Title: Magnetic resonance-guided Focused Ultrasound for the Treatment of Hypothalamic Hamartomas

Authors: Liming Qiu, Isaac Jonathan Pomeraniec, Ramya Raghupathi, H Isaac Chen, Marissa P Digiovine, Eva Catenaccio, Benjamin C Kennedy, Casey H Halpern

Email: liming.qiu@pennmedicine.upenn.edu

Abstract:

Introduction: Disconnective surgeries are a modern approach to epilepsy surgery to disrupt seizure networks with reduced surgical morbidities. Magnetic-resonance-guided focused ultrasound (MRgFUS) is a technology that allows incisionless conformal targeted thermoblation, providing safety advantages over traditional ablation techniques. Whilst most commonly used for its FDA approved indications of thalamotomy for Essential Tremor, MRgFUS has been increasingly investigated for other applications, including the treatment of hypothalamic hamartomas (HH) in case reports, and an ongoing early feasibility trial in the pediatric population.

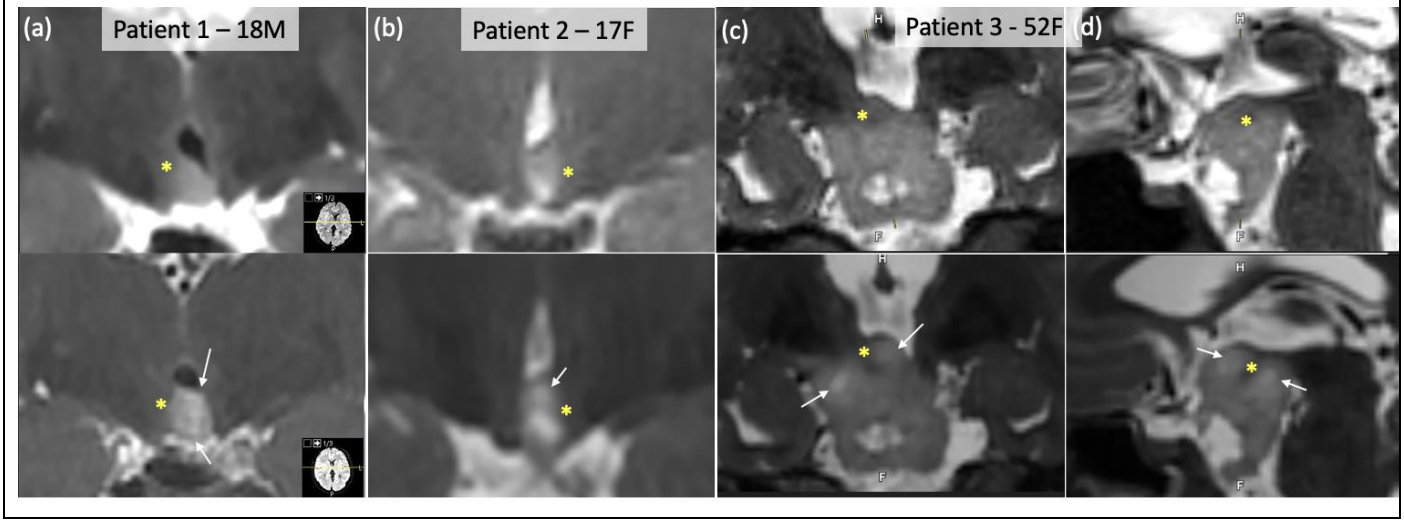
Methods: We present a case series of 3 patients who underwent MRgFUS disconnective ablation of HH as treatment of refractory epilepsy under the FDA Compassionate Use. All 3 subjects had received previous interventional procedures but still had recurrent seizures and were deemed good candidates for MRgFUS. Patient 1 is a 18 year-old male who underwent partial resection of HH at age 8 but still experienced at least 10-12 gelastic seizures daily as well as increased frequency of generalized tonic-clonic seizures. He also suffered memory and visual deficits from prior surgery. Patient 2 is a high-functioning 17 year-old female who had refractory gelastic seizures despite gamma knife radiosurgery at age 5. Patient 3 is a 52 year-old female with intellectual disability and high caregiver burden who experienced clusters of tonic and generalized seizures up to several times in a day despite partial debulking of a large type IV HH at age 8.

Results: All patients underwent MRgFUS disconnective ablation of HH under general anesthesia (Figure 1). Patient 1 no longer had generalized seizures at 1-year follow-up and gelastic episodes were greatly reduced (0-3/day), with no adverse effects. Patient 2 also had significant reduction in gelastic episodes at 5 months and change in quality of these episodes that no longer affected her social and occupational activities. Patient 3 experienced transient incomplete right abducens nerve palsy after treatment, which resolved after 2 days. At 6 weeks follow-up, she had 2 isolated seizure episodes, and no seizure cluster. All patients are still being followed for longer clinical outcomes.

Discussion: We demonstrated that MRgFUS is a safe and feasible approach for disconnective ablation of HH, of various sizes in selected patients. Given the incisionless, non-invasive, flexible targeting approach and ability to monitor and protect critical anatomical structures (Figure 1), MRgFUS may provide therapeutic benefits to patient with disabling seizures even if previous treatments have failed.

Conclusion: MRgFUS is a viable treatment option for treatment-refractory HH in appropriately selected patients.

Figure 1. Pre-surgical T2 sequence MRI (top row) and post-MRgFUS T2 MRI (bottom row) demonstrating successful ablations in 3 patients. Coronal images are displayed for (a) patient 1 and (b) patient 2, while (c) coronal and (d) sagittal images are displayed for patient 3. Arrows indicate the location of the disconnective ablation, and yellow * indicate critical structure (fornices) that were monitored and protected during the treatment procedure.



Acknowledgments: We thank Dr John Ragheb and Dr Gerald Grant for their invaluable inputs.

Conflicts of interest: *Enter disclosures or conflicts of interest*

Topic area: clinical **Preferred format:** poster

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: Optimization of MR-ARFI for transcranial ultrasound neuromodulation in human

Authors: Morteza Mohammadjavadi, Ryan T.Ash, Kim Butts Pauly, Gary H. Glover

Email: mortezmj@stanford.edu, rytash@stanford.edu, kimbutts@stanford.edu, gary.glover@stanford.edu

Abstract:

A major barrier to translating transcranial ultrasound stimulation (TUS) to human clinical trials is the need for confirmation of precise neuroanatomical targeting through the human skull which is strongly attenuating to ultrasound waves. MR acoustic radiation force imaging (MR-ARFI) has been demonstrated to provide reliable in vivo imaging of the focal spot. MR-ARFI combines low-intensity focused ultrasound (FUS) with motion-encoding gradients to create maps of the US beam profile from the phase difference between FUS on vs. off condition. Conventionally, 2DFT acquisitions have been employed with large pressures (2-3 MPa) (Mohammadjavadi et al, 2022). The 2DFT sequence was susceptible to motion artifacts from brain pulsatility (Kaye et al, 2013). The purpose of this study was to optimize MR-ARFI to allow reduced ultrasound exposure while at the same time being robust to bulk motion. In this study we introduce a timeseries of singe-shot spiral images while triggering the FUS on and off in blocks, analogous to fMRI block task designs. MR images were acquired on a 3T GE Signa MR scanner (GE Healthcare, Milwaukee, WI) using an 8-channel head coil with the 2DFT and single shot spiral readouts.

In Figure 1, image artifacts due to bulk- and pulsatile brain motion were significant with the 2DFT sequence (upper row), while the single-shot spiral time series acquisition substantially improved the motion artifacts (bottom row). A 500 kHz 4 element annular array (Neurofus System, UK) was coupled to the temporal bone of a human subject. During spiral scans, a free field value of 1.48 MPa (ISPPA = 68 W/cm2) at 60 mm depth was applied during motion encoding gradients of 12 ms and repeated for 50 time frames, interleaved with 50 frames without TUS, for a total exposure/slice of 12.75 J/cm2, using a conservative derating from Attali et al 2022. In contrast, the 2DFT exposure in our previous animal study used an in situ estimate at the focus of 2 MPa (ISPPA = 123 W/cm2), for a duration of 16 ms and repeated for 128 phase encodes for 2 images, with an exposure estimate/slice of 504 J/cm2. Thus, the time series approach allowed for a reduction in exposure/slice to 2.5% that in the animal study, while improving motion robustness with reduced scan time (80s vs. 205s).

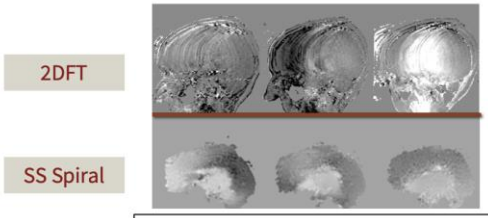


Figure1. Phase images obtained using 2DFT MR- ARFI pulse sequence in the (upper row) and SS Spiral shown in the (bottom row).

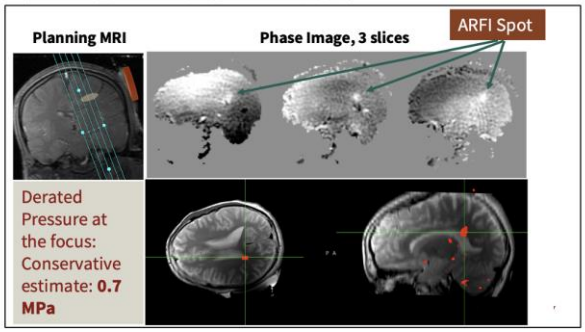


Figure2. MR-ARFI in human using 500kHz ultrasound frequency and derated pressure of 700 kPa. In the bottom row tSNR heatmap is overlaid on T2 anatomy image.

Acknowledgments: NIH MH131684, R01 EB032743

Conflicts of interest: No conflicts of interest.

Topic area: technical **Preferred format:** poster

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: **Enhancing Clinical Trial Design in Parkinson's Disease through Bayesian Hierarchical Modeling of Motor Responses to Transcranial Ultrasound Stimulation**

Authors: Nardin Samuel1*, Mandy Yi Rong Ding2*, Can Sarica1,2*, Leif Simmatis3, Ghazaleh Darmani2, Irene Harmsen1, Robert Chen2,4**, Andres M Lozano1,2**

1Toronto Western Hospital, Division of Neurosurgery, University of Toronto, Toronto, Ontario, Canada.
2Krembil Research Institute, University Health Network, Toronto, Ontario, Canada.
3Toronto Rehabilitation Institute, University Health Network, Toronto, Ontario, Canada.
4Edmond J. Safra Program in Parkinson's Disease Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, and Division of Neurology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada

Email: nardin.samuel@mail.utoronto.ca

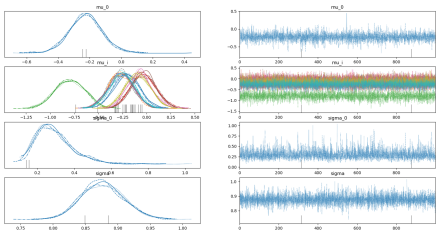
Abstract:

Introduction: Low-intensity transcranial focused ultrasound (TUS) is a promising neuromodulation tool for Parkinson's disease (PD) patients. We previously investigated the effects of accelerated theta-burst TUS (a-tbTUS) on neurophysiologic and clinical motor outcomes in PD, and reported a trend towards improved upper extremity (UE) rigidity in a subset of patients following active a-tbTUS. However, clinical findings from these studies are limited due to insufficient power. To address this gap, this study expands upon prior findings, by exploring grouping structures within intervention arms, with the goal of evaluating their impact on statistical power for subsequent clinical trials.

Methods: Bayesian simulation methods were used to characterize the structure of individual-level responses to a-tbTUS. Group-level and hierarchical Gaussian distributions were fitted to estimate the marginal and conditional mean structure of the data. These models were then fitted to the responses to sham and active a-tbTUS, and the clustering structure of the individuals from each dataset were assessed.

Results: Simulation-based analysis demonstrated distinct differences in clustering structure between sham and active a-tbTUS groups. Sham stimulation resulted in a wider range of overlapping responses with two clear modes consisting of 2 and 3 participants each, and the remainder not being separable. In contrast, active a-tbTUS yielded 3 clear modes each consisting of 3-4 individuals, suggesting individual differences in treatment response (see figure below). Hierarchal modeling demonstrarted reduced sampling variance of the mean, even at sample sizes less than 50 individuals per group.

Conclusion: Modern probabilistic methods for hierarchical inference have strong utility to derive generative models that can inform trial design. The findings from this study demonstrate that such modeling approaches can provide precise estimates of true means at small sample sizes. Future extensions of this work will explore incorporating individual-level patterns of clustering to inform sample size considerations for clinical trials investigating the motor effects of a-tbTUS in the setting of PD.



Acknowledgments:	*Enter acknowledgements*
Conflicts of interest:	The authors have no conflicts of interest to declare pertaining to this work

Topic area:	clinical	**Preferred format:**	oral

☐ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: Focused ultrasound-induced changes to animal pain behaviors and peripheral nerve structure

Authors: *1Zhao G, 1Thomas Z, 2Pacharinsak C, 3Kantarci H, 3Zuchero JB, 4Butts-Pauly K, 1Yeomans D, 1Anderson TA*
1Department of Anesthesiology, Perioperative and Pain Medicine, Stanford School of Medicine, Stanford, CA
2Comparative Medicine, Stanford University School of Medicine, Stanford, CA
3Neurosurgery, Stanford University School of Medicine, Stanford, CA
4Radiology, Stanford University School of Medicine, Stanford, CA

Email: tanders0@stanford.edu

Abstract:

Introduction
Moderate-to-severe acute pain is prevalent in many healthcare settings and associated with adverse outcomes. Opioids primarily block C fibers, not A-delta fibers and are associated with many adverse outcomes. Peripheral nerve blockade improves pain outcomes for some patient populations but has shortcomings limiting use. Focused ultrasound (FUS) is capable of inhibiting the peripheral nervous system and has potential as a pain management tool. In an in vivo acute pain model, we investigated focused ultrasound's effects on behavior and peripheral nerve structure.

Methods
FUS was applied directly to the sciatic nerve of rats just prior to a hindpaw incision; three control groups (FUSsham only, hindpaw incision only, FUS sham+hindpaw incision) were also included. For all four groups (intervention and controls), behavioral testing (thermal and mechanical hyperalgesia, hindpaw extension and flexion) took place for 24 weeks. Structural changes were assessed using transmission electron microscopy for controls and for 28 weeks after FUS application.

Results
Compared with controls, after FUS application, animals had increased mechanical nociceptive thresholds for 2 weeks, increased thermal nociceptive thresholds for 9 weeks, decreased hindpaw motor response for 1 week, and decreased hindpaw plantar sensation for 3 weeks. Histologically, FUS altered nerve structure significantly, but phasically, with nerve anatomy returning to normal by 20 weeks after FUS application.

Conclusion
FUS, using a distinct parameter set, reversibly inhibits C and A-delta peripheral nerve nociceptive, motor, and non-nociceptive sensory fiber-mediated behaviors, and alters nerve structure. FUS may have potential as a peripheral nerve blockade technique for acute pain management. However, further investigation is required to determine the significance of nerve structural changes.

References

1. Anderson TA, Pacharinsak C, Vilches-Moure J, Kantarci H, Zuchero JB, Butts-Pauly K, Yeomans D. Focused ultrasound-induced inhibition of peripheral nerve fibers in an animal model of acute pain. Reg Anesth Pain Med. 2023 Sep;48(9):462-470.
2. Anderson TA, Delgado J, Sun S, Behzadian N, Vilches-Moure J, Szlavik RB, Butts-Pauly K, Yeomans D. Dose-dependent effects of high intensity focused ultrasound on compound action potentials in an ex vivo rodent peripheral nerve model: comparison to local anesthetics. Reg Anesth Pain Med. 2022 Apr;47(4):242-248.

Acknowledgments: NA

Conflicts of interest: NA

Topic area: clinical **Preferred format:** oral

☐ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: **Transcranial low intensity focused ultrasound of the anterior nucleus of the thalamus in treatment resistant depression**

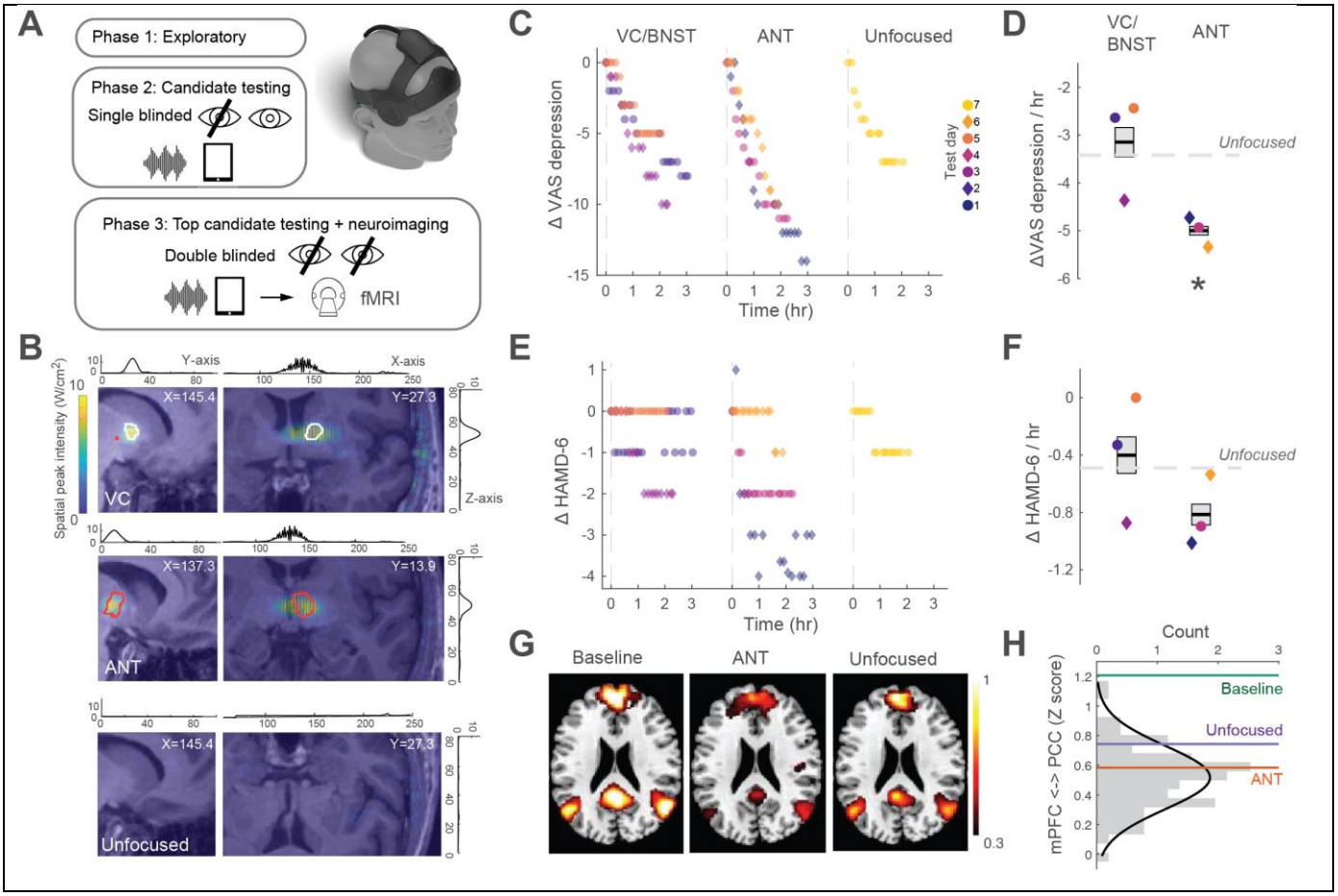
Authors: Joline M. Fan1,2, Kai Woodworth2, Keith R. Murphy3, Leighton Hinkley4, Josh L. Cohen2, Joanne Yoshimura2, Inhauck Choi2, Alex Tremblay-McGaw2, Joncarmen Mergarthan2, Cameron H. Good3, Peter Pellionisz2, Moses Lee2, Tommaso Di Ianni2,4, Leo P. Sugrue2,4, Andrew D. Krystal1,2

1Department of Neurology, University of California, San Francisco, CA; 2Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, CA; 3Attune Neurosciences, San Francisco, CA; 4Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA

Email: Joline.fan@ucsf.edu

Abstract:

Major depressive disorder (MDD) is a leading cause of disability worldwide with up to one third of cases being treatment resistant. Symptom heterogeneity suggests variability across the affected brain network, prompting efforts to personalize circuit-based neuromodulatory interventions. Transcranial low intensity focused ultrasound (LIFU) is an emerging, non-invasive method that has the potential to survey multiple regions and target deep structures within putative mood networks. To examine whether dynamically steered LIFU could be used to identify therapeutic subregions in MDD, we employed dual-phased array cross-beam focusing to stimulate subcortical mood-related circuitry. We report on a 46 year-old man with treatment resistant depression, who underwent an interventional assessment (Fig. 1A) aimed to 1) assess target regions that have therapeutic potential based on self-report and 2) objectively investigate the effects of a top candidate target using neuroimaging. Following an exploratory phase, serial testing was performed to assess the effects of stimulation on the ventral capsule (VC; Fig. 1B), bed nucleus stria terminalis (BNST) and anterior nucleus of the thalamus (ANT; Fig. 1B). Behavioral outcomes were collected using visual-analog scales (VAS) of depression and the 6-item Hamilton Depression Rating Scale (HAMD-6). All candidate regions were sonicated (ATTN201 device; Attune Neurosciences, Inc., San Francisco, CA) using the same stimulation parameters: 500 kHz fundamental frequency, 25 Hz pulse repetition frequency (PRF), 13% duty cycle (DC), and 300s pulse train duration. Alternating left and right lateralized regions were sonicated every 15 minutes, i.e. 10 min inter pulse-train interval for eight total pulse trains (four left and four right lateralized). Over the course of serial sonication, a reduction in VAS-depression and HAMD-6 was observed across all conditions (Fig. 1C-F). The effects of sonicating two regions, i.e. VC/BNST and ANT, were compared to unfocused stimulation. In contrast to the grouped VC/BNST condition, ANT sonication sessions led to a larger shift in VAS-D ($p=0.013$, one sample t-test; Fig. 1D) when compared to an unfocused sham stimulation. We subsequently evaluated the effects of sonication on the default mode network (DMN), an important resting-state network implicated in self-reflection and rumination. Resting-state fMRI following double-blinded ANT and unfocused stimulation revealed a reduction in DMN connectivity in the ANT condition, when compared to the atypically high levels of connectivity in the baseline condition, as well as the unfocused condition (Fig. 1G,H). In this N of 1 study, we demonstrate that LIFU directed to the ANT may have potential to elicit a subjective reduction in depression symptoms associated with changes in the DMN. Furthermore, we demonstrated that an intermittent stimulation paradigm may have the potential to progressively shift mood symptoms over time, when compared to an unfocused sham control. Further studies are needed to further explore the generalizability of these findings and to explore whether our result is due to selective engagement of ANT or of other nearby structures.



Acknowledgments: None

Conflicts of interest: Partially funded by Attune Neurosciences

Topic area: clinical **Preferred format:** oral

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: Neuronal and Inter-neuronal Responses to Transcanial Focused Ultrasound in Anesthetized Rats

Authors: Huan Gao, Sandhya Ramachandran, Kai Yu, and Bin He (Department of Biomedical Engineering, Carnegie Mellon University, Pittsburgh, PA)

Email: huangao@andrew.cmu.edu

Abstract:

Low-intensity transcranial focused ultrasound (tFUS) has shown abilities to unequally modulate activities of neuronal subpopulations and neural pathways. Previous studies demonstrated that tFUS could elicit excitatory effects in regular-spiking units (RSUs) during sonication with specific parameters and affect neural pathways, such as sensory and motor pathways. However, to understand the potential sustained neuronal effects and explanations for ultrasound-induced pathway modulation, post-sonication effects on neural activities and inter-neuronal correlations need to be investigated. In this study, 128-element random array ultrasound transducer H276 (f0: 1.5 MHz, axial specificity: 1.36 mm, lateral specificity: 0.46 mm) was used to stimulate at the somatosensory cortex (S1) of anesthetized wild-type rats (n=24). The recorded single neuronal units were sorted and categorized into regular spiking units (RSUs) and fast spiking units (FSUs) based on the waveforms, putatively deemed as excitatory and inhibitory neurons, respectively. We examined neuronal responses to different ultrasound pulse repetition frequency (PRF) levels of 30, 300, 1500, 3000, and 4500 Hz, and duty cycles (DC) of 0.6%, 6%, 30%, 60%, and 90%. We observed that while recording from S1, only RSUs show time-locked response ($p<0.01$ compared to pre stim) to the PRFs higher than 30Hz with mid-range of DCs. And both RSUs and FSUs exhibited delayed responses (0.2-0.3s, $p<0.01$) at high PRFs with a certain range of DCs, which indicate the selectivity of neuronal types to tFUS is parameter-independent while the responses are parameter-dependent.

Further,we simultaneously recorded from S1, primary motor cortex (M1) and posteromedial thalamic nucleus (POm) along the CTC pathway to explore the mechanism behind the ultrasound-induced delayed neuronal responses (N=9). The firing rates of RSUs in POm increased during 0.1-0.2s ($p<0.01$) with PRFs of 300Hz, 1500Hz and 3000Hz, while the FSUs did not change their spiking activities. A delayed response during 0.2-0.3s was also found in M1 FSUs. We further quantified the pairwise correlation between RSU and FSU in S1, M1 and POm using the directional spike time tiling coefficient (STTC) to determine the direction of activation along the CTC pathway due to ultrasound stimulation. As a result, RSUs correlation increases bidirectionally between S1 and M1, and between S1 and POm at the initial time-locked window (0-67ms). While the increase of FSUs correlation occurred bidirectionally between S1 and M1, and unidirectionally from POm to S1.

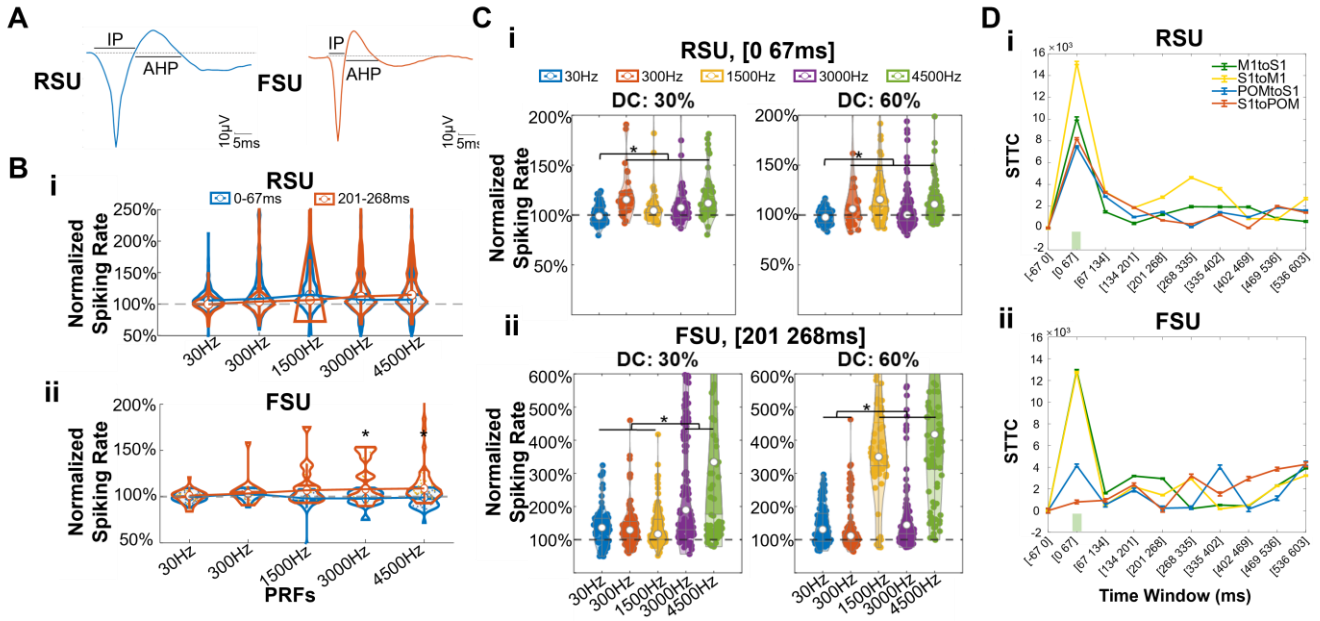


Figure 1 Neuronal and Inter-neuronal responses to tFUS. **(A)** Typical waveform examples of a regular-spiking unit (RSU, left) and a fast-spiking unit (FSU, right). **(B)** Unequal responses of RSUs (i) and FSUs (ii) to different PRFs (pulse duration is 200us) during sonication (0-67ms) and after sonication (201-208ms) (*p<0.05). **(C)** Normalized firing rates of RSUs during sonication (i,0-67ms) and FSUs after sonication (ii, 201-268ms) to five PRF levels with 30% and 60% DCs. **(D)** Neuronal correlation within RSUs (i) and FSUs (ii) along CTC pathway to 1500Hz PRF with 30% DC.

Acknowledgments: This work was supported in part by NIH grants NIH NS124564 and NS131069 (B.H.).

Conflicts of interest: N/A

Topic area: neuroscience **Preferred format:** poster

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: **Effects of muscle activation on theta burst transcranial ultrasound stimulation-induced plasticity in the motor cortex**

Authors: Negar Nasrkhani1*, Amitabh Bhattacharya1*, Rachel Chang1, Robert Chen1,2

1Krembil Research Institute, University Health Network, Toronto, Ontario, Canada. 2Edmond J. Safra Program in Parkinson's Disease Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, and Division of Neurology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada.

Email: Negar.nasrkhani@uhn.ca

Abstract:

Introduction: Low-intensity transcranial ultrasound stimulation (TUS) is a novel non-invasive brain stimulation (NIBS) method with deeper and more focal penetration compared to other NIBS, such as transcranial magnetic stimulation (TMS). The theta burst TUS (tbTUS) protocol enhances brain connections for 30-60 minutes post-stimulation, inducing long-term potentiation (LTP)-like effects in the primary motor cortex (M1). In LTP-inducing TMS protocols, M1 excitability is influenced by target muscle activation. Specifically, voluntary contraction of the target muscle before intermittent theta burst stimulation reverses its facilitatory effects to inhibitory, suggesting polarity-reversing metaplasticity. This study aims to understand how voluntary muscle contractions affect tbTUS-induced plasticity.

Hypothesis: Pre-tbTUS target muscle contraction will reverse tbTUS-induced facilitatory effects, while post-tbTUS muscle contraction will enhance tbTUS facilitatory effects.

Methods: The right first dorsal interosseous (FDI) muscle hotspot in the left M1 was targeted. The tbTUS paradigm used 80s of 5Hz bursts. FDI contraction involved 20% maximum voluntary index finger abduction for 180s. Four interventions (tbTUS alone, contraction before tbTUS, contraction during tbTUS, contraction after tbTUS) were performed in random order. Motor-evoked potential (MEP) amplitude, short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF) were measured using TMS before and at 5, 30, 60, and 90 minutes post-intervention from the FDI, abductor pollicis brevis (APB), and abductor digiti minimi muscles.

Results: Data was collected from 7 participants. FDI contraction before tbTUS reduced MEP amplitudes in FDI and APB muscles compared to tbTUS alone, while FDI contraction after tbTUS increased MEP size at 90 minutes post-stimulation. Changes in intracortical circuits, including an increase in SICI in pre-tbTUS contraction, and an increase in ICF in the post-tbTUS contraction, were associated with the altered plasticity.

Conclusion: tbTUS may be subject to polarity-reversing metaplasticity caused by muscle contraction. Data collection is ongoing.

Acknowledgments: *Enter acknowledgements*

Conflicts of interest: The authors have no conflict of interest to declare.

Topic area: neuroscience **Preferred format:** oral

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: **Subject-Specific Acoustic Holograms for Improved Targeting of Low-Intensity Focused Ultrasound (LIFU) Neuromodulation**

Authors: Ceren Cengiz, Mihir Pewekar, Ahmed Sallam, Wynn Legon, Eli Vlaisavljevich, and Shima Shahab

1)Department of Mechanical Engineering, Virginia Tech, Blacksburg, VA, 24061, USA
2)Fralin Biomedical Research Institute, Virginia Tech, Roanoke, VA, 24016, USA
3)Department of Biomedical Engineering and Mechanics, Virginia Tech, Blacksburg, VA, 24061, USA

Email: cerencengiz@vt.edu

Abstract:

Acoustic holographic lenses (AHLs) have lately emerged as a breakthrough technique for accurately regulating ultrasound fields, with more simplicity and affordability. AHLs function as 3D-printed phase plates, modulating the phase of the wavefront via uniquely created thickness maps. Their adaptability spans multiple domains, indicating promise, particularly for low-intensity focused ultrasound (LIFU) neuromodulation. Although their precise targeting and effective compensation of skull aberrations open up new opportunities for patient-specific medical applications, two key hurdles occur when incorporating AHLs into LIFU applications.

The primary hurdle is the computational burden of creating a thickness map of AHLs with increased skull heterogeneity in time reversal simulations. To address this, an innovative algorithm that combines a volumetric holographic technique with a gradient iterative optimization algorithm is presented, considerably improving the efficiency of AHL design. Numerical simulations are done to target four major brain structures: the anterior insula, hippocampus, caudate nucleus, and amygdala, with the goal of demonstrating the efficacy of AHLs across different brain geometries and depths. The findings are further corroborated through underwater hydrophone studies with a realistic skull phantom 3D made from segmented human CT images. The schematic representation of the concept is depicted in Fig. 1(a), alongside numerical simulation results illustrating the tailored pressure field distribution for the hippocampus target.

The second challenge is the actual application of AHLs to the skull; because of their uneven surface, these lenses are usually not easily adapted to the surface of the skull. In order to solve this, a unique hologram in the shape of a skull has been created for the integration of AHLs into particular areas of the skull. Between the skull and the hologram is a conforming layer (CL) that precisely mimics the surface morphology of the skull. The layer's material qualities are chosen to avoid prorogating media with excessive impedance mismatch. To take this layer into consideration while sonicating the target volume, a modified algorithm is created. The conceptual representation of the skull-shaped hologram is shown in Figure 1(b), where the speed of sound distribution for each layer is given as a benchmark.

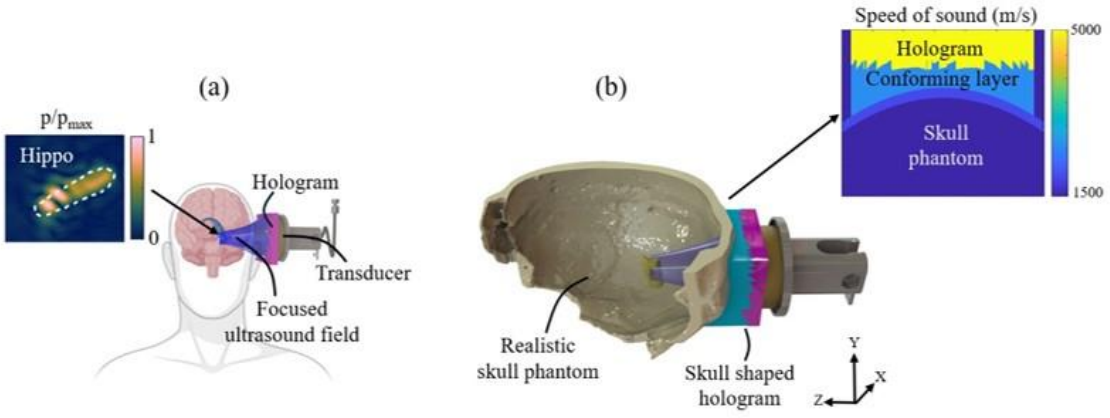


Figure 1. (a) Schematic representation of the concept and simulated pressure field distribution for the hippocampus target. (b) Conceptual representation of the skull-shaped hologram and speed of sound variation of each layer.

Acknowledgments: *Enter acknowledgements*

Conflicts of interest: *Enter disclosures or conflicts of interest*

Topic area: neuroscience **Preferred format:** oral

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: Inhibitory Effects of Transcranial Focused Ultrasound Stimulation on Amygdala During a Facial Expression Recognition Task

Authors: Yuanzhou Wei, Masahiko Haruno, Kazuki Enomoto

Email: ienshuu@outlook.com

Abstract:

Transcranial focused ultrasound stimulation (tFUS) is a novel non-invasive neuromodulation technique that uses ultrasound waves to stimulate brain structures. Compared to other non-invasive stimulation methods such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCs), tFUS has obvious advantages in terms of higher spatial resolution and stimulation of deeper brain regions.

The amygdala, which is a part of the limbic system deep in the brain, is known to be a central hub of processing emotional information. Although existing studies have reported modulatory effects of tFUS on cortical areas and the striatum, it remains unclear whether and how tFUS can modulate the activity in the amygdala and change behaviors.

Here, we conducted a tFUS experiment targeting the amygdala in healthy human participants performing a facial expression recognition task. In this task, participants were required to classify a presented facial expression into three categories (i.e., fearful, neutral, and happy). On the first day of the experiment, participants performed the task in the fMRI (functional magnetic resonance imaging) scanner. Based on the standard GLM analysis on SPM12, we determined the precise location of activity in the amygdala central nucleus. On the second day of the experiment, participants (n=25) received 40 seconds of low intensity (< 30 W/cm2) tFUS stimulation targeting the determined location in the amygdala followed by the same task as before (with different face stimuli) in the fMRI scanner. The task was similarly conducted within the control group (n=28), with the exception that the target location of tFUS in the control group was white matter between the amygdala/hippocampus and the cortex.

We observed a significant decline in the accuracy of fear expression recognition immediately following the stimulation, exclusively within the tFUS group ($p<0.05$). Then, we conducted a generalized least squared model analysis of behavioral data using “group” (tFUS:1 and control: 0) and other explanatory variables. After the stimulation, we observed significant negative effects on accuracy for the interaction terms ($p < 0.05$): fear*group. This suggests that tFUS exerted an inhibitory effect on the amygdala function of distinguishing fear expression, and this inhibition persisted for 16 fear-face trials.

These results showed that tFUS could disturb the amygdala function of emotional facial expression recognition. Since dysfunction of amygdala is associated with many psychiatric disorders, our research may contribute to developing a future tFUS-based therapy for psychiatric disorders.

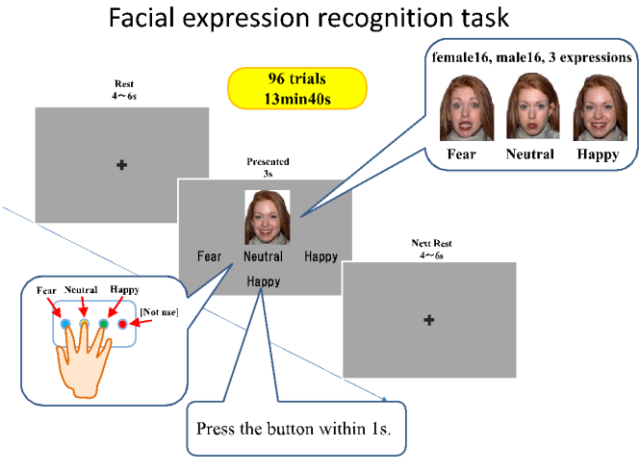


Fig1. The schema of facial expression recognition task

Acknowledgments: *Enter acknowledgements*

Conflicts of interest: No conflicts of interests

Topic area: neuroscience **Preferred format:** poster

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: **Offline 5Hz-rTUS over primary motor cortex (M1) did not alter cortical excitability – a partial replication study**

Authors: Carys Evans.1,2, Po-Yu Fong1,3,4, Benjamin R. Kop2, Bradley Treeby5, Eleanor Martin5,6, Lennart Verhagen2, John Rothwell1, Sven Bestmann1,7.

1. Department for Clinical and Movement Neuroscience, UCL Queen Square Institute of Neurology, University College London, UK
2. Donders Institute for Brain, Cognition, and Behaviour, Radboud University, Nijmegen, the Netherlands
3. Division of Movement Disorders, Department of Neurology and Neuroscience Research Center, Chang Gung Memorial Hospital at Linkou, Taoyuan City, Taiwan
4. Medical School, College of Medicine, Chang Gung University, Taoyuan, Taiwan
5. Biomedical Ultrasound Group, Department of Medical Physics and Biomedical Engineering, University College London, UK
6. Welcome EPSRC Centre for Interventional and Surgical Sciences, University College London, UK
7. Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, University College London, UK

Email: Carys.evans@donders.ru.nl

Abstract:

TUS is a relatively new form of non-invasive brain stimulation with high spatial resolution that can stimulate deep targets. 'Offline' TUS – where the primary measure of neuromodulation is measured after stimulation – can increase cortical excitability compared to sham when applied to the primary motor cortex (M1) in a 5Hz repetitive TUS sequence (5Hz-rTUS). In this pre-registered study (https://osf.io/p5n4q) we examined the test-retest reliability of offline TUS by partially replicating a study by Zeng and colleagues (2022). The original study observed modulation of M1 plasticity with 5Hz-rTUS with large effect sizes in a limited sample size (n=15), which has since been replicated by the same research group (Zeng et al., 2024). Extending beyond the original study, we used neuronavigation in a double-blind procedure to apply verum 5Hz-rTUS and sham-TUS across two sessions. We also explored the degree of M1 target exposure to TUS – the extent to which the acoustic focus intersects M1 – when transducer location is determined by TMS hotspot, a method used to specify stimulation site in the absence of individual MRI. Changes in participants MEP peak-to-peak amplitude (SI1mV), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) in response to TUS (verum vs. sham) were measured in the right first dorsal interosseous (FDI), abductor digiti minimi (ADM), and abductor pollicis brevis (APB). TUS transducer location was determined by TMS-hotspot for motor representations of the right FDI. Results did not reveal significant differences in motor excitability (SI1mV, SICI, ICF) across 5Hz-rTUS and sham-TUS conditions, indicating that the offline effect of 5Hz-rTUS on cortical excitability may not be robust. Null effects may be explained by variability in target exposure to TUS across participants, as post-hoc simulation data showed the acoustic focus did not consistently intersect M1 across participants. Future work using offline rTUS-TMS paradigms may benefit from individualised acoustic simulations to accurately position TUS over the target hand motor area. Reliability of neuromodulation effects may also be improved if higher TUS intensities are applied, as the replicated intensities applied here were low (Isppa_tc = ~3 W/cm2).

Acknowledgments: *Enter acknowledgements*

Conflicts of interest: *Enter disclosures or conflicts of interest*

Topic area: neuroscience **Preferred format:** *Select format*

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: **Investigation of Parameter-Dependent Cell-type Specific Effects of tFUS using an Awake Head-Fixed Rodent Model**

Authors: Sandhya Ramachandran, Huan Gao, Kai Yu, Bin He

Email: sandhyar@andrew.cmu.edu

Abstract:

Transcranial focused ultrasound is a promising neuromodulation technique with the ability to target brain structures with high precision. It has previously been found to elicit time-locked neural activity in regular spiking units (RSUs) in a pulse repetition frequency (PRF) sensitive manner, while fast spiking units (FSUs) only showed a delayed response with much weaker relationship with PRF. These results however are potentially influenced by the use of anesthesia, which significantly modulates neural activity. In this study, we develop an awake head-fixed rodent model for ultrasound stimulation, and test a variety of PRFs and burst duty cycles (DCs) to determine their effects on neuronal subpopulations without anesthesia.

To accomplish this we designed a head-fixation headpiece for rats compatible with our customized 128-element random array ultrasound transducer H276 (f0: 1.5 MHz, -3dB focal size: 1.36 mm axially, 0.46 mm laterally) for stimulating at S1, while an implanted 32-channel chronic electrode array records from the targeted neurons. Rat training protocols were developed to acclimate the rat to head-fixation for up to 1 hour. Following our protocol, we confirmed activation of recorded neurons from ultrasound stimulation in S1, observing increases of neural firing rate of up to 200% baseline in time-locked responses.

We proceeded to record from the S1 of awake rats (N=10), testing PRFs of 30, 300, 1500, 3000, and 4500 Hz, and 6%, 30% and 60% DCs at 1500 Hz, and then repeating the recordings under anesthesia in the same rats for comparison. In our awake model, we find overall higher responses than in the anesthetized model, reaching up to 200% baseline firing rate as compared to 140% baseline in the anesthetized model. In contrast to previous findings we observed slight time-locked activation at 3000Hz ($p < 0.005$), although the activation is much lower than in RSU. Both RSUs and FSUs showed delayed responses, but significant delayed responses in the awake model were present between 0.5-1s, while in the anesthetized model delayed responses appeared to be at 0.2-0.5s. Compared to the anesthetized model which shows an entirely positive correlation with PRF, in the awake model we find that that 4500Hz induces weaker excitation ($p < 0.005$). Focusing on the time-locked response, we observe that 1500Hz induces the strongest excitation, with over 50% of neurons (n = 297) responding up to 200% above baseline firing rate. Proceeding to test different duty cycles at 1500Hz PRF, we found that 30% and 60% DC induce significantly higher time-locked excitation than 6% DC ($p < 0.001$), with a 60% DC resulting in the highest average response. We conclude that overall anesthesia was not a major confound to our previous results such as the positive relationship between PRF and the cell-type specific responses of RSU and FSU. However, the awake model shows significant differences in delayed response dynamics, potentially due to greater FSU activity and circuit feedback, which should be considered while predicting in vivo responses to tFUS.

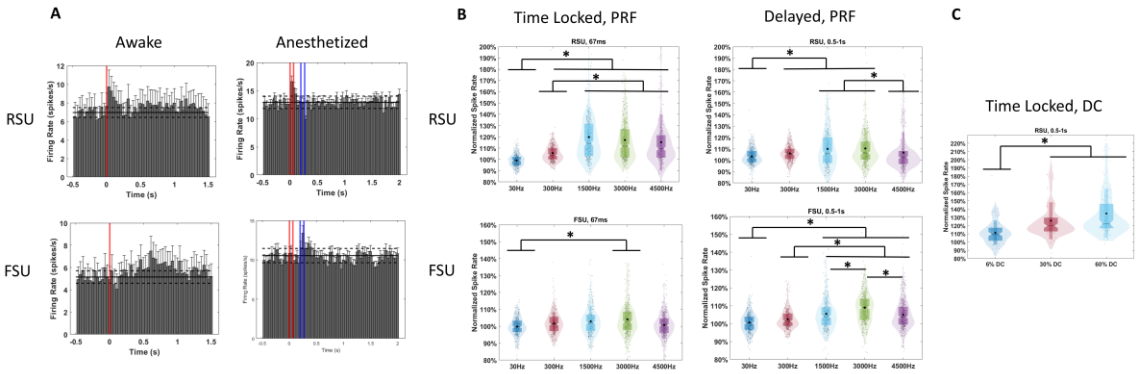


Figure 1. Neuronal subtype responses to tFUS in Awake and Anesthetized models. (A) Peri-stimulus time histograms showing a characteristic neuronal response from within RSU and FSU, in awake and anesthetized settings, demonstrating the different latency of delayed response. The red line shows the onset of tFUS, while additional lines in the anesthetized plots show the typically analyzed time segments for a time-locked and delayed response. (B) Violin plots showing the group level responses of neurons to tFUS with varying PRF from all recordings in each condition. The black asterisk marks show the mean of each group. The darker color within the figure is a traditional box plot, marking the quartiles and median. The ends of the narrow rectangle show the mean plus and minus one standard deviation. The lighter color shadow over the data shows the probability distribution of the data collected. The ends of that distribution mark the 1st and 99th percentile of the data. (C) Violin plots showing the group level responses of awake RSUs to varying DC.

Acknowledgments: Funded in part by NIH grants R01 NS124564 and RF1NS131069.

Conflicts of interest: N/A

Topic area: neuroscience **Preferred format:** poster

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

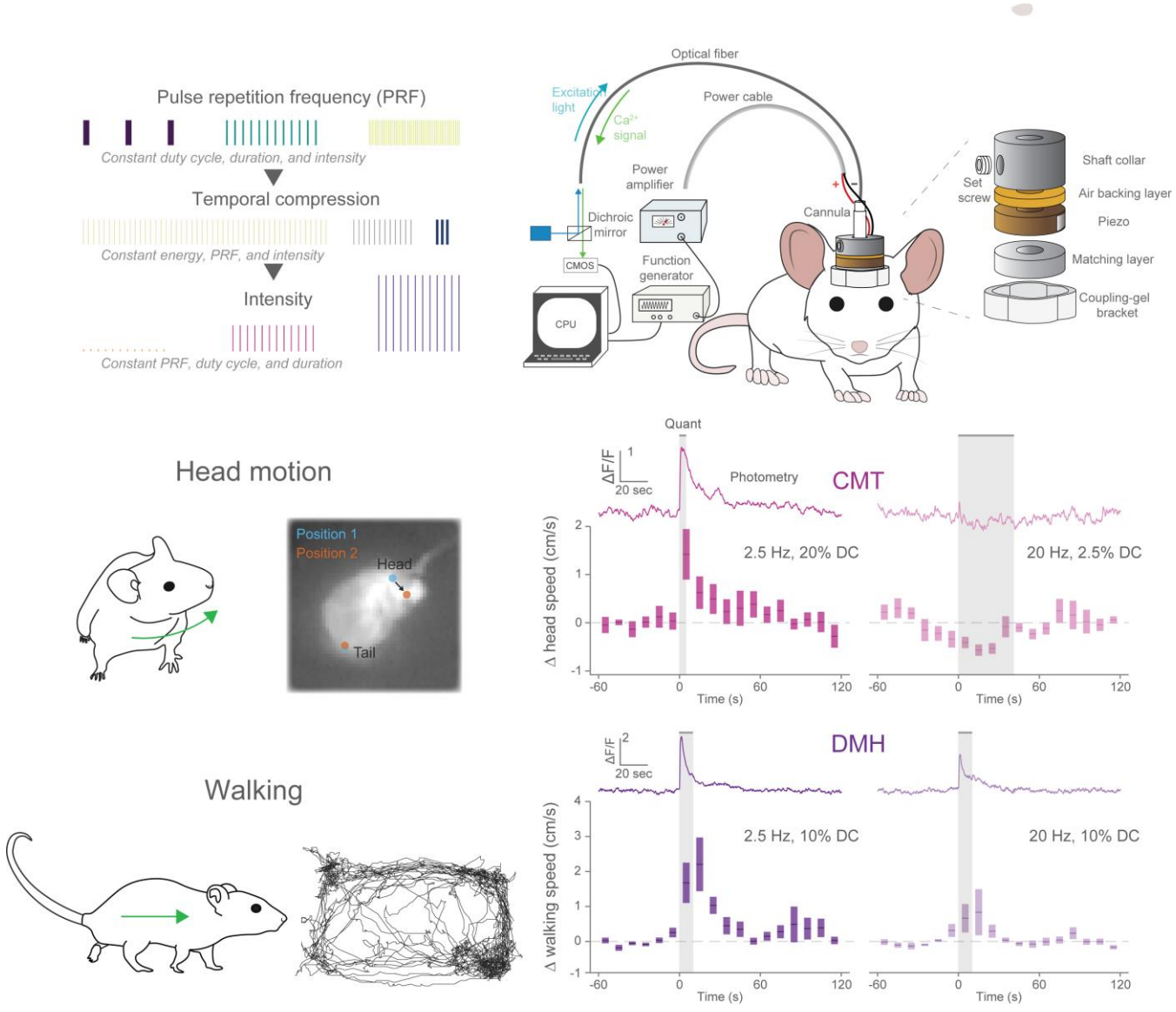
Title: Optimized ultrasound neuromodulation for non-invasive control of complex behavior and physiology

Authors: Keith R. Murphy, Jordan S. Farrell, Jonas Bendig, Anish Mitra, Charlotte Luff1, Ina A. Stelzer, Hiroshi Yamaguchi, Christopher C. Angelakos, Mihyun Choi, Wenjie Bian, Tommaso DiIanni, Esther Martinez Pujol, Noa Matosevich, Raag Airan, Brice Gaudillière, Elisa Konofagou, Kim Butts Pauly, Ivan Soltesz, Luis de Lecea

Email: keith@attuneneuro.com

Abstract:

Focused ultrasound can non-invasively modulate neural activity, but whether effective stimulation parameters generalize across brain regions and cell types remains unknown. We used focused ultrasound coupled with fiber photometry in freely behaving mice to identify optimal neuromodulation parameters in four different arousal centers of the brain, in an effort to yield overt changes in behavior. Applying coordinate descent, we found that optimal parameters for excitation or inhibition are highly distinct, and can generally be applied with high efficacy across brain regions and cell types. Optimized stimulations induced clear, target-specific behavioral effects, whereas non-optimized protocols of equivalent energy resulted in substantially less or no change in behavior. These outcomes were independent of auditory and heating confounds and, contrary to expectation, accompanied by a cyclooxygenase dependent and prolonged reduction in local blood flow and temperature with brain region specific valence. Together, these findings demonstrate that, with proper tuning, focused ultrasound can exhibit powerful effects on complex behavioral and physiological processes.



Acknowledgments: NIH (MH116470 and DA055056 to L.dL). K.R.M. was supported by the Ruth L. Kirschstein Postdoctoral Individual National Research Service Award (1F32HL149458-01A1) and the Multi-Institutional Training in Genetic/Genomic Approaches to Sleep

Disorders Award (5T32HL110952-08). J.S.F. is supported by a K99 from NINDS (K99NS126725). Relevant work in the laboratory of I.S. is supported by the NIH (NS121106) and the Lennox-Gastaut Syndrome Foundation.

Conflicts of interest: K.R.M. holds equity in, and is paid a salary by Attune Neurosciences

Topic area: neuroscience **Preferred format:** poster

☐ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: Ultrasound stimulation of the peripheral auditory system

Authors: Olivier Macherey (1), Emilie Franceschini (1), Vinay Parameshwarappa (1), Elena Brunet (1,2), Eric Debieu (1), Pierre-Olivier Mattéi (1), Yves Cazals (3)
(1) Université Aix-Marseille, CNRS, LMA, Turing Center for Living systems, Marseille, France
(2) Université Aix-Marseille, CNRS, IBDM, Turing Center for Living Systems, Marseille, France
(3) Université Aix-Marseille, INSERM, LNC, Marseille France

Email: macherey@lma.cnrs-mrs.fr

Abstract:

Cochlear implants (CIs) have restored hearing sensations to more than 1 million deaf people worldwide. CIs work by electrical stimulation of the spiral ganglion neurons (SGNs) but only provide limited speech perception in complex environments such as in the presence of noise. The poor spatial selectivity of electrical stimulation is believed to be the most limiting factor in CI performance, urging the need for research on alternative stimulation strategies. Here, we investigate if focused ultrasound (US) stimulation can stimulate spiral ganglion neurons (SGNs).

Ten anesthetized normal hearing guinea pigs were implanted with a recording electrode in their right inferior colliculus. The left bulla was opened and a focused US transducer was placed above the exposed cochlea. Burst US waves at frequencies ranging from 3 to 21 MHz were applied with pressure levels ranging from 0.08 to 1.32 MPa and durations ranging from 1 to 100 µs. US-evoked inferior colliculus potentials were obtained in all animals, showing an increase in amplitude as a function of pressure level and a non-monotonic variation in amplitude as a function of duration.

To investigate if the responses reflected direct neural stimulation, 4 additional guinea pigs were chronically deafened and tested one month later using the same protocol. In this case, no US-evoked response was obtained despite the fact that the neurons were still functional, as shown by electrically stimulating them using an electrode at the round window niche. This shows that the responses obtained in the normal hearing animals were mediated by hair cells.

One possible explanation is that the US waves sent on the bony shell of the cochlea induce bone vibrations containing energy in the hearing frequency range of the animal which then make the hair cells vibrate. To test this hypothesis, cochlear bone vibrations were measured postmortem with a laser vibrometer pointing on the apex of the cochlea in two guinea pig heads. The vibration signal lasted for several milliseconds (i.e. much longer than the US stimulus), showed the presence of energy in the hearing frequency range of the animal with an amplitude variation consistent with that observed electrophysiologially. From this set of experiments, it appeared that US waves can easily activate the auditory system of normal hearing guinea pigs but that the excitation process is mediated by hair cells and does not arise from direct neural stimulation.

Does this mean that spiral ganglion neurons cannot respond to US waves or that we did not use the right parameters to do so? To address this question, calcium imaging experiments were conducted on primary cultures of SGNs to optically monitor their activity during US stimulation. The US stimulus consisted of a 20 MHz sinusoidal signal and both acoustic pressure and pulse duration were varied. Calcium responses were consistently obtained across multiple experiments with success rates (%age of neurons responding) reaching 70-80% in some stimulus parameter conditions.

Acknowledgments: Project funded by CNRS and ANR (ANR-19-CE19-0015)

Conflicts of interest: The authors declare no conflict of interest

Topic area: neuroscience **Preferred format:** oral

☐ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: Modulating visual thalamus using transcranial focused ultrasound in a nonhuman primate model

Authors: Kai Yu, Bin He

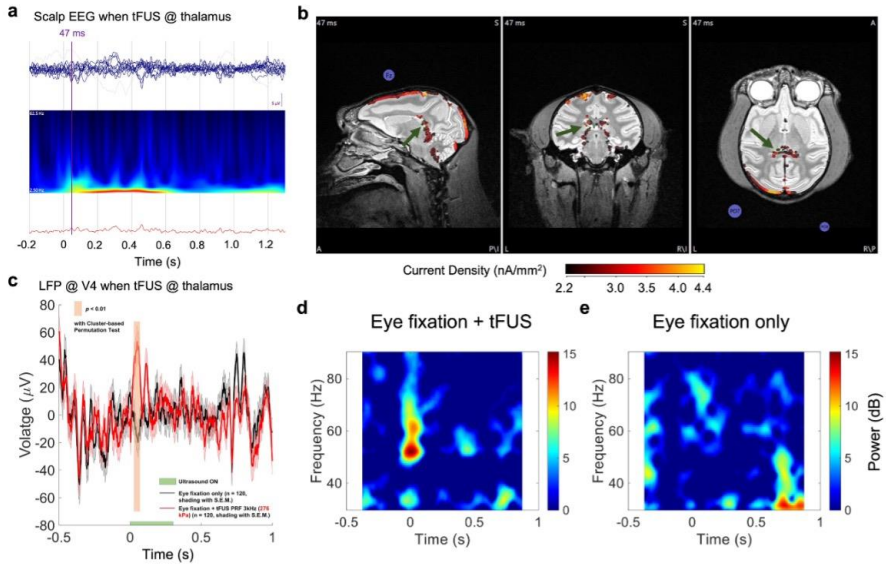
Email: yukai@cmu.edu

Abstract:

Visual thalamus serves as a pivotal relay center in the brain, transmitting sensory information to various cortical regions involved in processing visual stimuli. Utilizing transcranial focused ultrasound (tFUS) offers a non-invasive, high-precision approach to modulate neural activity in deep brain structures. Our previous investigations demonstrated remote cortical stimulation by tFUS at the frontal eye fields (FEF) in a nonhuman primate (NHP) model. In this present study, we aimed to explore the feasibility of localizing tFUS-induced brain activities in the thalamus and validating these responses through remote intracranial recordings from the V4, a region interconnected with the thalamus. In our study, we employed simultaneuous 12-channel scalp electroencephalography (EEG) and 96-channel intracranial recordings at V4 area on a head-fixed, behaving rhesus macaque monkey (M. mulatta) to investigate the neuromodulatory effects of tFUS targeting the thalamus without or with concurrent visual stimulation.

During experiments, tFUS stimulation (PRF: 40 or 3000 Hz, burst duty cycle: 8% or 60%, sonication duration: 400 ms) was delivered with a customized 128-element random array ultrasound transducer (f0: 700 kHz) and was directed to the thalamus following successful eye fixation by the monkey subject. As a result, we observed distinct EEG differences between trials with and without tFUS stimulation, characterized by an early peak in the mean global field potential (MGFP) at 47 ms post-tFUS onset. At this time point, EEG source reconstructions localized the evoked brain responses to the prefrontal and visual cortices, alongside the thalamic region. Moreover, intracranial recordings from the V4 also revealed significant differences in local field potentials (LFP) between tFUS stimulation and no-stimulation (i.e., eye fixation only) conditions. Without the presence of visual stimuli, tFUS stimulation at thalamus can also elicit a statistically significant evoked potential, reproducing a portion of spectral contents (50-65 Hz) in the gamma band. Furthermore, we examined the impact of tFUS focus within the thalamus on connected V4 activities elicited by coupled visual stimuli (a natural picture presented on screen for 400 ms). Spatially steered tFUS onto the pulvinar or thalamic reticular nucleus (TRN), part of the visual thalamus, exhibited distinct LFP responses at the V4, demonstrating the modulatory effects of excitatory/inhibitory tFUS parameters on visual processing.

Our findings provide compelling evidence that tFUS stimulation targeted at the visual thalamus elicits significant evoked potentials in the absence of visual stimuli, reproducing gamma band spectral contents indicative of neural activation. Furthermore, we also show that the tFUS stimulation can achieve subregional specificity when targeting at the thalamus. This study underscores the potential of tFUS as a promising tool for modulating visual thalamus activity and sheds light on its impact on downstream cortical regions in an NHP model.



Acknowledgments: This work was supported in part by NIH grants RF1NS131069, U18EB029354, and R01NS124564.

Conflicts of interest: B.H. and K.Y. are co-inventors of a pending patent application for tFUS technique. S.S. and M.S. have no competing interests to declare.

Topic area: neuroscience **Preferred format:** oral

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: High frequency focused ultrasound neuromodulation of the motor cortex causes lateralized motor responses in awake mice

Authors: Jonas Bendig, Seongyeon Kim, David Sulzer, Elisa E. Konofagou

Email: jb4781@columbia.edu

Abstract:

Focused ultrasound (FUS) is a noninvasive modality for neuromodulation in the central nervous system with a high spatial resolution and the ability to target deep brain structures. Rodent studies have shown motor responses following FUS but mostly failed to demonstrate consistent and target-specific effects. In addition, auditory artifacts of FUS have been linked to motor effects by various studies and the wide use of anesthetic agents further confounds existing positive results. Here, we used a high-frequency (4 MHz) transducer with a small focal area to investigate the target-specificity of FUS neuromodulation. Mice were implanted with a cranial window consisting of an ultrasound-transparent Polymethylpentene membrane. For the experiments, awake mice (n = 4) were head-fixed and allowed to move freely on a floating platform, while being recorded with a high-speed camera (200 fps). 20 pulses of continuous FUS (peak negative pressure (PNP) = 3.0 MPa, pulse duration (PD) = 40 ms) were administered to the right/left hindlimb motor cortex (-1.0 mm AP and +/-1.0 mm ML from Bregma with micro-adjustment in 0.1 mm steps in AP and ML direction to find maximum response on both sides). In separate experiments, mice were sonicated unilaterally at different pressures (PNP: 2.0 – 4.0 MPa) and different pulse durations (40 or 80 ms). The motor responses were classified by semi-automated tracking with Deeplabcut on 10 pulses without spontaneous movement. We found a contralateral motor response of the hind paws (Figure 1b, left stimulation: Total displacement ratio left/right = 138.5 % (± 20.2 %); right stimulation: Total displacement ratio left/right = 68.4 % (± 9.8 %); p = 0.0318 and p = 0.0075, respectively) with clear directionality dependent on the side of stimulation (Figure 1a, mean lateral displacement: 0.88 mm vs -0.62 mm (p = 0.0118, paired t-test) and stronger motor responses with higher pressures and longer pulse durations (Figure 1c/d, Friedman test = 0.0066). Off-target stimulation at +0.5 mm AP and +0.5 mm ML from the stimulation side had no effect on movement. Thermocouple measurements revealed a temperature increase of 1.51 °C (1.32 – 1.70, n = 2, PNP = 3 MPa, PD = 40 ms). In conclusion, we demonstrate that FUS neuromodulation to the motor cortex can induce target-specific contralateral motor responses in awake mice and that the magnitude of the response increases with the FUS pressure and longer pulse duration.

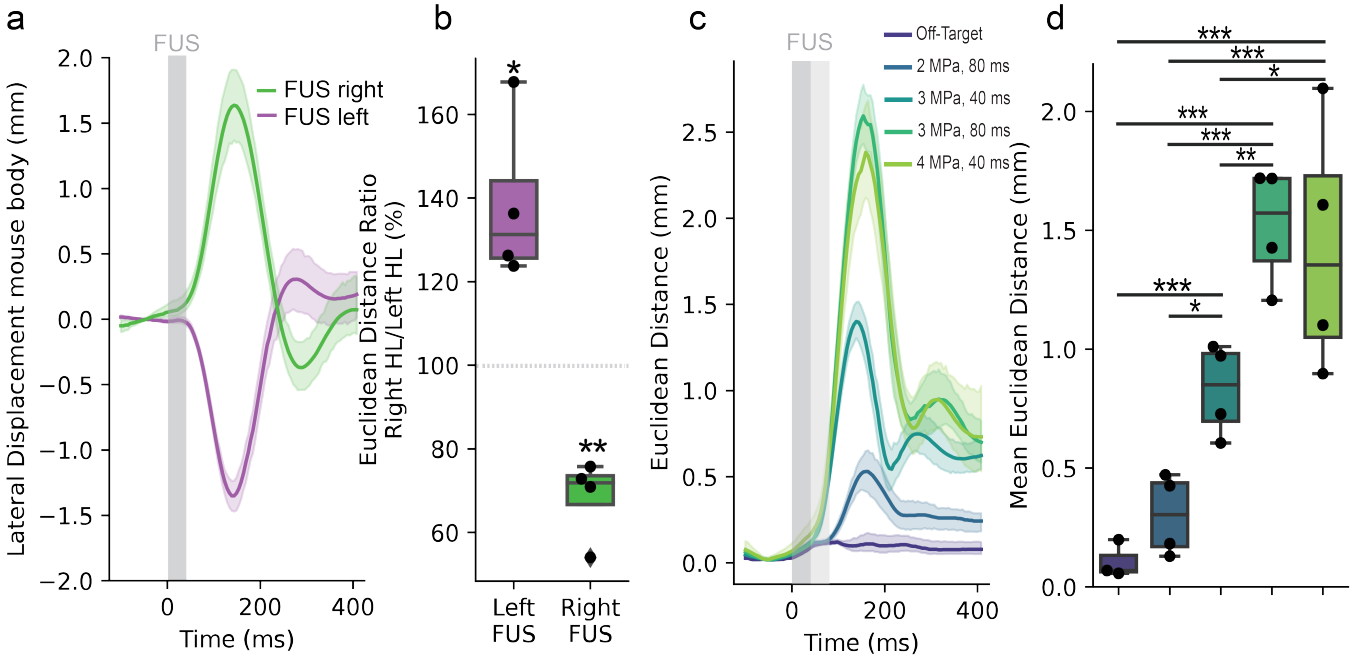


Figure 1. Effects of cortical high-frequency FUS neuromodulation. (a) Lateral Displacement of the whole mouse body following FUS to the left or right motor cortex area. **(b)** Ratio of mean Euclidean Distance traveled by right and left hindlimb between 50-250 ms following FUS to the left or right motor cortex area shows significantly lateralized responses (One sample t-test against 100 %) **(c)** Timecourses of Euclidean Distance traveled by mouse body following FUS neuromodulation of the left motor cortex area with different pressures and pulse durations. **(d)** Mean Euclidean Distance traveled by mouse body in 50-250 ms following FUS neuromodulation for the conditions shown in (c) reveals significantly stronger responses with higher pressures and longer pulse durations (posthoc Conover Test after significant Friedman Test, *p < 0.05; **p < 0.01; ***p < 0.001). Abbreviations: FUS - Focused Ultrasound, HL - hind limb.

Acknowledgments: The study was funded in part by R01EB027576

Conflicts of interest: None to declare

Topic area: neuroscience **Preferred format:** oral

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: *Transcranial ultrasonic stimulation of the human thalamus to study the function of sleep spindles for memory processing*

Authors: *Anastasiia Grigoreva*, Saman Seifpour*, Friederike Breuer*, Suhas Vijayakumar*, Maximilian Lueckel**, Til Ole Bergmann**

** Neuroimaging Center (NIC), Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz, Germany*
*** Leibniz Institut für Resilienzforschung (LIR), Mainz, Germany*

Email: *grigorea@uni-mainz.de*

Abstract:

Sleep benefits memory consolidation in multiple ways (Rasch and Born, 2013). It serves to extract the relevant gist from newly encoded information, determining what will be remembered or forgotten, stabilizes initially labile memories to make them resistant to decay and interference, and even improves newly acquired motor skills (Diekelmann and Born, 2010; King et al., 2017). A common principle of consolidation across memory systems is the reactivation of previously encoded representations. Besides their stabilization at the cellular level (synaptic consolidation), the reactivation of memory representations also serves their redistribution across neural structures at the network level (systems consolidation). Systems-level consolidation is best described for memories relying on the hippocampo-neocortical system (McClelland et al., 1995), for which the conjoint reactivation of neocortical representations constituting a memory engram via their hippocampal associations presumably leads to the establishment of direct intracortical associations (Klinzing et al., 2019; Winocur et al., 2010).

Neuronal oscillations reflect rhythmic fluctuations of neuronal excitability (Schroeder and Lakatos, 2009). During Non-REM sleep, the exceptionally low cholinergic tone enables the emergence of highly synchronized oscillatory activity in the thalamo-neocortico-hippocampal system, characterized by neocortical slow oscillations (SO; < 1 Hz), thalamic sleep spindles (~12-15 Hz), and hippocampal ripples (> 80 Hz), hierarchically interacting to subserve systems memory consolidation (Staresina et al., 2015; Bergmann and Staresina, 2017). The key mediating element for memory consolidation during sleep is presumably the sleep spindle, which opens windows of plasticity in a phase-dependent manner by means of highly synchronized thalamo-cortical input and associated Ca2+ influx into cortical neurons (Sejnowski and Destexhe, 2000), facilitating the concurrent input of hippocampal ripples into the neocortex. Indeed, spindles occur more often after declarative word-pair learning (Gais et al., 2002), but also hippocampus-dependent forms of motor learning (Ramanathan et al., 2015; King et al., 2017), and have been associated with the reactivation of hippocampo-neocortical memory traces (Bergmann et al., 2012a).

In this study, we will employ real-time EEG-triggered low-intensity focused transcranial ultrasonic stimulation (TUS) to probe the causal relevance of spindles (or spindle/SO complexes) and spindle-associated information reactivation and reprocessing during systems consolidation. Using spindle-triggered TUS, we will modulate ongoing spindle generation directly in the thalamus to increase spindle amplitude and consolidation of motor sequence memories. Using TUS pulsed at spindle frequency during spindle-free intervals, we aim to trigger thalamic spindle generation (similar to optogenetic stimulation in rodents (Latchoumane et al., 2017)) and thereby increase spindle density and improve motor memory consolidation.

Acknowledgments: *This work is supported by DFG Research Unit 5434 IADS (Information Abstraction During Sleep) – Project P08: Transcranial brain stimulation to study memory processing and synaptic plasticity during sleep, DFG Grant No. 468645090*

Conflicts of interest: *The authors have no conflicts of interest to declare*

Topic area: *neuroscience* **Preferred format:** *poster*

x Are you an early career researcher? (trainee, student, post-doc, etc) - PhD student

Title: Assessing various transducers' effectiveness with two distinct trajectories for precise deep brain targeting.

Authors: Ana Arantes, Samuel Pichardo, G. Bruce Pike, Alan Coreas, Conrad Rockel, Zelma Kiss

Email: Ana.arantes1@ucalgary.ca

Abstract:

Abstract
Assessing various transducers' effectiveness with two distinct trajectories for precise deep brain targeting.
Ana Arantes1,3, Samuel Pichardo1,2,3, G. Bruce Pike1,2,3, Alan Coreas1,2,3, Conrad Rockel1,2,3, Zelma Kiss1,3
1Department of Clinical Neurosciences, Cumming School of Medicine, Calgary, Alberta, Canada
2Department of Radiology, Cumming School of Medicine, Calgary, Alberta, Canada
3Hotchkiss Brain Institute, University of Calgary, Alberta, Canada

Background: Low-intensity focused ultrasound is a non-invasive neuromodulation technique with significant potential for enhancing treatment of neurological disorders. Numerous types of transducers have been developed in recent years with the goal of precisely reaching deep brain targets1. This study aims to compare the effectiveness of different transducers in achieving deep brain targeting on patients with different skull density using two distinct trajectories for precise deep brain targeting.
Methods: This study used MRI and CT scans from 7 patients along with the BabelBrain2 software to simulate the targeting of the ventral intermediate nucleus (Vim) region the thalamus using 4 distinct transducers. The transducers used were: cortical focus transducer (CTX_500)- 4 ring elements with focal length of 63.2 mm; H317- 128-element phased array with focal length of 135 mm; H246- flat ring-type device with 2 annular elements; BSonix- single-element with a focal length of 80mm. These transducers were positioned either on the top (parietal bone) or laterally (temporal bone) on the participants' heads. The Vim was visually identified by a neurosurgeon on the MRI image using the Brain Sight software (Rogue Research Inc). We ran 70 simulations using the following parameters: DC = 10%, Isspa = 10 W/cm2, FF =250 kHz, SD = 5 sec. Through the simulation we measured the Isspa at the Vim target. A criterion of success was if the intensity at target was 70% or more the maximal intensity in the brain.
Results: The intensity at target depends on the transducer used, trajectory selected, and participant's skull density. The only transducer that met the criteria when the transducer was placed on the top of the head was the H317, with an intensity at target ranging from 9.19 to 9.88 W/cm². When the transducer was placed laterally on the head (trajectory through the temporal bone) all transducer met the criteria. The range of intensity at the target were 8.87 to 9.99 W/cm², 8.67 to 9.83 W/cm², 9.17 to 9.61 W/cm², and 6.13 to 9.61 W/cm² for the H317, BSonix, CTX_500, and H246 transducers, respectively.

References
[1] Dell'Italia et al. Current State of potential Mechanisms Supporting Low Intensity Focused Ultrasound for Neuromodualtion. Frontiers in Human Neuroscience, 2022 Apr; 16. doi: 10.3389/fnhum.2022.872639.
[2] Pichardo S. BabelBrain: An Open-Source Application for Prospective Modeling of Transcranial Focused Ultrasound for Neuromodulation Applications. IEEE Trans Ultrasonics, Ferroelectrics, and Frequency Control. 2023 Jul;70(7):587-599. doi: 10.1109/TUFFC.2023.3274046.

Acknowledgments: *Enter acknowledgements*

Conflicts of interest: *Enter disclosures or conflicts of interest*

Topic area: neuroscience **Preferred format:** poster

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: **Transcranial ultrasound stimulation of subcortical visual pathways**

Authors: Ryan T. Ash [1], Patricia Limon[1], Morteza Mohammadjavadi[2], Martin Scott[3], Kim Butts Pauly[2], and Anthony M. Norcia[3]
1 Dept. of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, USA
2 Dept. of Radiology, Stanford University, Palo Alto, USA
3 Dept. of Psychology, Stanford University, Palo Alto, USA

Email: rytash@stanford.edu

Abstract:

Causal manipulations of neural activity in vivo -- originally with lesion studies, then with electrical microstimulation, and most recently with optogenetics -- have led to a revolution in our understanding of how different microcircuits drive cognition, emotion, and behavior. Unfortunately, the invasiveness of these methods has mostly limited their use to non-human subjects. Current methods for neuromodulation in human are limited by poor focality and depth penetration. Transcranial ultrasound stimulation (TUS) is an emerging tool to achieve noninvasive focal brain-wide neuromodulation with high focality (<1cm) and the ability to achieve high intensities in-depth. We previously targeted TUS to the lateral geniculate nucleus (LGN, visual thalamus) in a large mammal (sheep) (Mohammadjavadi, Ash et al., Scientific Reports 2022). Full-field light flash stimuli were presented with or without concomitant TUS in randomly interleaved trials. Similar to what has previously observed by Fry et al in cats (Science 1958), EEG visual-evoked potentials (VEPs) were reversibly suppressed by TUS to the LGN (n=6). No changes in VEPs were observed when TUS was delivered to a control site in the basal ganglia (n=6), ruling out auditory-somatosensory confounds and other non-specific TUS effects. We are now translating this paradigm into human. We implemented bilateral frequency-tagged steady-state visual evoked potentials (ssVEPs) (Ash, Norcia Psychophysiology 2023) and contrast increment detection psychophysics as robust readouts of left and right retinogeniculocortical pathway function. We are using a neuronavigated depth-steerable 4-element TUS transducer to target the LGN for neuromodulation. Our preliminary data suggests that VEPs can be reversibly suppressed with TUS to the human LGN. This work provides the foundation for a dissection of the roles of subcortical and deep cortical nuclei in cognition, emotion, and sensory processing in health and disease.

Acknowledgments: NEI K08EY035037-01, SFARI AR-BTI-Postdoctoral-00003163, and BBRF.

Conflicts of interest: none

Topic area: neuroscience **Preferred format:** poster

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: Systematic Examination of Peripheral Somatosensation during Transcranial Ultrasonic Stimulation

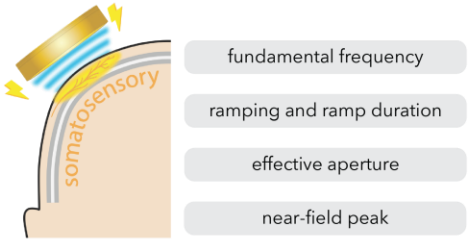
Authors: Benjamin R. Kop, Sjoerd W. Meijer, Soha Farboud, Hanneke den Ouden, Lennart Verhagen

Email: benjamin.kop@donders.ru.nl

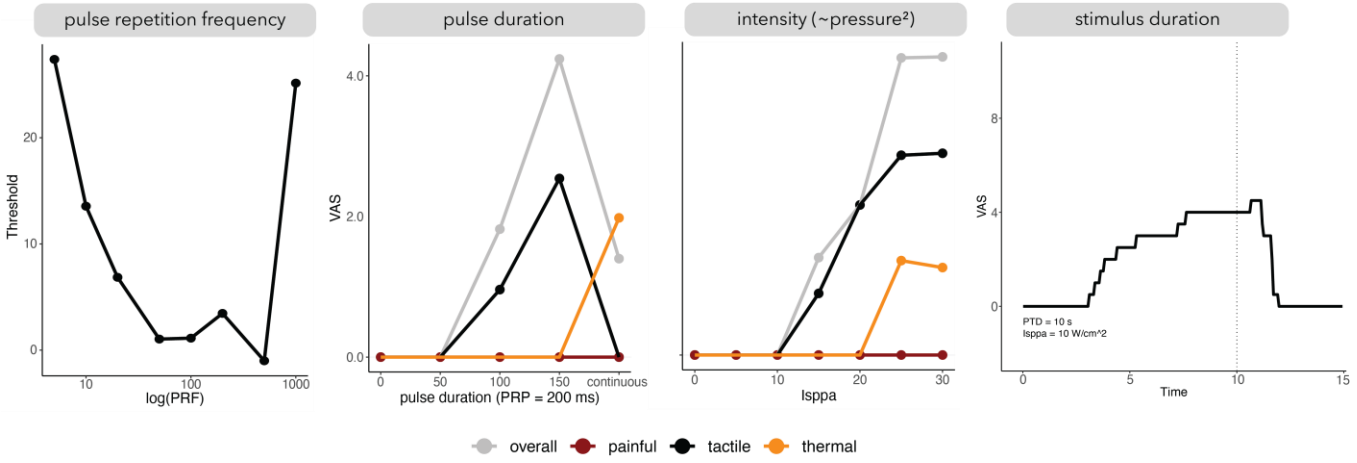
Abstract:

Transcranial ultrasonic stimulation (TUS) brings many opportunities for causal neuroscientific research and novel clinical interventions. However, rigorous experimental control is required for TUS to reach this potential. Similar to alternative forms of non-invasive brain stimulation, peripheral co-stimulation during TUS can confound results and lead to unsubstantiated inferences. Therefore, it is criticial to carefully account for both the auditory and somatosensory confounds that accompany TUS to facilitate the robust development and application of this technique. While multiple studies have specifically addressed the presence of the auditory confound and methods for its mitigation and control (Guo et al., 2018; Sato et al., 2018; Braun et al., 2020; Johnstone et al., 2021; Kop et al., 2024), peripheral somatosensory co-stimulation at the scalp during TUS has yet to be directly investigated. As the field moves towards the application of higher intensities, the next challenge will be to understand and control for somatosensory confounds during TUS.

In the present study, we first characterize the range of sensations experienced during commonly applied stimulation protocols. Further, we investigate potential methods for somatosensory confound mitigation by manipulating stimulation parameters while quantifying sensations through psychometric curves and visual analog scales. The parameters under investigation include fundamental frequency, intensity, pulse duration, pulse repetition frequency, ramping and ramp duration, stimulus duration, effective aperture, and near-field peak amplitude. The results also yield insight into the potential primary biophysical mechanism underlying peripheral somatosensation during TUS. Preliminary results indicate that somatosensory co-stimulation indeed varies with stimulation parameters in a manner that can be exploited to minimize the presence and salience of somatosensory confounds. For example, early preliminary data suggest there is a U-shape relationship between PRF and peripheral somatosensation, where neurophysiologically relevant frequencies elicit more salient sensations. Further, the somatosensory confound increases with increasing total dosage manipulated via pulse duration, stimulus duration, and intensity, but tactile sensations primarily arise from pulsing ultrasound.



preliminary results (n=1)



Acknowledgments: *Enter acknowledgements*

Conflicts of interest: NA

Topic area: neuroscience **Preferred format:** poster

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: Experimental characterisation and validation of an MR-Guided Transcranial Ultrasound System

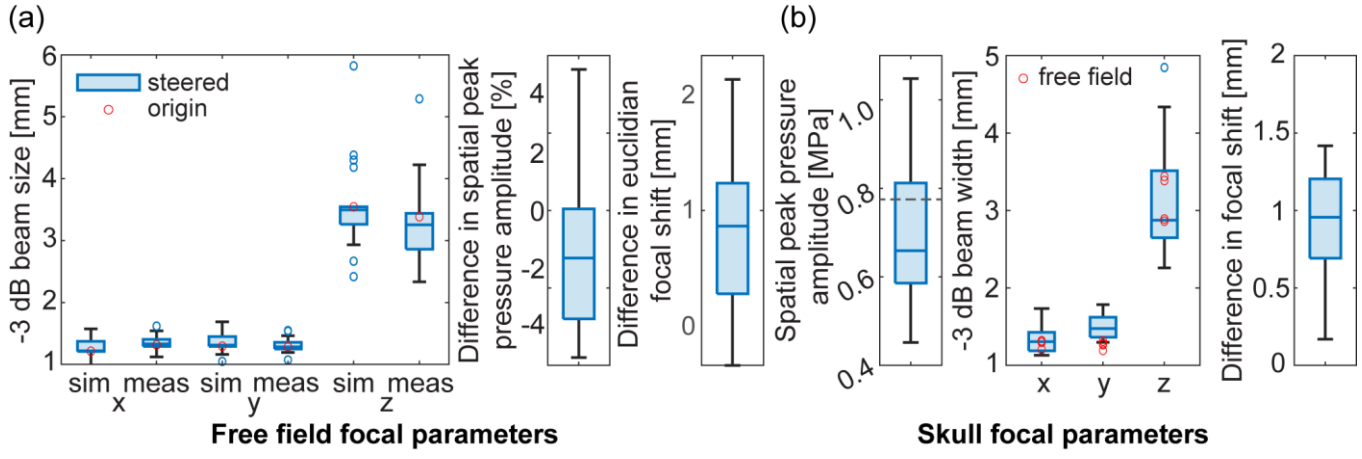
Authors: Eleanor Martin, Morgan Roberts, Ioana Grigoras, Olivia Wright, Tulika Nandi, Sebastian Rieger, Jon Campbell, Tim den Boer, Ben Cox, Charlotte Stagg and Bradley Treeby (University College London and University of Oxford)

Email: elly.martin@ucl.ac.uk

Abstract:

Modulating neural activity in deep brain structures with high spatial resolution and specificity is key for both neuroscience research and clinical applications. However, existing neuromodulation techniques are limited in both the depth and precision of targeting. We have developed a novel MR-guided transcranial ultrasound system designed which offers significant improvements in precision and flexibility of targeting in the deep brain.
A 256-element hemi-ellipsoidal array was constructed from pseudo-randomly distributed 3 mm planar elements operating at 555 kHz, designed to fit as a helmet over the human head. The array was driven using a Verasonics Vantage 256 with external power supply via custom electrical impedance matching network and twisted pair cables. Here we describe the charactersation of the system performance in free field together with experimental validation of the model-based treatment planning pipeline using ex-vivo human skull calvaria.

Acoustic field simulations were performed over a 16 cm steering range centred on the geometric centre of the array from which the spatial peak pressure and -3 dB focal dimensions were extracted. Fibre-optic hydrophone measurements were performed with the array driven using the same phases applied in simulation for a subset of positions up to 6 cm from the array centre. The results demonstrate a -3 dB focal size of 1.3 mm laterally and 3.4 mm axially at the geometric focus. This tight focus was well maintained across the range tested (Fig(a)). There was excellent agreement between measurement and simulation: spatial peak pressures were within 4%, and measured focal positions were within 2 mm of the planned position. For positions up to 5 cm from the array centre grating lobe height was less than 22%. This demonstrates the wide steering range and close to ideal performance of the array.
Experiments were conducted with 4 human skull calvaria, degassed and mounted using 3D printed mounts in the array derived from CT scans of the skulls. Treatment plans were executed for 4 focal positions for each skull, at the geometric centre and 2 cm in each cartesian direction. Fibre-optic hydrophone measurements were acquired along lines passing through the location of spatial peak pressure. On average the measured spatial peak pressure was within 21% of the planned pressure, and the focal position within 0.9 mm. The mean -3dB focal dimensions were (x, y, z) = (1.3, 1.5, 3.1) mm (Figure), with an average difference of (dx, dy, dz) = (0.2, 0.2, 0.7) mm from the planned -3dB focal dimensions, and (dx, dy, dz) = (0.1, 0.2, 0.6) mm from the corresponding -3dB free field focal dimensions (Fig(b)). These findings confirm the targeting accuracy of the array and the associated treatment planning software and workflow.
In summary, the large aperture and sparse element distribution of the array results in a small focal region and wide steering range, allowing significantly higher specificity in targeting of deep brain nuclei compared to existing systems.



Acknowledgments: This work was supported by the EPSRC, UKRI, the Wellcome Trust, and the NIHR Oxford Health Biomedical Research Centre.

Conflicts of interest: B.E.T., E.M., O.W., and M.R. are authors of or have a financial interest in patent filings related to the technology described in this study.

Topic area: technical **Preferred format:** *Select format*

☐ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: Evaluating the Efficacy of Pseudo-CT Images for Precision Focused Transcranial Ultrasound Applications

Authors: Maria Miscouridou (1), Alisa Krokhmal (2), Aaron Hess (3), Jon Campbell (3), Charlotte Stagg (3), Bradley Treeby (1)
(1) University College London, UK. (2) Moscow State University, Russia. (3) Wellcome Centre for Integrative Neuroimaging, FMRIB

Email: maria.miscouridou.16@ucl.ac.uk

Abstract:

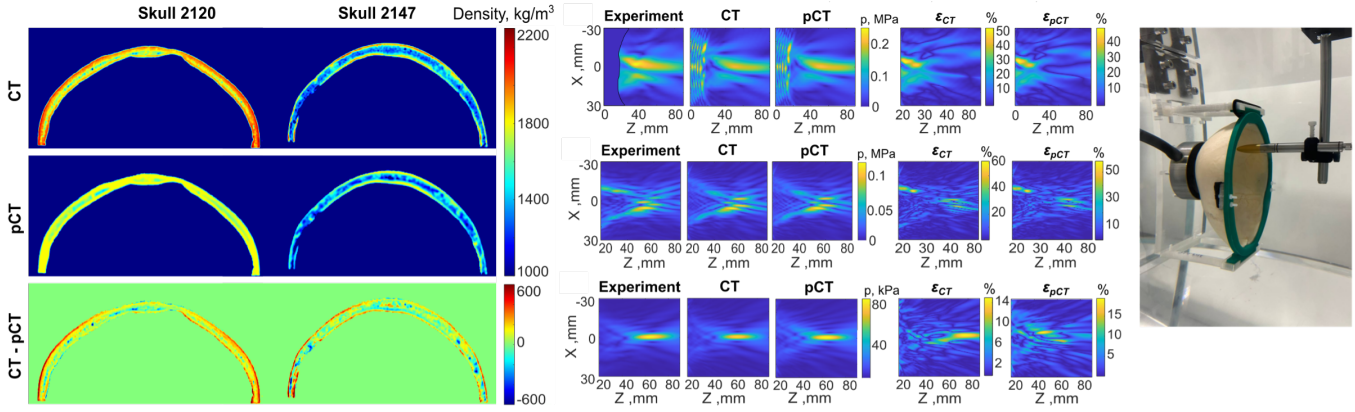
Ultrasound simulations are increasingly being used for Transcranial Ultrasound Stimulation (TUS) to aid with guidance and dosimetry. Current approaches are based on mapping acoustic properties from x-ray Computed Tomography (CT) images of the individual subject. However, CT images are not always available and they expose patients to harmful ionizing radiation. Previous work (https://doi.org/10.1109/TUFFC.2022.3198522) has shown the benefits of using pseudo-CT images generated from MR (Magnetic Resonance) images, with either machine learning or classical methods, and have These highlighted the usefulness of sequences like PETRA (Pointwise Encoding Time Reduction with Radial Acquisition) that image the bone. In this work, we explore a classical method to translate from ex-vivo PETRA images to pseudo-CTs, and comparing their acoustic simulations to experimental results performed on two ex-vivo skulls.

To obtain the mapping from PETRA to CT, we used a dataset of 3 subjects with two scans each, a PETRA scan taken on a Siemens 3T scanner (MAGNETOM Prisma, Siemens, Germany) and a low-dose CT scan (GE Revolution scanner). The MR images were debiased using N4ITK (https://doi.org/10.1109/TMI.2010.2046908) and then coregistered to the CT scans with FSL. Then, histogram normalization was applied to shift the soft-tissue peak to 1. Skull and head masks were obtained by segmenting the image using SPM12, followed by morphological operations in MATLAB. The first principal component of voxels only in the bone mask is described by the linear relationship pCT = -2815.1 * MRI + 2779.4. For the pseudo-CT generation, voxels in the head mask were assigned to 42 HU (Hounsfield Units), background/air was assigned to -1000 HU and voxels in the skull mask were converted with the above linear mapping. The average MAE (mean absolute error) of the pCTs compared to the CTs is 376 ± 32 HU in the skull mask.

To perform simulations, high-dose CTs were also acquired on Siemens SOMATOM Force CT scanner. Simulations were set up on the open-source k-Wave toolbox. The area surrounding the skull was modeled to replicate the properties of water at 20°C. To determine the bone density ρ, we calculated the cranial tissue densities from the HU of the CT and pCT, using their equivalent calibration files. The sound speed map was calculated as c = ρ * 1.333 + 166.7. In the experimental setup, three transducers were used to create the acoustic fields, a H115 model driven at 270 kHz, a single-element H104 transducer at 500 kHz, and another single-element H101 transducer at 750 kHz and 1 MHz.

Across all skulls and all frequencies, and the mean difference in focal position is 2.1 ± 3.4 mm. For one of the skulls, the pressure error for CT varies from -18 to 1% and for pCT it ranges from -6 to 11%, while for the other skull, the CT error ranges from -37 to 50%, and for pCT from -39 to 56%.

These results demonstrate that acoustic simulations based on mapping pCT images from PETRA MRIs can give comparable results to simulations based on ground truth CT.



Acknowledgments: This work was supported by the Engineering and Physical Sciences Research Council, UK (EP/S026371/1, EP/S021612/1). The Wellcome Centre for Integrative Neuroimaging is supported by core funding from the Wellcome Trust (203139/Z/16/Z). CJS holds a Senior Research Fellowship, funded by the Wellcome Trust (224430/Z/21/Z).

Conflicts of interest: No conflicts of interest

Topic area: technical **Preferred format:** poster

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: Feasibility testing of individualized transcranial ultrasonic stimulation of the human basal forebrain with concurrent functional neuroimaging.

Authors: Suhas Vijayakumar1, Maximilian Lueckel2, Jennifer Weinberg1, Dorina Laurila-Epe1, Til Ole Bergmann1,2

1 Neuroimaging Center (NIC), Focus Program Translational Neuroscience (FTN), Johannes Gutenberg University Medical Center, Mainz, Germany;
2 Leibniz Institute for Resilience Research, Mainz, Germany

Email: suhas.vijayakumar@uni-mainz.de

Abstract:

Transcranial ultrasonic neuromodulation (TUS) has recently emerged as a promising intervention for neurological and psychiatric disorders due to its unique ability to stimulate deeper brain structures. However, TUS is primarily used in isolation, and simultaneous data acquisition with neuroimaging techniques like functional magnetic resonance imaging (fMRI) is not well established. This makes it difficult to examine the immediate, online effects of TUS on brain activity. Individuals with Alzheimer's and Parkinson's disease exhibit degeneration in the basal forebrain (BF), leading to memory and cognitive impairment. Situated deep in the brain with cholinergic projections to various cortical areas, the BF is an appropriate target for TUS neurostimulation.

Our study aimed to:
(1) Optimize MR sequences for the best temporal signal-to-noise ratio (tSNR) in the presence of an ultrasound transducer.
(2) Develop a concurrent TUS-fMRI workflow in humans, including transducer coupling mechanisms optimized for the MR environment.
(3) Provide evidence of individualized online neuromodulation of the BF.

We acquired a T1-weighted structural image in healthy participants, followed by an additional structural image using a Pointwise Encoding Time Reduction with Radial Acquisition (PETRA) sequence to reconstruct a pseudo-CT image for individualized acoustic simulations. Functional MRI scans were acquired before, during, and after sonication. We tested multiband-multi echo MR sequences, varying the number of echoes, multiband factor, repetition time (TR), and in-slice acceleration. Multiple transducer coupling mechanisms were tested to target the BF through the temporal bone window using a coupling gel pad and ultrasound gel. The transducer location was planned using acoustic pressure simulations (k-plan) and achieved using online MR-informed neuronavigation (Localite).

TUS was delivered with a four-element annular array transducer with a fundamental frequency of 545kHz (SonicConcepts) for 30 trials (focal depth=approximately 60mm, pulse interval=35s, pulse duration=80ms, pulse repetition frequency=2.5Hz, pulse train duration=5.2s, duty cycle=20%).

The fMRI sequence with 3 echoes (TE1=21ms, TE2=51.94ms, TE3=82.88ms), multiband factor=4, TR=1499ms, and no in-slice acceleration yielded the best tSNR results. The largest change in average BF connectivity due to stimulation ("after > before") was observed in the insula, IPL, cingulate cortex, and lateral occipital lobe in both hemispheres. Preliminary analysis did not reveal a strong TUS-evoked BOLD response when comparing "stimulation > rest," but subthreshold activation of the BF was observed only in the ipsilateral hemisphere to sonication which could be a result of low intracranial intensities (~2.67 W/cm2).

We demonstrated the technical feasibility of combining individualized low-intensity TUS with fMRI for BF neuromodulation. Additional data will be collected with a further optimized setup and suitable control conditions to provide proof of target engagement.

Acknowledgments: We received funding supporting this work from the Boehringer Ingelheim Foundation (grant on "Methods Excellence in Neurostimulation"), the European Innovation Council (EIC Pathfinder project CITRUS, Grant Agreement No. 101071008), and the Ministry of Science and Health of the State of Rhineland-Palatinate, Germany ("ACCESS" grant).

Conflicts of interest: None

Topic area: technical **Preferred format:** poster

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: Feasibility of Transcranial Displacement Imaging In Vivo

Authors: Samuel G Blackman, Jad El Harake, and Elisa E. Konofagou

Email: sgb2155@columbia.edu

Abstract:

Background, Motivation and Objective

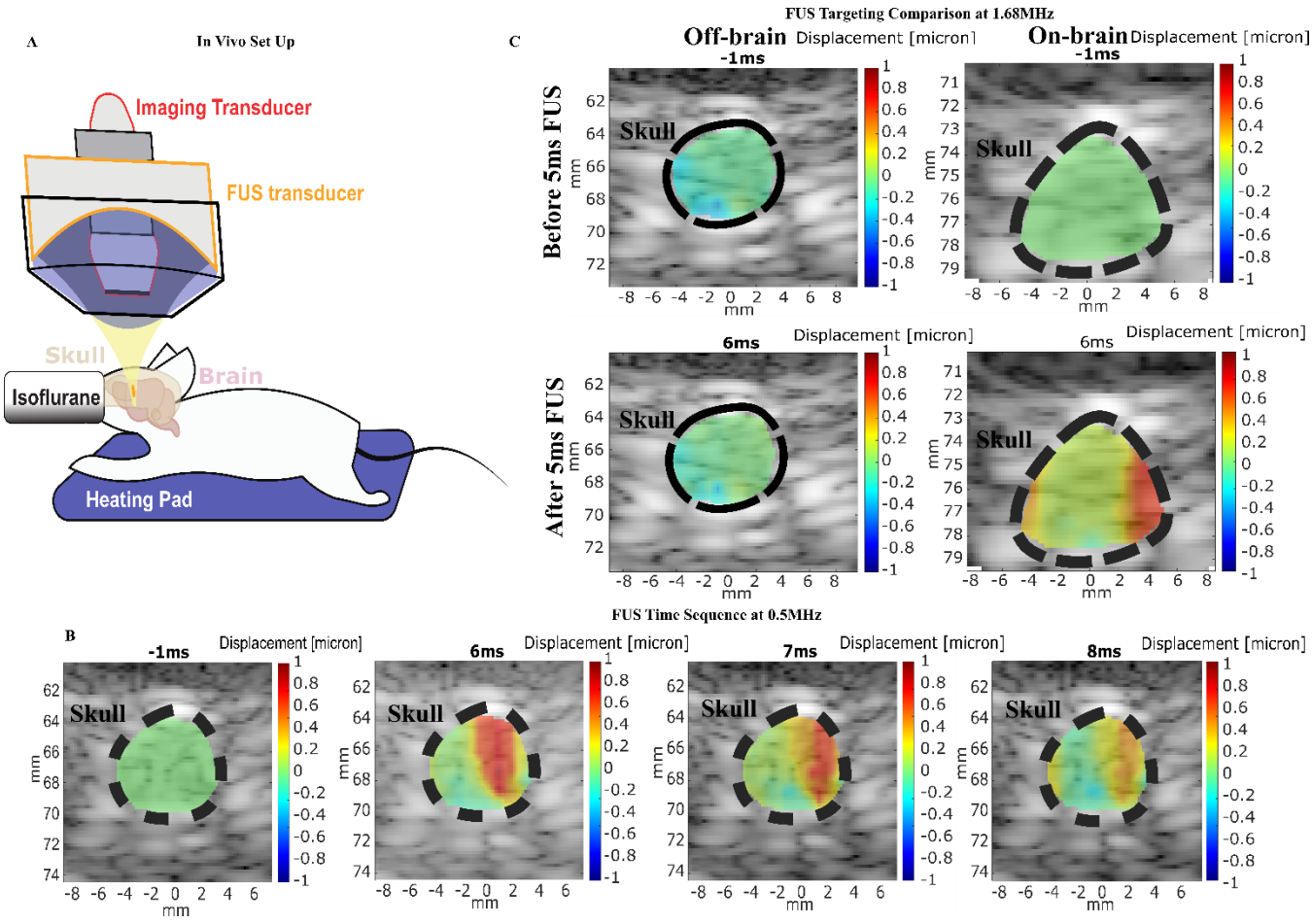
Measurement of micron-scale displacement in the brain is of interest for monitoring the bioeffects of focused ultrasound (FUS). Displacement has been associated with vascular response of the brain to FUS, and can be used as a proxy for tissue stiffness in harmonic motion imaging and for temperature in thermal strain imaging.

Statement of Contribution/Methods

A 2.5 MHz Philips P4-2 imaging transducer was coaxially aligned with a Sonic Concepts H204 FUS transducer (0.5MHz) and positioned in a water bath coupled to the shaved head on an anesthetized mouse (n = 2 mice) (Fig. 1a). Single, 5ms FUS pulses were applied at a center frequency of either 0.5 or 1.68 MHz. In addition to on-brain sonication, off-brain targeting where the FUS focus was beneath the brain was investigated as an active control (Fig. 1c, left column). Brain displacement was estimated using 1D cross-correlation on recontstructed RF signals from diverging wave imaging at 1 kHz with 5-angle compounding. Delay-and-sum (DAS) and sliding-window minimum variance (MV) beamformers were compared.

Results/Discussion

Normalized cross-correlation was capable of measuring displacements with high (>0.95) correlations in the murine brain using both MV and DAS. Manual segmentation was used to isolate the brain displacements and eliminate spurious displacement observed in coupling media. We demonstrated the ability to localize displacement produced by the FUS transducer at both harmonics, visualizing the transmission of shear waves resulting from the FUS-induced displacement (Fig. 1cb 0.5 MHz timecourse shown). On-brain sonication at 1.68 MHz similarly resulted in visible shear waves (Fig. 1c, right column). In contrast, the 1.68 MHz off-brain control, where the transducer was translated down by 5 mm, resulted in the removal of the observed shear waves from the image (Fig. 1c, left column). This control case confirmed that shear waves resulted from the displacement at the focus of the transducer, and not from an interaction between the FUS and the imaging transducer.



Acknowledgments: Funding from the NIH (R01EB027576)

Conflicts of interest: None to report

Topic area: technical **Preferred format:** oral

☒ Are you an early career researcher? (trainee, student, post-doc, etc)

Title: *Maximising participant comfort for whole-head transcranial ultrasound neuromodulation*

Authors: *Morgan Roberts, Eleanor Martin, Ioana F Grigoras, Olivia Wright, Tulika Nandi, Sebastian Rieger, Jon Campbell, Tim den Boer, Ben T Cox, Charlotte J Stagg & Bradley E Treeby*

Email: *morgan.roberts.18@ucl.ac.uk*

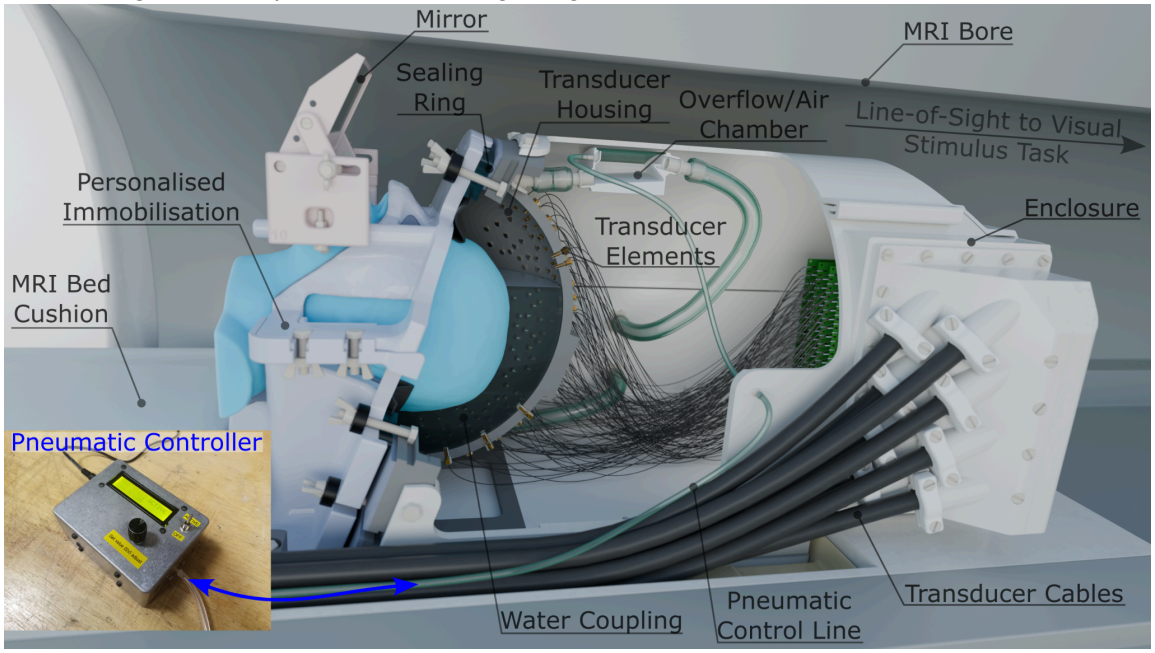
Abstract:

Transcranial ultrasound (TUS) neuromodulation is a groundbreaking technique with potential applications in various neurological and psychiatric disorders. TUS is often used concurrently with functional magnetic resonance imaging (fMRI), to measure its effects on brain activity. In whole-head TUS studies, participant comfort is crucial for maximising fMRI data collection duration and quality. Comfortable participants are less likely to move, which supports accurate targeting of small structures in the deep brain. Previous studies in clinical populations have used an invasive neurosurgical frame to immobilise the head [1], but this is not appropriate for practical studies in healthy volunteers, where maximising comfort is essential.

We developed an advanced MRI-compatible TUS system that utilises personalised immobilisation hardware to repeatably position participants relative to the transducer array. A water layer couples the participants to the transducer array. To minimise discomfort caused by the contact force of the immobilisation hardware on the face and neck, we incorporated silicone cushions at the interfaces and optimised the shape and material properties of the hardware.

The hydrostatic pressure exerted by the water coupling layer on the scalp caused significant discomfort, by pushing the participant against the immobilisation hardware. To alleviate this issue, we designed a custom pneumatic controller, connected to a sealed air chamber above the water layer via an airline. By maintaining the air pressure at 99500 Pa, just below atmospheric pressure, we reduced the hydrostatic pressure of the water. This reduced the contact force exerted by the immobilisation hardware on the participant, enhancing comfort.

Our results demonstrate that participants can comfortably tolerate fMRI sessions of up to 60 minutes using our optimised system, with an average head motion of 0.25 +/- 0.001 mm during scans. As concurrent TUS/fMRI studies in healthy volunteers are crucial for further developing and understanding TUS neuromodulation, participant comfort is essential for gathering high-quality and high-quantity data. The techniques presented in this study represent a significant step towards achieving this goal.



[1] - Bancel, T. et al. Sustained reduction of essential tremor with low-power non-thermal transcranial focused ultrasound stimulations in humans. Brain Stimulat. 17, 636–647 (2024).

Acknowledgments: *We thank the WIN radiographers, the Oxford Radiology Research Unit Team at Churchill Hospital, and the Radiology Department at Great Ormond Street Hospital. This work was supported by the EPSRC, the Wellcome Trust, and the NIHR Oxford Health Biomedical Research Centre.*

Conflicts of interest: *B.E.T., E.M., O.W., and M.R. are authors of or have a financial interest in patent filings related to the technology described in this study. B.E.T. is a developer of the commercially available k-Plan treatment planning software used in this study and holds a financial interest in the software. The remaining authors declare no competing interests.*

Topic area: *technical* **Preferred format:** *poster*

☐ Are you an early career researcher? (trainee, student, post-doc, etc)
YES