September 7-10, 2021

Contents

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Message from Program Committee

Dear FUN Conference Attendees.

Although we wish we were seeing each other in person, it's been a blast organizing this virtual conference. We have a great lineup of speakers for two hours each day. The presentations cover technical, mechanistic, clinical, and neuroscience topics. They are mixed up across the days so that attendees are encouraged to see presentations across topics.

Each day, there will be a period between the oral presentations and the poster presentations for social interactions. It will take place in the poster hall immediately after the oral presentations. Poster presenters will stand by their posters for one of the three days.

We are very grateful to our sponsors. Their booths in gather.town are centrally located, so we encourage you to drop by and say hello. Their products and services make our work possible and their contributions help us to learn and engage with each other at FUN21.

We have been overwhelmed with the quality of the submitted abstracts. Thank you all, for your wonderful contributions. With such talented people and exciting work, the future of this field is bright! We will be giving out three awards: best oral presentation, best poster presentation, and best overall presentation. Thank you to Hong Chen and the Awards Committee!

An unusual aspect of this meeting is the scavenger hunt/raffle for trainees. The raffle prizes will be 50 euros and will be announced on Friday. To gain entry to the raffle, trainees have to send an email to fun.conference2021@gmail.com with a screenshot of themselves and two people from the organizing committee, three sponsor booth representatives, someone from Asia, North America, and Europe, a faculty and a trainee. The emails must be sent by Thursday Sept 9 12 pm CET/ 2 pm PT.

On Friday, we will have presentations by ITRUSST. We will report on ongoing discussions for safety, planning, and standardisation of ultrasonic neuromodulation in humans. We will close this day by presenting the organisation and aims of ITRUSST.

We are very grateful to the organizing committee, in particular Benjamin Kop who organized the gather.town conference hall.

In closing, we are particularly grateful for the new tools we have to organize such an event (zoom and gather.town). But, we are looking forward to the day when we can meet in person and overhear a trainee say, “So this is what a conference is really like!”

Kim Butts Pauly
Lennart Verhagan
The Organizing Committee

Program Committee & Co-Moderators

Kim Butts Pauly
Charles Caskey
Elsa Fouragnan
Samuel Pichardo
Jerome Sallet
Bradley Treeby
Lennart Verhagen
Christopher Butler
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Martin Prieto
Hong Chen
Mikhail Shapiro

Neuroscience:

David Howett
Miriam Klein-Flugge
Elsa Fouragnan
Jerome Sallet
Julien Claron

Technical:

Samuel Pichardo
Laura Curiel
Ryan Jones
Apoutu N'Djin
Gianmarco Pinton

Clinical:

Chris Butler
Ellen Bubrick
Fidel Vila-Rodriguez
Robert Chen

Program-at-a-Glance

Day 1

	Time (pm CET)	Time (am PT)	Time (pm Seoul, Tokyo)	First Author	Title (Link)
Tuesday Sept 7th	3:00	6:00	10:00		Introduction
					Moderators: Charles Caskey and Martin Prieto
	3:05	6:05	10:05	Elisa Konofagou	Modulation of the central and peripheral nervous system
	3:25	6:25	10:25	Steffen Tretbar	TRUST - a new 3D Transcranial Ultrasound neuro Stimulation system
	3:40	6:40	10:40	Xue Xia	Time course of low-intensity transcranial ultrasound on the excitability of ipsilateral and contralateral human primary motor cortex
	3:55	6:55	10:55	Thomas Tiennot	Bifocal Acoustic Lens For Personalized Simultaneous Multisite Deep Brain Stimulation
	4:10	7:10	11:10		Sponsor Video
					Moderators: Hong Chen and Robert Chen
	4:15	7:15	11:15	Kai Yu	In vivo cell-type selectivity of transcranial focused ultrasound stimulation
	4:30	7:30	11:30	Keith Murphy	Deep brain optical recording of ultrasound neuromodulation reveals cell type selective parameter space
	4:45	7:45	11:45	Zhihai Qui	Transcranial ultrasound stimulates neurons in targeted region in mouse brain
	5:00	8:00	12:00		Social time in gather.town
	5:30	8:30	12:30		Poster session

Day 2

	Time (pm CET)	Time (am PT)	Time (pm Seoul, Tokyo)	First Author	Title (Link)
Wednesday Sept 8th	3:00	6:00	10:00		Introduction
					Moderators:Fidel Vila-Rodriguez and Samuel Pichardo
	3:05	6:05	10:05	Ellen Bubrick	TUS in the Treatment of Epilepsy
	3:25	6:25	10:25	Chien-Chen Chou	Neuronavigation-Guided Low-Intensity Focused Ultrasound in Patients with Epilepsy
	3:40	6:40	10:40	Hao Wang	Ultrasound inhibits amyloid formation through membrane structure modulation
	3:55	6:55	10:55	Stephen Lee	FUS-induced median nerve stimulation alters pain sensation in humans
	4:10	7:10	11:10		Sponsor Video
					Moderators: Mikhail Shapiro and Miriam Klein-Flugge
	4:15	7:15	11:15	Erica McCune	Monitoring Cavitation Activity and the effect of Tissue Temperature During Focused Ultrasound Neuromodulation
	4:30	7:30	11:30	Yaoheng Yang	Sonothermogenetics Enables Noninvasive and Cell-type Specific Deep Brain Neuromodulation
	4:45	7:45	11:45	Quanxiang Xian	Sonogenetic deep brain stimulation in freely moving mice
	5:00	8:00	12:00		Social time in gather.town
	5:30	8:30	12:30		Poster session

***An overview of oral abstracts can be seen on page 14**

***An overview of posters and poster sessions can be seen on page 36**

Day 3:

	Time (pm CET)	Time (am PT)	Time (pm Seoul, Tokyo)	First Author	Title (Link)
Thursday Sept 9th	3:00	6:00	10:00		Introduction
					Moderators: Elsa Fouragnan and Ellen Bubrick
	3:05	6:05	10:05	Apoutou N'Djin	Spatio-temporal dynamics of neural responses causally induced by single-pulse focused ultrasound
	3:25	6:25	10:25	Ke Zeng	Induction of Human Motor Cortex Plasticity by Theta Burst Transcranial Ultrasound Stimulation
	3:40	6:40	10:40	Jan Kubanek	Effective ultrasonic neuromodulation
	3:55	6:55	10:55		Sponsor
					Moderators: Chris Butler and Apoutu N'Djin
	4:00	7:00	11:00	Hyungmin Kim	Image-based guidance for focused ultrasound neuromodulation
	4:15	7:15	11:15	Siti Yaakub	Pseudo-CTs from T1w MRI for planning of low-intensity ultrasound stimulation
	4:30	7:30	11:30	Jak Loree-Spacek	Development of in vitro Ultrasound Neuromodulation System with Concurrent Measurement of Evoked Local Field Potential
	4:45	7:45	11:45	Catherine Swytink-Binnema	Preliminary results on the reproducibility of focused-ultrasound based neuromodulation in an in vitro electrophysiological system
	5:00	8:00	12:00		Social time in gather.town
	5:30	8:30	12:30		Poster session

Day 4:

	Time (pm CET)	Time (am PT)	Time (pm Seoul, Tokyo)	First Author	Title (Link)
Friday Sept 10th	3:00	06:00	10:00		Award Winners Announcement
					ITRUSST Presentation, Moderated by Lennart Verhagen
					Modeling
					Safety
					Reporting
					Practice-practical guide
					Equipment
					Clinical

***An overview of oral abstracts can be seen on page 14**

***An overview of posters and poster sessions can be seen on page 36**

Poster Sessions

For an overview of all posters, please see page X.

Tuesday September 7, 2021

3. Transcranial neuromodulation array for simultaneous multifocal imaging

Rebecca Jones, Charles Caskey, Paul Dayton, Omer Oralkan, Gianmarco Pinton

4. An open source system for logging and monitoring FUS transmission

Adrienne A Hawkes, Michelle Sigona, Kianoush Banaie Boroujeni, Louie Treuting, Thilo Womelsdorf, Charles F Caskey

5. A Novel Metric for Assessing Audibility of Transcranial Ultrasound Neuromodulation Signals

Mi Hyun Choi, Gerald Popelka, Kim Butts Pauly

6. Development of a Computational Tool to Guide Transcranial Ultrasound Signal Parameter Selection and Reporting

Karanpartap Singh, Mi Hyun Choi, Gerald Popelka, Kim Butts Pauly

11. Transcranial Ultrasound Stimulation in Anterior CingulateCortex Impairs Information Sampling and Learning in Loss Contexts

Kianoush Banaie Boroujeni, Michelle K Sigona, Robert Louie Treuting, Adrienne Hawkes, Charles F. Caskey, Thilo Womelsdorf

12. Adapting the Proteus Platform to Support Image-Guided Focused Ultrasound Neuromodulation Experimentation in a Pre-Clinical Commercial Device

Aidan Johnson, Chris Krasnichuk, Amine Benaceur, Marc Santos, Rajiv Chopra, Samuel Pichardo

13. Ultrasound modulation of macaque prefrontal cortex selectively alters credit assignment-related activity and behavior

Folloni, D., Fouragnan, E., Wittmann, M.K., Roumazeilles, L., Tankelevitch., L., Verhagen, L., Attali, D., Aubry, J-F., Sallet, J., Rushworth, M.F.S

14. Implementation of Optimized Isoflurane Protocol in Focused Ultrasound Neuromodulation Using Random Pulse Repetition Frequency Modulation for Skull Vibration Reduction

Jake Hesselink, Aidan Johnson, Zelma Kiss, Samuel Pichardo

20. BEST Toolbox: Brain Electrophysiological recording & STimulation Toolbox

Umair Hassan, Steven Pillen, Christoph Zrenner, Til Ole Bergmann

21. TUS in DBS-implanted patients: In vitro safety assessment and evaluation of stimulation effect on continuous LFP recordings through DBS electrode

Can SARICA, Anton Fomenko, Jean-Francois Nankoo, Ghazaleh Darmani, Artur Vetkas, Andres M. Lozano, Robert Chen

29. State-Dependent Modulation of Pain Circuits of Nonhuman Primates using an Integrarted MRI Guided Fcoused Ultrasound System at 3T

LM Chen, PF Yang, T Manual, M Sigona, H Luo, AT Newton, A Mishra, JC Gore, W Grissom, CF Caskey

30. MorphoSONIC: a morphologically structured intramembrane cavitation model reveals fiber-specific neuromodulation by ultrasound

Théo Lemaire, Elena Vicari, Esra Neufeld, Silvestro Micera

39. Experimental validation of k-Wave simulations of ultrasound propagation through ex-vivo human skull

Eleanor Martin, Bradley Treeby

40. Regional pharmacological neuromodulation by FUS-mediated disruption of blood plasma protein binding

Wonhye Lee, Hyun-Chul Kim, and Seung-Schik Yoo

Wednesday September 8, 2021

2. Acoustic Coupling Pads for the Control of Ultrasound Exposure
Samantha Schafer, Mark E. Schafer

7. Displacement of intracranial electrodes induced by focused ultrasound stimulation
Min Gon Kim, Kai Yu, Xiaodan Niu, Bin He

10. Concurrent TUS-TMS-EMG to quantify the online effects of varying TUS duty cycle and intensity on corticospinal excitability in humans
Tulika Nandi, Umair Hassan, Angela Radetz, Til Ole Bergmann

15. Modulating cerebellar-M1 connectivity using transcranial focused ultrasound
Jean-Francois Nankoo, Anton Fomenko, Julianne Baarbé, Yanqiu Wang, Xue Xia, Nasem Raies, Stephanie Tran, Andres Lozano, Robert Chen

18. Sonication of thalamic circuits changes brain oscillations during non-stimulus conditions in a way analogous to changes in anesthetic level
Morteza Mohammadjavadi, Pooja Gaur, Yamil Saenz, Ryan T.Ash, Kim Butts Pauly

19. Using Lenses to Focus Ultrasound to the Human Hippocampus: Modelling and Validation
Xinghao Cheng, Christopher R. Butler, Robin O. Cleveland

22. Quantitative Acoustic Output Measurement System for Low Intensity Focused Ultrasound
Mark E. Schafer, James Gessert, Samantha Schafer

23. Precomputation of hundreds of transducer positions for real-time, patient-specific simulation-based tFUS neuronavigation and planning
Bastien Guerin, Mohammad Daneshzand, Jason Stockmann, Jian Li, David Izquierdo, Ciprian Catana, Tina Chou, Brian L. Edlow, Darin Dougherty, Aapo Nummenmaa

28. TUSX: an accessible toolbox for transcranial ultrasound simulation
Ian S. Heimbuch, Marco Iacoboni, Andrew C. Charles

31. Precise Targeting of Transcranial Focused Ultrasound Using Image Guidance and Array-Based Steering
M Anthony Phipps, Thomas Manuel, Huiwen Luo, Pai-Feng Yang, Allen Newton, Li Min Chen, William Grissom, Charles F Caskey

38. Sensing mechanical force in the central nervous system.
Scott Hansen, Hao Wang, E. Nicholas Petersen

41. Ultrasound holograms to enhance deep-brain neuromodulation
Diana Andrés, Sergio Jiménez-Gambín,Noé Jiménez, Francisco Camarena, José María Benlloch

Thursday September 9, 2021

1. Human Skull imaging with Ultrashort TE and Zero TE MRI sequence
Fanrui Fu, Erpeng Dai, Gerald R. Popelka, Pejman Ghanouni, Kim Butts Pauly

8. The essential role of neuron multiphysics in ultrasound neuromodulation and anaesthesia.
Casey Adam, Miren Tamayo-Elizalde, Celine Kayal, Ari Ercole, Sonia Contera, Hua Ye, Antoine Jerusalem

9. Differential brain network effects following anterior versus posterior hippocampal perturbation with transcranial ultrasound stimulation in primates
David Howett, Christopher Petkov, Matthew Rushworth and Jérôme Sallet

16. Transcranial ultrasound stimulation using a learned mapping from MR to pseudo-CT images
Maria Miscouridou, Antonio Stanziola, José Angel Pineda-Pardo, Bradley Treeby

17. Long-term study of motivational and cognitive effects of low-intensity focused ultrasound neuromodulation in the dorsal striatum of nonhuman primates
Fabian Munoz, Anna Meaney, Aliza S. Gross, Katherine Liu, Antonios N. Pouliopoulos, Dong Liu, Elisa Konofagou, Vincent P. Ferrera

24. Deep brain neuromodulation in disorders of consciousness: challenges and opportunities
Monti MM, Cain J, Spivak N, Schnakers C

26. Imaging assessment of mechanical and thermal effects during focused ultrasound sequences
Hermes A. S. Kamimura; Niloufar Saharkhiz; Stephen A. Lee; Elisa E. Konofagou

27. Noninvasive ultrasound neuromodulation induces long term depression in rat hippocampus
Xiaodan Niu, Kai Yu, Bin He

32. Low intensity, CW focused ultrasound reversibly alters heart and respitory rate in anesthetized mice
Ethan Bendau, Christian Aurup, Hermes Kamimura, Elsa Konofagou

33. Pulsing, ramping, masking and the auditory artefact.
Ainslie Johnstone, Tulika Nandi, Elly Martin, Sven Bestmann, Charlotte Stagg, Bradley Treeby

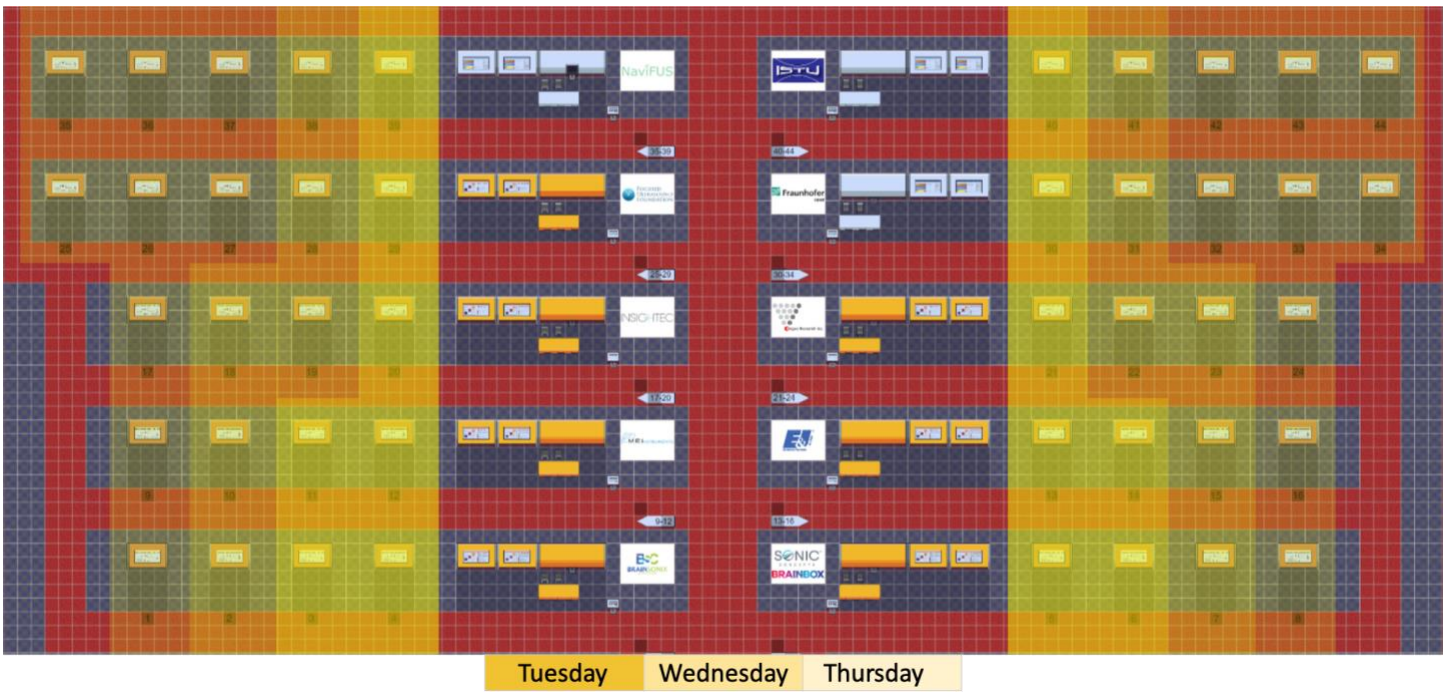
37. Balancing open-label exploratory clinical trials with double-blinded RCT in the development of the new field of research. Lessons from rTMS and tFUS.
Alexander Bystritsky, M.D., Ph.D.

42. The ultimate acoustic energy deposition (uAED): A theoretical performance metric for the assessment of tFUS strategies and hardware

Bastien Guerin, Kyungho Yoon, Jason Stockmann, Tina Chou, Brian L. Edlow, Darin Dougherty, Aapo Nummenmaa

43. Computational Analysis of Off-target Ultrasound Neuromodulation Effects

Hossein Salahshoor, Mikhail G. Shapiro, Michael Ortiz



Information attendees

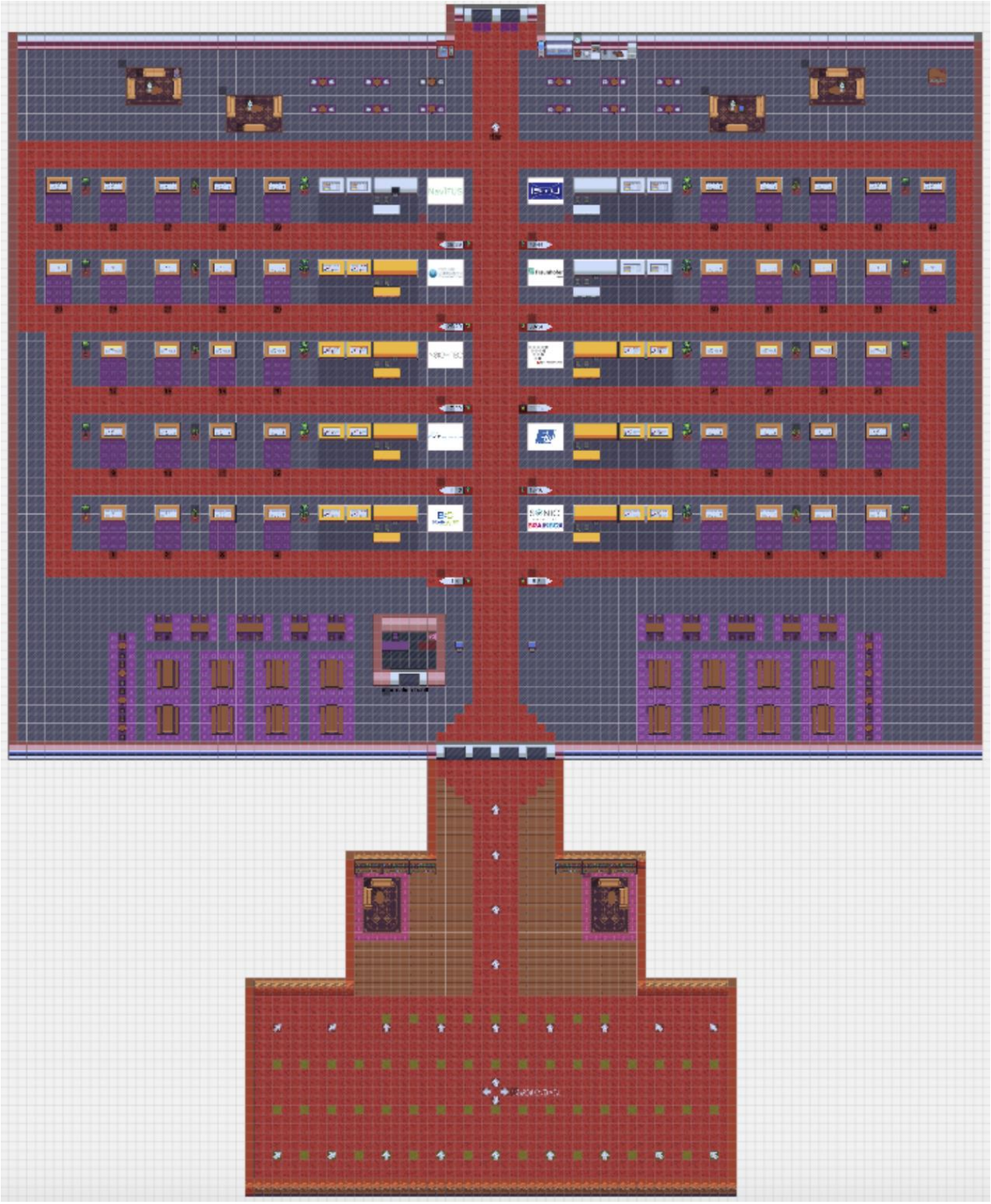
All oral presentations will be done on zoom. The link to the zoomroom will be in an email close to the date of the conference. The format will be a webinar format. All presenters will be invited to be panelists. The audience attendees will not be seen or heard, but they will be able to post questions. Moderators will introduce the speakers, read questions posted by the audience, and ask the questions of the speakers.

Presentations will be uploaded on a private YouTube channel and viewable for 4 weeks after the conference.

Poster sessions will take place in the virtual environment of Gather.Town. When your poster session is scheduled, the poster presenter's avatar should stand in the shaded square in front of your poster. This is a 'private space' where your audio/video and poster will only be shared with others standing in the same shaded area (capacity = 9 people).

Poster Hall Map

overview



Oral Presentation Abstracts

Date: Tuesday Sep 7, 2021 Location: Zoom Category: Oral presentation
Time: 3:05 pm (CET)

Modulation of the central and peripheral nervous system

Elisa Konofagou
Columbia University

Elisa E. Konofagou designs and develops ultrasound-based technologies for automated estimation of tissue mechanics as well as drug delivery and therapeutics. Her group has worked on the design of algorithms that can estimate minute deformation as a result of physiological function, such as in the heart and vessels, and displacements induced by the ultrasound wave itself, such as in tumors and nerves, while she maintains several collaborations with physicians in order to translate these technologies to the clinical setting. She has also developed novel techniques in order to facilitate noninvasive brain drug delivery as well as modulation of both the central and peripheral nervous systems.

Date: Tuesday Sep 7, 2021 Location: Zoom Category: Oral presentation
Time: 3:25 pm (CET)

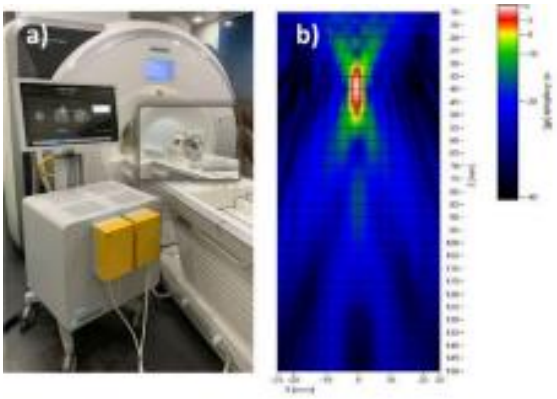
TRUST - A new 3D TRanscranial Ultrasound neuro STimulation system

S. Tretbar1, C. Risser1, C. Degel1, H. Hewener1, K. Butts-Pauly3, A. Melzer2, M. Fournelle1,1Ultrasound Department, Fraunhofer IBMT, Sankt Ingbert, Germany2Innovation Center Computer Assisted Surgery, Leipzig, Germany3Stanford University, USA

Deep brain stimulation (DBS) is an established method for therapy of brain-related neurological disorders. Placing the electrode involves brain surgery with related risks such as brain hemorrhage or infection. Ultrasound may present a noninvasive alternative. While therapy based on high intensity focused ultrasound (HIFU) will permanently damage malignant brain tissue via ablation, LIFU (low intensity focused ultrasound) therapy is based on an acoustic stimulus having a neuromodulatory effect while remaining in the energy range of diagnostic ultrasound. In both cases, a successful therapy requires the precise application of spatially confined acoustic energy though the skull. In addition, it is very advantageous to reach multiple target areas as flexibly as possible throughout the brain. In order to allow a systematic assessment of the influence of ultrasound parameters (burst length, exposure time, frequency, amplitude, etc.) on brain physiology, we developed a new MR-conditional ultrasound neuro stimulation research system.

Our TRUST system consists of a multi-channel electronics platform and two matrix array transducers with 3D beam steering. The 256 transmit channels of the system can be individually programmed and have a maximum power of 16 W/channel. Depending on the chosen voltage and sonication duration, duty cycles of up to 100% can be realized. The matrix ultrasound arrays have 256 elements in a circular configuration with a pitch of 3.08 mm and a frequency of 480 kHz. The matrix array transducers are divided into two separately connected apertures of 128 elements each (inner circle and outer ring) that can independently be driven by the system. For example, in the investigation of cross-beam approaches allowing higher resolution focusing, one of the rings from each of two perpendicular-positioned transducers can be activated. The flat matrix array probes allow integration into an MRI system head coil and are equipped with MR-sensitive fiducials for easy localization in MR planning data. Each probe is equipped with active cooling. The user interface allows definition of the focusing properties by simply choosing a focal point in the brain. As an alternative, pre-defined custom delay patterns can be prescribed, which will allow for compensation of phased aberration due to propagation through the skull bone. Arbitrary temporal patterns can be defined both on the level of the individual signal burst (using pulse wave modulation) and with respect to pulse/pause patterns.

The performance of the TRUST system (figure 1a) and probes were assessed in sound-field scans. With a transmit voltage of +/- 90V, a focal pressure (peak-to-peak) of more than 8 MPa was obtained when measured according to protocols described by standards for acoustic safety (IEC 60601-2-37). The inter-element variability in acoustic output was less than 20% (standard deviation). The array allows steering in a range of approximately +/- 20°, with grating lobes higher than -6 dB appearing for higher steering angles. The focus size strongly depends on the chosen focus depth and can reach approximately 3mm x 20mm in lateral and axial dimension respectively (for focusing to a depth of 40 mm, see figure 1b). The system safety was assessed both for compliance with medical device standards (IEC 60601-1 electrical safety testing by certified lab) and thermal aspects. Temperature probes are integrated into the transducer and on the cable and are monitored in real-time, so that the system is disabled if predefined critical temperature levels are reached. Furthermore, initial MRI compatibility testing (3T MR) has been carried out (no probe attraction and the impact of the system and probes on MR SNR has been assessed for different sequences)



Date: Tuesday Sep 7, 2021 Location: Zoom Category: Oral presentation
Time: 3:40 pm (CET)

Time course of low-intensity transcranial ultrasound on the excitability of ipsilateral and contralateral human primary motor cortex

Xue Xia 123, Anton Fomenko 24, Jean-François Nankoo 2, Ke Zeng 2, Yanqiu Wang 12, Jian Zhang 1, Andres M Lozano 24, Robert Chen 23*
1 School of Psychology, Shanghai University of Sport, Shanghai, China
2 Krembil Research Institute, University Health Network, Toronto, ON, Canada
3 Division of Neurology, Department of Medicine, University of Toronto, Toronto, ON, Canada
4 Division of Neurosurgery, Department of Surgery, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada

Low-intensity transcranial ultrasound stimulation (TUS) is a promising non-invasive brain stimulation technique that can modulate the excitability of cortical and deep brain structures with a high degree of focality. Previous human studies showed that TUS decreases transcranial magnetic stimulation (TMS) induced motor cortex (M1) excitability, but whether the effects persist beyond sonication and whether TUS affects the excitability of other interconnected cortical areas is not known. In the present study, we investigated the time course effect of TUS of the left M1 on the ipsilateral and contralateral (right) M1 excitability using a combined TMS-TUS stimulation paradigm. We tested 22 human subjects and TMS motor evoked potentials used to index M1 excitability. Since a previous study showed that the neuromodulatory effect of the TUS presented in a blocked design was stronger than in an interleaved design, we tested the time course of TUS in both types of design. Left M1 excitability was tested at 400 ms before the onset of a TUS (baseline); 490, 502, 520, 550, 600, 700, 1000, 1500, 2000, and 2500 ms after the onset of TUS; and 490 and 550 ms after the onset of sham TUS. The right M1 excitability was tested at 400 ms before the onset of left M1 TUS (baseline); 100, 300, 490, 502, 520, 550, 600, 700, 1000, 1500, 2000, and 2500 ms after the onset of TUS; 490 and 550 ms after the onset of sham TUS. We showed that suppression of left M1 excitability persisted for at least 20 ms after a 500 ms sonication period, and the effects were stronger with blocked design compared to interleaved design. There was no significant effect on contralateral M1 excitability. Furthermore, since the TUS transducer is activated with an amplified radiofrequency signal when sonicating, we also investigated whether it may alter the temporally and spatially overlapping TMS-induced electromagnetic field. We conducted an electromagnetic field quantification in proximity to the TUS-TMS stimulator to rule out device interference as a possible confounding mechanism of MEP modulation. The results showed that the ultrasound transducer did not affect the magnitude or time course of the TMS-induced electromagnetic field. The suppressive effects of TUS on ipsilateral M1 cortical excitability outlast the sonication duration. The absence of contralateral effects suggests that there is little tonic interhemispheric inhibition in the resting state.

Date: Tuesday Sep 7, 2021 Location: Zoom Category: Oral presentation
Time: 3:55 pm (CET)

Bifocal Acoustic Lens For Personalized Simultaneous Multisite Deep Brain Stimulation

T.Tiennot1, D. Attali1,2,3, A. Houdouin1, M. Tanter1, J.F. Aubry1
1 Physics for Medicine Paris, INSERM U1273, ESPCI Paris, CNRS UMR 8063, PSL Research University, Paris, France.
2 GHU PARIS Psychiatrie & Neurosciences, site Sainte-Anne, Service Hospitalo-Universitaire, Pôle Hospitalo-Universitaire Paris 15, F-75014 Paris, France
3 Université de Paris, F-75005 Paris, France

Objectives: Ultrasound neuromodulation is an emerging technique for the modification of the neural activity in the central and the peripheral nervous systems [1]. Compared to existing techniques, its high spatial resolution and penetration depth makes it suitable to reach structures deep in the human brain with a mm-scale precision. However, the human skull is not transparent to ultrasound due to the refraction, reflection, absorption and scattering of the incoming ultrasound beam [2]. Several methods have been developed to compensate for these distortions but rely on multi-element transducers [3] and remain expensive. Recently, several works based on a single-element transducer coupled with an aberration-corrective lens have been proposed, but remained limited to the targeting of a single structure inside the brain [4] or lack of demonstration on real human skulls [5]. Here we present acoustic lenses that both compensate for human skull aberrations and enable the simultaneous targeting of multiple structures deep inside the brain.
Methods: Numerical simulations were performed to design bifocal lenses for four cadaveric human skulls. These lenses were manufactured and experimental pressure scans were acquired to validate their design.
Results: Typical experimental result is displayed in Fig 1. The average absolute shift between the maximum intensity spots and the targets was 0.22mm±0.26mm for the four skulls. According to the metrics of [6], the mean (pmeanerr ± SD), root-mean-square (pSDerr ± SD), pressure error (pRMS ± SD) and the cross correlation (pxc ± SD) fields were pmeanerr =4.74±0.75%, pSDerr =0.0087±0.0019%, pRMS=5.86±0.91% and pxc=96.54±0.71%, which demonstrates the accuracy of lens-based transcranial bifocal targeting.
Conclusion: Future work will focus on including more skulls to even more demonstrate the versatility of the technique and its possible translation in human studies for non-invasive simultaneous multisite deep brain stimulation.

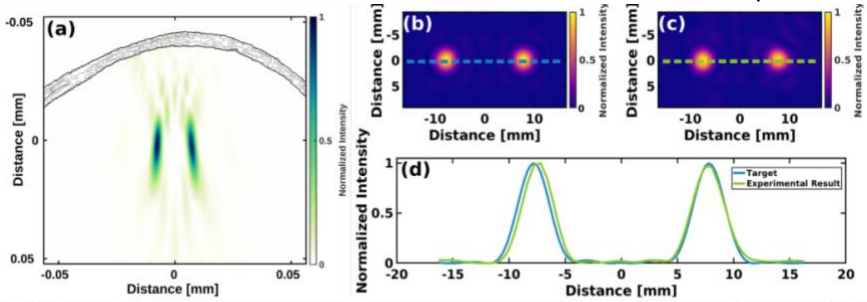


Figure 1: (a) Representation of a simulated intensity field overlaid on a CT-skull contour plot. (b-c) Cross-section of normalized intensity distribution obtained (b) in simulations in water (i.e. our target) and (c) experimentally across a human-cadaveric skull. (d) Comparison of 1D cross-section of simulated and experimental normalized intensity fields displayed in (b) and (c).

References:
1. Blackmore J, Shrivastava S, Sallet J, Butler CR, Cleveland RO. Ultrasound neuromodulation: A review of results, mechanisms and safety. Ultrasound Med Biol. 2019;45(7):1509–36.
2. Pinton G, Aubry J-F, Bossy E, Muller M, Pernot M, Tanter M. Attenuation, scattering, and absorption of ultrasound in the skull bone: Absorption of ultrasound in the skull bone. Med Phys. 2012;39(1):299–307.
3. Bancel T, Houdouin A, Annic P, Rachmilevitch I, Shapira Y, Tanter M, et al. Comparison between ray-tracing and full-wave simulation for transcranial ultrasound focusing on a clinical system using the transfer matrix formalism. IEEE Trans Ultrason Ferroelectr Freq Control. 2021;PP:1–1.
4. Maimbourg, Guillaume, et al. "3D-printed adaptive acoustic lens as a disruptive technology for transcranial ultrasound therapy using single-element transducers." Physics in Medicine & Biology. 2018; 63.2.
5. Jiménez-Gambín S, Jiménez N, Benlloch JM, Camarena F. Holograms to focus arbitrary ultrasonic fields through the skull. Phys Rev Appl [Internet]. 2019;12(1).
6. Xu R, O'Reilly MA. Simulating transvertebral ultrasound propagation with a multi-layered ray acoustics model. Phys Med Biol. 2018;63(14):145017.

Date: Tuesday Sep 7, 2021 Location: Zoom Category: Oral presentation
Time: 4:15 pm (CET)

In vivo cell-type selectivity of transcranial focused ultrasound stimulation

Kai Yu, Xiaodan Niu, Esther Krook-Magnuson, and Bin He
K.Y., X. N. and B.H. are with Department of Biomedical Engineering, Carnegie Mellon University, Pittsburgh, PA, USA. E.K.-M. is with Department of Neuroscience, University of Minnesota, Minneapolis, MN, USA. K.Y. and X. N. contributed equally.

Low-intensity transcranial focused ultrasound (tFUS) has been evidenced as a noninvasive brain stimulation tool for safely and reversibly modulating brain circuits with high spatiotemporal precision. While efforts are devoted to uncovering the mechanism of tFUS neuromodulation, it remains unclear whether the tFUS exhibits the same modulation effects in different neuron populations in the in vivo brain.
To address this question, we firstly examined the tFUS stimulation effect on different functional neuron types in wild-type Wistar rats (N = 19) by tuning the ultrasound pulse repetition frequency (PRF). The neuronal cell types, such as regular spiking units (RSU, presumably as excitatory neurons) and fast spiking units (FSU, presumably as inhibitory neurons), were identified based on features of their action potentials that were concurrently recorded from the primary somatosensory cortex (S1) through intracranial multi-electrode array. Two anesthetic methods, i.e., ketamine/xylazine cocktail (N = 9) and isoflurane (N = 10), were used to sedate the animal subjects for a reliable tFUS targeting; multiple sham conditions were employed to rigorously control confounding factors, e.g., potentially audible sound, electromagnetic interference to the electrical recordings, skull bone conduction and potential ultrasound-electrode interaction. Through multiple studies, we repeatedly observed significant effects of the tFUS PRF on changing firing rates of the RSUs during the sonication (146 RSUs, $p = 0.006$ in the ketamine/xylazine group; 245 RSUs, $p = 1.65e-8$ in the isoflurane group). On the contrary, the FSUs demonstrated homogenous responses to all the PRF levels (53 FSUs, $p > 0.3$ in the ketamine/xylazine group; 347 FSUs, $p > 0.1$ in the isoflurane group). Notablly, the interaction between the neuronal cell type and ultrasound PRF varied significantly across the two anesthesia methods ($p = 3.37e-9$). Such a phenomenon disappeared in the control studies by flipping acoustic aperture away from the scalp, targeting ultrasound to an anterior brain location or directing ultrasound onto the electrode shank. Moreover, we investigated such functional neuron-type-specific responses to the PRF change while maintaining a constant burst duty cycle (i.e., 60%) for the administered tFUS conditions (N = 7). Similarly, by maintaining the amount of energy delivered and tuning the PRF can still elicit significant responses of RSUs (174 RSUs, $p = 1.69e-14$), while the FSUs' spiking activities do not exhibit significant change (243 FSUs, $p > 0.09$). Furthermore, we tested this functional neuron-type specificity hypothesis in transgenic mouse models with parvalbumin (PV, inhibitory interneuron, 53 single units) and CaMKII-alpha (excitatory pyramidal neuron, 50 single units) cortical neurons identified by their response to optical stimulation (wavelength = 465 nm). Significant differences were also observed between these two optotagged neuron types in response to two levels of tFUS PRF ($p < 0.01$), in which the CaMKII-alpha neurons exhibited significantly higher spiking rates at a high ultrasound PRF level (i.e., 300 Hz) than those at a low PRF condition (i.e., 30 Hz), whereas the PV neurons preferred a low PRF condition (i.e., 30 Hz).
In summary, we observed that tFUS modulation effects have unequal impact to the excitatory and inhibitory neuron populations in the in vivo brain. By leveraging this functional neuron-type-specific stimulation capability of tFUS, we may gain a better understanding and thus enable more efficient explorations of the tFUS parameter space to achieve effective excitatory/inhibitory neuromodulation and treat neurological disorders noninvasively.

Date: Tuesday Sep 7, 2021 Location: Zoom Category: Oral presentation
Time: 4:30 pm (CET)

Deep brain optical recording of ultrasound neuromodulation reveals cell type selective parameter space

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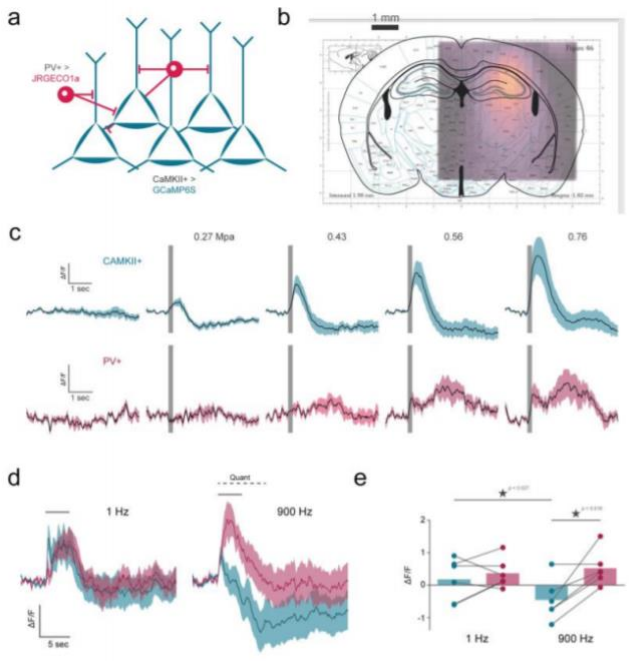
Focused ultrasound is a powerful tool for modulating deep brain activity, but the existence of bidirectional cell type selectivity across parameter space remains unknown. Here, we developed a focused ultrasound integrated fiber photometry system in freely behaving mouse model for measuring activity of subcortical genetically labeled cell types in response to focused ultrasound. Simultaneous imaging of excitatory and inhibitory neurons of the hippocampus revealed distinct parameter sets for net excitation or bimodal modulation of excitatory and inhibitory cells. Non-invasive positron emission tomography (PET) imaging of fluorodeoxyglucose across the brain demonstrated a highly concentrated effect at the target and confirmed net modulatory effects. Finally, we demonstrate that optimized parameters for parvalbumin+ neuron excitation with + pyramidal neuron inhibition result in seizure attenuation/suppression in a kainate model of epilepsy. Collectively, these data demonstrate that ultrasound parameters may be selected to bias directional response of discrete cell types in brain regions and can be leveraged in the design of therapeutic platforms for ultrasound neuromodulation.

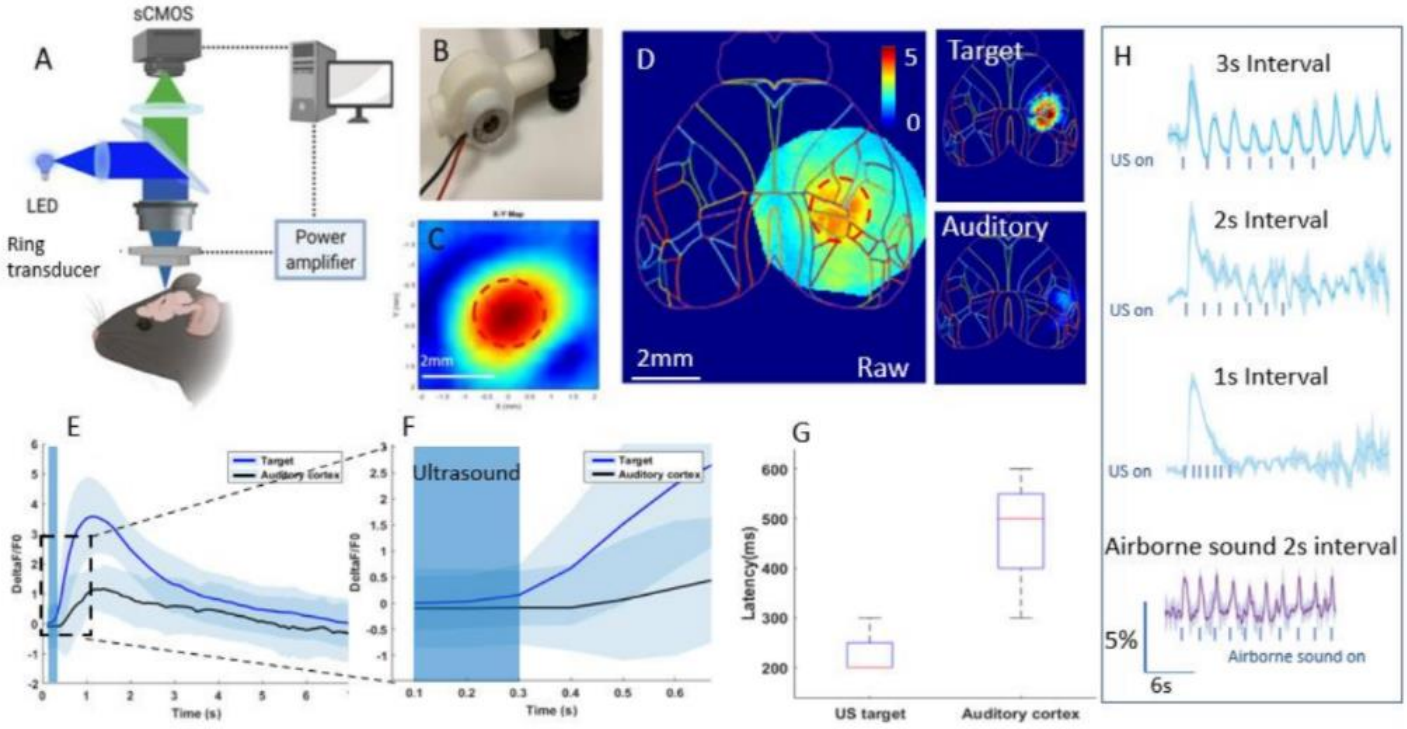


Date: Tuesday Sep 7, 2021 Location: Zoom Category: Oral presentation
Time: 4:45 pm (CET)

Transcranial ultrasound stimulates neurons in targeted region in mouse brain.

Zhihai Qiu, Mihyun Choi, Ningrui Li, Kim Butts Pauly

Recent work demonstrated smoothed waveforms reduce the auditory confound in mice and that deaf mice respond to ultrasound (Mohammadjavadi 2019). However, there are still lingering questions about the lack of response at the ultrasound focus on GCaMP fluorescence imaging (Sato 2018). In the present study, a widefield GCaMP fluorescence microscope was developed for visualizing neural activity in mouse brain in vivo (Figure A). A ring transducer was used to generate focused ultrasound in the mouse brain while allowing realtime imaging of neural activities through the hole in the center (Figure B and C). We used the localized semi-nonnegative matrix factorization (LocaNMF) method (Saxena 2020) to decompose the acquired images by the spatial and temporal response into multiple components, including the target and auditory components. Our results showed that smoothed waveforms suppress the auditory component and produce highly localized stimulation in the targeted brain regions (Figure D). The neural response in the targeted region is higher than the auditory components (Figure E). The latency (as measured by 0.5% response elevation) in the target region is on average 205 ms, as compared to an average latency of 495 ms in the auditory cortex. In addition, repeated stimulation can induce robust responses. If the stimulation interval is shorter than 2s, adaptation effects were clearly observed. In contrast, airborne sound stimulation (5kHz, 60dB) with 2 seconds interval did not exhibit adaptation effects (Figure H). Collectively, our data clearly showed that ultrasound can induce targeted neurostimulation effects.



Date: Wednesday Sep 8, 2021 Location: Zoom Category: Oral presentation
Time: 3:05 pm (CET)

TUS in the Treatment of Epilepsy

Ellen J. Bubrick, MD, FAES

Epilepsy is one of the most common neurologic disorders, affecting 3.5 million Americans, and >65 million people worldwide. Approximately 2/3rds of patients with epilepsy are seizure free on antiseizure medication, but 1/3rd have drug-resistant epilepsy (DRE). The burden of DRE is high; ongoing seizures impair quality of life, can be very debilitating, and are often associated with significant morbidity and even mortality. Though the population affected by this disorder is large with high morbidity, there are few new treatments, pharmacologic or non-pharmacologic, coming down the pipeline to address this disabling disorder. Surgical resection or laser ablation are suitable for only a small percentage of patients with DRE. Neuromodulation is very effective in some neuropsychiatric disorders (Deep Brain Stimulation for tremor, Transcranial Magnetic Stimulation (TMS) and Electroconvulsive Therapy for depression), and could potentially offer an alternative treatment for DRE. Invasive neurostimulatory devices such as Responsive Neurostimulation and Vagal Nerve Stimulation are of some benefit in epilepsy, but these require permanent implanted hardware, and clinical responses vary. Noninvasive TMS, though highly effective for some psychiatric illnesses, has produced disappointing outcomes in epilepsy, largely due to its inability to reach deeper structures in the brain commonly responsible for seizure onset, such as the hippocampus. High intensity FUS has been transformative in treating tremor as it can treat deep targets such as the thalamus by thermal ablation. Low intensity focused ultrasound (LIFUS) waves can be transmitted through the skull and modulate deep structures with a sharply focused beam without causing tissue destruction. Epilepsy rodent models have shown LIFUS can suppress seizure activity on EEG. Human studies have shown modulation of auditory, visual, sensory and motor functions by positioning the beam focus over correlating cortex. Therefore, LIFUS may be a promising alternative treatment for DRE when surgery is not favored. We will discuss our pilot safety trial using LIFUS targeting the hippocampus in subjects with temporal lobe DRE.

Date: Wednesday Sep 8, 2021 Location: Zoom Category: Oral presentation
Time: 3:25 pm (CET)

Neuronavigation-Guided Low-Intensity Focused Ultrasound in Patients with Epilepsy

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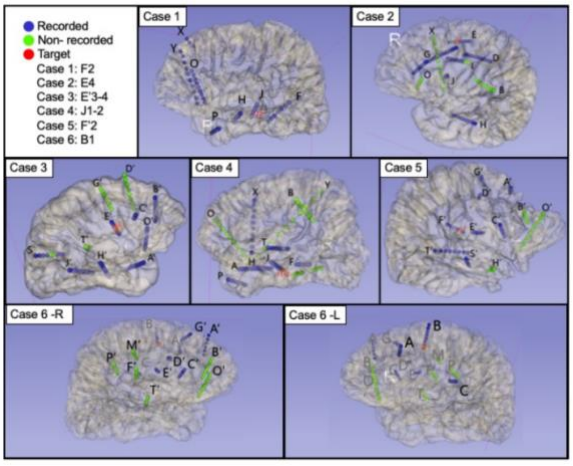
The benefits of low-intensity focused ultrasound (LI-FUS) on epilepsy have been demonstrated in the rats with pentylenetetrazol-induced seizures. However, the effects of LI-FUS on patients with epilepsy has not been well established. Therefore, we prospectively enrolled six patients with drug-resistant epilepsy undergoing stereo-electroencephalography (SEEG) to investigate not only the safety but also the neuromodulatory effects of LI-FUS in humans. LI-FUS was delivered to the epileptogenic area, which was selected accoding to the SEEG results, using a neuronavigation-guided focused ultrasound system (ceiling ISPTA level = 2.8 Watts/cm2, duty = 30%, modulating duration = 10 minutes). Continuous SEEG were recorded before and after the procedure, including the 10 minutes during sonication. Clinical seizures and adverse events after LI-FUS were also monitored. The results showed that two patients had a decrease in seizure frequency in the 3-day follow-up. However, there was an increase in the frequency of subclinical seizures in one patient. From the view of adverse events, scalp heating during LI-FUS in one patient and transient functional neurolgocal disorder in one another patient were noticed. There was no lesion or brain edema in post-treatment MRI. For better evaluating the effects of LI-FUS on epileptic network, we used node strength to analysis the connectivitiy between electrodes of SEEG. We found that node strength after LI-FUS was signigicantly changed compared to that before treatment. The effects on node strength were varied in frequency band, and transient lasting for 30-60 minutes. From this study, we provided evidence that LI-FUS can be safely delivered in the local brain region in patients with epilepsy. We also found inconsistent and transient neuromodulatory effect on epileptic network from LI-FUS. A larger sample cohort and pursuing optimal sonication parameters will be required to elucidate the neuromodulatory effects of LI-FUS on seizure control.



Date: Wednesday Sep 8, 2021 Location: Zoom Category: Oral presentation
Time: 3:40 pm (CET)

Ultrasound inhibits amyloid formation through membrane structure modulation

Hao Wang

Alzheimer's Disease (AD) is characterized by the presence of β-Amyloid (Aβ) plaques, tau tangles, inflammation, and loss of cognitive function. Amyloid precursor protein (APP) clusters with the enzymes β- and g-secretase in ganglioside (GM1) lipids to generate Aβ-peptide. The distance between APP and g-secretase determines the amount of Aβ to be produced and the amount of plaques formed. Here we show that both APP and g-secretase are mechanosensitive and they respond to different thresholds of shear force. APP is highly sensitive to mechanical force and is trafficked nanoscopic distances out of GM1 clusters into a disordered region of the membrane under low intensity fluid shear (0.1 dynes/cm2) in cultured primary neurons. In contrast g-secretase requires high intensity fluid shear (15 dynes/cm2) to traffic out of GM1 clusters suggesting an minimum production of Aβ peptide with mild shear. Mild sonication of whole mouse brains show similar trafficking of APP out of GM1 clusters, away from its enzyme g-secretase, which doesn't respond to ultrasound. Concomitantly both cholesterol and Aβ level in ultrasound treated brain tissue decreased. Apart from Aβ production, we show that tau phosphorylation and inflammation are also regulated by mechanical shear through similar membrane-mediated pathways. We propose a molecular mechanism for ultrasound where mechanical force disrupts clustering of amyloid producing enzyme with its substrate. Without access to its substrate, the enzymes are mechanically inhibited. These results indicate that ultrasound has the potential to be an effective therapeutic approach for neurodegenerative diseases like AD.

Date: Wednesday Sep 8, 2021 Location: Zoom Category: Oral presentation
Time: 3:55 pm (CET)

FUS-induced median nerve stimulation alters pain sensation in humans

Stephen A. Lee, Hermes A.S. Kamimura, Elisa E. Konofagou

The peripheral nervous system manages and translates all sensory signals, including noxious pain, to the brain. Noxious thermal stimuli at the skin can elicit pain via TRPV1 channels in free nerve endings of c-fiber neurons. Evidence shows focused ultrasound (FUS) has neuromodulatory attributes that can alter both brain and nerve signals. Thus, the objective of this study was to investigate whether direct nerve FUS neuromodulation can alter pain sensation levels.
Eleven (n=11) normal human volunteers were enrolled in this study. We used a dual-mode ultrasound system to both target with displacement imaging and stimulate the median nerve at the distal region of the forearm (Fig. 1a). The imaging transducer (7.8 MHz, 104-element, phased array) and the stimulation transducer (1.1 MHz, 4- element, concentric array) both driven by a Vantage system (Verasonics). FUS (5-ms pulse) was delivered at various pressures to achieve adequate nerve displacement. We used a custom-built thermal stimulation device (Fig. 1b) to induce noxious pain through TRPV1 channels activation in the C6 dermatome, innervated by the median nerve. Fig. 1c shows the heat pulse signal (5-s baseline at skin temperature (30-32oC), 2-s rise to the subjects' perceived threshold for pain (37-40oC). Subsequently, there was 2-3 minute-interval (randomized) in between pulses to allow for cessation of peptidergic release, i.e., upregulation of peptides (calcitonin gene-related peptide, substance P, BDNF) in the skin, responsible for changing the magnitude of response to a stimulus. Altogether, the subject received 15 thermal stimulations with FUS pulses randomized with sham pulses. Subjects were asked to rate their pain sensation based on the Wong-Baker pain rating scale. It was found that the interframe displacement induced during FUS is correlated with significant differences in reported pain sensation between FUS and sham pulses. Fig. 1d shows FUS decreased subjective pain ratings significantly two subjects ($p < 0.05$) and trending in another subject but not significantly ($p = 0.0839$). Subjects were grouped into a 0-3 micron and 4-7 micron group (Fig. 1e). A 2-way ANOVA indicated the decrease in pain ratings between the two groups were significantly different. This study provides the basis for a feasibility study in chronic pain patients leading to the potential development of a FUS-based therapeutic for pain control.

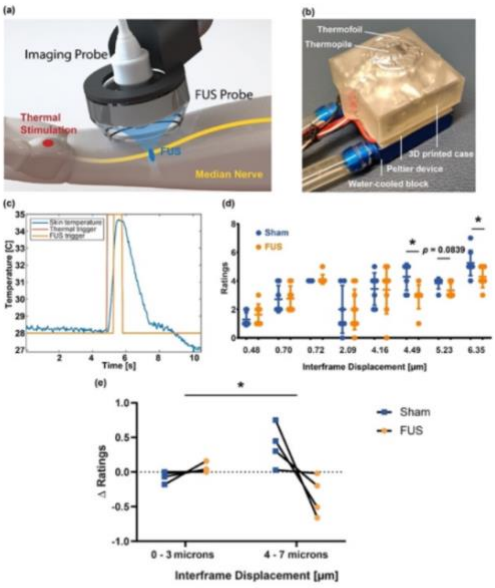


Figure 1. (a) Experimental setup illustration with location of thermal and FUS stimulation sites. (b) Closed-loop custom thermal stimulation device. (c) Representative thermal trace from the center thermopile of one 35°C stimulation with thermal and FUS trigger timings. (d) Summary statistics (Mann-Whitney t-test), within each subject, of 8 subjects receiving 15 randomized thermal/FUS or thermal/Sham stimulations. Data is displayed in increasing interframe displacement of the nerve measured by ultrasound displacement tracking. (e) 2-way Anova of the change in ratings due to FUS or sham grouped by peak interframe nerve displacement. ($p = 0.0309$).

Date: Wednesday Sep 8, 2021 Location: Zoom Category: Oral presentation
Time: 4:15 pm (CET)

Monitoring Cavitation Activity and the effect of Tissue Temperature During Focused Ultrasound Neuromodulation

Erica P. McCune [1], Stephen A. Lee [1], Elisa E. Konofagou [1,2], [1] Department of Biomedical Engineering, Columbia University, New York, USA, [2] Department of Radiology, Columbia University Medical Center, New York, USA

Introduction/Background:
Focused ultrasound neuromodulation applied to the peripheral nervous system can induce therapeutic effects, such as decreasing perceived pain. Peripheral FUN often relies on the use of high negative pressures, making cavitation a potential safety concern. In addition, heat may accumulate in tissue during FUS and tissue temperature naturally varies between patients. To ensure safety during these neuromodulatory procedures, cavitation should be monitored and factors influencing its activity must be well understood. Previous studies have shown a dependence of inertial cavitation thresholds on tissue shear modulus, which changes with temperature, but the direct effect of non-ablative temperatures on cavitation is not well characterized. This study investigated cavitation activity and its change with tissue temperature during peripheral FUS neuromodulation to ensure safety.
Methods:
A 1.1-MHz, 4-element FUS transducer (SonicConcepts, WA, USA) applied pulses of 5 ms, 4 MPa peak negative pressure for 10s at 15 Hz or 30 Hz PRF to the sciatic nerve in the mouse hind limb. Cavitation was recorded at 7.8 MHz with a concentric imaging transducer (ATL, Philips). Displacement imaging verified the sciatic nerve targeting. A water bath with a Peltier device controlled tissue temperature (Fig. 1a). Consecutive sonications (n=6) were performed at a constant temperature (30°C or 38°C) at both PRFs. In a second experiment, sonication occurred at five temperatures with a ramping pattern (30°C to 38°C to 30°C) at 15Hz PRF and at three decreasing temperatures at 30Hz PRF (38°C to 30°C). Each set of consecutive sonications occurred in a new limb in all experiments. Passive acoustic maps (PAM) were computed with a time exposure acoustic (TEA) algorithm and the time averaged cavitation dose was separately calculated for broadband and harmonic frequencies.
Results/Discussion
Averaged TEA PAM show increased average cavitation of 1.9 dB at 15 Hz and 7.3 dB at 30 Hz between 30°C and 38°C (Fig. 1b). During temperature ramping, The stable cavitation dose (SCD) increased by 2.0 dB and the inertial cavitation dose (ICD) by 2.8 dB between 30°C and 38°C at 15 Hz. SCD decreased by 7.0 dB and ICD by 9.3dB between 38°C and 30°C at 30Hz (Fig. 1c). The verage cavitation dose at a constant temperature increased by 2.9dB for the SCD and 0.1dB for the ICD at 15Hz and by 2.9dB for the SCD and 16.5dB for the ICD at 30Hz between 30°C and 38°C (Fig. 1d). This confirms prior literature showing higher temperatures increase harmonic magnitudes from nonlinear propagation, which may be reflected in the SCD changes reported here. These findings demonstrate the occurrence of cavitation during FUS with a magnitude dependence on tissue temperature. Thus, both temperature elevation and cavitation need to be monitored during FUS.

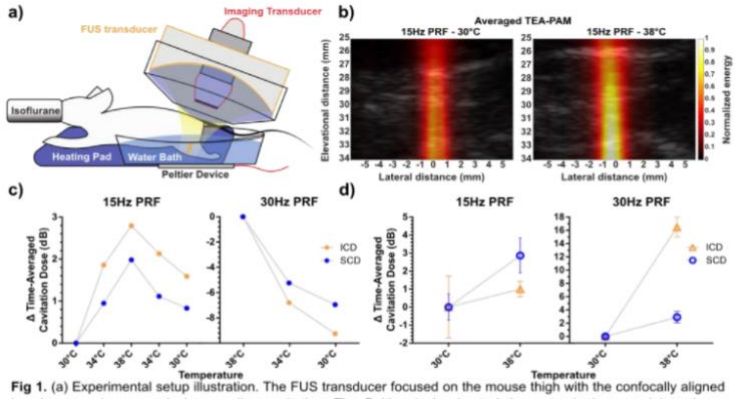


Fig 1. (a) Experimental setup illustration. The FUS transducer focused on the mouse thigh with the confocally aligned imaging transducer passively recording cavitation. The Peltier device heated the water bath to modulate tissue temperature. (b) Comparison of PAM activity between 30°C and 38°C for 15Hz PRF during the constant temperature experiment. Activity in both maps is normalized to the maximum intensity found in the 38°C PAM. (c) Time-averaged SCD and ICD across temperature for the ramp-up/ramp-down experiment. (d) Time-averaged SCD and ICD (n=6) for the 30°C and 38°C constant temperature experiment.

Date: Wednesday Sep 8, 2021 Location: Zoom Category: Oral presentation
Time: 4:30 pm (CET)

Sonothermogenetics Enables Noninvasive and Cell-type Specific Deep Brain Neuromodulation

Yaoheng Yang1, Christopher Pham Pacia1, Dezhuang Ye1, Lifei Zhu1, Hongchae Baek1, Yimei Yue1, Jinyun Yuan1, Mark J. Miller1, Jianmin Cui1, Joseph P. Culver1, Michael R. Bruchas2, and Hong Chen1*; 1. Washington University in St. Louis, Saint Louis, MO. 2 University of Washington, Seattle, WA

Background, Motivation and Objective: Critical advances in the investigation of brain functions and treatment of brain disorders are hindered by our inability to selectively target neurons in a noninvasive manner in the deep brain. Sonogenetics, which uses focused ultrasound (FUS) to selectively control a specific type of neurons that have been genetically modified to express ultrasound-sensitive ion channels, has the potential to overcome this challenge. All reported sonogenetic studies utilized mechanosensitive ion channels. However, these studies did not provide direct evidence of neuronal activation in vivo and did not demonstrate behavior modulation in freely moving mice. This study aimed to develop sonothermogenetics for noninvasive, deep-penetrating, and cell-type- specific neuromodulation by combining a thermosensitive ion channel TRPV1 with FUS-induced brief, non-noxious thermal effect.
Methods: The sensitivity of TRPV1 to FUS sonication was evaluated in vitro. It was followed by in vivo assessment of the success rate of sonothermogenetics in the activation of genetically defined neurons in the mouse brain by two-photon microscopic calcium imaging. Behavioral response evoked by sonothermogenetic stimulation at a deep brain target was recorded in freely moving mice that were sonicated by the customized miniature wearable focused ultrasound. Immunohistochemistry staining of ex vivo brain slices was performed to evaluate the safety of FUS sonication.
Results/Discussion: TRPV1 was found to be a sonothermogenetic actuator. FUS sonication at the mouse brain in vivo selectively activated neurons that were genetically modified to express TRPV1 (Fig. 1A). Temporally precise activation of TRPV1-expressing neurons was achieved with its success rate linearly correlated with the peak average temperature within the FUS-targeted brain region as measured by in vivo magnetic resonance thermometry. FUS stimulation of TRPV1-expressing neurons of the Parkinsonian circuit at the striatum repeatedly evoked rotating locomotor behavior in freely moving mice (Fig. 1B). FUS sonication was confirmed to be safe based on inspection of neuronal integrity, inflammation, and apoptosis markers.
Conclusions: Sonothermogenetics is a noninvasive and cell-type-specific neuromodulation approach with the capability to target the deep brain.

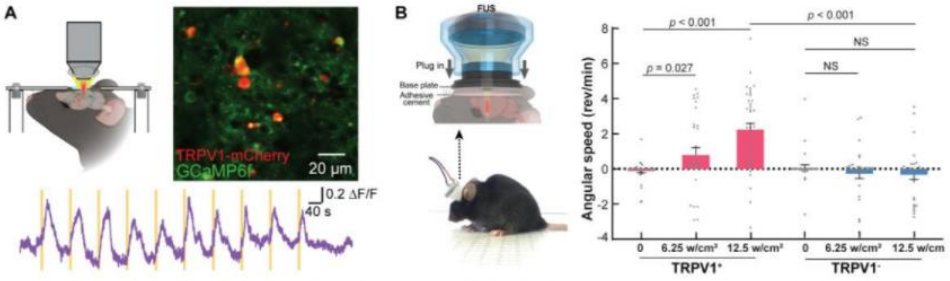


Figure 1. (A) Sonothermogenetics in the mouse brain in vivo. The mouse head was fixed in the stage for simultaneous FUS stimulation and two-photon Ca^{2+} imaging. The coexpression of TRPV1 and GCaMP was observed in vivo. FUS can repeatedly activate neurons expressing TRPV1. The orange bar indicates the FUS on time. (B) Experimental setup for *in vivo* sonothermogenetic stimulation of the striatum in freely moving mice (left panel). The miniaturized wearable FUS transducer was plugged into a base plate adhered on the mouse head. The comparison of the mean angular rotation speed of $TRPV1^+$ mice versus $TRPV1^-$ mice with FUS stimulation at I_{spta} = 0, 6.25, and 12.5 w/cm^2. The positive and negative values indicate rotation in the contralateral and ipsilateral directions, respectively. Error bars represent the standard error of the mean.

Date: Wednesday Sep 8, 2021 Location: Zoom Category: Oral presentation
Time: 4:45 pm (CET)

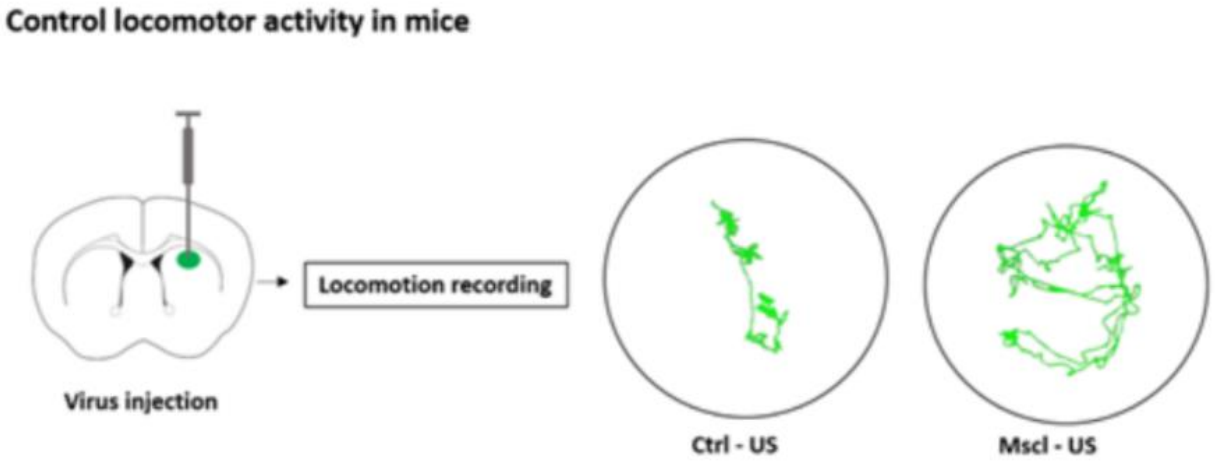
Sonogenetic deep brain stimulation in freely moving mice

Quanxiang Xian, Zhihai Qiu, Suresh Kanna, Shashwati Kala, Jinghui Guo, Lei Sun

Background, Motivation and Objective
Controlling specific targeted neural activity via physical intervention is a effective method to gain causal Insight into brain functions and treat brain diseases. Ultrasound stimulation (US) is a promising modality for probing brain function and treating brain diseases. It can be non-invasively steered and focused into millimeter-scale regions across the human skull, facilitated to produce controlled manipulation of neuronal activity. However, this method lacks selectivity. Sonogenetics, which focuses on the genetic modulation of ultrasound-sensitive neurons and their specific responses to ultrasound via the expression of MS receptors, has non-invative property ane enhanced spatial focus. Modulating animal's behavior with sonogenetics approach may enhance our new understanding of cell pathophysiology and almost certainly lead to development of novel neuropsychiatric diseases and non-neural diseases treatments.

Statement of Contribution/Methods
Methods we used included ultrasound stimulation, virus injection, fiber photometry, behavior tests, immunocytochemical staining.

Results/Discussion
In this study we demontrated a sonogenetics approach which can address specific cell types in vivo. Mscl-G22S (a mutant of mechanosenstive channel of large conductance) is a mechanosensitive ion channel isolated from the Escherichia coli and can be selectively modulated by low intensity ultrasound stimulation. Here we report the first in vivo behavioral demonstration of a functional sonogenetics in intact animals. Transcranial Mscl G22S-mediated ultrasound stimulation increased animal's locomotion activity through activation of the neurons of dorsal striatum, induced stronger whisker movement by activation of excitatory neurons in the sensory cortex. We conclude that ultrasound can modulate the behavior in mice which expresses mscl-G22S. Achieving manipulation of behavior with ultrasound control of neuronal subtypes in this way may find application across a broad range of neuroscience and disorders.



Date: Thursday Sep 9, 2021 Location: Zoom Category: Oral presentation
Time: 3:05 pm (CET)

Spatio-temporal dynamics of neural responses causally induced by single-pulse focused ultrasound

N'Djin, W.A.1, Suarez Castellanos I.M.1, Aubier T.1, Perier M.1, Carpentier A.2,3
1 LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ Lyon, F-69003, Lyon, France
2 AP-HP, Neurosurgery department, Pitie Salpetriere hospital, F-75013 Paris, France
3 Sorbonne university, GRC23, Interface Neuro Machine team, F-75013 Paris, France

Low energy Focused Ultrasound (FUS) could be a promising alternative to standard neurostimulation strategies. While FUS should allow stimulation of brain regions with high selectivity/specificity, the associated spatio-temporal dynamics of basic neural responses remain to be described, to better control highly integrated responses. In this work, the spatio-temporal characteristics of Ca2+ fluxes triggered causally by single-pulse FUS exposures were investigated in vitro.
Experiments were performed on human neural progenitors (ReNcell-VM) and labelled with a Ca2+-sensitive fluorescent dye (Fluo-4). The FUS stimulation platform was built on an inverted microscope that included micromanipulators to position a FUS source (custom-made FUS transducer; radius of curvature: 11 mm; ø: 15 mm) (**Fig a**). The transducer was operated at its fundamental frequency (f0 = 727 kHz) and its harmonics, to explore the impact of the focal spot size on the stimulation selectivity. Single FUS pulses (duration = 0.2-20 ms, psar < 2 MPa) were applied, while the resulting neural activities were recorded using fluorescence microscopy imaging (ORCA-Fusion, Hamamatsu, 10 fps). The spatio-temporal Ca2+ dynamics induced by FUS were compared to those obtained by a gold standard chemical stimulation (KCl perfusion).
Ca2+ fluxes were successfully induced by FUS in human neural cells in vitro. Following FUS exposures, strong and sustained elevations in intracellular Ca2+ were immediately observed in localized areas within the FUS focus. These fluxes propagated across the surrounding neural network at an estimated velocity of 15 µm·s -1, over > 100-200 µm and dozens of seconds (**Fig b**). Neural responses induced by FUS stimulations exhibited similarities in their dynamics (propagation velocity through interconnected neurons, rate of change of florescence intensity) with those observed in the responses to KCl stimulation (**Fig. c-d**). They were, however, concentrated in the FUS focal area, while responses to diffuse KCl perfusion were spread throughout the FOV.
These investigations highlighted that Ca2+ fluxes can be causally, selectively and transiently induced by single-pulse FUS stimulations in a human neural model. These conditions are compatible with signal transmissions across multiple interconnected neurons. Overall, the complex data obtained from these recordings should be crucial to improve our knowledge and control of FUS neurostimulation phenomena, in order to consolidate the transfer of FUS techniques for future applications in deep brain neurostimulation. Project support: French Research Agency (ANR-16-TERC-0017), FUS Foundation (Centers of Excellence, 2019-2021).

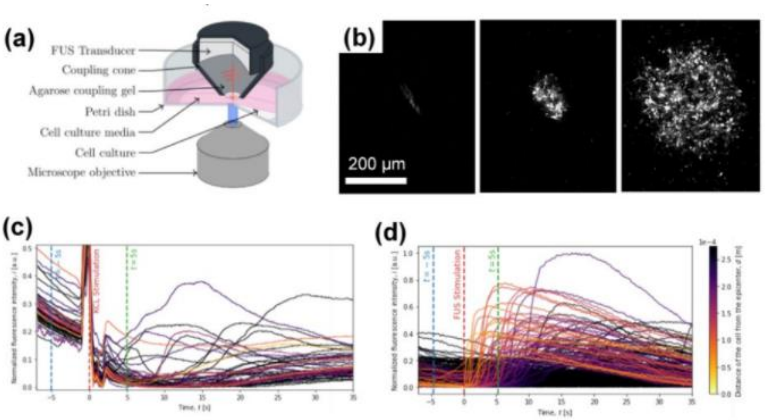


Fig. 1: **(a)** Mixed - FUS/fluorescence microscopy imaging – platform: experimental setup. **(b)** Single-pulse FUS-induced Ca2+ fluxes in in-vitro Human neural cells: selective response propagating across the neural network at t = 0.2 s, t = 1.0 s, and t = 8.0 s after FUS exposure. **(c, d)** Individual traces of normalized fluorescence intensity versus time for every neural cells exhibiting a response in the FOV. **(c)** Chemical-induced response (spatially diffuse KCL perfusion). **(d)** FUS-induced response (spatially selective FUS targeting).

Date: Thursday Sept 9, 2021 Location: Zoom Category: Oral presentation
Time: 3:25 pm (CET)

Induction of Human Motor Cortex Plasticity by Theta Burst Transcranial Ultrasound Stimulation

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Background and Hypothesis: Transcranial ultrasound stimulation (TUS) is a novel, non-invasive neuromodulation method that is beginning to be applied in human subjects. We hypothesize that long-term potentiation (LTP)-like plasticity can be induced in the human motor cortex by repetitive TUS.

Materials and Methods: Three repetitive TUS protocols, theta burst patterned TUS (tbTUS), regularly patterned TUS (rTUS) and sham TUS, were delivered to motor cortex in 15 healthy subjects in separate sessions in random order. The tbTUS and rTUS had same total sonication duration and total time of stimulation. Motor evoked potentials (MEPs) evoked by single and paired pulse TMS were recorded before and at 5 min, 30 min and 60 min after TUS. Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were measured with paired pulse TMS. The effects of motor cortex tbTUS on movement performance in a visuo-motor task and the effects of ipsilateral occipital cortex tbTUS on motor cortex excitability were also assessed.

Results: MEP amplitudes significantly increased at 5 min (43.4%) and 30 min (27.5%) and returned to baseline level at 60 min after tbTUS. SICI was significantly attenuated at 5 min and 30 min, and ICF was significantly enhanced at 5 min after tbTUS. The movement time on a visuomotor task was significantly shortened after tbTUS without affecting task attention. In contrast, rTUS, sham TUS and occipital tbTUS had no effect on the MEP amplitudes elicited by both single and paired pulse TMS. In addition, the MEP amplitudes elicited by lateral-medial directed TMS were unchanged after tbTUS.

Conclusions: The tbTUS protocol is capable of inducing LTP-like plasticity in human for at least 30 min. The plasticity occurred at the cortical level and involved both inhibitory and excitatory cortical circuits. This LTP-like plasticity was specific to tbTUS and could not be due to sensory confounds associated with TUS. tbTUS is a novel paradigm to induce cortical plasticity in human and has the potential to be developed for neuromodulation treatment for neurological and psychiatric disorders, and to advance neuroscience research.

Date: Thursday Sept 9, 2021 Location: Zoom Category: Oral presentation
Time: 4:00 pm (CET)

Image-based guidance for focused ultrasound neuromodulation

Hyungmin Kim, Korea Institute of Science and Technology

Non-pharmacological and non-invasive neuromodulation of selective brain areas would provide unprecedented opportunities in neuroscience and neurotherapeutics. Transcranial focused ultrasound (tFUS) has emerged as a novelneuromodulation modality with its exquisite spatial selectivity and depth penetration compared to conventional non-invasive neuromodulation methods, such as transcranial magnetic stimulation (TMS) and transcranial current stimulation (tCS). In order to maximize the spatial selectivity of tFUS, image-based guidance is widely adopted, especially for larger animal and human studies. However, many researchers still rely on image-based guidance solutions developed for TMS. I would like to summarize technical achievements in image-based guidance for tFUS developed by research groups worldwide and discuss the future development directions.

Date: Thursday Sept 9, 2021 Location: Zoom Category: Oral presentation
Time: 4:20 pm (CET)

Pseudo-CTs from T1w MRI for planning of low-intensity transcranial ultrasound stimulation

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Introduction: Individual skull models of bone density and geometry are important when simulating the expected acoustic field in transcranial ultrasound (TUS). Computed tomography (CT) images have good contrast between bone and soft tissue, and CT Hounsfield units (HU) have been used to estimate skull acoustic properties [1]. However, obtaining CT images in research participants is prohibitive due to exposure to ionising radiation. 2D convolutional neural network (CNN) methods have been proposed to synthesise pseudo-CT (pCT) from ultra-short echo time magnetic resonance (MR) images for use in TUS planning [2]. In this study, we used a 3D CNN to synthesise pCT from T1-weighted MR images. We performed simulations using real CT and compared them to simulations using pCT in 37 individuals from a healthy control database.

Materials & Methods: Low-dose CT (100 keV) and T1-weighted MR images from 37 healthy control subjects (mean age ± SD = 38.1 ± 11.4) were downloaded from the CERMEP-IDB-MRXFDG database [3]. Images were rigidly realigned and resampled to the MNI152 1mm space. CT images were thresholded at 300 Hounsfield units (HU) to obtain bone only. Our 3D CNN was based on a U-Net [4] with shuffle convolutional layers [5] and implemented in PyTorch. We trained on 256 x 256 x 32 patches from the MR images, used the Adam optimizer and L2 loss, and performed a four-fold cross-validation. We used the k-Wave MATLAB Toolbox [6], [7] for our simulations. We targeted the dorsal anterior cingulate from a position over the frontal pole, keeping the transducer approximately perpendicular to the skull surface. We simulated the TUS burst (pulse length = 30 ms, pulse repetition frequency = 10 Hz, total duration = 20 s) with a 250 kHz single element transducer. The free field maximum pressure was 0.82 MPa. The skull was estimated from CT images by thresholding at 300 HU and truncating values above 2400 HU. CT HU were linearly mapped to acoustic properties (sound speed, density, attenuation coefficient) according to [8]. All other media in the image were treated as homogeneouswith acoustic properties of water. We present here preliminary results from fold 1 of our cross-validation.

Results: Our CNN produced pCT images with mean absolute errors of 254.4 ± 48.3 HU compared to real CT
images in bone (>300 HU). The TUS intensity at focus was attenuated by 84.3 ± 2.1% (range = 81.0 – 86.9%) in CT and 82.1 ± 1.2% (range = 80.9 – 84.3%) in pCT simulations. Table 1 summarises the TUS metrics at the acoustic focus in water, CT, and pCT simulations. Mechanical indices were not significantly different, but TUS
intensities were less attenuated in simulations using pCT than CT (paired t-test: p = 0.001). Figure 1 shows the MR, CT skull and pCT skull of an example subject from the database, with the corresponding simulated TUS pressure field overlaid on the MR.

Discussion: This study highlights the importance of obtaining subject-specific simulations since individual variations in skull density and geometry can influence the extent of attenuation and focusing of TUS. Our 3D CNN method to synthesise pCT from MR images can be used in TUS simulations, although estimates tend to be more conservative (i.e. less attenuation) than simulations using real CT scans. This may be due to the high mean absolute errors (pCT HU tend to be lower than CT HU). Further work is ongoing to improve the output of the CNN,complete the cross-validation, to generalise the method for use in MR images obtained independently of the training data, and to compare against existing methods for skull imaging e.g., ultra-short echo time MR.

References: [1] Aubry et al., 2003; [2] Su et al., 2020; [3] Mérida et al., 2020; [4] Ronneberger et al., 2015; [5] Shi et al., 2016; [6] Treeby and Cox, 2010; [7] Treeby et al., 2012; [8] Marsac et al., 2017.

Table 1. Simulated TUS acoustic intensity metrics at the focus given as mean ± SD across all 37 database subjects for CT and pCT. MI: mechanical index. I_{SPPA}: spatial peak pulse average intensity. I_{SPTA}: spatial peak temporal average intensity.

Simulation	Water	CT	pCT
MI	1.65	1.23 ± 0.08	1.26 ± 0.05
I_{SPPA} [W/cm^2]	22.6	3.56 ± 0.47	4.05 ± 0.27
I_{SPTA} [W/cm^2]	6.78	1.07 ± 0.14	1.22 ± 0.08

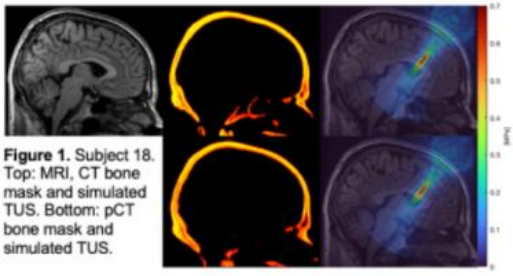

Figure 1. Subject 18. Top: MRI, CT bone mask and simulated TUS. Bottom: pCT bone mask and simulated TUS.

Date: Thursday Sept 9, 2021 Location: Zoom Category: Oral presentation
Time: 4:35 pm (CET)

Development of in vitro Ultrasound Neuromodulation System with Concurrent Measurement of Evoked Local Field Potentials

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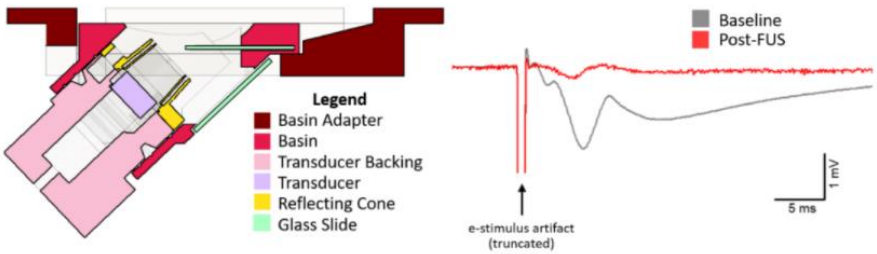
INTRODUCTION. In this communication, we describe the development of a system that we used to Ultrasonically modify electrical activity of rat brain slices in vitro. We present details on the technical development of this system to complement our concurrent report of the results obtained in experiments("Preliminary results on the reproducibility of focused-ultrasound based neuromodulation in an in vitro electrophysiological system," C. Swytink-Binnema et al., submitted to this conference for oral presentation).
METHODS. The first phase of development involved conceptualization of a novel reflecting cone collimator. We performed simulations to produce an optimal design of such a collimator; we initially used Rayleigh's integral and an approach inspired by ray tracing, and later incorporated multiphysics finite element modelling (COMSOL Inc., Massachusetts, USA). We obtained viable optimized designs using a multi-objective genetic algorithm from MATLAB 2019A (Mathworks, California, USA). The second phase of development comprised fabrication and validation. We 3D-printed prototypes of three modular pieces using the Form 3 (Formlabs, Massachusetts, USA): the transducer assembly, the reflecting cone, and the experiment basin. 200 kHz flat cylindrical PZT transducers with diameter 10 mm were selected for our devices (DL47: DeL Piezo, Florida, USA). Transducer efficiency was established with radiation force methods using an absorber devised for sub-MHz ultrasound emissions (Precision Acoustics, UK). Transducer impedance variation over the power range was recorded using a low-power coupler. The acoustic field distribution produced by the transducer plus reflecting cone was measured with a 1 mm needle hydrophone (NH1000: Precision Acoustics, UK) mounted on a 3-axis robotic arm (UMS3 Scanning Tank: Precision Acoustics, UK). In the third phase of development, we iterated on each of the hardware pieces to meet the needs of our planned experiments. We adapted the basin to improve optical compatibility with microscope components and adjusted the transducer design to minimize electrical interference with electrophysiology equipment. We incorporated an acoustic intensity profile mask to aid with positioning of brain slices. Finally, we developed a software console to control the driving hardware based on prescribed sonication parameters, and a method for synchronizing the electrical and ultrasonic stimulation sequences.
RESULTS. Left attached figure shows a cross-sectional schematic diagram of the final design. Right attached figure shows an example of an evoked local field potential in a hippocampal rat brain slice being modulated by pulsed FUS. Ultrasound sequence parameters used to achieve this modulation effect were: fundamental frequency = 192.5 kHz, pulse repetition frequency = 500 Hz, burst duration = 500 ms, inter-stimulation interval = 4.0 s, duty cycle = 30%, spatial-peak temporal-average intensity (I_SPTA) = 0.25 mW/cm2.
CONCLUSION. We have developed a modular and thoroughly-characterized system to enable our ultrasound neuromodulation experiments. In the near future, we will corroborate pressure field measurements with arecently-acquired calibrated hydrophone.

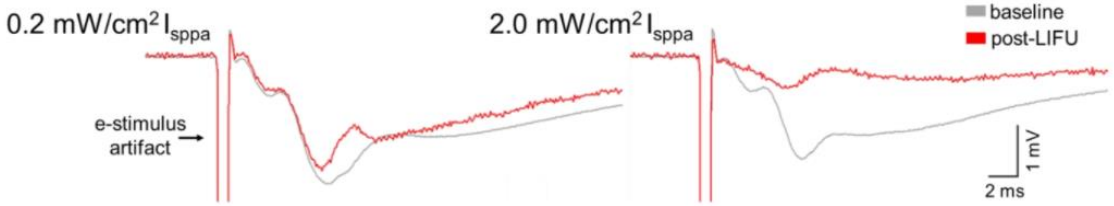


Date: Thursday Sept 9, 2021 Location: Zoom Category: Oral presentation
Time: 4:50 pm (CET)

Preliminary results on the reproducibility of focused-ultrasound based neuromodulation in an in vitro electrophysiological system.

CA Swytink-Binnema (1), JDM Loree-Spacek (1), S Pichardo (1, 2), GB Pike (1, 2, 3), ZHT Kiss (3).
1. Biomedical Engineering, University of Calgary (Alberta, Canada)
2. Dept. of Radiology, University of Calgary
3. Dept. of Clinical Neuroscience, University of Calgary

Intro: Low-intensity focused-ultrasound (LIFU) is a neuromodulation technique that offers a novel, non-invasive method to reversibly alter brain activity. Thus, LIFU presents several advantages over current neuromodulationmethods. Despite its tremendous potential, the use of LIFU as a research tool or therapy is currently limited because we lack key fundamental knowledge about its mechanism of action. To effectively characterize LIFU, it isessential to establish a versatile and reproducible in vitro experimental system where the electrophysiological mechanisms involved can be dissected.
Objectives: Our objectives were to: (1) develop a custom in vitro LIFU experimental system, (2) assess its reliability, and (3) determine the neuromodulatory effect of LIFU on evoked local field potentials (LFPs) in rat brain slices.
Methods: LFPs were elicited in acute hippocampal and cortical rat brain slices using an electrophysiology system configured for extracellular recordings (Axon Axopatch 200B, Molecular Devices). LFPs were evoked with a 0.2 ms electrical current pulse at 4 s inter-stimulus intervals. A custom-built 200 kHz ultrasound transducer (calibrated with a radiation force method) and focusing conegenerated pulsed LIFU. The focal point encompassed both the stimulating and recording electrodes. In these experiments, we used a pulse-repetition frequency of 500 Hz and a 30% duty-cycle. Each LIFU application consisted of five sonications, each 500 ms long and preceding the electrical pulses by 1010 ms. LIFU was applied at intensities ranging from ~1 uW/cm^2 to 78 mW/cm^2 I_sppa. As a negative control, an air barrier was positioned in front of the transducer, impeding propagation of ultrasound to the slice.
Results: Of 44 brain slices (19 cortical, 25 hippocampal) tested in this protocol, LFPs were transiently decreased or eliminated by LIFU in 25 slices (9 cortical, 16 hippocampal). In slices that did show a response, the effect was related to LIFU intensity. Higher LIFU intensities could eliminate the LFP response, and more time was required for the LFP to return to baseline. At lower intensities, the LFP response remained, but with decreased amplitude. If the intensity was decreased further, the effect could be eliminated. Sham LIFU (N=3), produced by blocking the ultrasound, did not alter LFPs. Interestingly, when a fiber volley, field EPSP, and population spike could be clearly discerned in the LFP response in hippocampal slices, they sometimes responded differently to LIFU, suggesting LIFU has different effects on each of these components.
Conclusion: We have developed a reproducible method of studying LIFU neuromodulation in a brain slice preparation. These preliminary results suggest that LIFU interrupts signal transmission, decreasing the LFP response, dependent on the intensity of LIFU applied. Next, we will validate our acoustic pressure measurements using hydrophones calibrated for low-frequency emissions. Future work will explore the LIFU parameter space systematically to characterize effects of LIFU parameters such as sonication duration and pulse repetition frequency. Further, we will probe mechanisms of action using various blockers and agonists.



Poster Presentation Abstracts

Date: Thursday Sep 9, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 1

Category: Poster presentation

Human Skull imaging with Ultrashort TE and Zero TE MRI sequence

Fanrui Fu, Erpeng Dai, Gerald R. Popelka, Pejman Ghanouni, Kim Butts Pauly; Stanford University

Introduction: With magnetic resonance guided focused ultrasound (MRgFUS), skull imaging is used for subject suitability screening and for correction of ultrasound aberration. Skull images are currently obtained with CT, which exposes patients to ionized radiation. Acquiring skull images with MRI can free the subject from ionizing radiation and save time and effort on imaging registration. The purpose of this work was to evaluate ultrashort TE (UTE) and Zero TE (ZTE) MRI sequences for determining phase aberration corrections. In addition, noise reduction by averaging and deep learning were evaluated.

Methods: CT images were obtained from a GE Revolution CT with the following parameters: slice thickness 0.625mm, data collection diameter 32cm, KVP 120, current 350mA. UTE images were obtained from a GE Signa Premier 3T with the following parameters: FOV 22cm, slice thickness 0.8mm, TE 32µs/2.4ms, TR 11ms, Flip angle 18, NEX 2, BW 125 kHz, scan time 15 mins. NormUTE was generated by subtracting two UTE images that have different TEs, normalized by their sum. ZTE images were obtained from a GE Signa Premier 3T with the following parameters: FOV 22cm, slice thickness 1.3mm, Flip angle 1, NEX 2 and 4, BW 64 kHz, scan time 2:30s and 5 mins. Denoising with deep learning was applied to the ZTE images. InvZTE images were obtained by inverting the image intensity and then scaling intensity values to the CT Hounsfield unit range (0-2000). The InSightec console was used for calculating phase aberration corrections from CT and InvZTE images from the same subject, and the corrections were compared element by element.

Results: Example images are shown in Figure 1. Both InvZTE and NormUTE demonstrate good differentiation between cortical bone and cancellous bone, but the InvZTE is preferred over the normUTE because scan time is shorter, acoustic noise is much less, and the image acquisition is more robust. Results from the InSightec console aberration calculations are shown in Figure 2. Correction terms based on 2 and 4 average InvZTE were essentially the same. Correction terms based on 2 average DL InvZTE and 4 average non DL InvZTE were essentially the same.

Discussion: Two average InvZTE shows excellent depiction of cortical and cancellous bone, depiction of internal bone structure, essentially the same phase aberration correction terms as the longer scans within a reasonable scan time of 5 mins.

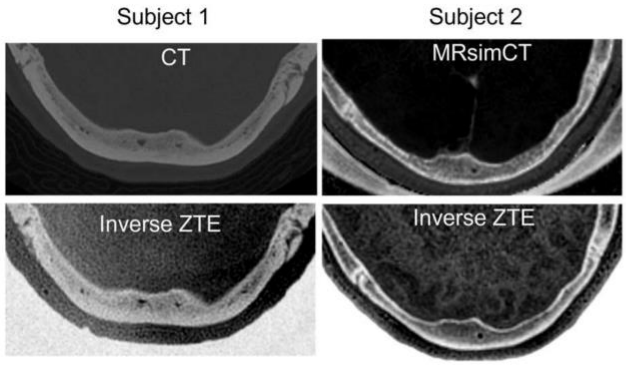


Fig. 1 CT, MRsimCT, and inverse ZTE images from two subjects.

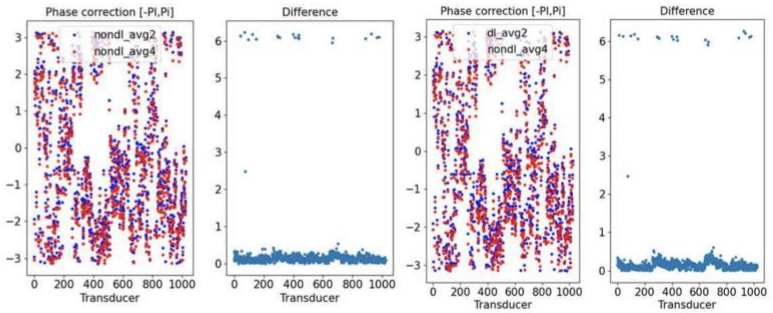


Fig. 2 Insightec console simulation for ZTE images with and without Deep learning noise reduction.

Date: Wednesday Sep 8, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 2

Category: Poster presentation

Acoustic Coupling Pads for the Control of Ultrasound Exposure

Samantha Schafer, Dexel Univerisity, Sonic Tech, Inc; Mark E. Schafer, Drexel Univerisity

Background: Ultrasound neuromodulation studies often require unexposed control groups to limit placebo or other confounding effects. Ultrasound transducers produce an audible clicking sound when energized, thereby inducing an auditory cue. A method is needed for controlling ultrasound exposure while maintaining this auditory cue, so the subjects are blinded to the exposure condition (single- blinded). The operator should also be unaware of the exposure condition so they cannot provide subtle cues to the subject (double-blinded). Methods such as disabling the transducer electrical drive signal or improperly mounting the transducer on the subject's head do not solve this problem. We have developed acoustic coupling pads that facilitate single-blind and double-blind experiments by selectively transmitting ultrasound into the subject without affecting the audible sound from the transducer.

Materials and Methods: The pads were made from a skin-safe two-part silicone with little to no ultrasonic attenuation (Dragon Skin NV-10). The material was dyed white with a skin-safe silicone dye (Silc-Pig) to hide the inner contents of the pad. This material provided the necessary acoustic properties, mechanical stability and flexibility. The acoustic requirements included low loss (~5%) and little refractive bending of the beam due to sound speed differential (therefore sound speed within 20% of tissue). Mechanically, the gel pads conformed to both the front of the transducer and the surface of the skull and were compressible so as to fill the gap in between the two. In order to inhibit the transmission of ultrasound, a foam disk (open cell polyethylene foam wrap) was imbedded into the pad during the manufacturing process. The design goal for acoustic attenuation was -40dB (factor of 10,000 in intensity). Pads are assigned individual serial numbers so that testing can be unblinded at a later date.

Results: Ten sets of transmit pads and non-transmit pads (see Figure) were fabricated. Acoustic transmission loss was measured in a water tank with a 60mm diameter, 80mm focus circular disk transducer operated at 650kHz and a standard hydrophone (Reason TC4038). Transmit pads had an average of -0.5dB loss (2% variation); non-transmit pads met the required -40dB loss (average: -46.6dB). An operator experienced with ultrasound treatments was asked to inspect and handle both types of pads, and was unable to distinguish them by visual inspection or casual physical manipulation, as would be the case clinically. A subject well experienced with ultrasound neuromodulation treatments was exposed to a typical treatment regimen, once using the transmit pad and once using the non-transmit pad. The subject was asked to discern between the two, and was not able to distinguish any audible difference.

Conclusion: The acoustic coupling pads create identical testing situations for single-blind and double-blind studies for neuromodulation treatments so that neither the patient nor the operator administering the treatment can distinguish which patient group received the ultrasound treatment and which did not.

Date: Tuesday Sep 7, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 3

Category: Poster presentation

Transcranial neuromodulation array for simultaneous multifocal imaging

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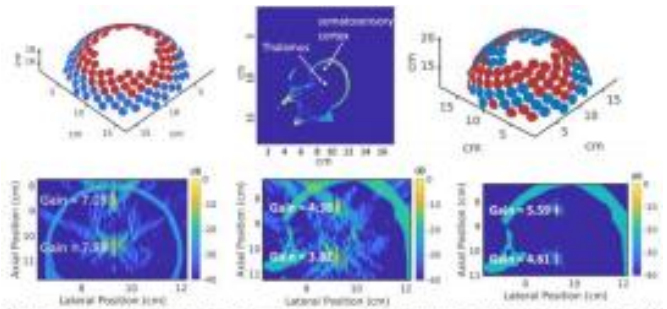
Within a brain circuit, neurons are recruited from different parts of the brain to perform an action. So to be able to accurately study different brain pathways, multi-focal stimulation is required. Macaque monkeys can be used as a model for the human brain, but focusing ultrasound waves through the skulls of larger animals is challenging due to the geometry of the skull, particularly when focusing to regions near the surface of the skull due to increased angle of incidence. To simultaneously focus to different regions in a macaque monkey brain, we have designed a multifocal neuromodulation array with an imaging aperture to allow for simultaneous stimulation and imaging.

To model neuromodulation of a macaque monkey, 3D simulations were performed using Fullwave, an ultrasound simulation tool based on finite difference methods in the time domain. CT scans of macaque monkeys were converted to acoustic maps and used as inputs into the simulation tool. These helmet designs were evaluated based on gain and resolution of the target region. Each design includes 128 10mm diameter elements arranged in a spherical helix pattern, with a 65-mm imaging aperture at the top of the array. Each array design was tested for the ability to focus to the geometric focus of the array and a shallower target, near the skull. Initial helmet designs included a large sector array, where elements that face the geometric focus of the spherical helix extend across the upper hemisphere, a small sector array where elements are positioned in a tightly packed distribution along the spherical helix, and a multifocal small sector design (Fig 1a) where elements are rotated to point towards different regions. The large and small sector arrays did not focus to the shallow target as well as they did to the geometric focus, but the multifocal design was able to focus to both targets with a small gain differential between the two focal points. Using this design, both focal points were stimulated at the same time, with 64 elements focusing to each location. To increase the amount of energy delivered due to the decrease in the number of elements focusing to each focus, the element size was increased to 15mm. This resulted in gains of 7.89 and 7.03 and focal volumes of 2.24 and 1.16 mm^3 at -3 dB at the geometric and shallow focal points, respectively (Fig 1d).

To test the ability of the array to focus to specific brain location, the somatosensory cortex and thalamus were found using a labeled CT scan (Fig 1b), and positioned so that the thalamus was at the geometric focus, and the somatosensory cortex is directly above that. Due to the different skull position, this decreased the gain to 3.87 at the thalamus and 4.38 at the somatosensory cortex (Fig. 1e). So to counteract this decrease in gain, we performed an optimization step to improve the placement of the elements based on specific brain targets. To optimize our array, two phase aberration correction simulations were performed to find the average intensity at each element from a shallow and deep focal point. Based on these simulations, the elements were arranged in a pattern that allowed for better delivery of sound to each focal point through the skull (Fig 1c). Then, we implemented phase aberration correction on emission with the optimized array, allowing for us to correct for aberration caused by the skull geometry (Fig 1f). This improved the gain slightly to 4.61 at the thalamus and 5.59 at the somatosensory cortex, but decreased the focal volume to 0.96 mm^3 at both locations as well as decreasing the amount of energy located in regions surrounding the focal points, decreasing the likelihood of stimulating additional regions. This simulation-based array design process thus results in an ultrasound neuromodulation array that can simultaneously stimulate different brain regions with high gains and small focal volumes while maintaining an imaging aperture.



a) The multifocal array design with red elements facing the shallow focus and blue facing the geometric focus b) The rotated labeled CT scan c) The optimized array design d) The resulting intensity plot for the multifocal array design e) resulting intensity plot from the multifocal array for the rotated and labeled CT scan and f) the resulting intensity plot from the optimized and phase aberration corrected multifocal array design

Date: Tuesday Sep 7, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 4

Category: Poster presentation

An open source system for logging and monitoring FUS transmission

Adrienne A Hawkes, Michelle Sigona, Kianoush Banaie Boroujeni, Louie Treuting, Thilo Womelsdorf, Charles F Caskey

During focused ultrasound (FUS) neuromodulation procedures, knowledge of the electrical current delivered to the transducer is important to ensure that intended FUS exposures have been delivered. While many amplifiers are equipped with a built-in meter for monitoring power output, they do not log power delivery versus time and often report an instantaneous power value integrated over an unknown time frame resulting in imprecise online dosimetry estimates. A method to monitor FUS exposure in real-time is desirable for quality control of FUS dosimetry and safety. Here, we present an open-source method to estimate FUS power in real-time using a programmable USB oscilloscope. Our system provides an affordable method to log, analyze, and monitor power during both event-based FUS studies and studies with FUS exposures of multiple seconds. We developed software for a digital oscilloscope (PicoScope 5424B, Pico Technology, St Neots, United Kingdome) to monitor power during FUS neuromodulation by sampling the signal from the forward and reverse ports of a bi-directional coupler (ZABDC50-150HP+, Mini-Circuits, Brooklyn, NY) placed between the amplifier and transducer (H115, Sonic Concepts, Seattle, WA). We designed two programs to monitor different FUS stimulation schemes: a 250 kHz, 40 second burst with a PRF of 10 Hz and 30% duty cycle at a sampling frequency of 1.5 MHz, and a 250kHz, 300 milliseconds burst with a PRF of 1.5 kHz and 50% duty cycle at a sampling frequency of 5 MHz. Prior to experiments, we created a calibration curve between the signal sampled at the coupler and the free-field peak negative pressure (PNP) to determine the input amplitude necessary to achieve the desired PNP. We also created a calibration curve between the input signal and the signal sampled at the coupler to estimate the root-mean square (RMS) voltage that should be measured given the provided input amplitude. When the PicoScope receives a trigger, it begins sampling, computes RMS voltages from the measured coupled voltages, and reports these values in real-time. This live feedback estimates delivery of current to the transducer. When the procedure is finished, PicoScope exports the expected and measured voltages and the corresponding timestamps, storing a manageable amount of data while still providing useful information about the delivered signal. Our power monitoring system has been successfully incorporated into two different FUS neuromodulation procedures. During FUS neuromodulation studies using 40-second FUS exposures, the power monitor reported the RMS voltage at 1 Hz on-screen while logging the signal. This allowed experimenters to manually monitor the real-time value and analyze stored measurements to ensure the integrity and quality of the FUS exposure (Fig. 1A). During event based stimulations with durations of 300 msec, the monitor provided quantitative feedback about the power that could not be detected on the amplifier's built-in integrating power meter (Fig. 1B). The power monitor system described here helps ensure consistent delivery, overcomes limitations of built-in meters, and provides a method to log the power delivered during FUS neuromodulation sessions. Real-time feedback of the FUS stimulations can help ensure that intended exposures are delivered while detecting transmission errors that can occur due to equipment failure or user error. Because the monitor stores the measured power values, experimenters can track the number and amplitude of stimulation events across experiments. Overall, the software developed here provides a method to monitor and log the coupled voltage during FUS procedures in real-time. Monitoring the coupled voltage improves quality of FUS delivery and ensures integrity and safety of FUS exposure.

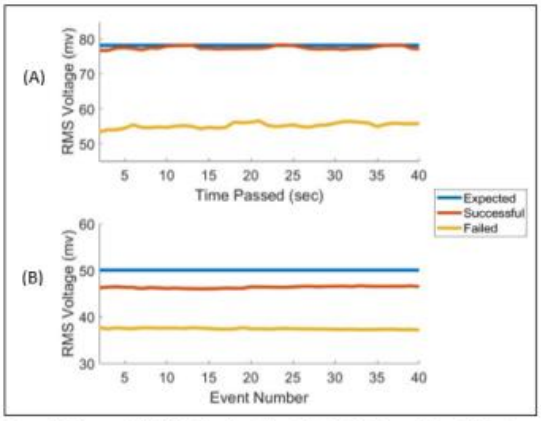


Figure 1. The expected RMS voltage is estimated using the linear relationship between measured coupled voltage and the amplitude of the input signal. The results marked in yellow and red depict RMS voltages computed from the measured coupled voltage. The red depicts the results of a trial in which the signal was considered to have been sucessfully transmitted. The yellow depicts the results of a trial in which the signal was not considered to have been sucessfully transmitted. If the measured RMS voltage was below 20% of the expected value, the connection was considered faulty. (A) The results of two FUS neuromodulation studies using 40-second FUS stimulations. (B) The results of two FUS neuromodulation studies using event-based FUS stimulations.

Date: Tuesday Sep 7, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 5

Category: Poster presentation

A Novel Metric for Assessing Audibility of Transcranial Ultrasound Neuromodulation Signals

Mi Hyun Choi (Department of Bioengineering, Stanford University), Gerald Popelka (Department of Otolaryngology, Stanford University), Kim Butts Pauly (Department of Radiology, Stanford University)

Introduction: It has long been known that transcranial ultrasound stimulation (TUS) produces cochlear microphonics (Foster and Wiederhold, 1978). More recently, this was shown to obfuscate observations of direct effects of various TUS signals on neural activity at targeted non-auditory brain regions (Guo et al., 2018; Sato et al., 2018; Salahshoor et al., 2020). To address this issue, we introduce a novel metric for quantifying susceptibility to auditory confounds in mice.
Methods: Our metric was developed by comparing the signal power of experimental auditory brainstem responses (ABRs) to computational time-based frequency analyses of sample ultrasound signals (Figure 1) weighted by mouse hearing sensitivity.
Results: The comparison showed a significant linear correlation between the computational and experimental values ($R^2 = 0.98$) (Figure 2). Using this relationship, audibility in terms of the frequency spectrum of the ultrasound signal was defined as ≥ three standard deviations above the mean experimental ABR power from sham conditions.
Conclusions: This metric can aid researchers performing in vivo studies on mice by helping them select ultrasound signal parameters that avoid inadvertent auditory activation. Furthermore, the method for developing this metric is easily generalizable to other species with additional ABR measurements in response to TUS.

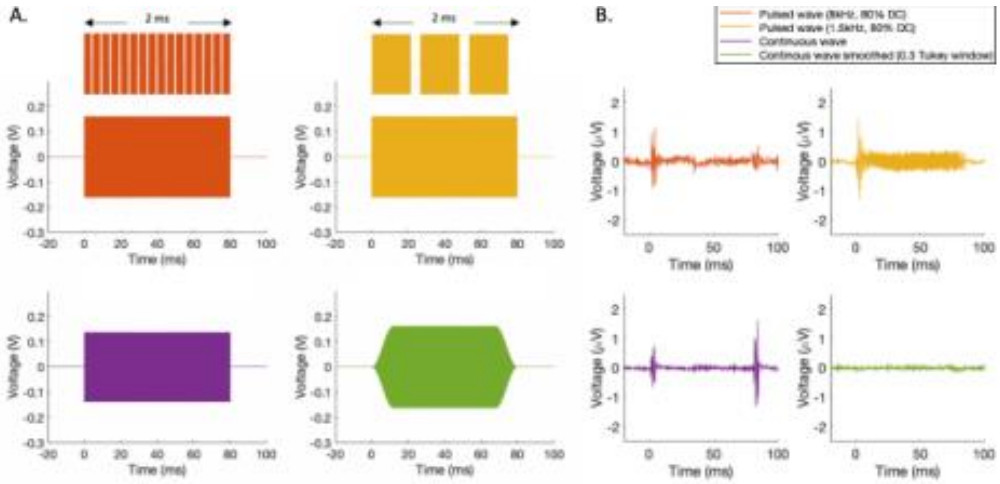


Figure 1. A) Sample signals used to develop the metric, and B) respective representative ABRs.

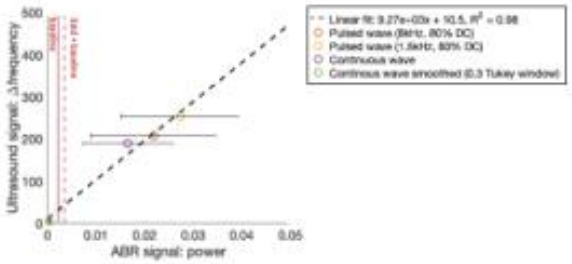


Figure 2. Correlation between computational ultrasound signal analysis and experimental ABR power at onset.

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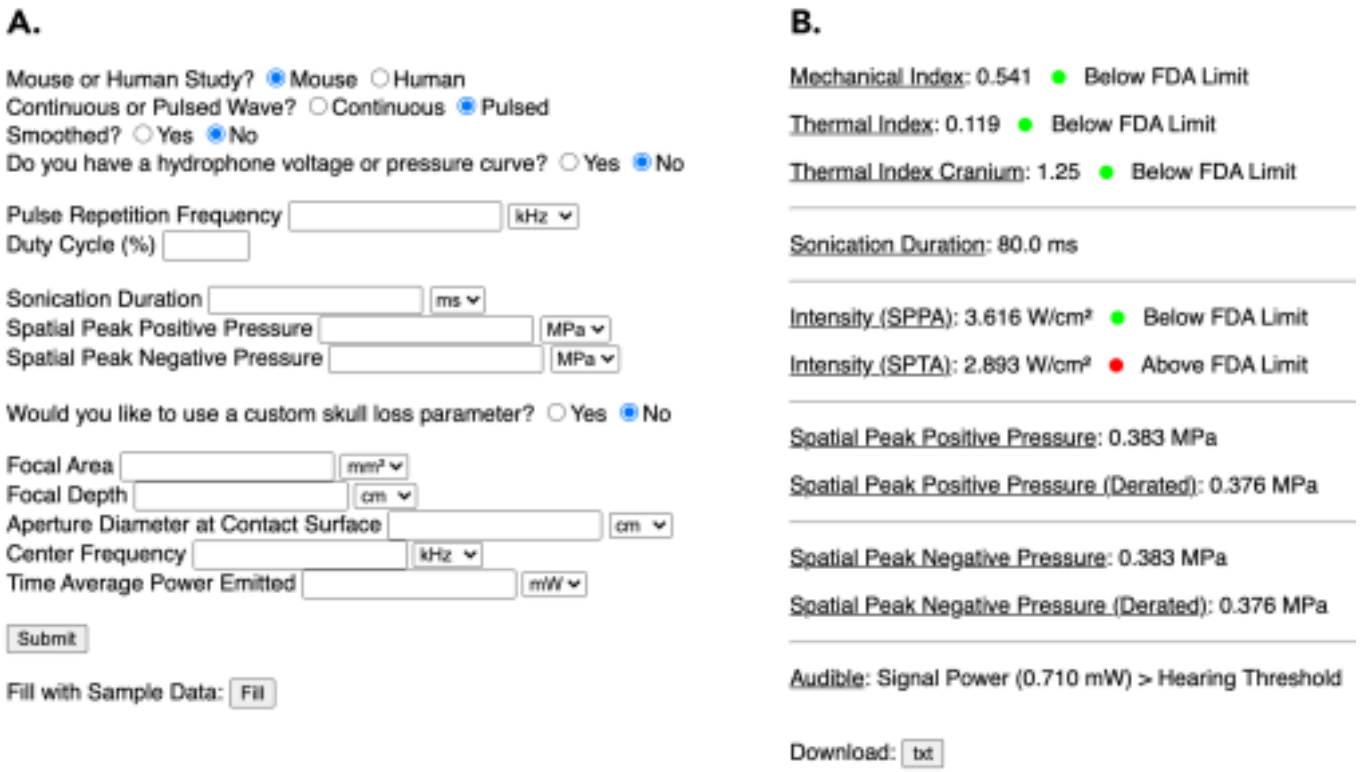
Category: Poster presentation

Development of a Computational Tool to Guide Transcranial Ultrasound Signal Parameter Selection and Reporting

Karanpartap Singh (Department of Electrical Engineering, California Polytechnic State University), Mi Hyun Choi (Department of Bioengineering, Stanford University), Gerald Popelka (Department of Otolaryngology, Stanford University), Kim Butts Pauly (Department of Radiology, Stanford University)

Previous studies have demonstrated that transcranial ultrasound stimulation (TUS) leads to varying levels of suppression or excitation of neural activity at the targeted brain region depending on signal parameters – including signal intensity, signal duration, pulse repetition frequency, and pulse duration (Yoo et al., 2011; King et al., 2013; Kim et al., 2014; Plaksin et al., 2016; Yu et al., 2019). However, many studies underreport or inconsistently report these metrics (Pasquinelli et al., 2019), preventing the field from converging on a clear relationship between sonication parameters and respective neural effects. To advance TUS as a neuromodulatory tool that can create predictable neural responses, there is a need for systematic testing and reporting of safe and confound-free parameters and brain regions. A safety metric based on FDA guidelines for mechanical and thermal indices (Nelson et al., 2009) and an audibility metric for assessing unintended auditory activation confounds in mice were incorporated into a web-based computational tool (https://sr.karanps.com), written in Python and hosted through the Flask library. When users either manually input experimental parameters (Figure 1A) or upload hydrophone measurements, the tool provides a standardized report on key TUS parameters (Figure 1B). The report also includes an ideal reconstruction of the inputted signal for confirmation as well as an assessment of the signal's audibility in mice. This tool is easily accessible to aid in the selection of appropriate, safe, and inaudible signals for neuromodulation and can be used to guide standardized parameter reporting across studies, facilitating reproducibility and inter-study comparisons. Any feedback regarding the tool's features or functionality is welcome and can be emailed to sr@karanps.com.



Date: Wednesday Sep 8, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 7

Category: Poster presentation

Displacement of intracranial electrodes induced by focused ultrasound stimulation

Min Gon Kim, Kai Yu, Xiaodan Niu, Bin He; Department of Biomedical Engineering, Carnegie Mellon University, Pittsburgh, PA, USA

Background and Objective: Transcranial focused ultrasound (tFUS) has gained significant attention as an emerging neuromodulation technique for noninvasive brain stimulation with a high specificity and a deep penetration. Inspired by the notable features along with promising experimental evidence in many applications, efforts have been made to elucidate the underlying biophysical mechanisms by combining tFUS with multi- channel intracranial electrophysiological recordings to monitor the activity of large populations of neurons with high temporal resolution. Nonetheless, the physical interactions between tFUS and the electrode may compromise a reliable assessment of neuronal electrophysiological recordings. In this work, we aim to investigate the displacement of the intracranial electrode arrays induced by tFUS, using high-frequency ultrasound (HFUS)-based displacement tracking and analysis.

Methods: We developed a HFUS system and integrated it with tFUS neuromodulation experimental setup as presented in Figure 1. To verify this proposed method, we measured and compared performance of the integrated system with theoretical estimation. We examined the displacements induced by several ultrasound pressure levels onto the silicon-based microelectrode array in ex vivo brain tissue using the developed approach.

Results: The developed approach was capable of tracking and analyzing the motion of a solid sphere in a tissue- mimicking phantom and the measured displacements were comparable to theoretical analysis. Figure 2 illustrates the statistical comparisons of the averaged peak displacements of the microelectrode array in ex vivo brain induced by neuromodulatory ultrasound sequence (fundamental frequency of 500 kHz, pulse duration of 200 µs, peak-to-peak pressure greater than 131 kPa) against the baseline measurements (peak-to-peak pressure of 0 kPa) as a negative control group.

Conclusion and Significance: The experimental results revealed the relationship between various pressures and displacements of the multi-electrode array in ex vivo brain. The developed approach can be applied for determination of a vibration-free threshold of ultrasound parameters in multi-channel intracranial recordings for a reliable assessment of electrophysiological activities of living neurons.

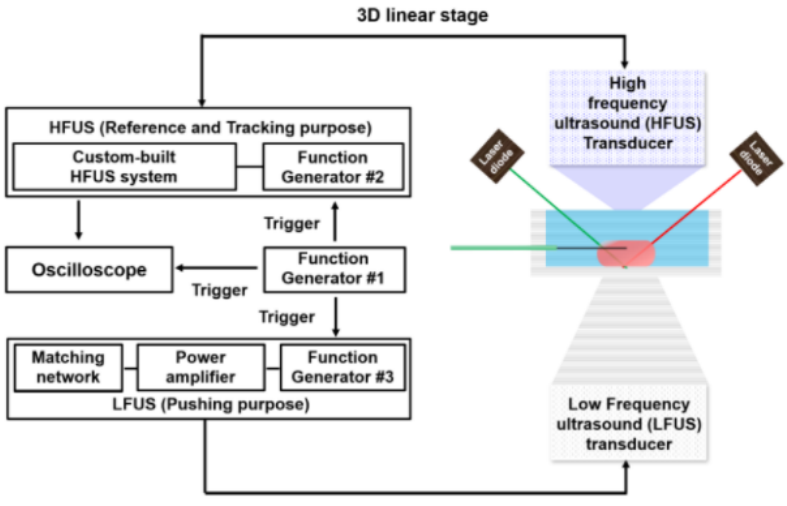


Figure 1. The experimental setup consists of HFUS transducer with custom-built HFUS system, a 3D linear stage, LFUS transducer with a commercially available driving system, and an oscilloscope.

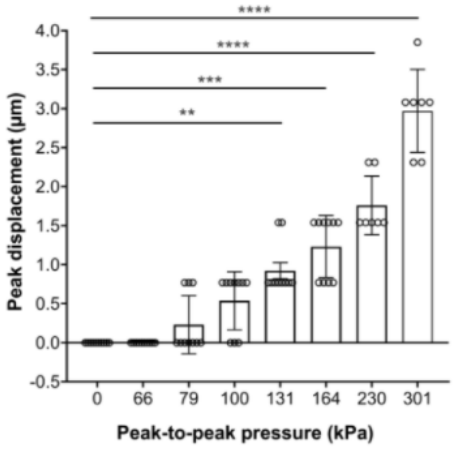


Figure 2. Focused ultrasound-induced axial displacement of the silicon-based microelectrode array in *ex vivo* brain tissue. ($p = 0.004 < 0.01$ **, n = 10 for 131 kPa; $p < 0.001$ ***, n = 10 for 164 kPa; and $p < 0.0001$ ****, n = 7 for each 230 and 301 kPa).

Date: Thursday Sep 9, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 8

Category: Poster presentation

The essential role of neuron multiphysics in ultrasound neuromodulation and anaesthesia.

Casey Adam (1), Miren Tamayo-Elizalde (1), Celine Kayal (1), Ari Ercole (2), Sonia Contera (3), Hua Ye (1), Antoine Jerusalem (1)
(1) Department of Engineering Science, University of Oxford
(2) Department of Medicine, University of Cambridge
(3) Department of Physics, University of Oxford

A growing body of research has demonstrated that ultrasound (US) stimulus can alter neuron activity in a reversible and non-invasive manner. This research is leading the development of US neuromodulation therapies, where a mechanical stimulus at US frequencies is applied to modulate the electrical activity of the brain in order to treat neurodegenerative disorders. However, such therapies are in their infancy and the intrinsic mechanisms by which mechanical stimuli alter the electrophysiological activity of the brain at the cellular scale is still poorly understood.

Action potentials (APs) have traditionally been solely considered as an electrical process. However, it has now become clear that APs are also mechanical in nature (and more generally through thermodynamic considerations: chemical, pH, and heat). These mechanical and electrophysiological properties are collaboratively and concurrently participating in the functional action of individual neurons. Therefore, the coupling mechanism of different physical phenomena in neurons is likely to play an important role in neuromodulation, and new frameworks are needed to adequately characterise the “multiphysics” of neurons.

To this end, we designed an experimental multiphysics setup combining confocal microscopy, nanoindentation, and patch clamp measurements [1]. Using this setup, the electrical activity of a single neuron can be measured with either Calcium imaging or patch clamp, and the mechanical properties of the neuron by the nanoindenter. The latter was also fitted with two piezos to allow for mechanical stimulation at low frequencies and high (ultrasonic) frequencies. Here, we applied mechanical stimuli at US frequencies to single dorsal root ganglion-derived neurons and measured changes in the AP with patch clamp. We found that mechanical stimuli with frequencies ~1 MHz (but not at ~300 kHz and below) shorten the time to depolarisation and repolarisation during the AP, thus shortening the overall AP duration. This presentation will also show how these results hold in the presence of anaesthetics, in particular isoflurane, whose influence on neuronal membranes ion channels, and cytoskeleton has still not been fully identified.

Overall, this multiphysics setup paves the road towards the analysis of single-cell scale mechanisms involved in US neuromodulation. A deep understanding of the mechanisms involved is needed to fully establish US neuromodulation’s efficacy and specificity [2]. The ability of adding environmental factors such as anaesthetics to the setup is particularly useful in the identification and control of sonication and drug parameters for clinical use.

[1] M. Tamayo-Elizalde, H. Chen, M. Malboubi, H. Ye, A. Jerusalem, "Action potential alterations induced by single f11 neuronal cell loading". Progress in Biophysics and Molecular Biology (2021).
[2] H. A. S. Kamimura et al. “Ultrasound Neuromodulation: Mechanisms and the Potential of Multimodal Stimulation for Neuronal Function Assessment”. Frontiers in Physics 8 (2020).

Date: Thursday Sep 9, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 9

Category: Poster presentation

Differential brain network effects following anterior versus posterior hippocampal perturbation with transcranial ultrasound stimulation in primates

David Howett [1], Christopher Petkov [1], Matthew Rushworth [2*] and Jérôme Sallet [2, 3*]

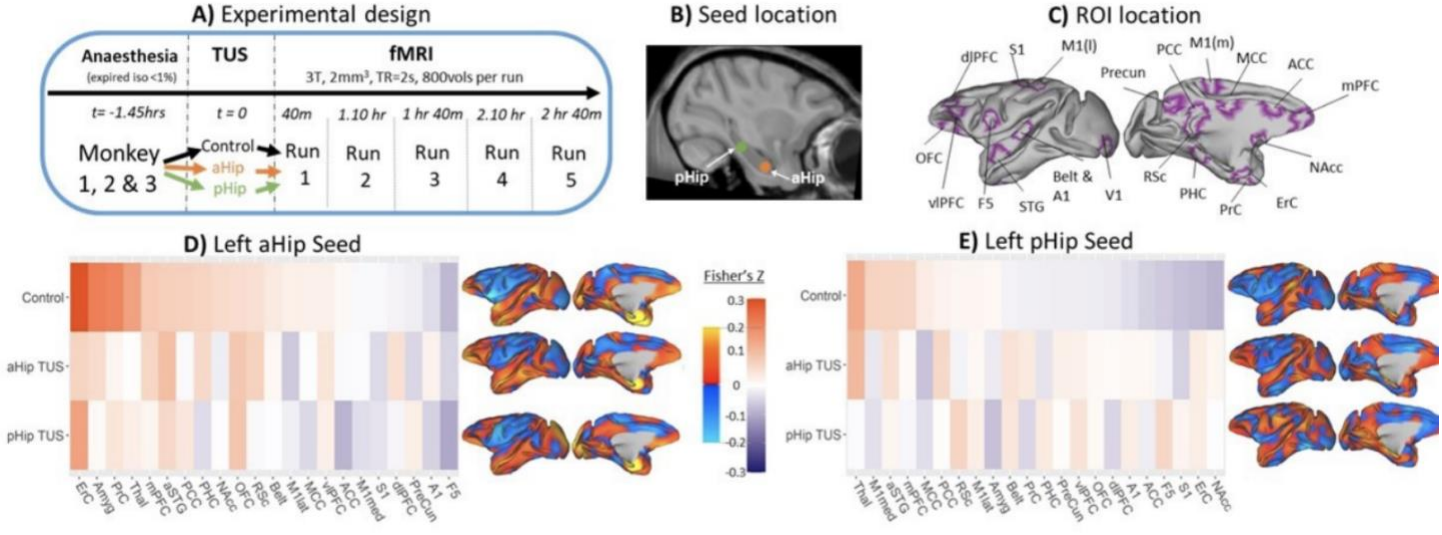
1. Department of Biosciences, Newcastle University
2. Department of Experimental Psychology, Oxford University
3. Université de Lyon, INSERM U1208

There is a need to develop focal noninvasive methods of causally unravelling the function of the hippocampus in health and its dysfunction (hyperactivity) in diseases such as Alzheimer's and Schizophrenia. TUS has the potential to meet this demand as a translatable and non-invasive perturbation method. Here, we demonstrate that TUS targeting of the anterior (aHip) and posterior hippocampus (pHip) differentially modulates the functional coupling of hippocampal networks using resting-state fMRI.

Three anaesthetised macaques underwent low-intensity aHip and pHip 'offline' TUS (250 kHz, 30ms bursts every 100ms for 40s), as well as a control condition. Site-specific effects of TUS on aHip and pHip hippocampal coupling were compared to control using resting-state fMRI. Data were pre-processed using a macaque-optimised pipeline (MrCat toolbox) and analysed using seed-based connectivity analyses of the whole brain and an apriori defined 'fingerprint' for the anterior and posterior hippocampus (fig 1 A-C).

Hippocampal TUS reduced the coupling magnitude of the hippocampus with its apriori defined networks and in some instances reverse the direction of coupling altogether. Bilateral stimulation of the hippocampus (both sites) reduced aHip and pHip coupling with the medial temporal lobe, anterior cingulate and medial frontal cortex and increased coupling in parahippocampus, ventrolateral and orbital frontal cortex (fig 1D-E). Opposing effects of aHip and pHip stimulation were observed in occipital, medial frontal and medial parietal areas. aHip and pHip connectivity patterns were also impacted by the stimulation of the pHip and aHip respectively, though those alterations were distinct from the effects of TUS. Altogether the observed effects were not explained by inadvertent stimulation of areas along the TUS trajectory plane, differences in temporal variability of the BOLD signal or differences in anaesthesia depth or timelines.

In summary, TUS can transiently and reversibly alter neural activity in disparate extent of the same subcortical structure with high spatial specificity. These observations build upon previous work that demonstrates the utility of TUS as a translational tool for causally manipulating the brain. The reduction in the magnitude of functional coupling induced by hippocampal TUS may have therapeutic implications for conditions that are characterised by hippocampal hyperactivity (such as Schizophrenia and Alzheimer's Disease).



Date: Wednesday Sep 8, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 10

Category: Poster presentation

Concurrent TUS-TMS-EMG to quantify the online effects of varying TUS duty cycle and intensity on corticospinal excitability in humans

Tulika Nandi (1), Umair Hassan (1,2), Angela Radetz (1), Til Ole Bergmann (1,2)
(1) Neuroimaging Center (NIC), Focus Program Translational Neuroscience (FTN), Johannes Gutenberg University Medical Center, Langenbeckstr. 1, 55131, Mainz, Germany
(2) Leibniz Institute for Resilience Research, Wallstraße 7-9, 55122, Mainz, Germany

Transcranial ultrasound stimulation (TUS) can produce both excitatory/facilitatory and inhibitory effects at the level of neuron populations (Munoz et al., Curr. Behav. Neurosci. Reports 2018). In rodents, motor cortex TUS can elicit a muscle contraction, i.e., an excitatory effect (Kim et al., Brain Stimul. 2014; King et al., Ultrasound Med. Biol. 2013), while in humans no overt motor response can be observed. Instead, transcranial magnetic stimulation (TMS) of the primary motor cortex (M1) can be used to elicit muscle responses and quantify corticospinal excitability changes using the amplitude of the motor evoked potential (MEP) in the electromyogram (EMG). Concurrent TUS-TMS-EMG studies in humans have so far reported suppression, but no facilitation of the MEP amplitude during TUS (Fomenko et al., Elife 2020; Legon et al., Sci. Rep. 2018). To some extent, population level excitatory versus inhibitory effects may be driven by differences between species and brain regions. However, recent work suggests that, by adjusting the stimulation parameters, inhibitory and excitatory neurons can be differentially stimulated, in the same species and brain region (Yu et al., Nat. Commun. 2021).

TUS for neuromodulation is often applied in a pulsed manner, with the temporal pulse pattern leading to a very large parameter space (Fig. 1). In addition to the fundamental TUS frequency, we can vary pulse repetition frequency (PRF) and duty cycle (DC), i.e., the percentage of TUS 'on' time within each cycle of the PRF. Also, the intensity can be quantified in two ways – either by averaging over a single pulse (Isppa – spatial peak pulse averaged) or by averaging over an entire trial that includes both TUS-on and -off periods (Ispta – spatial peak temporal averaged). So far, only a small part of this parameter space has been systematically examined.
The aim of this neuronavigated concurrent TUS-TMS-EMG study is to investigate whether both facilitatory and inhibitory online effects can be elicited in the human M1 by varying the TUS parameters of Isppa and DC (and thus Ispta), as theoretical models suggest that the same DC can produce excitatory or inhibitory effects at different intensities (Planksin et al., eNeuro 2016). Using a 250 kHz 2-element transducer (CTX-250-2chan, NeuroFUS Pro, BrainBox, UK), we will apply TUS at a PRF of 1000 Hz, with the DC and intensity varied as shown in Fig. 2, leading to eight conditions. We will vary the Isppa in such a way that we can sample the same Ispta at different duty cycles. This allows us to disentangle the differential effects of Ispta and Isppa at each duty cycle. Each trial will last for 400 ms, with a 4-6 s inter-trial interval and MEPs measured at 390 ms after TUS onset. Based on the findings from this study, we hope to selectively tune TUS effects to be either excitatory or inhibitory in future studies.

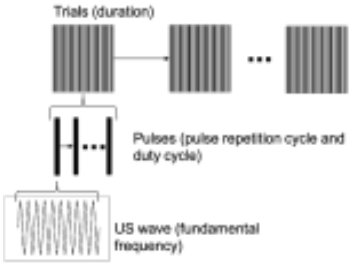


Figure 1: The ultrasound wave (250 kHz) is applied in short pulses which are repeated at 1000 Hz to form trials which last 400 ms.

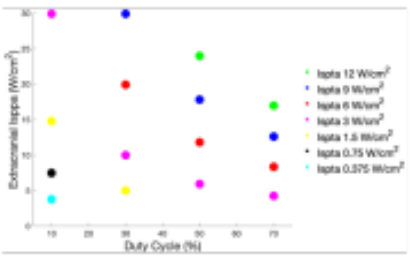


Figure 2: Duty cycle and intensity combinations. Isppa – intensity spatial peak pulse averaged, Ispta – intensity spatial peak temporal averaged

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Category: Poster presentation

Transcranial Ultrasound Stimulation in Anterior CingulateCortex Impairs Information Sampling and Learning in Loss Contexts

Kianoush Banaie Boroujeni 1, Michelle K Sigona 2, Robert Louie Treuting 1, Adrienne Hawkes 2, Charles F. Caskey2, Thilo Womelsdorf 1,2
1 Department of Psychology, Vanderbilt University, Nashville, TN 37240.
2 Department of Biomedical Engineering, Vanderbilt University, Nashville, TN 37240.

Learning the relevance of visual objects in changing environments requires monitoring the motivational values of objects as well as strategic sampling of information to deploy attention to objects with highest expected values. These motivational and attentional demands are closely associated with neural activity in the anterior cingulate cortex (ACC) and the anterior striatum (aSTR), but it has remained unclear what their specific contributions are to instantiate motivational tracking and attentional deployment. Here, we address this question by interfering with the ACC and aSTR using transcranial ultrasound stimulation (TUS), while two rhesus monkeys performed a visual feature learning task that orthogonally varied motivational costs and attentional load.

The TUS protocol used 250 kHz 1.2 MPa free-field peak negative pressure, a long duration (40 second) and low repetition pulse frequency (10 Hz) with a duty-cycle of 30% to disrupt either ACC or aSTR. We completed a 12-week protocol on two rhesus monkeys with two sham control and two stimulation sessions in each area per week. In each session, monkeys performed six baseline learning blocks of ~55 trials each. Then, the experiment was paused and ACC or striatum was targeted bilaterally for TUS using a custom-designed neuronavigational setup with real-time tracking of the transducer focus in a 3D space with the co-registered monkey's brain. Then, the experiment resumed and monkeys completed another 18-24 learning blocks.

We found that TUS of the ACC, but not of the striatum or any sham TUS condition, impaired learning performance and prolonged information sampling in task conditions that imposed high attentional load and high motivational costs for incorrect responses. Trial-by-trial analysis showed that subjects were impaired when incurring multiple losses but successfully learned after gains. These findings suggest that the ACC is causally important for overcoming motivational challenges in cognitively demanding situations. This ACC function becomes evident in less efficient information sampling supporting recent suggestions that the ACC plays a fundamental role in directed exploration and the guidance of attention to behavioral relevant information. Taken together, this study validates TUS as a versatile transcranial neuromodulation technique for cortical and subcortical areas in the primate brain.

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Booth number: 12

Category: Poster presentation

Adapting the Proteus Platform to Support Image-Guided Focused Ultrasound Neuromodulation Experimentation in a Pre-Clinical Commercial Device

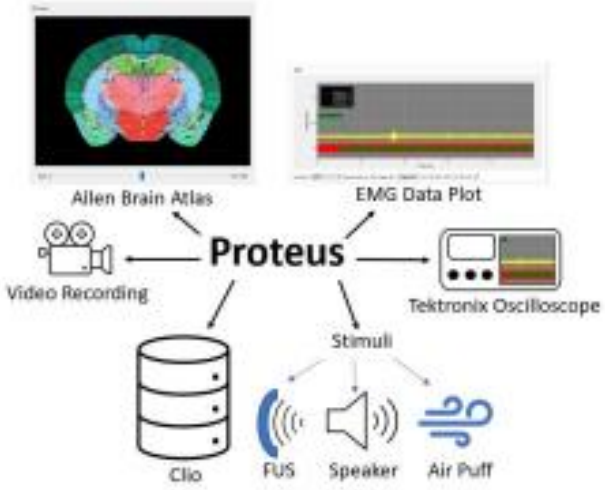
Aidan Johnson 1, Chris Krasnichuk 2, Amine Benaceur 3, Marc Santos 4, Rajiv Chopra 5, Samuel Pichardo 6
1 Electrical and Computer Engineering, University of Calgary
2 Electrical and Computer Engineering, Lakehead University
3 Software Engineering, University of Calgary
4 Physical Sciences Platform, Sunnybrook Research Institute
5 Radiology and the Advanced Imaging Research Center, UT Southwestern Medical Center
6 Radiology and Clinical Neurosciences, Cumming School of Medicine, University of Calgary

Transcranial focused ultrasound (tFUS) neuromodulation is an emerging technique for stimulating different brain areas non-invasively. This technique is one of the central research topics being explored in our laboratory and this study presents the adaptation of our Proteus software platform to support neuromodulation experimentation for pre-clinical focused ultrasound research with FUS Instrument's RK-50 device.

Proteus is a software platform for image-guided focused ultrasound therapy used primarily for academic research. In this work, Proteus was adapted to support neuromodulation with FUS Instrument's RK-50 stereotactic device. A user-centered design (UCD) methodology was followed to capture and code user feedback around its development. Improvements based on this feedback centered on redesigning the user interface, adding video recording of the experiments, and interfacing with an oscilloscope for collecting EMG and microphone data. Also, a data management subsystem based on the HDF5 library was developed to handle the curation of multiple types of different experimental data, such as EMG and audio data.

The figure below shows the new modules that were added to the Proteus platform for the RK-50 system to support the neuromodulation mode. Based on the UCD-derived analysis, the interface was redesigned to include visual plots of the recorded EMG and Audio data, a workflow assistant to help guide the user through an experiment and 2D orthogonal views for their treatment points overlaid upon a stereotactic rodent brain atlas from the Allen Brain Institute. Furthermore, the new subsystem for data management named CLIO was developed to support multiple background software services capable of capturing large amounts of data without affecting the response time of the FUS hardware. On top of focused ultrasound stimuli, audio and air-puff stimuli were incorporated into the system to support user requirements around having different sham stimulation for their experiments.

The adaptation of the Proteus platform to support neuromodulation for pre-clinical experimentation in a commercial focused ultrasound device has been successful. This project improved Proteus to further focused ultrasound research, facilitating the ability for new investigators and experts in the field to conduct pre-clinical neuromodulation experiments seamlessly.



Date: Tuesday Sep 7, 2021
Time: 5:30 pm (CET)

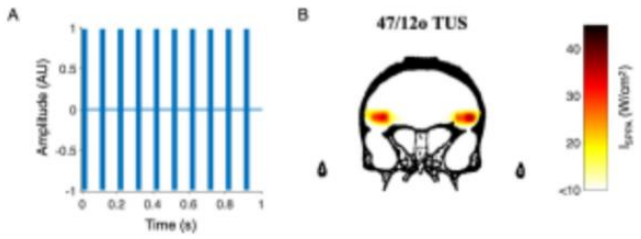
Location: Gathertown
Booth number: 13

Category: Poster presentation

Ultrasound modulation of macaque prefrontal cortex selectively alters credit assignment-related activity and behavior

Folloni, D., Fouragnan, E., Wittmann, M.K., Roumazeilles, L., Tankelevitch., L., Verhagen, L., Attali, D., Aubry, J-F., Sallet, J., Rushworth, M.F.S

Transcranial ultrasound stimulation (TUS) has the potential to crucially contribute to our understanding of what role neural activity associated with specific brain area plays on behavior. In previous separate studies I showed that TUS targeted to subcortical or cortical areas was able to non-invasively modulate either neural activity (Folloni et al., 2019; Verhagen et al., 2019) or behavior (Fouragnan et al., 2019; Khalighinejad et al., 2020; Bongioanni et al., 2021). However, it is still unknown whether TUS manipulation results in simultaneous changes in both neural activity and behavior. Now, for the first time, in a novel series of experiments (Folloni et al., under review) I show that this technique can be successfully combined with neuroimaging (fMRI) and computational modelling to elucidate its simultaneous impact on brain and behavior. Here, I trained macaque monkeys while they were in an MRI scanner to perform a probabilistic decision-making task in which they had to learn the value of three choice options and use this information to guide future behavior (Folloni et al., under review). Animals had to observe the outcome of their previous choice and learn to assign credit to the correct option that led them to a obtain a reward, a type of learning often referred to as "credit assignment". Previous, invasive lesion and correlational imaging studies have linked the orbitofrontal cortex (OFC) and area 47/12o with such type of learning and the ability to track the history of past choice outcomes (Chau et al., 2015; Walton et al., 2010). Here, I decided to causally test the role of area 47/12o in credit assignment by non-invasively disrupting its activity using TUS immediately before the animals entered the MRI scanner to perform the task. By combining TUS with fMRI I was able to look at simultaneous TUS-induced changes in both neural activity and behavior. Moreover, I exploited the non-invasive properties of TUS, to compare within the same animals, the effects of 47/12o TUS with a no stimulatio condition (sham) and a active control condition where TUS was applied to the adjacent anterior prefrontal cortex (aPFC). The TUS protocol used in these experiments consisted of a 40s ultrasonic stimulation with a rectangular envelope over a train of pulses: the pattern displayed was repeated 40 times. Within the ultrasonic stimulation pulse train, each pulse had a pulse duration (PD) of 30 ms, a pulse repetition interval (PRI) of 100 ms, for a duty cycle (DC) of 30%. The pulse repetition frequency within the stimulus duration (PRF) was 10Hz PRF=1/PRI. First, I examined win-stay/lose-shift (WSLS) behavior that provides a direct index of credit assignment by examining whether a choice's outcome on one occasion influences whether the choice will be taken on the next occasion that it is available. Compared to sham, 47/12o TUS impaired the animals' ability to perform WSLS behavior. At the neural level, such 47/12o TUS-induced behavioral impairment was associated with a significant reduction in the pattern of activity underlying WSLS within 47/12o and OFC. Instead, when TUS was applied to the control area aPFC both behavior and neural activity remained unchanged compared to the sham condition. In a second set of analyses, I looked at how macaques computed and represented the values of their choices based on the conjoint history of choice and reward and how they used this information to guide future behavior. After 47/12o TUS the animals learned choice values in a different way and this effect was linked to lower learning rates and less accurate decisions. In addition, I found a significant impact of 47/12o TUS on the animals' ability to form choice-outcome contingency compared to sham. Again, the control condition aPFC TUS was no different compared to sham. Next, to examine the neural effect of 47/12o TUS me and my colleagues fitted a reinforcement learning model to the behavioral data and regressed the whole-brain fMRI signal onto the model's value estimates of the three choice options. In a sham condition, choice value-related activity was observed in anterior cingulate cortex (ACC) and anterior medial frontal cortex (aMFC). This activity was, however, significantly reduced after 47/12o but not aPFC TUS. Therefore, disrupting credit assignment in 47/12o results in alteration of value-related activity in the interconnected ACC and aMFC. Behaviorally, this resulted in poorer decision-making as the choice values now only reflected an average value of the environment regardless of the specific choice taken. Thanks to the non-invasive features of the TUS protocol used in these experiments I think that TUS bears a unique potential for translation across several species including humans and for its application to patients.



TUS protocol (A) and estimated peak intensities and spatial distributions of ultrasound based on a high-resolution macaque whole-head CT scan (B) (from Folloni et al., *under review*).

Date: Tuesday Sep 7, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 14

Category: Poster presentation

Implementation of Optimized Isoflurane Protocol in Focused Ultrasound Neuromodulation Using Random Pulse Repetition Frequency Modulation for Skull Vibration Reduction

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Background
Focused ultrasound (FUS) neuromodulation can modulate neural activity at specific locations throughout the brain non-invasively. Current studies in mice often record motor responses to FUS neuromodulation, though the success rate of these responses can be quite variable. Isoflurane anesthetic has also been shown to extinguish motor responses at concentrations above 0.5%. Additionally, FUS delivery has been shown to cause vibrations in the skull related to the pulse repetition frequency (PRF) of the signal, which creates an auditory confounder of this procedure.

Objective
The plane of anesthesia changes rapidly with isoflurane levels, depending on breathing rate, gas flow rate, and animal size. Further, isoflurane can accumulate within tissue over time. To mitigate the influence of these variables, the current study aims to present a reliable timing protocol for the reduction of isoflurane and the consistent acquisition of motor responses. This protocol will then be applied to acute trials in which the PRF has been randomized. We hypothesize that a random PRF will prevent constructive interference of internal reflections of the FUS beam, mitigating the production of skull vibrations while maintaining the effect of neuromodulation.

Methods
Pulsed FUS of 477 kHz with 80 ms pulses, 31.5% duty cycle, 1.5 kHz PRF and 12.6 W/cm2 intensity (spatial peak temporal average intensity, water-conditions), was delivered to targets at the visual and motor cortices of C57BL/6 mice. Motor responses were recorded with video and electromyography. Animals (n=6) inhaled 2% isoflurane in oxygen flowing at 0.8L/min. Isoflurane was reduced to 0.2% for 2 minutes before treating a target with 5 pulses, with 15 seconds between pulses. Isoflurane was then returned to 2% for 5 minutes. This was repeated for 5 treatments per target and 2 sham treatments. In random PRF studies, only the visual target was treated, using the above conditions, as well as a FUS stimulation using a PRF randomly fluctuating around 1.5 kHz, a sham condition, and an audio tone matching the PRF, all repeated in a random pattern.

Results
This protocol yielded 57.2 ± 12.4% and 67.7 ± 22.5% motor responses from the motor and visual targets, respectively, both significantly higher than sham trials (10.4 ± 8.7%; $p < 0.001$). Random PRF trials are ongoing.

Conclusion
These preliminary results indicate that the present anesthetic protocol facilitates consistent motor response rates.
Future work will continue to refine this approach and apply it to acute studies investigating the mitigation of auditory confounders of this technique.

Date: Wednesday Sep 8, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 15

Category: Poster presentation

Modulating cerebellar-M1 connectivity using transcranial focused ultrasound

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Although established non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS), can target the cerebellum, they lack the spatial focality to allow detailed investigations of the cerebello-cortical networks. Transcranial low intensity focused ultrasound (TUS) is a novel stimulation technique that uses acoustic waves to alter neuronal excitability. TUS can reach deeper brain structures with greater focal width than TMS. This makes TUS particularly well-suited to target functional subregions of the cerebellum. Here, we investigated the effects of cerebellar TUS (cbTUS) on motor cortical (M1) excitability.

Hypotheses: 1) Longer TUS duration will induce greater inhibition of M1 excitability; 2) TUS will transiently lower M1 excitability post-sonication; 3) cbTUS of cerebellar lobule VIII will have a greater inhibition and longer lasting effects compared to TMS-based scalp coordinates.

Methods: In Experiment 1, 500 ms of cbTUS was applied at 3cm lateral and 1cm below the inion. Motor evoked potentials (MEPs) were measured using TMS applied to M1. MEPs were measured at pre-TUS, after 150ms, 300ms, and 450ms of TUS, and 150ms post-TUS. In Experiment 2, the effects of cbTUS when stimulating the same location as Experiment 1, was compared to lobule VIII. MEP were measured at pre-TUS, after 150ms, and 450ms of TUS, and at 5ms, 50ms, 150ms, 1000ms and 2000ms post-TUS.

Results: In Experiment 1 we found that cortical excitability is significantly reduced 150 ms after 500 ms of TUS (26% decrease in excitability). In Experiment 2, we found that the time point of peak inhibition is dependent on the cerebellar lobule being stimulated. When targeting lobule VIII the peak inhibition was found 450 ms after the start of TUS (38% decrease in excitability).

Conclusion: Our results show that cbTUS can effectively modulate motor cortical excitability. This study is the first investigation of cerebellar TUS in humans, and provides the first step towards modulating specific lobules of the cerebellum non-invasively.

Date: Thursday Sep 9, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 16

Category: Poster presentation

Transcranial ultrasound stimulation using a learned mapping from MR to pseudo-CT images

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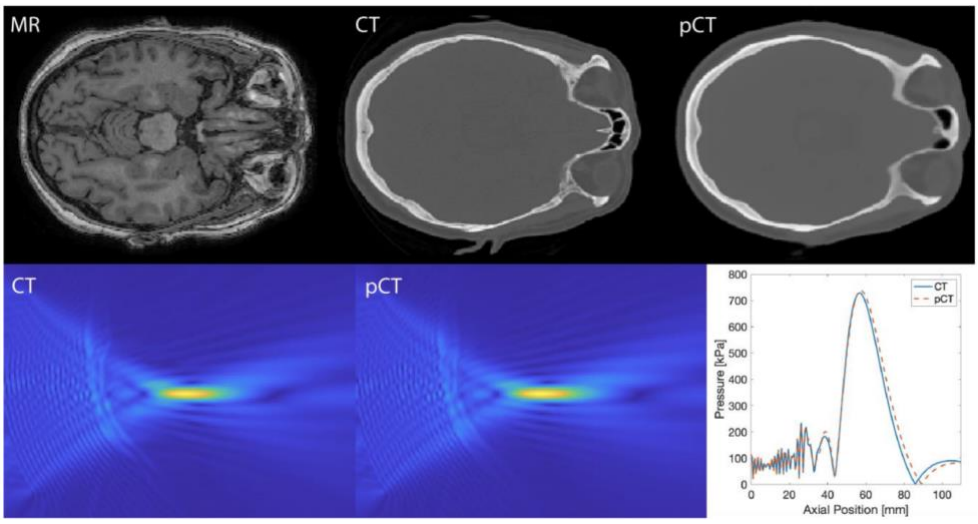
Ultrasound simulations are increasingly being used for transcranial ultrasound stimulation (TUS) to aid with guidance and dosimetry. Current approaches are based on mapping acoustic properties from x-ray computed tomography (CT) images of the individual subject, however, CT images are not always available. In this work, we explored using a convolutional neural network to perform image-to-image translation from a T1-weighted magnetic resonance (MR) image to a pseudo-CT (pCT) that can be used for TUS simulations.

A dataset of 55 patients who had undergone MR-guided focused ultrasound surgery (MRgFUS) at the Centro Integral en Neurociencias A.C. (HM CINAC) in Spain was used. Each patient had a CT image and a T1-weighted MR image (fast-spoiled gradient echo). The image pairs were co-registered using FSL, and the MR images were bias-corrected and histogram normalised. A mask was also generated from the MR images to segment the head.

A five-level convolutional U-Net was developed following Han (doi.org/10.1002/mp.12155) and trained using mean absolute error (MAE) on the pixels belonging to the extracted mask. The network was trained using transverse slices, which were then stacked together to create the final 3D volume used for simulation. 50 skulls were used for training (giving 7350 2D slices), and 5 for validation (723 2D slices). A range of hyper-parameters was investigated. A representative slice from the validation set is shown in the figure.

The acoustic performance of the pCT vs the ground truth CT was evaluated using 3D k-Wave simulations. The acoustic properties were mapped from Hounsfield units. The transducer was defined as a 64 mm f/1 focused bowl targeted at the approximate position of the visual cortex. For the skulls tested so far (see figure for an example), the difference in focal volume and the difference in peak pressure were both less than 10%. This suggests that using MR to generate pCTs for acoustic simulations is a promising avenue.

In future work, we will extend the size of the dataset, perform statistical analysis of the acoustic and imaging difference metrics, explore the use of multiple slices as input to the network, and investigate different transducer positions.



Date: Thursday Sep 9, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 17

Category: Poster presentation

Long-term study of motivational and cognitive effects of low-intensity focused ultrasound neuromodulation in the dorsal striatum of nonhuman primates

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Noninvasive brain stimulation using focused ultrasound (FUS) has many potential applications as a research and clinical tool, including incorporation into neural prosthetics for cognitive rehabilitation. To develop this technology, it is necessary to evaluate the safety and efficacy of FUS neuromodulation for specific brain targets and cognitive functions. It is also important to test whether repeated long-term application of FUS to deep brain targets improves or degrades behavioral and cognitive function. To this end, we investigated the effects of FUS in the dorsal striatum of nonhuman primates (NHP) performing a visual-motor decision-making task for small or large rewards. Over the course of 2 years, we performed 129 and 147 FUS applications, respectively, in two NHP. FUS (0.5 MHz @ 0.2 – 0.8 MPa) was applied to the putamen and caudate in both hemispheres to evaluate the effects on movement accuracy, motivation, decision accuracy, and response time. Sonicating the caudate or the putamen unilaterally resulted in modest but statistically significant improvements in motivation and decision accuracy, but at the cost of slower reaction times. The effects were dose (i.e., FUS pressure) and reward dependent. There was no effect on reaching accuracy, nor was there long-term behavioral impairment or neurological trauma evident on T1-weighted, T2-weighted, or susceptibility-weighted MRI scans. Sonication also resulted in significant changes in resting state functional connectivity between the caudate and multiple cortical regions. The results indicate that applying FUS to the dorsal striatum can positively impact the motivational and cognitive aspects of decision making. The capability of FUS to improve motivation and cognition in NHPs points to its therapeutic potential in treating a wide variety of human neural diseases, and warrants further development as a novel technique for non-invasive deep brain stimulation.

Date: Wednesday Sep 8, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 18

Category: Poster presentation

Sonication of thalamic circuits changes brain oscillations during non-stimulus conditions in a way analogous to changes in anesthetic level

Morteza Mohammadjavadi, Pooja Gaur, Yamil Saenz, Ryan T.Ash, Kim Butts Pauly

Objectives: It has been shown that the level of arousal in anesthetized animals can be changed through transcranial ultrasound stimulation (TUS) of the thalamus (Yoo et al., 2011). To investigate the effect of sonication and brain anesthetic level in a large animal model, we analyzed the spontaneous EEG activity of the frontal cortex during sonication.

Methods: Male sheep (N=4) were anesthetized with tiletamine and zolazepam at 4 mg/kg, intramuscularly. The anesthesia was maintained with a combination of isoflurane (0.3% to 0.7%) delivered by facemask and telazol delivered continuously by intravenous infusion. Platinum monopolar 30-gauge subdermal 10-mm long needle electrodes were implanted subdermally on the head positioned to overlie the frontal and occipital cortices. Animals were positioned in a 3T MRI scanner with an MR-compatible ultrasound transducer (ExAblate 2100, Insightec Ltd) coupled to the skin. The lateral geniculate neucleus (LGN) on one side was identified with T2-weighted MRI. MR acoustic radiation force imaging (MR-ARFI) was used to confirm focal sonication (in a position away from the experimental target). TUS pulses (PW 300 ms pulse duration, 50% duty cycle, 550kHz center frequency, at in situ estimated ISPTA values between 1 and 10 W/cm2) were applied to LGN for 40 min, followed by 60 min sonication to a location approximately 10 mm anterior to the LGN and including a portion of the medial putamen and immediately adjacent internal capsule (trials of TUS were interleaved with flashing light conditions in this order: No-stimulus, Light Only, TUS Only and Light+TUS). Multi-taper spectrograms were computed using 10 s periods of spontaneous activity within each 20 minute block of sonication recorded from the frontal midline electrode. The trials from each block were then concatenated into a single 200-second epoch data for time-frequency decomposition. To quantify the power shift in the spectrum, a power spectrum-based parameter, power fast slow (PFS), was derived to compare the logarithmic ratio of high-frequency components (40 to 47 Hz) with the total (1 to 47 Hz) band. This method has been compared to the Bispectral (BIS) index, a quantified EEG index to monitor the level of anesthesia in the operating room, and showed similar performance (Miller et al., 2004).

Results and Conclusions: The results are shown in Figure 1. The results from quantifying spectral analysis of EEG suggest that sonicating visual thalamus causes a shift in spontaneous EEG power analogous to the one from awakening from anesthesia, without any changes in vital sign measurements (MBP, HR).

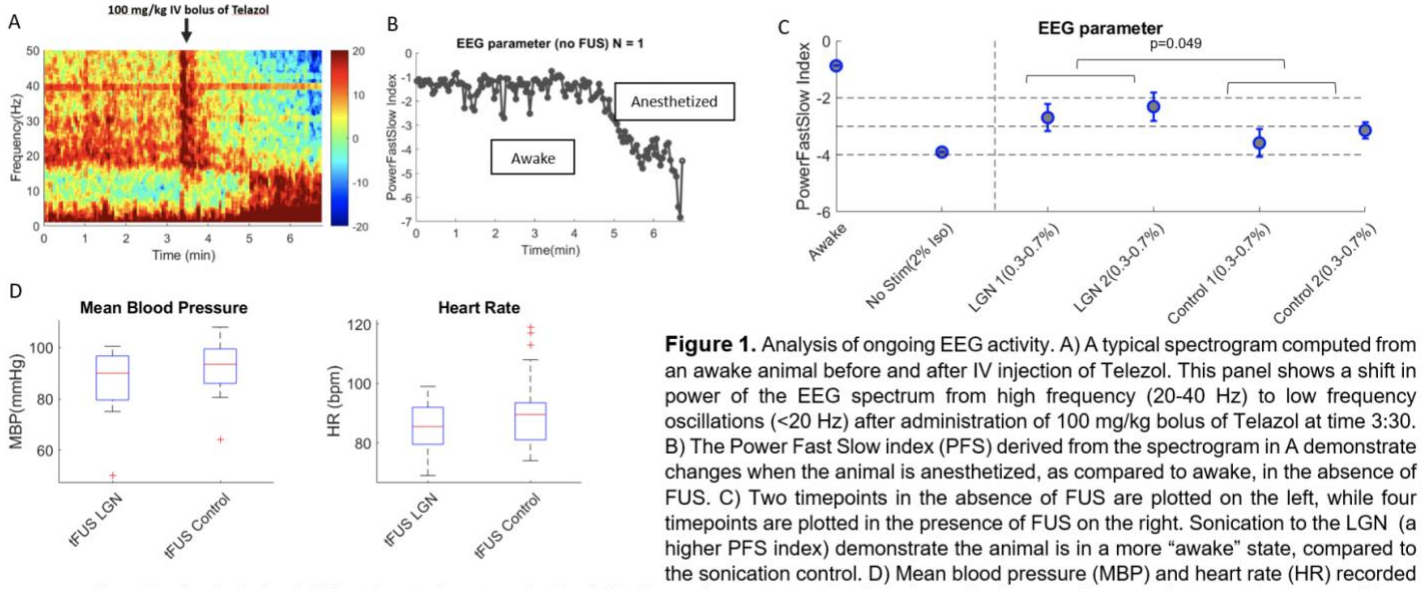

Figure 1. Analysis of ongoing EEG activity. A) A typical spectrogram computed from an awake animal before and after IV injection of Telezol. This panel shows a shift in power of the EEG spectrum from high frequency (20-40 Hz) to low frequency oscillations (<20 Hz) after administration of 100 mg/kg bolus of Telazol at time 3:30. B) The Power Fast Slow index (PFS) derived from the spectrogram in A demonstrate changes when the animal is anesthetized, as compared to awake, in the absence of FUS. C) Two timepoints in the absence of FUS are plotted on the left, while four timepoints are plotted in the presence of FUS on the right. Sonication to the LGN (a higher PFS index) demonstrate the animal is in a more "awake" state, compared to the sonication control. D) Mean blood pressure (MBP) and heart rate (HR) recorded from 4 animals during LGN and control spot sonication. This figure demonstrates that there is no significance difference between the two conditions.

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Time: 5:30 pm (CET) Booth number: 19

Using Lenses to Focus Ultrasound to the Human Hippocampus: Modelling and Validation

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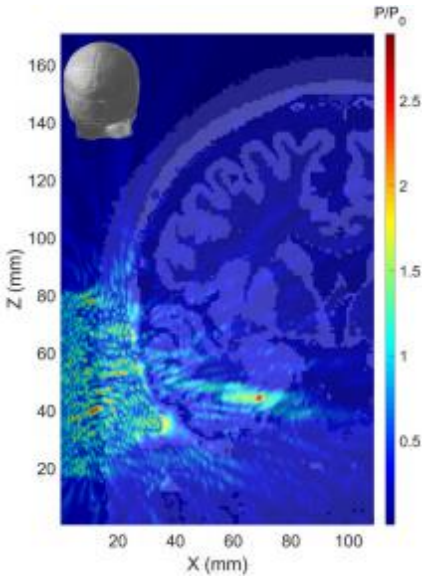
The goal of this paper is to develop a procedure for designing lenses for use with single element transducers to allow stimulation of deep brain targets in human by ultrasound. The two sites that were considered were the hippocampus (a site of interest in memory function) and the perirhinal cortex which is a neighbouring site that can be used as control for neurostimulation studies.

Anonymised T1-weighted MR images were segmented and used as the 3D simulation space and simulations were carried out using the k-Wave toolbox. For the lens design, a virtual source was placed at the target location and the radiated field captured on a surface outside the head. Phase-conjugation was employed to design lenses for an unfocused transducer with a range of diameters, frequencies and lens materials. The lens and transducer were then incorporated into the model and forward propagation employed to predict the acoustic field in the head. The simulation results suggested that the optimal configuration was a 65 mm diameter, 500 kHz transducer fitted with a PDMS lens. Targeting was accurate to within 1 mm with a focal volume less than 200 mm^3. In comparison, using a single element transducer with a fixed radius of curvature produce a focal volume greater than 1300 mm^3.

The lens design was validated on an ex-vivo skull sample. The skull's CT scan was binarised and imported into k-Wave for the lens design. A mould for the lens was 3D printed and then used to cast the PDMS lens. Pressure measurements were taken in a water tank. The measured focus was within 2.3 mm and the amplitude within 4% of the simulations. This work demonstrates that a lens can be employed to target the hippocampus for transcranial ultrasound stimulation studies and suggests that other targets will be amenable to this approach.

Figure: Simulated pressure field for a 500 kHz unfocused transducer with a target specific lens, demonstrating targeting of the hippocampus. The colour scale is the gain relative the source pressure.



Date: Tuesday Sep 7, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 20

Category: Poster presentation

BEST Toolbox: Brain Electrophysiological recording & STimulation Toolbox

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Non-invasive brain stimulation (NIBS) experiments involve many recurring procedures that are not sufficiently standardized in the community. Given the diversity in experimental design and experience of the investigators, automated but yet flexible data collection and analysis tools are needed to increase objectivity, reliability, and reproducibility of NIBS experiments. The Brain Electrophysiological recording and STimulation (BEST) Toolbox is a MATLAB-based open-source software, allowing the user to design, run, and share freely configurable multi-protocol, multi-session NIBS studies, including transcranial magnetic, electric, and ultrasound stimulation (TMS, tES, TUS). Interfacing with a variety of recording and stimulation devices, the BEST toolbox analyzes incoming EMG and EEG data and sets stimulation parameters on-the-fly to facilitate closed-loop protocols and real-time applications. Its functionality is continuously expanded and includes e.g., TMS motor hotspot search, threshold estimation, motor evoked potential (MEP) and TMS-evoked EEG potential (TEP) measurements, dose-response curves, paired-pulse and dual-coil TMS, rTMS interventions, TUS interventions, real-time EEG- triggered TMS or TUS, interleaving of concurrent TMS-fMRI, and many more. The BEST toolbox is powered by state-of-the-art signal processing algorithms and comes with a user- friendly graphical user interface (GUI) that facilitates data collection, live and interactive data analyses and visualization, student training, study comparison and replication, data sharing, and open science. In addition to supporting multimodal brain stimulation experiments, the BEST Toolbox features a TUS parameters planner (Figure 1), remote configuration of the TPO (NeuroFUS Pro, SonicConcepts/BrainBox, US/UK) via an independent API (https://github.com/umair-hassan/neurofus-api), RF wattmeter readout for in loop testing of the triggered sonication, and combination of TUS with other state-of-the-art stimulation modalities, such as real-time brain-state dependent brain stimulation. The BEST Toolbox empowers students, researchers, and clinicians to use complex multimodal methods, such as EEG-triggered TMS and TUS, to test their hypotheses in a plug-and-play manner. The integrated storage of experimental parameters and data ensures full transparency and reproducibility, while the full automation of procedures (such as closed-loop threshold hunting) increases objectivity and reliability of data collection and parameter estimation. Documentation and open source repository are available at www.best-toolbox.org.

Date: Tuesday Sep 7, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 21

Category: Poster presentation

TUS in DBS-implanted patients: In vitro safety assessment and evaluation of stimulation effect on continuous LFP recordings through DBS electrode

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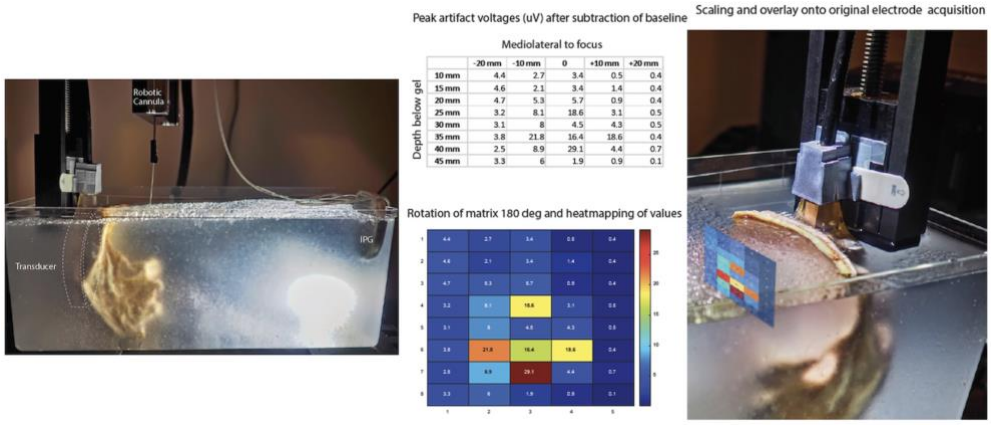
*equal first author contribution; **equal senior author contribution

Background: Transcranial ultrasound stimulation (TUS) is a promising modality of non-invasive human neuromodulation. A reliable method of targeting deep brain nuclei during TUS and confirming target engagement has yet to be described.
Objective: In this study, we investigated the safety of TUS on deep brain stimulation (DBS) systems, as well as the effects of acoustic waves on local field potential (LFP) sensing.

Methods and Materials: To simulate the human brain tissue, we created two phantom models by filling a polycarbonate box with a semisolid gel made of polyacrylic acid salt with (W SKULL) or without (NO SKULL) a partially-cut human cadaver skull. For temperature experiment, two DBS electrodes, each tied with a thermal sensor (GE model MA1000BF), were placed 60 and 80 mm away from the transducer (NeuroFUS CTX-500) into the phantom (NO SKULL). Two stimulation sessions (1 min and 30 mins) were performed under continuous TUS (500 kHZ, 60 mm focus, 0.2 ms burst length, 1 ms period). For motion detection, we captured a 50 FPS video (OLYMPUS OM-D EM-10) of the electrode embedded inside the phantom gel (NO SKULL) and performed a motion analysis by using CvMob software. We used a Medtronic Percept PC implantable pulse generator, which is designed for LFP sensing (250 Hz sampling rate), to identify, if any, stimulation artefacts by using its internal sensing ability. A 3-axis robotic arm (Acertara) used to place the electrode in different spatial locations as in a grid at a distance of 60 mm (W SKULL). Same stimulation parameters were used as in temperature experiment except continuous stimulation was replaced by intermittent 1 sec sonications. Spatial heatmaps were created by peak artefact voltage changes with sonication.

Results: With 1 min stimulation, there was no change in the temperature on the lead at 80 mm, while the electrode at 60 mm focus heated by 0.386 C. 30 minutes of stimulation increased the temperature at electrodes placed at 60 mm and 80mm by 1.463 and 0.091 C, respectively. Motion associated with sonication was not detected within the 50 uM pixel limit. We identified a stimulation artefact (a negative peak at the beginning of sonication followed by a positive peak at the end of sonication) after each sonication around the stimulation focus, of which the peak voltage change reaches to 28.1 uV (Figure 1).
Conclusion: Our results showed that short-duration TUS does not increase the temperature around the DBS electrode to hazardous levels. The motion of the electrode due to acoustic waves were within the acceptable limits. These findings highlight the possibility of utilization of TUS in DBS-implanted patients and may pave the way for neuroscientific studies aiming to compare the neuroimaging (i.e., fMRI) and neurophysiological (i.e., EEG, EMG) outcomes of DBS and TUS. The LFP artefact with TUS maybe due to sub-milimeter oscillations of electrode. Its capture has the value to be used as a feedback for the target-sonication engagement and may increase the accuracy of deep brain TUS targeting.



Date: Wednesday Sep 8, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 22

Category: Poster presentation

Quantitative Acoustic Output Measurement System for Low Intensity Focused Ultrasound

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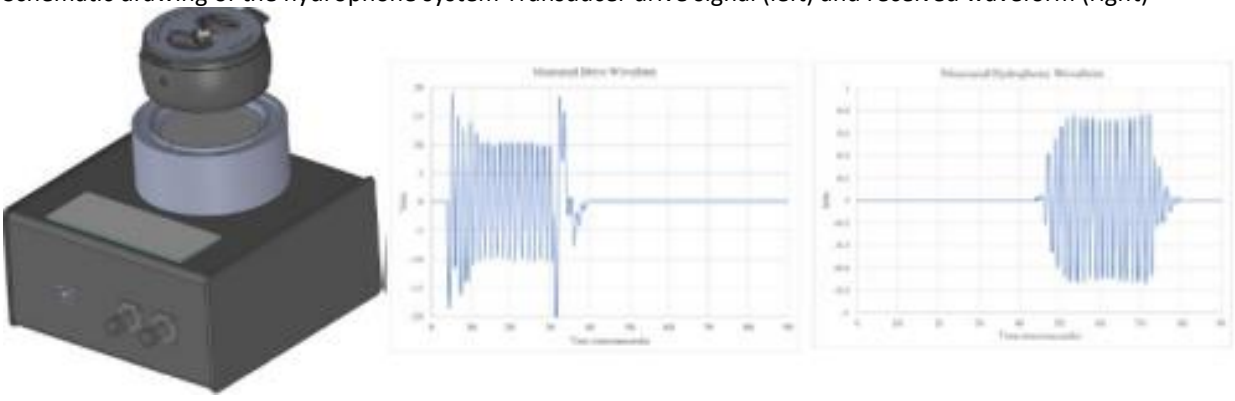
Background: It is important that ultrasound exposures for neuromodulation be conducted with the intended level of ultrasound energy. If the energy is too low, the treatment may be ineffective; if too high, there may be unintended negative biological effects. When the ultrasound treatment system is first delivered and installed at the treatment facility, it is presumed to be in complete working order. From that point forward, it is important that test procedures are in place to ensure that the output remains consistent, without imposing undue burden on the user or their facility. Results need not be absolutely calibrated, but must be repeatable and correlate to acoustic exposure.

Materials and Methods: To meet this need, we have developed a hydrophone-based acoustic output measurement system with no moving parts. The top of the system mates directly with the ultrasound treatment transducer to align the acoustic axis, and acoustical coupling requires less than 20ml of water (see Figure). The system is interconnected between the transmit electronics and the transducer via BNC connectors, to measure the transmitter electrical power, frequency, and transducer electrical impedance. Control and analysis software run on a laptop connected via USB. A piezopolymer hydrophone is embedded in a low loss castable silicone and positioned along the acoustic axis of the transmitting transducer at a depth beyond the focal plane. This ensures a plane wave field at the hydrophone. The hydrophone assembly is fully shielded from electromagnetic interference and contains a preamplifier and temperature sensor. Waveforms are sampled at 20MHz and transferred to the laptop.

Results: Under program control from the laptop computer, the system first disconnected the transducer from the drive electronics and measured the transmitter voltage and drive frequency. It then measured the electrical impedance of the transducer at that frequency. Finally, it reconnected the transmitter and drive electronics and measured the transmitted ultrasound wave as well as the change in the electrical drive signal when connected to the transducer (see Figure). All data were stored with a timestamp for later review. Experimental data showed that the system produced stable readings after repeated test cycles. The transducer output was reduced 5% by adding a resistor to the circuit; the shift was detected and the software alerted the operator.

Conclusion: The overall test process was rapid enough that it could be used before and after each clinical treatment, assuring exposure consistency over the course of a clinical study. The device is compliant with the goals of the ITRUSST Equipment Committee recommendations.

Schematic drawing of the hydrophone system Transducer drive signal (left) and received waveform (right)



Date: Wednesday Sep 8, 2021
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Location: Gathertown
Booth number: 23

Category: Poster presentation

Precomputation of hundreds of transducer positions for real-time, patient-specific simulation-based tFUS neuronavigation and planning

Bastien Guerin[1,2], Mohammad Daneshzand[1,2], Jason Stockmann[1,2], Jian Li[1,2,3], David Izquierdo[1,2], Ciprian Catana[1,2], Tina Chou[1,2,4], Brian L. Edlow[1,2,3], Darin Dougherty[1,2,4], Aapo Nummenmaa[1,2]
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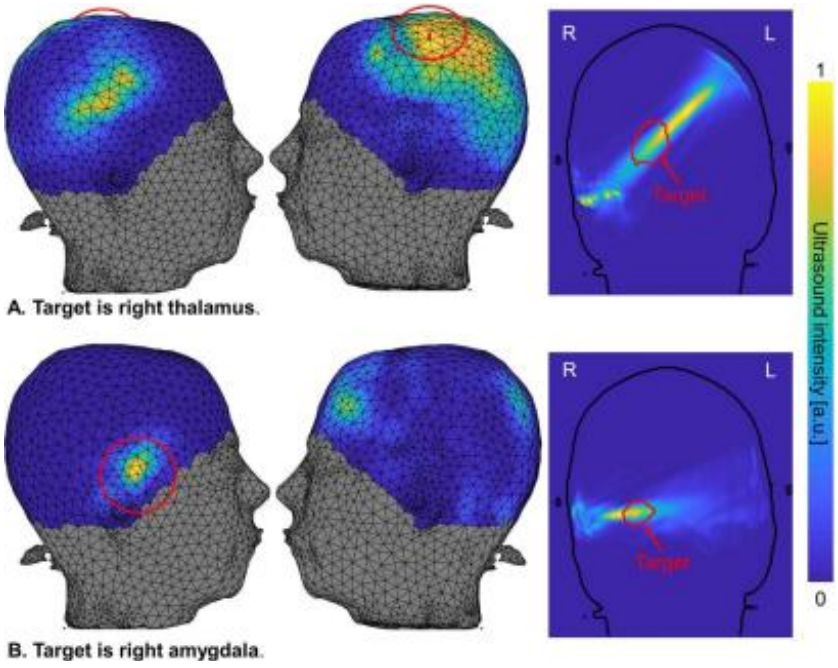
PURPOSE: We pre-calculated ~1000 transducer positions in two patients to 1) determine the optimal transducer placement for targeting the thalamus/amygdala ahead of sonication and 2) real-time neuronavigation.

METHODS: We derived acoustic parameters using CT data, using linear scaling of the HU. We meshed the skin surface and rejected vertices not directly above the brain cavity, resulting in 932 and 962 vertices for patients 1 and 2, respectively. We simulated the ultrasound beam created by a transducer with 200kHz/61mm/80mm frequency/aperture/radius placed at those locations and aligned to the local scalp normal using an FDTD simulator accelerated on a GPU.

RESULTS: Each transducer position took ~1.5min to solve, resulting in ~24 hours total compute time for each patient. Fig. 1 shows results for patient #2. The left/middle columns show scalp maps of ultrasound intensity in the thalamus and amygdala. The red transducer contour shows the optimal placement solution. The right column shows the optimal beam. For this patient (#2), the optimal transducer placement was contralateral to the target for the thalamus and ipsilateral for the amygdala. These conclusions were reversed for patient #1 (not shown). Targeting the thalamus yielded a broad region of near-optimal transducer locations, whereas only a small region was found to be optimal for the amygdala target.

CONCLUSIONS: Pre-calculation of transducer positions ahead of sonication is feasible, yields patient-specific optimal transducer placements that cannot be intuited easily (e.g., the laterality of the optimal placements can be opposite in different patients) and enable real-time simulation-based neuronavigation when combined with an optical tracking system.



Date: Thursday Sep 9, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 24

Category: Poster presentation

Deep brain neuromodulation in disorders of consciousness: challenges and opportunities

Monti MM, Cain J, Spivak N, Schnakers C

Disorders of consciousness (DOC) such as the Vegetative State (VS) and the Minimally Conscious State (MCS) describe conditions of severe disability and complete dependence, typically acquired after severe brain injury, which can last from days to decades. These conditions are also associated with great emotional and financial strain on families, increased burn-out rates of care-taking personnel, and pose complex medical, legal, and ethical questions. On the basis of a theoretical understanding of DOC as a functional and/or structural “disconnection” of thalamo-cortical circuits, experimental interventions are typically aimed at upregulating thalamic output. Yet, despite great advances in our understanding of these conditions, there is no accepted treatment for chronic DOC. Surgical interventions for direct thalamic stimulation (e.g., deep brain stimulation) have shown remarkable results, but are inapplicable to more than 85% of patients, while non-invasive indirect approaches (e.g., transcranial direct current stimulation) show some promise, but their efficacy remains debated. In light of the above, we launched a first-in-man clinical trial, in both acute (n = 11) and chronic (n = 10) DOC, aimed at evaluating the feasibility and initial safety and efficacy of non-invasive focused ultrasound neuromodulation of thalamus. First, with respect to safety we observed no Serious Adverse Events, confirming the safety record of this technique. Second, although this feasibility trial was open label with no sham control, both cohorts exhibited significant improvement in neurobehavioral measurements (i.e., Coma Recovery Scale – Revised, CRS-R, and CRS-R-index) following ultrasound. In the chronic cohort, which received two doses of ultrasound at a weeks distance, a significant linear trend was observed, suggesting an additive effect of multiple sonications. Despite these exciting initial data, and the opportunity that this technique affords to the treatment of conditions involving deep-brain neuclei, several challenges remain with respect to how this approach can best be deployed in the clinical context.

Date: Thursday Sep 9, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 26

Category: Poster presentation

Imaging assessment of mechanical and thermal effects during focused ultrasound sequences

Hermes A. S. Kamimura; Niloufar Saharkhiz; Stephen A. Lee; Elisa E. Konofagou

Focused ultrasound (FUS) can produce mechanical and thermal effects on tissues. Acoustic parameters can be adjusted to primarily produce one effect or the other, providing different neuromodulatory results. Comparable with electrical stimulation, we have shown that single FUS pulses applied to the mouse sciatic nerve can produce motor evoked responses. In contrast, fast-repeated pulses produce tissue temperature elevation followed by motor inhibition. The assessment of the contribution of each effect can provide important feedback on the optimum acoustical parameters for ultrasound neuromodulation.

In this study, we describe a dual imaging method based on harmonic motion imaging (HMI) and thermal strain imaging (TSI) for the evaluation of tissue-mimicking displacement and temperature increase caused by FUS [1]. A plane-wave imaging sequence interleaved with 1.1 MHz FUS pulses at a frame rate of 1 kHz was used to monitor tissue displacement as an index for acoustic radiation force. Simultaneous temperature evaluation was obtained through TSI, where cumulative apparent displacement indicated sound speed changes in tissue due to temperature elevation.

We demonstrated that the interleaved sequence (Fig. 1a) detected tissue displacements up to 70.6 ± 1.5 µm with temperature elevations up to 1.8°C (Fig. 1b). The interleaved sequence adopted an AM tissue motion, which allowed the evaluation of tissue displacement in the presence of tissue heating. Interestingly, the TSI estimation allowed an evaluation of tissue temperature during the FUS pulse, much less susceptible to tissue motion than thermocouple readings [2]. Simulation results using the Bioheat equation show that the temperature estimates were consistent with the TSI assessment.
Future studies will investigate the proposed pulse sequence to evaluate safety and mechanisms in ultrasound neuromodulation in the human peripheral nerve.

[1] Kamimura et al. IEEE OJ-UFFC, (accepted for publication). DOI: 10.1109/OJUFFC.2021.3085539
[2] Kamimura et al., IEEE TUFFC,67(1):70-80, 2020. DOI: 10.1109/TUFFC.2019.2940375

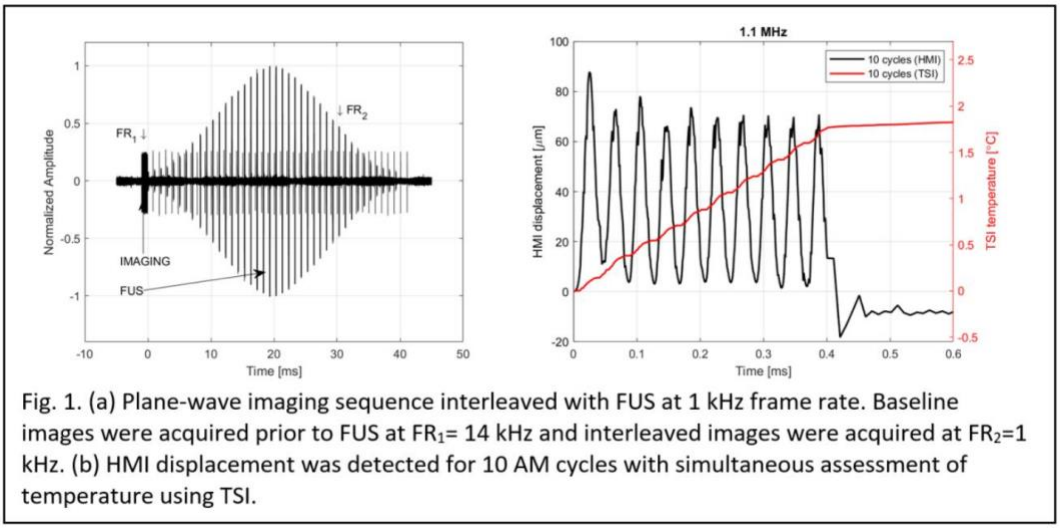


Fig. 1. (a) Plane-wave imaging sequence interleaved with FUS at 1 kHz frame rate. Baseline images were acquired prior to FUS at FR_1= 14 kHz and interleaved images were acquired at FR_2=1 kHz. (b) HMI displacement was detected for 10 AM cycles with simultaneous assessment of temperature using TSI.

Date: Thursday Sep 9, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 27

Category: Poster presentation

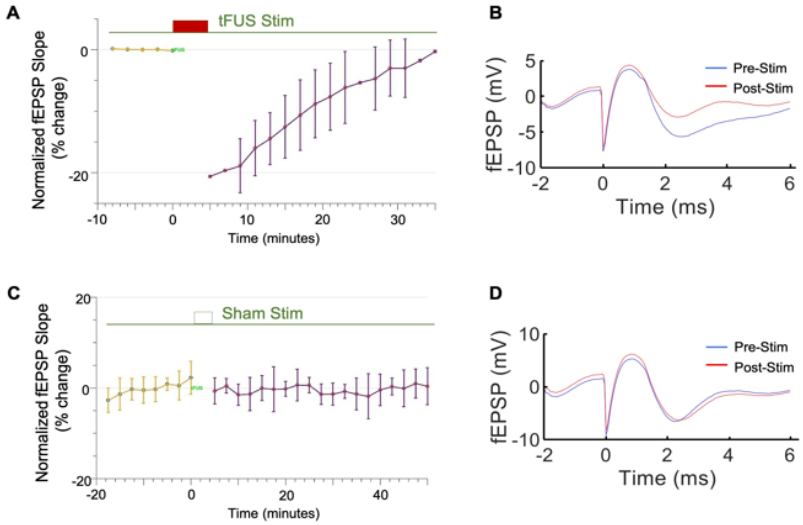
Noninvasive ultrasound neuromodulation induces long term depression in rat hippocampus

Xiaodan Niu, Kai Yu, Bin He

Abstract Transcranial focused ultrasound (tFUS) neuromodulation is a promising emergent non-invasive therapy for the treatment of neurological disorders. Many studies have demonstrated the ability of tFUS to elicit transient changes in neural responses. However, the mechanisms of sustained network changes induced by tFUS remain unclear.

The overall goal of this study is to examine the ability of pulsed tFUS to encode frequency specific modulation into the target neural tissue. We use the long-term potentiation/ long term depression (LTP/LTD) model in the rat hippocampus, the medial perforant path (mPP) to dentate gyrus (DG) pathway, to explore whether tFUS is capable of encoding frequency specific information to induce plasticity. Single-element focused ultrasound transducers were used for tFUS stimulation with fundamental frequency of 0.5 MHz and nominal focal distance of 38 mm (Olympus Scientific Solutions Americas, Inc., USA). tFUS stimulation is directed at mPP. Measurement of synaptic connectivity is achieved through the slope of field excitatory post synaptic potentials (fEPSPs), which are elicited using bipolar electrical stimulation electrodes and recorded at DG using extracellular electrodes to quantify degree of plasticity. We applied pulsed tFUS stimulation with total duration of 5 minutes, with 5 levels of pulse repetition frequencies (i.e. 3000 – 10,000 Hz), each administered at 50 Hz sonication frequency (i.e. inter-sonication interval: 20 msec) at the mPP. Baseline fEPSP is recorded 10 minutes prior, and 30+ minutes after tFUS administration.

In N = 16 adult wildtype rats, we observed sustained depression of fEPSP slope after 5 minutes of tFUS focused at the presynaptic field mPP. Across all PRFs, no significant difference in maximum fEPSP slope change was observed, average tFUS induced depression level was observed at 19.6%. When compared to low frequency electrical stimulation (LFS) of 1Hz delivered at the mPP, the sustained changes induced by tFUS stimulation show no statistical difference to LFS for up to 24 minutes after tFUS stimulation. When both the maximum depression effects and the duration of sustained effects are both taken into account, PRF 3 kHz can induce significantly larger effects than other PRFs tested. tFUS stimulation is measured with spatial-peak pressure amplitude of 99 kPa, which translates to an estimation of 0.43 ℃ temperature increase, rendering thermal effects an unlikely mechanism. Overall, the results suggest the ability of tFUS to encode sustained changes in synaptic connectivity through mechanisms of frequency encoding similar to the effects of LFS to elicit transient calcium fluctuations and downstream phosphatase cascades. Future studies will examine different sonication frequencies, and their effect of delivering sustained synaptic changes.



Date: Wednesday Sep 8, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 28

Category: Poster presentation

TUSX: an accessible toolbox for transcranial ultrasound simulation

Ian S. Heimbuch, Marco Iacoboni, Andrew C. Charles. University of California, Los Angeles

Introduction

Normally, the complicated nature of acoustic simulation makes it infeasible for most research groups, hindering interpretation and safety for transcranial ultrasound studies. We present here an open-source MATLAB toolbox to perform acoustic simulations using conventional subject-specific medical images for transcranial ultrasound experiments. This toolbox, Transcranial Ultrasound Simulation Toolbox (TUSX), consists of an integrated processing pipeline that takes in structural MR or CT images, processes them for accurate simulation, and runs the simulations in the existing open-source acoustics toolbox k-Wave.

Methods

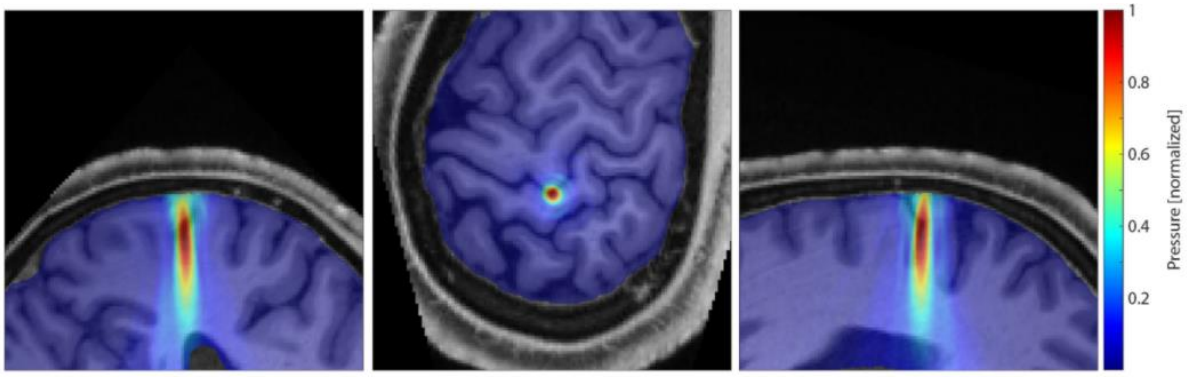
TUSX takes in a binary 3D skull volume (MR or CT) and scales it using linear interpolation to a higher resolution, which is necessary for accurate simulation. The location, trajectory, and other parameters of an ultrasound transducer is set by the user. The volume is then rotated such that the transducer trajectory is in line with the computational grid. This rotation improves accuracy by reducing the effect of staircasing along the skull edge, which would otherwise cause aberrant interference patterns.1 The skull volume is smoothed at multiple steps (before and after rotation) using morphological image processing. The proper acoustic parameters are then applied to each part of the volume. By default, a homogenous skull medium is used. Users can also independently supply heterogenous media volumes (e.g. apparent bone density derived from CT2). Additional k-Wave parameters are then set at proper values for the given volume. TUSX then executes the time domain 3D acoustic simulation via k-Wave,3 which uses a k-space pseudospectral method. The toolbox can execute the simulation via k-Wave's MATLAB implementation or export it for use in k-Wave's compiled C++ version for improved performance.4

Results

For a novel user performing simulations of transcranial ultrasound, TUSX greatly simplifies performing k-Wave acoustic simulations compared to k-Wave alone. It saves the user significant labor processing image volumes, placing ultrasound sources, and researching the necessary acoustic and k-Wave parameters for accurate transcranial simulations.

Conclusions

Since skull morphology varies highly between individuals, variations in skull thickness and shape result in equally varied intensity levels and foci location following skull transmission of ultrasound. As such, having access to estimations of in-tissue intensities in each research participant is crucial for both safety and interpretation of results. TUSX lowers the barrier to entry for transcranial ultrasound researchers to include acoustic simulation in their projects. By publishing it as an open-source code repository (TUSX.org), we hope TUSX will expand with the needs of the ultrasound community.



Slices from example tUS simulation overlaying a T1-weighted image. In-brain pressures shown only. Slice coordinate: hand knob. For this simulation, the volume has been reoriented by TUSX before simulation such that the ultrasound trajectory is orthogonal to the computational grid. Reorientation can help avoid having the ultrasound pressures interface with the skull at curvature; this 'staircasing' has been noted as the most serious cause of error in previous investigations of acoustic simulation accuracy.[1]

Date: Tuesday Sep 7, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 29

Category: Poster presentation

State-Dependent Modulation of Pain Circuits of Nonhuman Primates using an Integrarted MRI Guided Fcoused Ultrasound System at 3T

LM Chen, PF Yang, T Manual, M Sigona, H Luo, AT Newton, A Mishra, JC Gore, W Grissom, CF Caskey. Vanderbilt University Medical Center, Vanderbilt University Institute of Imaging Science

In the clinical management of pain, there is an unmet need for a non-invasive method that can precisely target and modify the neural activity within brain regions engaged in pain while providing simultaneous feedback on treatment effects. We have developed an integrated magnetic resonance (MR) image guided focused ultrasound (MRgFUS) stimulation system for targeted and high precision modulation of pain regions and circuits with fMRI feedback at 3T. Our goals are (a) to optimize our MR-ARFI system to provide realtime feedback of the beam target, and (b) to evaluate the modulation of FUS on neural activity of ACC and PVG as well as their corresponding pain circuits in two brain states (pain processing and at rest) with functional MRI (fMRI). We observed bidirectional and state-dependent functional modulation of pain circuits in three monkeys studied to date. Three macaque monkeys have been scanned at 3T under light isoflurane (~1%) anesthesia. 128-element transducer array was positioned on the top of the head, and a pair of surface coils were positioned on both sides of the head for acquiring ARFI and MRI/fMRI data. T1w and T2w structural images along with multiple runs (n=10) of fMRI data were acquired. Within each functional run, three experimental conditions (i) painful heat alone, ii) painful heat with FUS, and iii) FUS alone) were randomly presented in 16-sec on and 30-sec off epochs (7 epochs for each condition) one one hand. In total 498 (TR = 2s) volumes were acquired in 3T MRI scanner using a single shot GE-EPI sequence (TE=16ms, 1.43x1.43x2 mm3 voxel size). The standard pre-processing and normalization of fMRI data to the macaque template (NMT_v2.0) were done using FSL and custom Matlab code. The GLM analysis was performed to quantify stimulus-driven activation at the group level using three different conditions. Thresholded activation maps ($t>1.5$, $p < 0.05$, FDR corrected) were overlaid on the NMT template for display (Fig 1A&B). Widespread but distinct circuit activation maps were identified for heat + FUS versus FUS alone conditions. Robust BOLD fMRI signal changes were detected at the target and off-target known regions involved in pain processing, and regions that are not part of the pain circuits(Fig 1C&D). Concurrent presentation of pulsed FUS (650 kHz) at the target (ACC or PVG) drastically suppressed the pain responses at the target, compared to that during painful heat stimulation alone. However, the FUS-induced fMRI activation map did not completely overlay with that evoked by painful stimulation, indicating that ACC and PVG have their own casually interconnected brain pain networks. In summary, we found that FUS suppressed responses to heat stimulation and excited the two targets at resting state. MRgFUS has the potential to become a valuable tool for identifying pain regions for therapy. MR-ARFI provided realtime validation of FUS targeting while fMRI monitored the FUS modulation of the target and functional circuits.

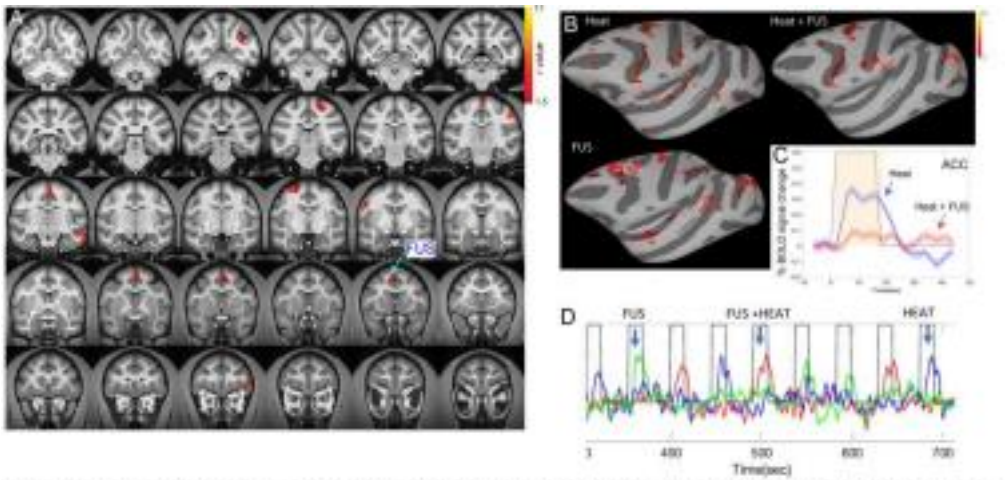


Figure 1. FUS stimulation of ACC during heat stimulation or at rest. A) BOLD fMRI activation evoked by FUS stimulation of left ACC. B) Inflated brain showing activation maps during three experimental conditions. C) Epoch-averaged % BOLD signal changes at the ACC targets during two conditions (Hot and Heat+FUS). D) Representative BOLD signal changes during three different stimulation epochs.

Date: Tuesday Sep 7, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 30

Category: Poster presentation

MorphoSONIC: a morphologically structured intramembrane cavitation model reveals fiber-specific neuromodulation by ultrasound

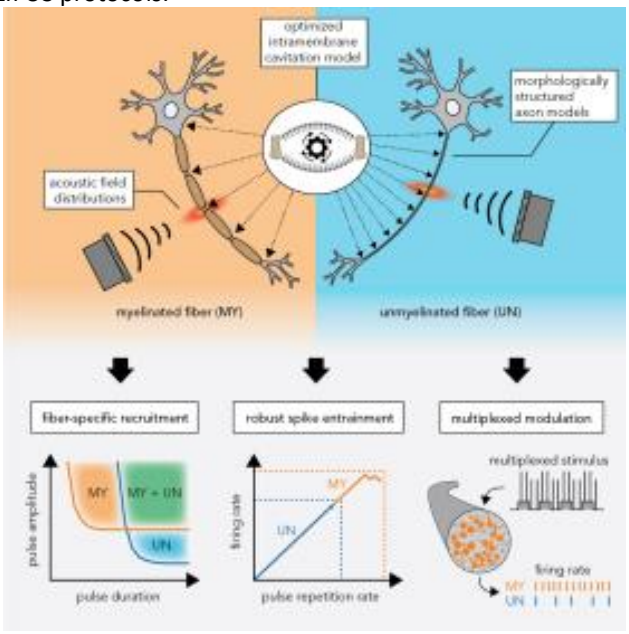
Théo Lemaire, Elena Vicari, Esra Neufeld, Silvestro Micera

Objective.
Low-Intensity Focused Ultrasound Stimulation (LIFUS) is emerging as a promising technology for the remote modulation of neuronal activity, but an incomplete mechanistic characterization hinders its clinical maturation. Intramembrane cavitation has been proposed as a candidate mechanism, but it has only been studied in single or two-compartment computational models of brain neurons. Here, we developed a computational framework to investigate this mechanism in multi-compartmental, morphologically structured neuron models, and used it to study ultrasound neuromodulation of peripheral nerve fibers.

Approach.
We recast NEURON's internal cable representation to enable the simulation of multi-compartment models with temporally and spatially varying membrane capacitance. This allowed to seamlessly incorporate the multi-Scale Optimized Neuronal Intramembrane Cavitation (SONIC) paradigm across an arbitrary number of connected compartments, while simultaneously ensuring numerical stability and accuracy. Within this framework, we then implemented single-cable models of myelinated and unmyelinated peripheral axons in order to compute their response to spatially-varying pressure fields.

Results.
We predict that by engaging mechanoelectrical bilayer coupling, LIFUS can exploit fiber-specific differences in membrane conductance and capacitance to selectively recruit myelinated and/or unmyelinated axons in distinct parametric subspaces. This fiber-specific neuromodulation is conserved across a wide range of acoustic field distributions and allows to design specific LIFUS protocols to modulate the spiking activity of different fiber types concurrently and independently over physiologically relevant regimes.

Significance.
These theoretical results consistently explain recent empirical findings and suggest that LIFUS can simultaneously yet selectively engage multiple neural pathways, opening up opportunities for peripheral neuromodulation currently not addressable by electrical stimulation, such as the specific targeting of nociceptive and sensory fibers. More generally, our framework can be readily applied to other neural targets in order to investigate electrophysiologically relevant LIFUS neuromodulatory effects and guide the development of application-specific LIFUS protocols.



Date: Wednesday Sep 8, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 31

Category: Poster presentation

Precise Targeting of Transcranial Focused Ultrasound Using Image Guidance and Array-Based Steering

M Anthony Phipps (1,3), Thomas Manuel (1.2), Huiwen Luo (1,2), Pai-Feng Yang (1,3), Allen Newton (1,3), Li Min Chen (1,3), William Grissom (1,2,3), Charles F Caskey (1,2,3)
(1) Vanderbilt University Institute of Imaging Science, Nashville, TN, USA, (2) Biomedical Engineering, Vanderbilt University, Nashville, TN, USA, (3) Department of Radiology, Vanderbilt University Medical Center, Nashville, TN, USA

Transcranial focused ultrasound (FUS) is being explored for a number of research and clinical applications in neuroscience due to its ability to non-invasively modulate functions of precise brain regions and circuits. The ability to target and localize the beam to these specific brain regions with a minimum amount of acoustic energy is important to avoid damage or off-target effects from FUS. Optical tracking of the FUS transducer is often used to estimate the beam position and MR acoustic radiation force imaging (MR-ARFI) can measure displacement generated at the focus. Here we present a method to guide the transducer with optical tracking and then electronically correct for tracking error and steer the FUS beam to brain targets based on a single MR-ARFI localization scan.

A 128-element FUS array was rigidly affixed to an optical tracking tool whose position and orientation were measured by an infrared camera. We computed the rigid transformation between the transducer's coordinate system and optically tracked space using hydrophone measurements followed by MR-based bias correction. Using fiducial-based registration we navigated the focus to a target and measured the beam location using MR-ARFI. We compare the optically tracked position to the MR-ARFI focus to calculate the FUS transducer steering coordinates required to correct for errors that occur due to optical tracking, registration, and sound transmission through the skull. Validation of the method was performed in gel phantoms and demonstrated in vivo feasibility by targeting the macaque insula and thalamus from a single transducer position.

Registration of the transducer coordinate system to the MR image space resulted in an average in vivo distance from the estimated focus location to the center of the MR-ARFI focus of 2.1mm. To demonstrate in vivo feasibility, we targeted a region between the macaque thalamus and insula and validated steering using MR-ARFI (Fig 1). The targeted points in the brain were within the MR-ARFI displacement map. The method described here allows for eliminating tracking error and rapidly targeting multiple individual brain regions with FUS without the need for multiple localization scans.

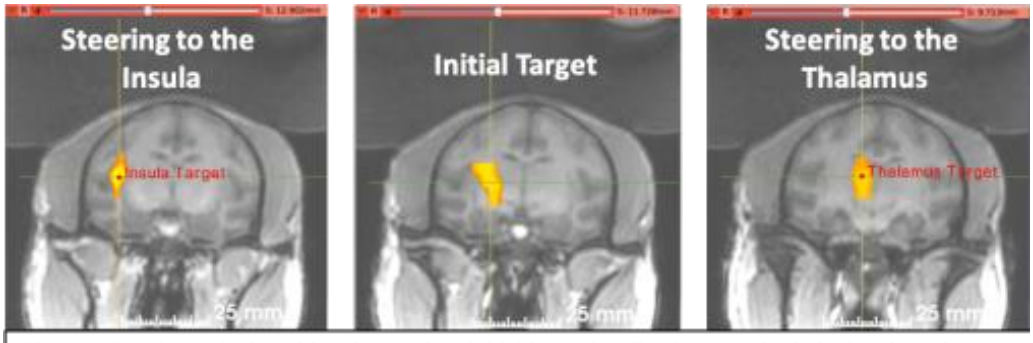


Fig 1: Using the optical tracking data and an initial beam localization scan both the insula and thalamus were targeted and successfully sonicated. The MR-ARFI displacement maps are shown in color overlaid on anatomical images. These maps have been cropped and thresholded to show the focus.

Date: Thursday Sep 9, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 32

Category: Poster presentation

Low intensity, CW focused ultrasound reversibly alters heart and respitory rate in anesthetized mice

Ethan Bendau (1), Christian Aurup (1), Hermes Kamimura (1), Elsa Konofagou (1,2)
(1) Department of Biomedical Engineering
(2) Department of Radiology, Columbia University, New York, NY

Background
Rising temperature as an effect of focused ultrasound (FUS) neuromodulation is an unavoidable result of ultrasound absorption by the treated tissue. Although many studies seek to reduce this temperature rise by employing various pulsing schemes, it has been suggested that sufficiently large FUS-induced changes in temperature can influence neuromodulation results. Our previous work has shown that continuous-wave focused ultrasound, causing changes in temperature within a safe range (<5oC), can modulate cardiorespiratory activity in mice. However, the extent to which the thermal and mechanical effects contribute to the effects has not been shown. In this study, low-intensity FUS was used to produce focal temperature rise in the brain of anesthetized mice while monitoring heart and respiratory rates. The changes in heart and respiratory rate due to FUS were compared to a separate cohort subjected to intracranial optical heating. The regulation of autonomic activity using FUS has not been previously demonstrated and we have shown that it can be used to transiently control heart and respiratory rates.

Materials and Methods
Continuous-wave focused ultrasound, generated by a single-element, 2 MHz FUS transducer (focal size: 1 mm lateral by 8.7 mm axial) was delivered to sodium pentobarbital-anesthetized wild-type C57BL/6 mice in the hypothalamus, a brain region related thermal and autonomic regulationHeart rate (HR) and respiratory rate (RR) were monitored via electrocardiography and respiratory pressure sensing. In a separate group, a 200-µm optical fiber coupled to a 50-mW laser (λ = 650nm) and controlled by an Arduino microcontroller was inserted into the brain at the same target. The duration and inter-stimulus interval of stimulus delivery was 60 s for both FUS and laser heating. For each mouse, the experiment lasted for up to 15 stimulus exposures or until it showed signs of consciousness. Changes in temperature due to FUS and laser heating were measured by thin wire thermocouples inserted at the skull/brain interface and in the target region. Targeting of a motor-related region encompassing the primary motor cortex (M1) and caudate putamen (CP) was used as a negative control.

Results
The increase in temperature over 60 s due to FUS at 425 kPa and 850 kPa was approximately 0.25 degrees C and 1.7 degrees C, respectively. The power output of the laser was adjusted via pulse-width modulation to produce a temperature increase of 0.25 degrees C at 1 mW and 1.7 degrees C at 38 mW, respectively. During both FUS and laser heating of the hypothalamus, the heart rate significantly decreased by up to 4 beats per minute during heating at 1.7 oC, while breathing rates significantly increased by up to 6 brpm. FUS in the negative control regions resulted in little or inconsistent changes in vital signs, despite similar temperature increases.

Conclusion
Modulation of cardiorespiratory activity in mice exposed to continuous-wave focused ultrasound targeted to the hypothalamus, producing both mechanical and thermal effects, has been shown to compare closely to modulation of the same region by laser heating acting purely via a thermal mechanism. The results indicate that the FUS- induced changes in heart and respiratory rate are primarily due to a local increase in temperature and are dependent on whether the hypothalamus is targeted. These results demonstrate the neuromodulatory impact of focused ultrasound in a regime where thermal effects of FUS dominate over its mechanical effects, and, further, that the effects of FUS-mediated changes in temperature can be explored further as a potential mechanism of FUS modulation

Date: Thursday Sep 9, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 33

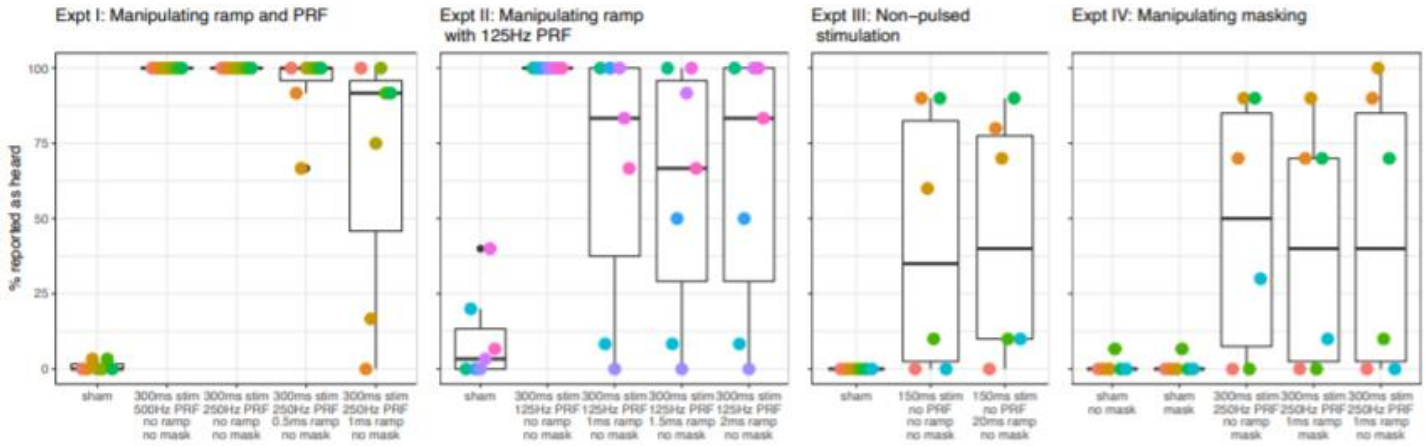
Category: Poster presentation

Pulsing, ramping, masking and the auditory artefact.

Ainslie Johnstone (1), Tulika Nandi (2,3), Elly Martin (1), Sven Bestmann (1), Charlotte Stagg (2), Bradley Treeby (1).

1: University College London, 2: University of Oxford, 3: Johannes Gutenberg University Medical Center.

Recently, the presence of an auditory confound has been noted when applying transcranial ultrasound stimulation (TUS) in both small animal models and humans (Mohammadjavadi et al., 2019; Braun et al., 2020). This prevents participant blinding, and causes excitation of auditory corticies which may interact with brain readouts or behaviour. Here, we investigate auditory perception of different stimulation protocols, and the effectiveness of mitigating it through different combinations of ramping and masking.
16 participants (5 female) took part in one or more different experiments across multiple days. Experiments manipulated the pulse repetition frequency (PRF), duty cycle, and ramp (see figure). In the final experiment, both active and sham pulses were masked using an intermittent 1s square wave matching the PRF. The mask was played over headphones at a fixed level, near the upper limit of tolerability. Real and sham stimulation was delivered randomised and double-blind, and participants were asked to report audition of the ultrasound stimulation using a mouse click. TUS was delivered using a H115-2AA transducer operating at 270 kHz driven by a 2-channel TPO (Sonic Concepts). The output power and element phase was adjusted to give a focal pressure in water of 700 kPa (~16 W/cm2) and a focal distance of 43 mm. The duty cycle for the ramped conditions was adjusted so that all stimuli had the same time-averaged intensity. The participant was positioned in a chin rest, and the transducer was manually positioned over the inion and held in place using rubber straps. Acoustic coupling was achieved using a gel coupling pad and ultrasound gel. All pulsed stimuli, without masking or ramps, were clearly heard by all participants. The sound was reported as being tonal in nature, scaling in frequency in line with the PRF. Adding a ramp of 1 to 2 ms prevented perception for some participants (Expt I & II). If stimuli was still audible it was reported as quieter, in some cases towards the limit of perception. Some participants reported using non-audible cues (such as perceived vibrations) to identify active conditions. Masking did not reduce perception over-and-above ramping (Expt IV). Non-pulsed stimulation, regardless of ramping, produced similar levels of audibility as pulsed stimulation with ramps (Expt III). Non-pulsed stimulation, if heard, was perceived as high-pitched pops or clicks. One participant reported this as very unpleasant. These results show that commonly used pulse configurations for human TUS are audible for a substantial proportion of participants. The resultant auditory processing may interact with brain or behavioural measures. Additional procedures are required to ensure blinding across all participants.



Date: Thursday Sep 9, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 37

Category: Poster presentation

Balancing open-label exploratory clinical trials with double-blinded RCT in the development of the new field of research. Lessons from rTMS and tFUS.

Alexander Bystritsky, M.D., Ph.D.

The development of new technology is challenging and has many obstacles, both scientific and financial. Looking at rTMS as the first non-invasive focused brain stimulation technique, it took many years to find appropriate locations, stimulation parameters, and clinical indications. Sound research methodology requires a sham-controlled double-blind approach for establishing efficacy. However, the experiments using this methodology are generally very complicated and expensive to perform. Researchers and developers of such devices struggle to obtain the financial support needed for these experiments that provide evidence for specific hypotheses. This is why the appropriate targeting, duration and exploration of the parameters were not done for rTMS. Much of this work is currently being done by researchers in academic medical centers, many years after the commercialization of the devices has occurred, as a result of which providers and payors are set in their way. This results in a lower effectiveness of treatments with the devices and often resistance of insurance companies to pay for the treatments. We will discuss different strategies and financial opportunities for the further development of tFUS. We believe that more open-label, exploratory, clinical experiments are needed to determine and optimize the effects of this new technology. The research institutes, funding agencies, private and public entities should support these new technologies and actively participate in these explorations.

Date: Wednesday Sep 8, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 38

Category: Poster presentation

Sensing mechanical force in the central nervous system.

Scott Hansen, Hao Wang, E. Nicholas Petersen
Department of Molecular Medicine, Scripps Research, Jupiter FL

Almost all cell types in the central nervous system (CNS) are sensitive to mechanical force. The utility and mechanism of sensing CNS force is still poorly understood. One way force influences protein function is through sorting of select proteins into nanoscopic lipid clusters comprised of either cholesterol and ganglioside (GM1) lipids or the signaling lipids phosphatidylinositol 4,5-bisphosphate (PIP2) and phosphatidic acid (PA). Shear causes proteins to move from GM1 clusters to the PIP2 clusters. I will discuss recent findings that show ultrasound applied to mouse brains alters the sorting of Alzheimer's and inflammatory proteins into mechanosensitive lipid compartments. First, the force deforms the ordered GM1 lipids. Second the deformation disrupts the interaction of palmitate, a saturated lipid, with GM1 lipids allowing the proteins to move. The amount of cholesterol in the membrane sets the threshold. Due to the short distances, the process can be very rapid (<3 ms).

Date: Tuesday Sep 7, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 39

Category: Poster presentation

Experimental validation of k-Wave simulations of ultrasound propagation through ex-vivo human skull

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Accurate modelling of the propagation of ultrasound through the skull is critical for the prediction of in situ acoustic parameters within the brain during transcranial ultrasonic neuromodulation, as well as for aberration correction and targeting of specific brain regions. While accurate simulation of the amplitude and spatial distribution of acoustic pressure after propagation through anatomical skull bone phantoms has been demonstrated, the mapping of the geometry and acoustic properties of real skull bone from medical images poses additional challenges which must be overcome. Here we present preliminary results of experimental validation of k-Wave simulations of the propagation of ultrasound through ex vivo human skull calvaria at four frequencies between 270 kHz and 1 MHz.

Acoustic fields were generated by a 2-element spherically focusing annular array transducer (H115 Sonic Concepts) driven at 270 kHz and 400 kHz with a 60 us burst, and by a single element spherically focusing ultrasound transducer (H101, Sonic Concepts) driven at 750 kHz and 1 MHz with both a 2 cycle burst and a 30 cycle burst. All source conditions were first characterized in free field using a calibrated 0.2 mm needle hydrophone in order to derive the equivalent source for k-Wave simulations. Acoustic properties of the skull were mapped from clinical CT scans of the skull, together with images of an electron density phantom acquired at the same settings. The skull medium was registered with the physical transducer position using CAD files of the 3D printed skull mounts used in the experiments.For each source condition, a degassed skull calvaria was mounted approximately 1 cm from the transducer surface, and the acoustic pressure was measured on a plane just inside the skull. The measured post skull acoustic pressure was propagated using the angular spectrum approach and compared with k-Wave simulations of the acoustic field generated by the source and passing through the skull.

In general there was greater aberration of the acoustic field at higher frequencies, with significant focal splitting and distortion at 750 kHz and 1 MHz (Fig. 1a), which was accompanied by larger differences between measured and simulated pressure distributions. In all cases, the simulated and measured arrival time of pulses at both the measurement plane and at the position of the spatial peak pressure agreed closely (Fig 1b), indicating that the speed of sound mapping, and registration between measurement and simulation was correct. Differences between measured and spatial peak pressure amplitude were within 15%, indicating that the absorption coefficient was also a reasonable estimate of the bulk attenuation of the skull. There were greater differences in the volume and spatial distribution of the -6 dB regions as frequency increased, for example with up to 59% and 55% of voxels lying at the same location in simulation and measurement at 750 kHz and 1 MHz respectively.
These results suggest that for this particular skull, the acoustic properties mapped from CT images acquired using these particular settings, enable prediction of pressure amplitude with similar error magnitude as previous validation studies performed using geometric phantoms. Further investigation will be performed with additional skull samples.

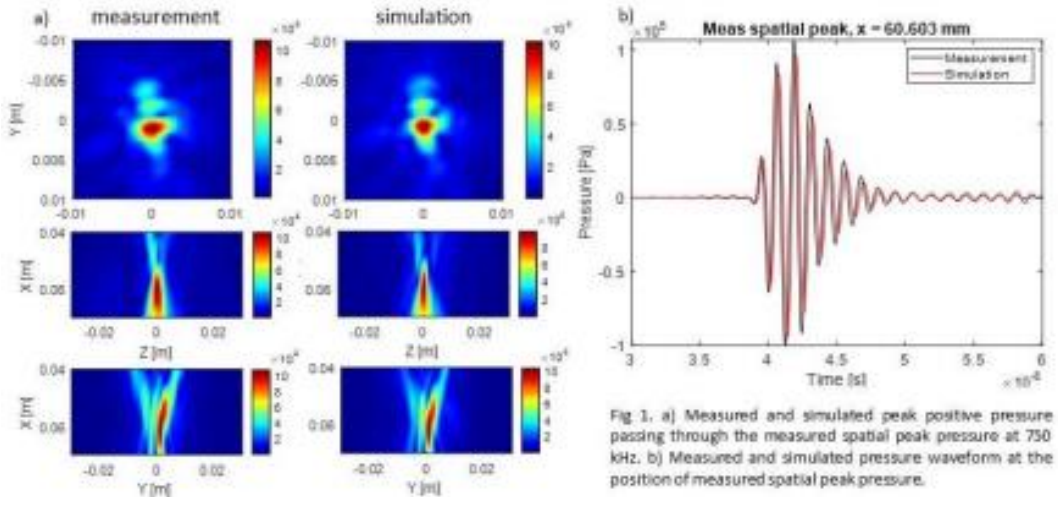

Fig 1. a) Measured and simulated peak positive pressure passing through the measured spatial peak pressure at 750 kHz. b) Measured and simulated pressure waveform at the position of measured spatial peak pressure.

Date: Tuesday Sep 7, 2021
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Category: Poster presentation

Regional pharmacological neuromodulation by FUS-mediated disruption of blood plasma protein binding

Wonhye Lee, Hyun-Chul Kim, and Seung-Schik Yoo

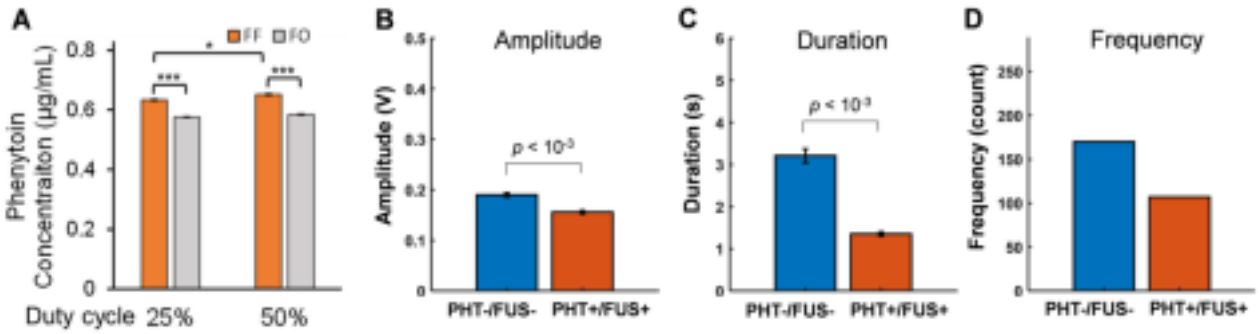
Region-specific enhancement of drug delivery to the brain, without increasing systemic drug dose or actively disrupting the blood-brain barrier, has been sought after as a new mode of regional neuromodulation, enabling pharmacological treatment of various central nervous system disorders. We present low-intensity transcranial focused ultrasound (FUS) technique that reversibly disrupts plasma protein binding (PPB) of a drug to enhance local drug concentration and corresponding drug delivery across the vasculature. We examined the effects of transcranial FUS on region-specific disruption of PPB with phenytoin (PHT; sodium channel blocker, molecular weight 252 Da), an antieplileptic agent that heavily binds to albumin, and evaluated if the regional increase of parenchymal PHT uptake results in the suppression of focal temporal lobe epilepsy (TLE) in rodents.

First, equilibrium dialysis was conducted on the sonicated cocktail of PHT/albumin in phosphate-buffered saline for 30 min, using duty cycles of 25% and 50% and pulse durations of 50, 75, and 100 ms at 5 W/cm^2 spatial-peak pulse-average intensity (Isppa) with 600 kHz fundamental frequency. A parameter set of 50% duty cycle with 50 ms pulse duration yielded 16.1% elevation in the unbound PHT concentration compared to unsonicated control (Fig. A; FF: at FUS focus, FO: at outside focus), showing the highest free unbound PHT level among the tested parameter sets.

Chronic focal TLE rats werultre prepared using unilateral intrahippocampal kainic acid (KA) injection [Raedt et al. 2009 Acta Neurol Scand]. Then, using the parameter set identified from the equilibrium dialysis results, multiple sessions of FUS (twice per week) were administered to the epileptic brain region (ipsilateral hippocampus) of chronic TLE rats receiving therapeutic doses of PHT. Starting ~12 weeks after the KA injection, electroencephalography (EEG) was acquired from the animals using a wearable telemetry device with video monitoring, and the amplitude/duration/frequency of epileptographic EEG events associated with behavioral seizures were quantified. Each animal underwent a total of 24 h EEG/video recording across 2-week period before and after the intervention, comparing PHT-only (PHT+/FUS-) and both PHT/FUS (PHT+/FUS+) conditions.

Although preliminary, PHT+/FUS+ condition significantly reduced all of the amplitude/duration/frequency of EEG ictal signatures compared to those measures from PHT-/FUS- (Figs. B–D). PHT treatment alone (PHT+/FUS-), on the other hand, reduced the amplitude/frequences of EEG ictal signal without decreasing its duration. Histological analysis was conducted to evaluate potential tissue or vascular damages, which showed that the FUS itself did not damage the sonicated tissues. Trypan blue intravenous injection after the sonication did not reveal undesired disruption of the blood-brain barrier.

The proposed method of acoustic disruption of PHT-PPB may provide an elegant and unprecedented option for suppressing seizure activity associated with focal epilepsy. Similar FUS protocols may also be applicable to increase regional delivery of a wide range of neuromodulatory drugs that have a high affinity to plasma proteins.



Date: Wednesday Sep 8, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 41

Category: Poster presentation

Ultrasound holograms to enhance deep-brain neuromodulation

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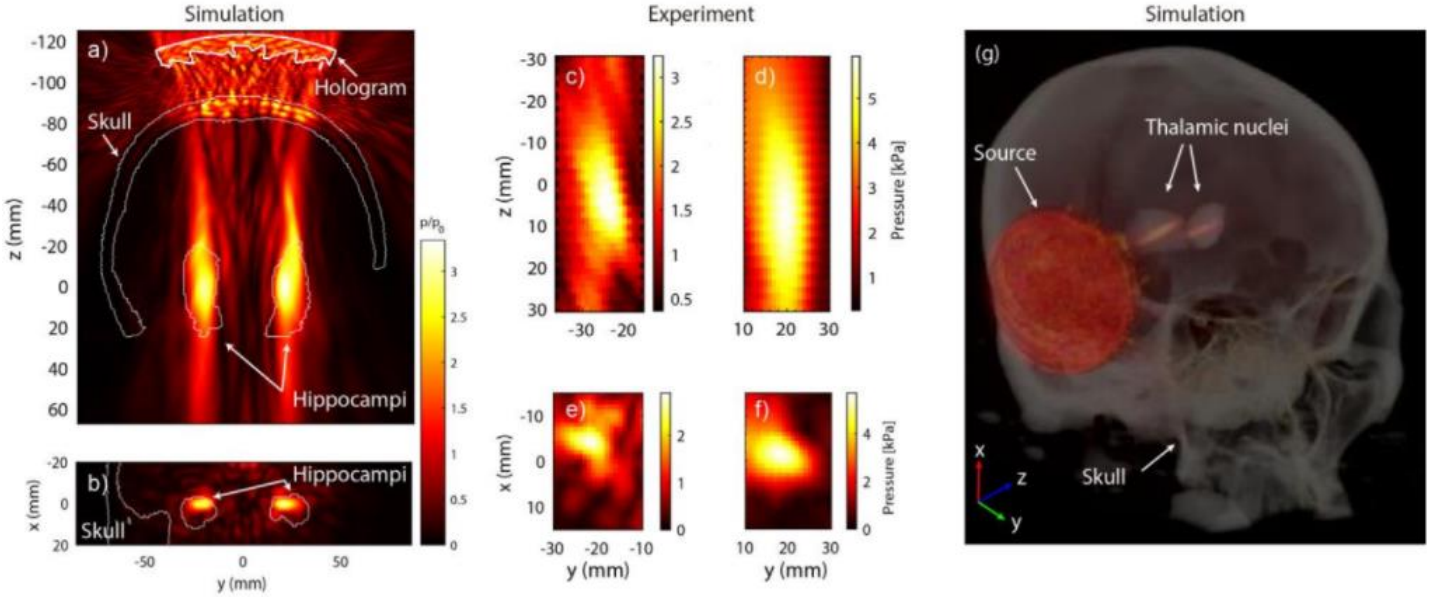
Transcranial focused ultrasound is widely used for neuromodulation at moderate intensity. To achieve a good treatment, it is important to have a control of the transducer focus location relative to the target of interest, but when ultrasound propagates through the skull it suffers from aberrant and attenuating effects that result in an undesired defocusing and uncertainty of the focus shape and location. Moreover, some nuclei of interest for neuromodulation are symmetrical in both brain hemispheres and current technologies are not capable of producing a simultaneous sonication of these structures.
In this work, we present the capability of acoustic holograms to control the focus shape and location even through the skull. First, time reversal simulations were done to adapt ultrasound focus to deep-brain targets of interest for neuromodulation, such as hippocampus, thalami, putamen and caudate nuclei. Second, holograms were 3D-printed and experimentally validated with an ex-vivo skull in water. We have simulated acoustic holograms to focus on both hippocampi, putamen and caudate nuclei from the parietal bone. Transcranial measurements completely agreed with numerical calculations. We have also created holograms to optimize the covered target volume when sonicating through the temporal bone window while avoiding skull heating, specifically for the thalamic nuclei. Results show that more than 20 % of the volume of bilateral targets within the brain can be covered with a single hologram while minimizing the sonicated non-objective brain tissue.

Acoustic holograms are a robust and low-cost system to focus ultrasound beams through the skull into deep-brain nuclei for precise and selective neuromodulation applications.



Date: Thursday Sep 9, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 42

Category: Poster presentation

The ultimate acoustic energy deposition (uAED): A theoretical performance metric for the assessment of tFUS strategies and hardware

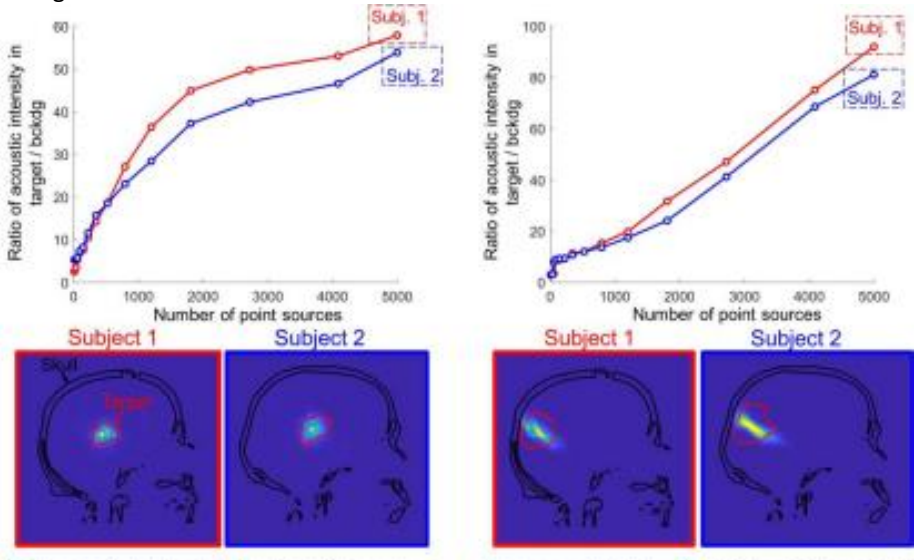
Bastien Guerin [1,2], Kyungho Yoon [3], Jason Stockmann [1,2], Tina Chou [1,2,5], Brian L. Edlow [1,2,4], Darin Dougherty [1,2,5], Aapo Nummenmaa [1,2]
[1] Harvard Medical School, Boston MA. [2] A. A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown MA. [3] Korea Institute of Science and Technology, Seoul, Republic of Korea. [4] Department of Neurology, Massachusetts General Hospital, Boston MA. [5] Department of Psychiatry, Massachusetts General Hospital, Boston MA

PURPOSE: We introduce the ultimate acoustic energy deposition (uAED), i.e. the best tFUS performance of any ultrasound hardware system for a specific brain target and frequency.

METHODS: At low intensity, ultrasound wave propagation is approximately linear. By Huygens's principle, the pressure field created by an arbitrary ultrasound source distribution placed outside the head can therefore be represented, inside the head, by a weighted combination of the fields created by a large number of points sources placed on the head' surface (skin). We place thousands of point sources on the scalp of two subjects, for whom we have a CT volume. Each point source is an isotropic ultrasound emitter at 200 kHz. We simulate the scattering and absorption of each point source' complex pressure distribution using a GPU-accelerated FDTD code based on the linearized Westervelt-Lighthill equation (acoustic maps derived from CT). Then, we calculate the complex weighted combination of those fields that maximizes the ratio of the total acoustic intensity in the target region and the rest of the brain.

RESULTS: Panels A & B show the approach to the uAED in two subjects at 200 kHz for deep and shallow target brain regions, as we increase the number of point sources in the basis set. The approach to the ultimate is slower for the shallow target (it is not reached with 5000 point sources). For that shallow target the uAED distribution displays a typical "lensed pattern" caused by the local skull curvature.

CONCLUSIONS: The uAED in cortical targets (shallow) seems to be lensed, indicating that the ultimate tFUS strategy may be obtained using a focused tFUS transducer matching the local skull curvature. For deep targets, the uAED conforms to the target' shape, indicating that a helmet similar to those used in HIFU applications may be advantageous. The uAED, like the ultimate signal-to-noise ratio in MRI, is an absolute benchmark performance metric that could prove useful for the development and comparison of neuromodulation tFUS strategies.



A. Approach to the uAED in the left thalamus (deep target)

B. Approach to the uAED in the right parietal cortex (shallow target)

Date: Thursday Sep 9, 2021
Time: 5:30 pm (CET)

Location: Gathertown
Booth number: 43

Category: Poster presentation

Computational Analysis of Off-target Ultrasound Neuromodulation Effects

Hossein Salahshoor, Mikhail G. Shapiro, Michael Ortiz; California Institute of Technology

Ultrasound neuromodulation (UNM) has recently received significant attention as a promising tool for neuroscience, where a region in the brain is targeted by focused ultrasound (FUS), which, in turn, causes excitation or inhibition of neural activity. Despite its great potential in neuroscience, several aspects of UNM are still unknown. An important question pertains to the off-target effects of UNM and their dependency on stimulation parameters [1-3]. To understand these effects, we pursue a computational analysis of UNM in both humans and rodents with recourse to explicit finite element method, where we account for the intiricate geometry and the viscoelastic mechanical behaviors of individual tissues. We demonstrate that, upon subjecting a region on the scalp above the skull to focused ultrasound (FUS) pressure, the bone acts as a waveguide for ultrasound- induced shear waves, carrying them away from the FUS target. As we demonstrate in our human study [4], this phenomenon help explain the off-target auditory responses observed during neuromodulation experiments [1-3].

We further invstigate the off-target UNM effects in a mouse subject by characterizing the resultant displacements, pressure and shear stresses at different locations on the mouse skin as a function of FUS frequency. Tissue motion at these locations can potentially cause sensory effects. Our findings reveal that shear stresses, but not pressures, exhibit a consistent and significant dependence on the FUS frequency, with lower frequencies leading to stronger shear effects. These findings appear to mirror the frequency dependence of UNM effects in rodents [5], making it challenging to distinguish them from direct neuromodulation. Our findings could help explain the off-target responses observed during neuromodulation experiments and inform the development of mitigation and sham control strategies.

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