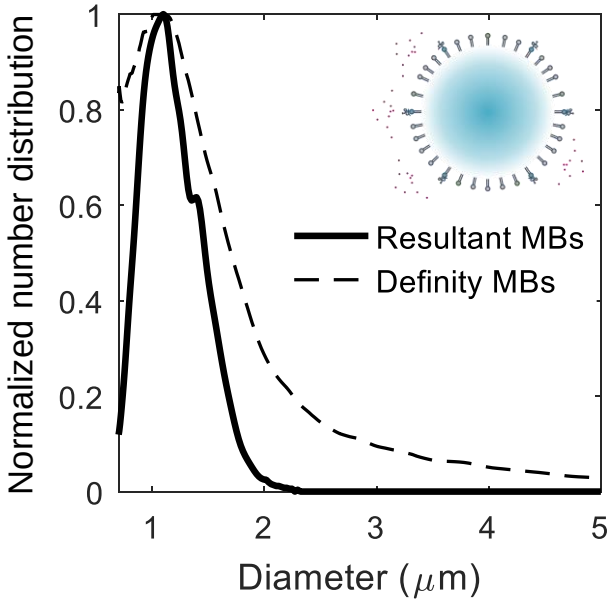


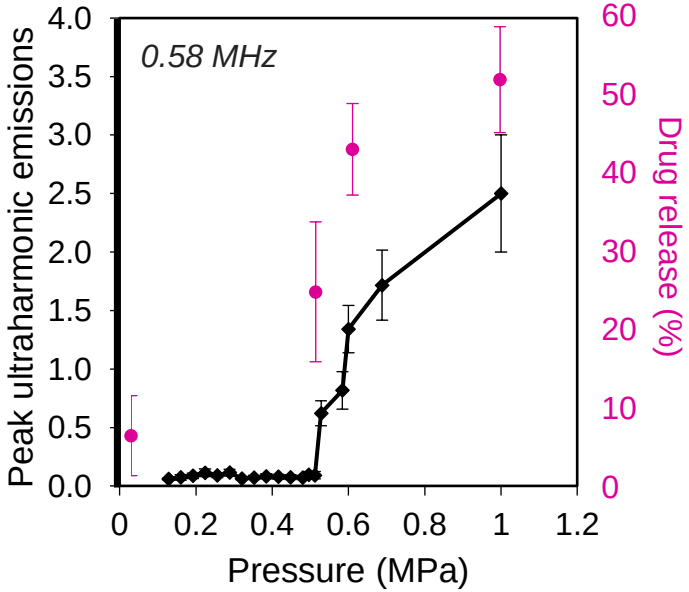
Lea-Banks *et al.* 2020. *Theranostics*, 10(6), pp. 2849–2858.

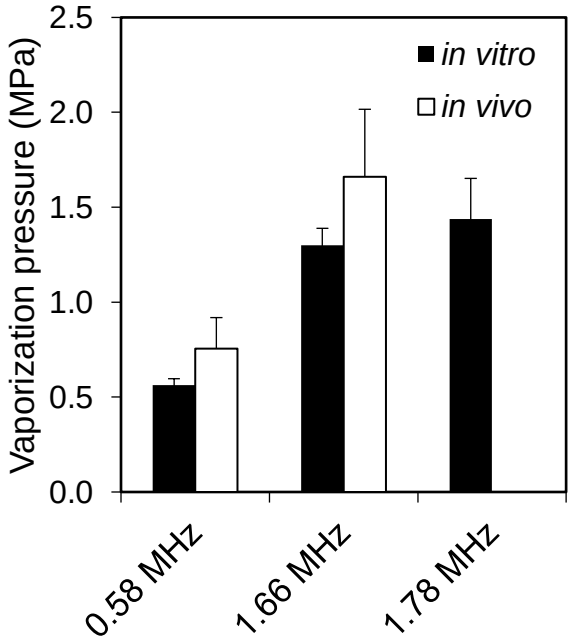


- Pentobarbital (PB)

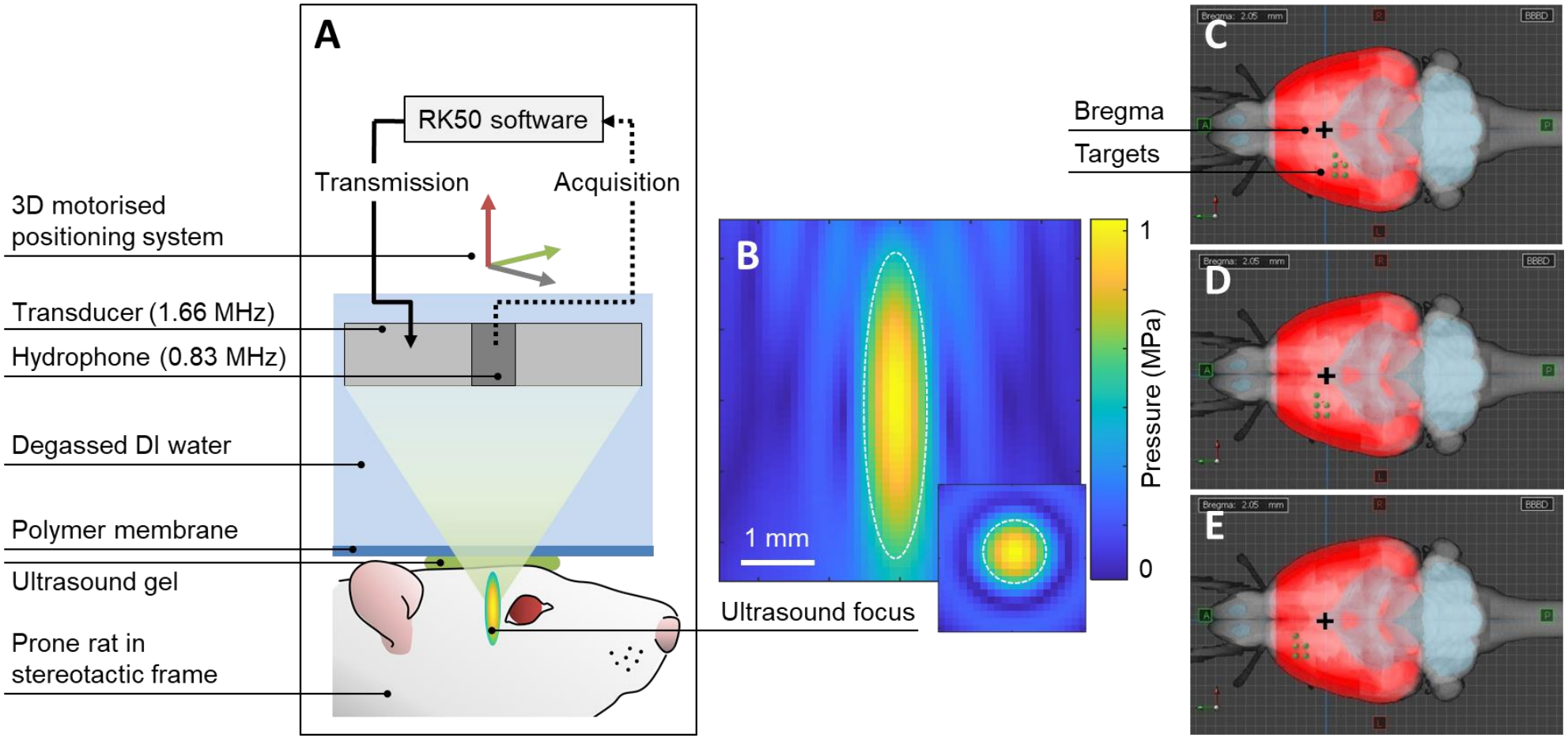




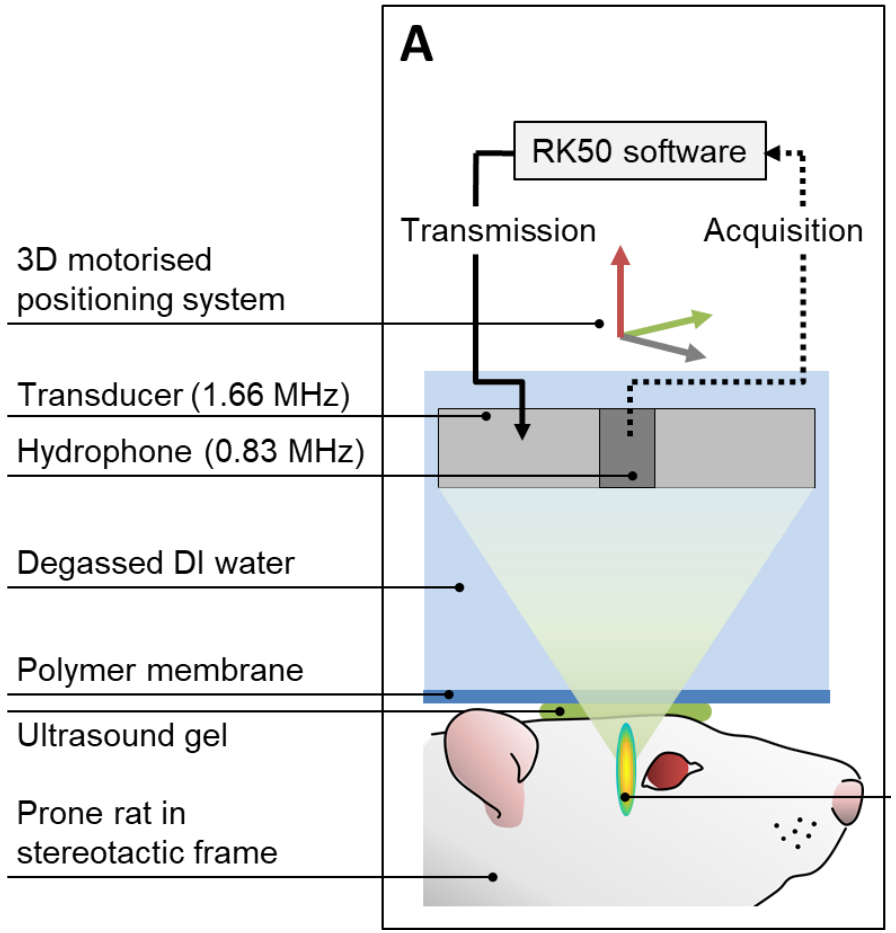


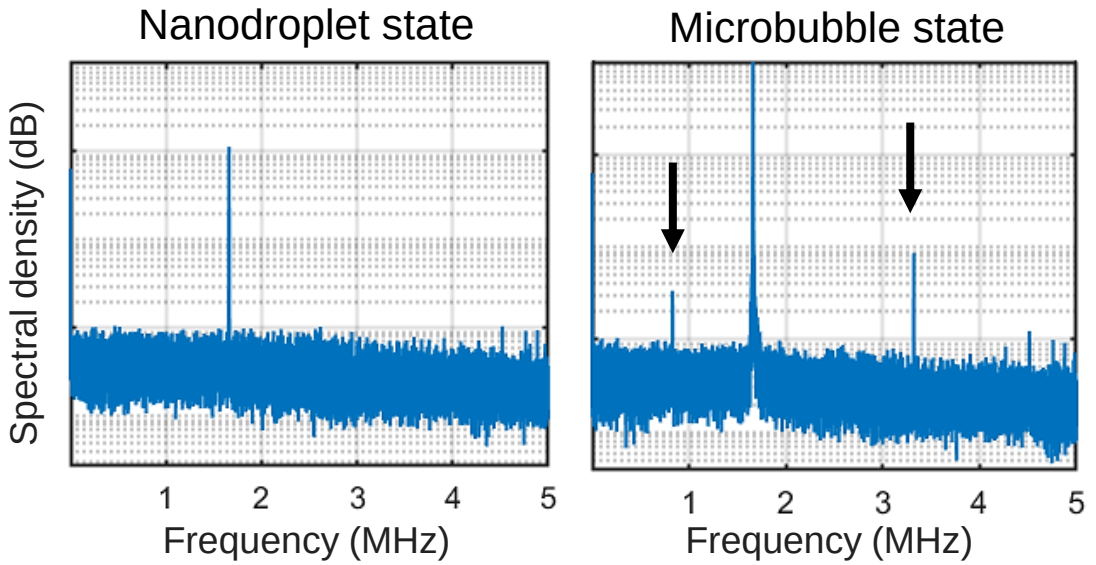


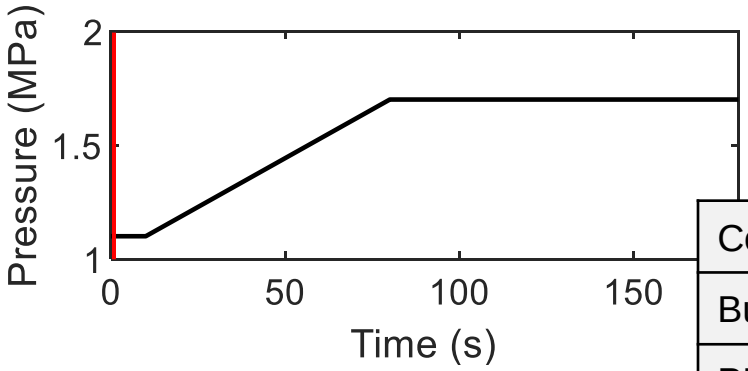
Lea-Banks *et al.* 2020. *Theranostics*, 10(6), pp. 2849–2858.



Lea-Banks *et al.* 2021. *Journal of Controlled Release*, 332, pp. 30–39.

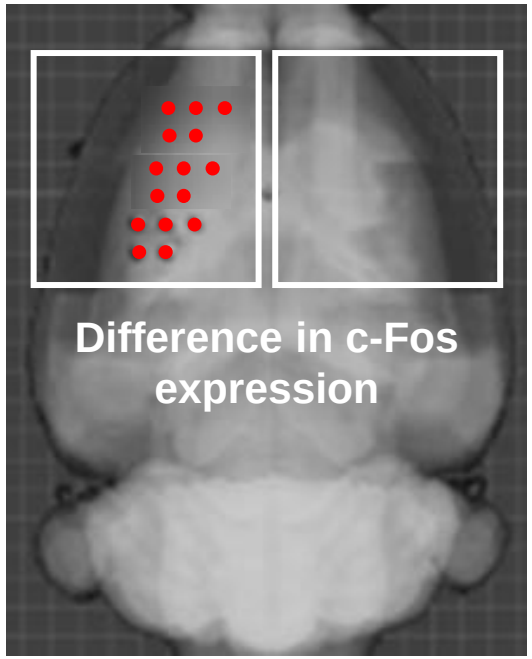


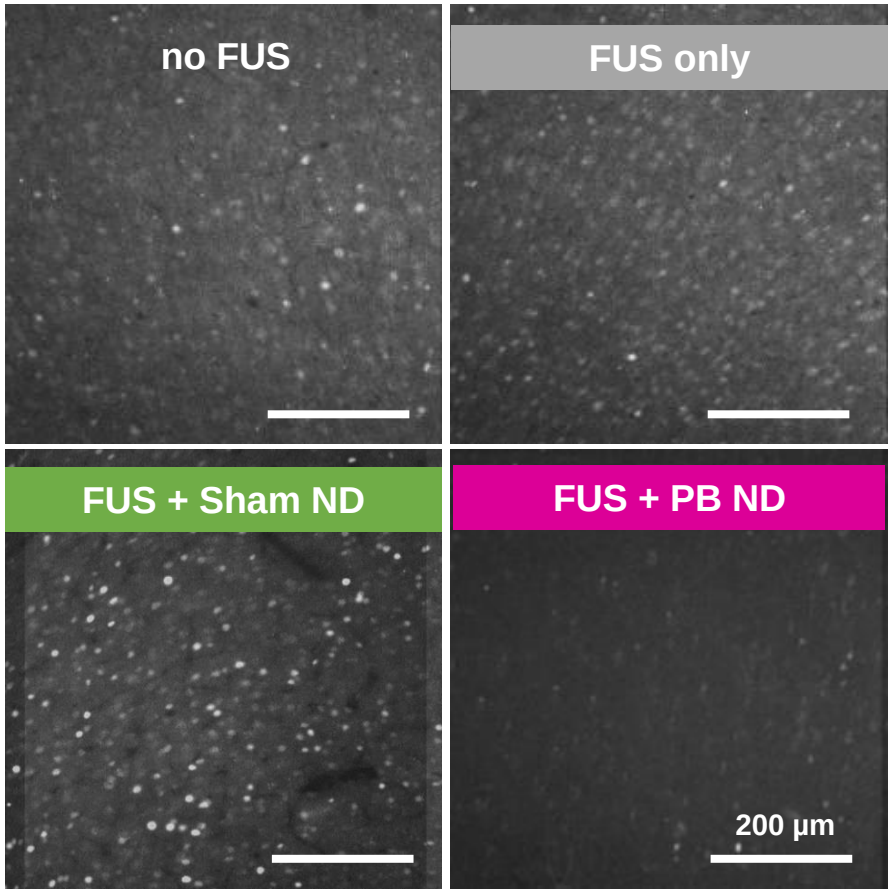


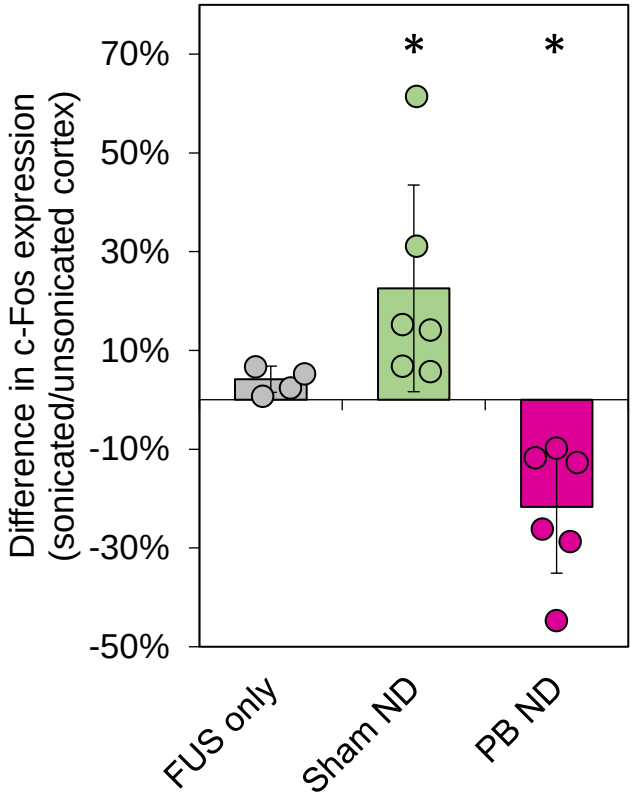


Centre frequency	1.66 MHz
Burst length	10 ms
PRF	1 Hz
Injectate (**x3**)	500 µL (4x10^{10} ND, 12 µg PB)

Lea-Banks *et al.* 2021. *Journal of Controlled Release*, 332, pp. 30–39.

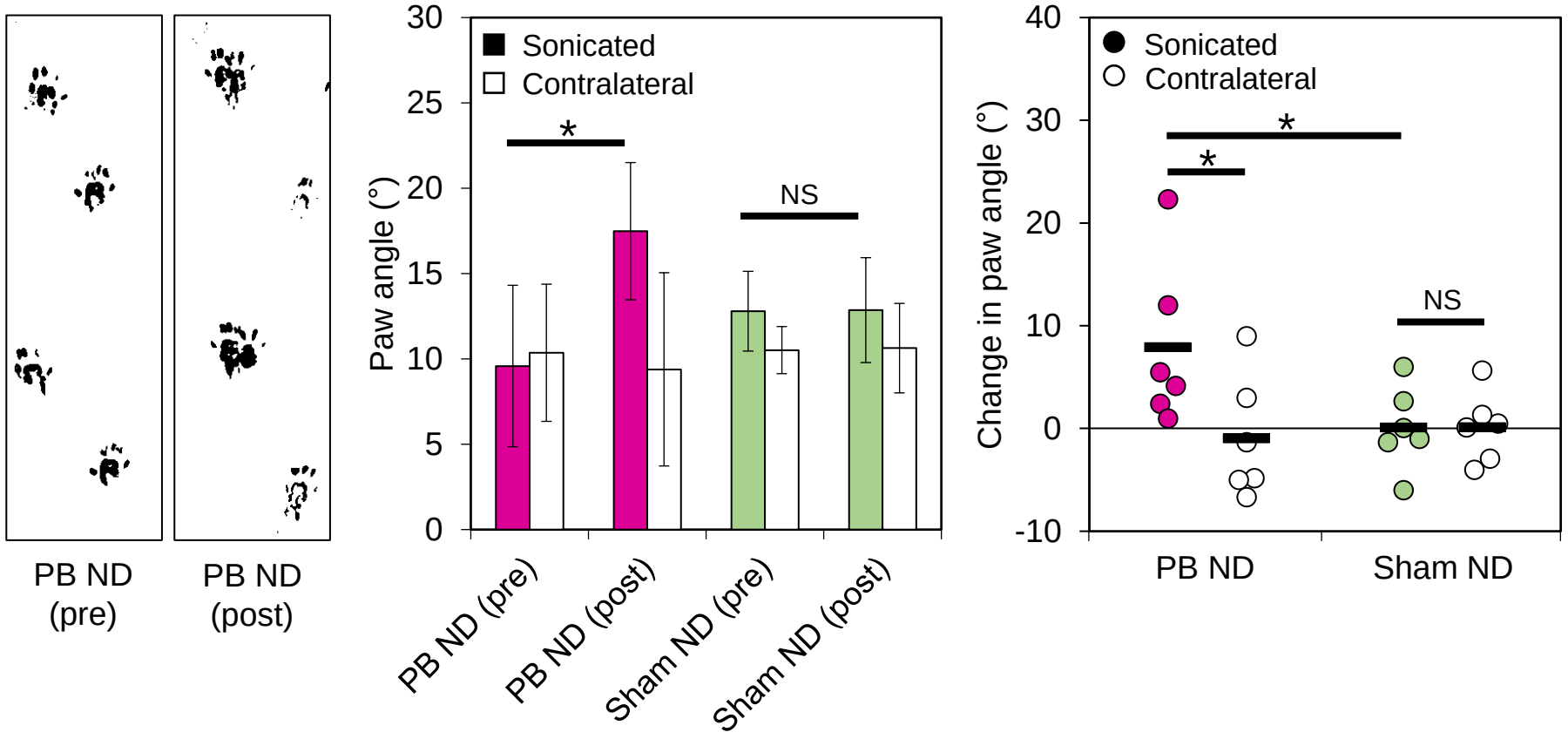






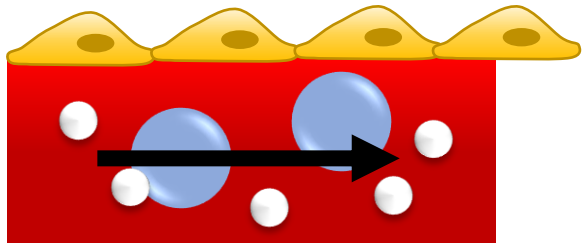
c-Fos expression was significantly different in the sonicated brain region following FUS + sham ND, and FUS + PBND

Lea-Banks *et al.* 2021. *Journal of Controlled Release*, 332, pp. 30–39.



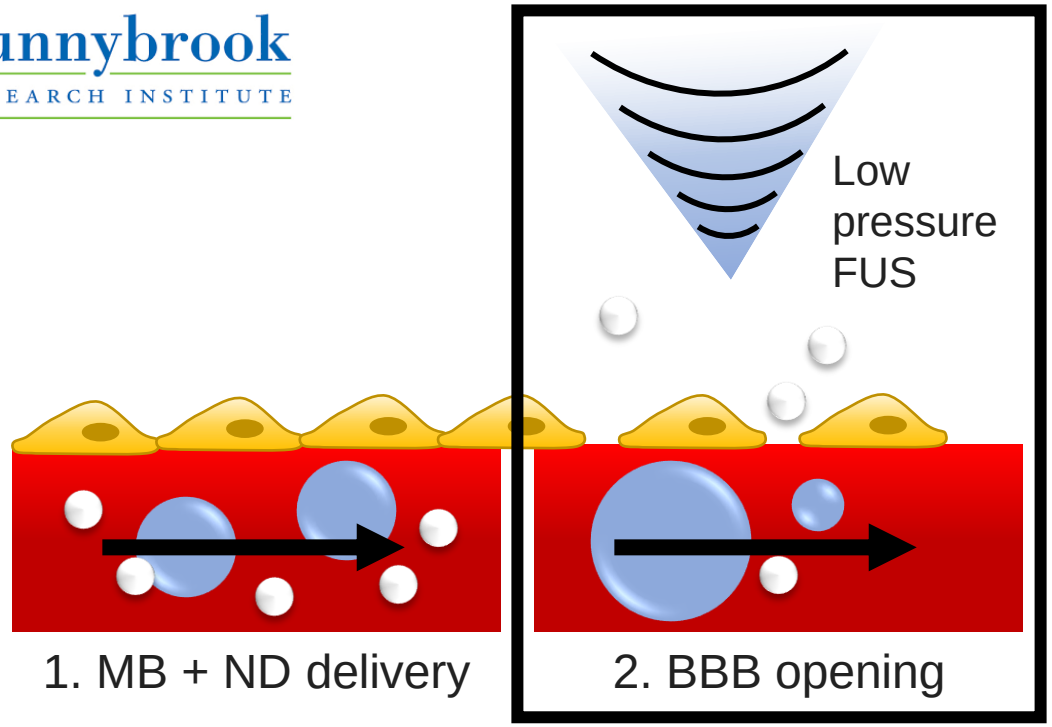
A temporary, asymmetric sensorimotor deficit was measured following FUS + PBND targeted at the motor cortex

Lea-Banks *et al.* 2021. *Journal of Controlled Release*, 332, pp. 30–39.

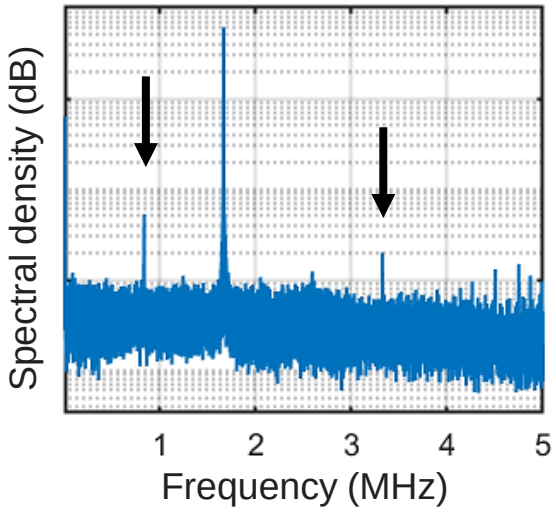


1. MB + ND delivery

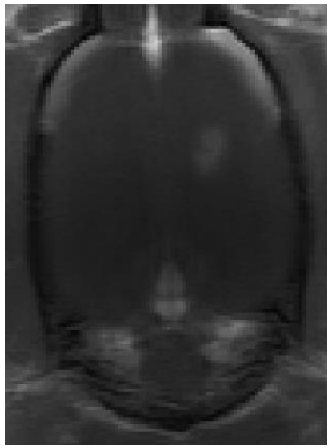
Centre frequency	1.66 MHz
Burst length	10 ms
PRF	1 Hz
Injectate (**x1**)	500 µL (4x10^{10} ND, 12 µg PB)



MB-mediated BBB opening was achieved with low pressure FUS and verified with contrast-enhanced MRI and Evans Blue extravasation

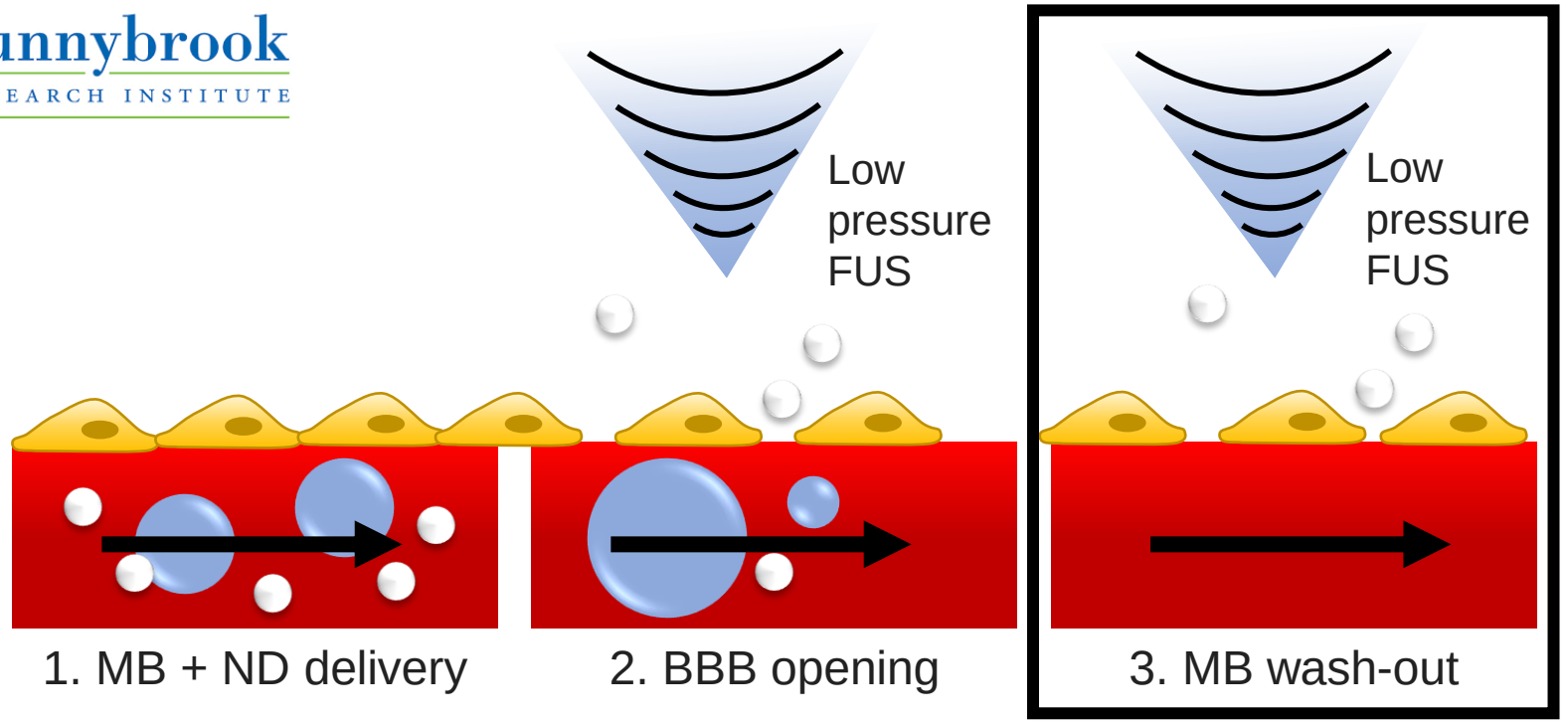


0 min

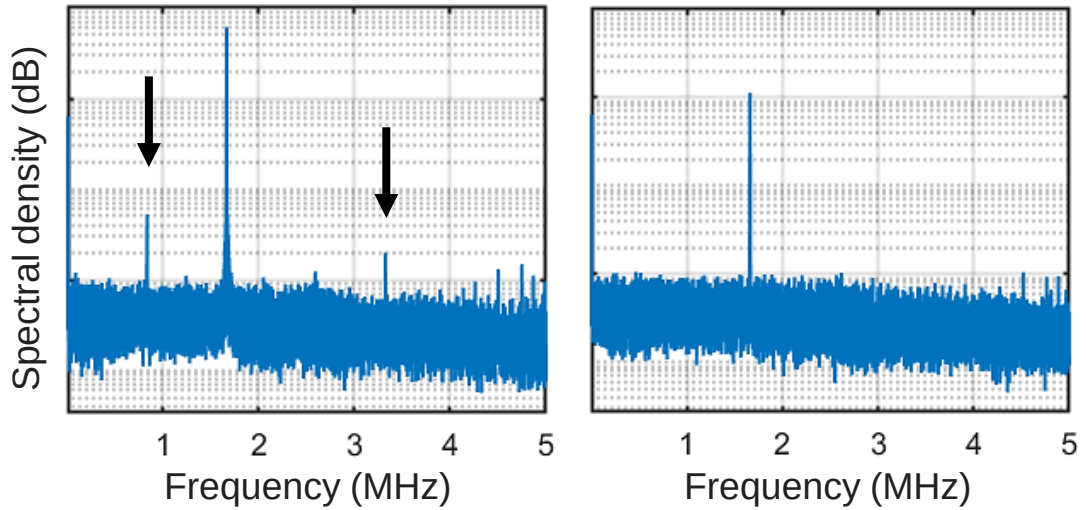


T1-w contrast

Evans Blue

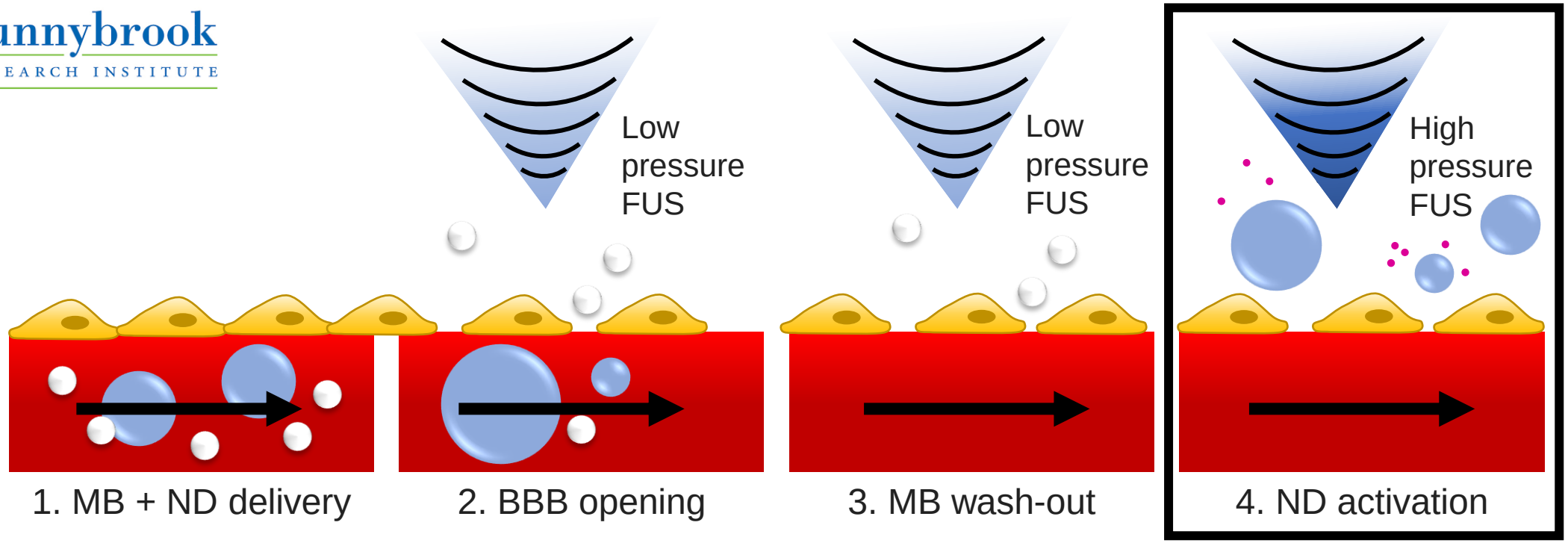


MB clearance was verified with low pressure FUS 20 min after injection

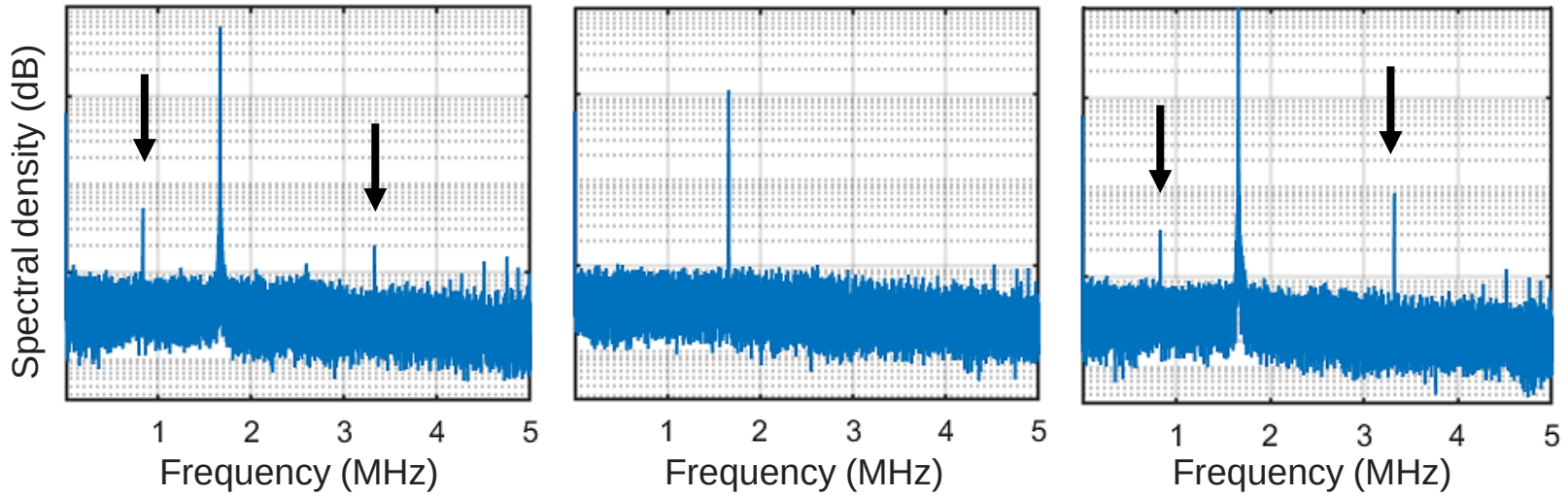


0 min

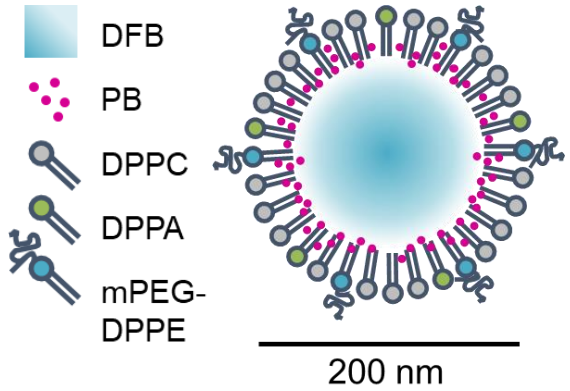
20 min

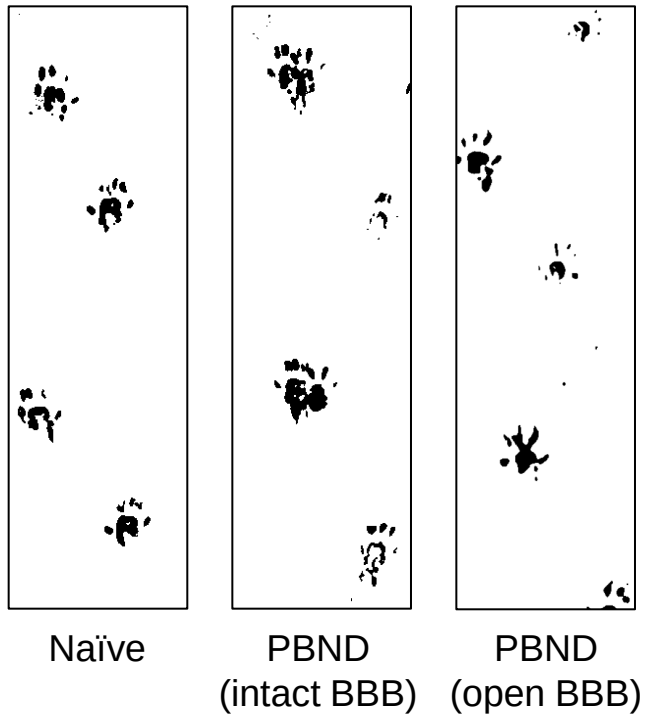


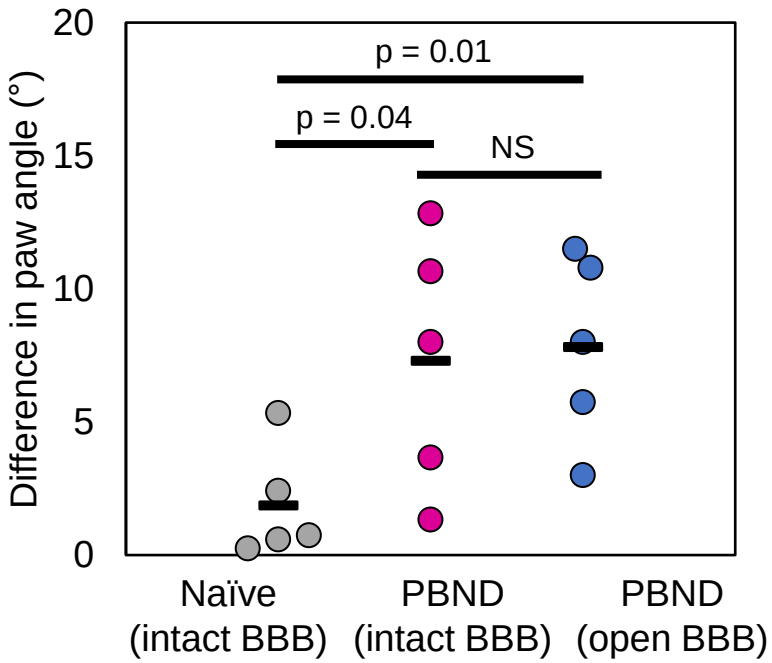
Extravasated PBND remained acoustically activate 30 min after injection



0 min 20 min 30 min





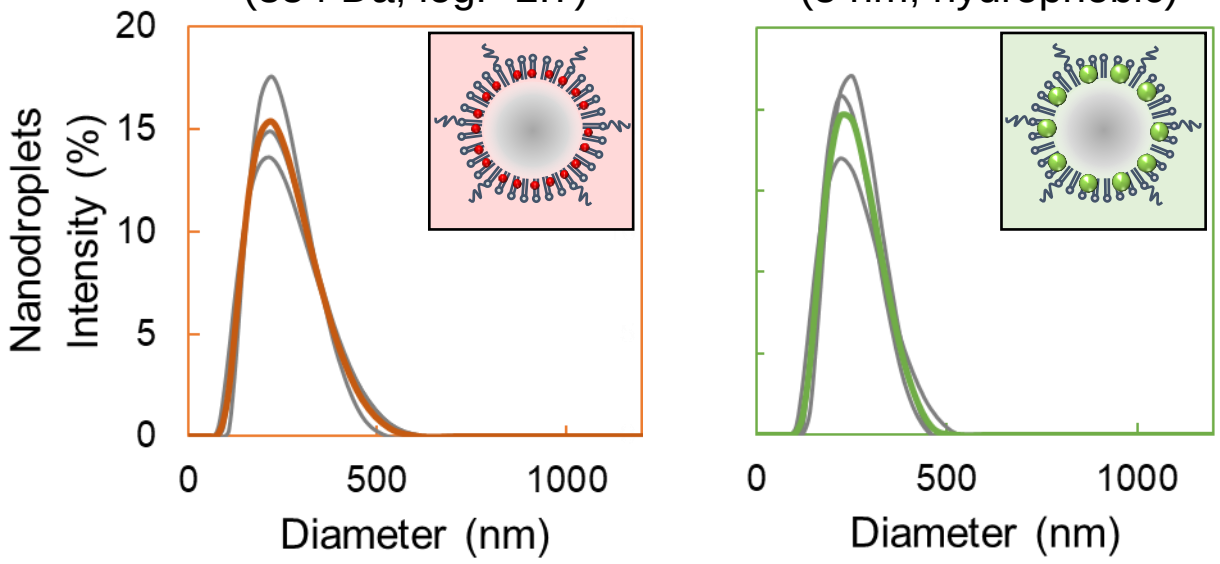


Sensorimotor deficit following FUS + PBND (1/3 dose) with open BBB was comparable to FUS + PBND (full dose) with intact BBB

Sunnybrook
RESEARCH INSTITUTE

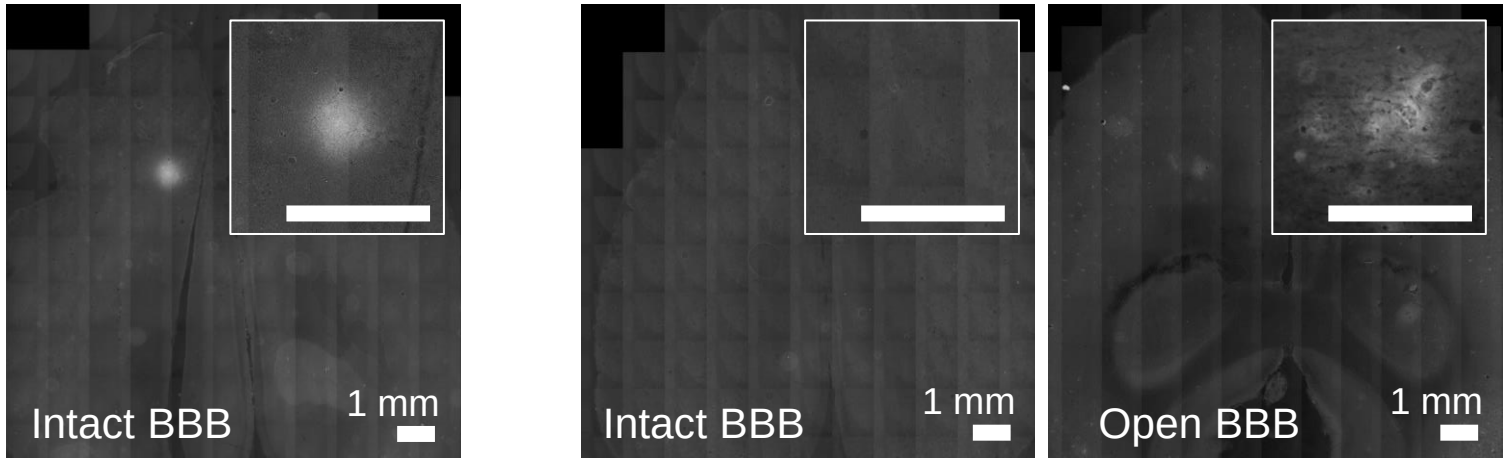
Nile Blue
(354 Da, logP 2.7)

Quantum Dots
(5 nm, hydrophobic)

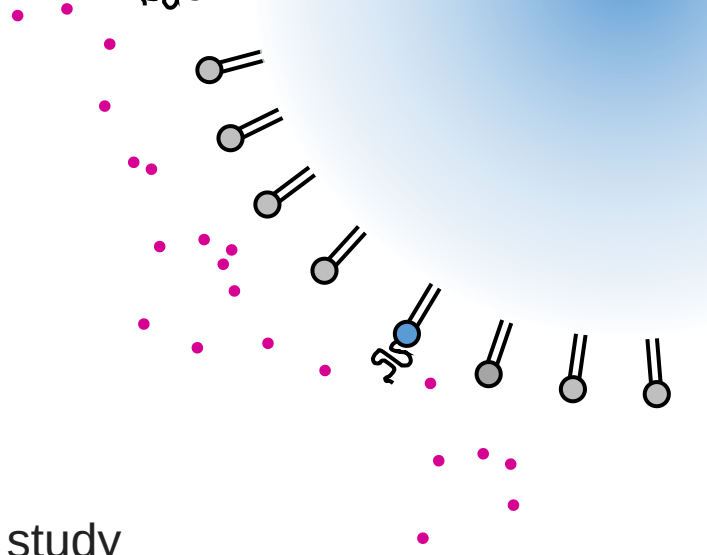


ND can be used to carry and deliver large agents across the open BBB

Brain sections



Sunnybrook
RESEARCH INSTITUTE



Conclusions

Nanodroplets, combined with transcranial FUS, offer an adaptable tool to study neuromodulation, through the controlled release of small molecule anesthetics.

Vaporization causes local release of the payload whilst simultaneously emitting unique acoustic emissions.

Opening the BBB with FUS and microbubbles is a potential strategy to deliver nanodroplets, loaded with large therapeutics, into the brain.

Acknowledgements

Focused Ultrasound Lab, Sunnybrook
Dr. Meaghan O'Reilly
Dr. Dallan McMahon
Dr. Ryan Jones
Lulu Deng
Ginni Ting
Hannah Lee
Shawna Rideout-Gross
Kristina Mikloska
Jennifer Sun

Division of Neurosurgery, Sunnybrook
Mustansir Diwan

SickKids Hospital, Toronto
Dr. Nesrin Sabha

Dr. Ying Meng, MD

Dr. Sheng-Kai Wu

Dr. Clement Hamani, MD

Dr. Kullervo Hynynen

National Institute of Biomedical Imaging and Bioengineering

CIHR IRSC

Chaires de recherche du Canada
Canada Research Chairs
Canada