Title: Axonal excitability to ultrasound stimulation

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Abstract:

Focused ultrasound is increasingly recognized as a promising non-invasive modality for neuromodulation of brain circuits. However, the question of whether ultrasound can directly excite axons, fundamental for its application to treat peripheral neuropathologies and modulate long-range brain connectivity, remains unresolved. Recent findings disagree on whether the effect of axonal ultrasound stimulation is excitatory or inhibitory, and this uncertainty hinders clinical translation, as the field lacks a standardized approach to achieve predictable neuromodulatory effects.

In this study, we determined the direct effects of ultrasound on axons by employing an experimental model that isolates the neural components from other tissues. We employed a nerve-on-a-chip platform (Gribi et al., 2018) adapted to deliver controlled ultrasound stimulation to systematically explore the impact of the acoustic parameters and define optimal parametric regimes. To validate in vitro findings and explore functional responses, we extended our investigation to an anesthetized rodent model, which allowed us to monitor both neural and muscular activation as indicators of effective neuromodulation. Additionally, we performed biophysical simulations to investigate the mechanical (stretching, bending, transversal compression) and thermal effects of the acoustic pressure field on the axonal structure.

Our findings demonstrate that axons are directly excitable by ultrasound. Clear excitability patterns emerged when exploring the stimulation parameter space defined by pressure amplitude and pulse duration. Moreover, the evoked neural activity is locked with the pulse stimulation and the activation levels are dose dependent. Within an optimized parametric regime, ultrasound stimulation consistently elicits neural responses (success rate > 80%) enabling robust firing behaviours for pulsed protocols (20 Hz to 100 Hz pulse repetition frequency). Furthermore, the in vivo investigation confirms the neural activations observed in vitro and the resulting induction of muscular twitches. The simulations of mechanical and thermal effects provide insights into the biophysical mechanisms that may underlie the axonal response to ultrasound, enhancing our understanding of its therapeutic potential and guiding future applications.

Acknowledgments: *Enter acknowledgements*

Conflicts of interest: The authors declare that there is no conflict of interest regarding the publication of this abstract.

Topic area: mechanisms **Preferred format:** oral

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

Title: A study on the mechanisms and effective parameters for sciatic nerve neuromodulation in vivo

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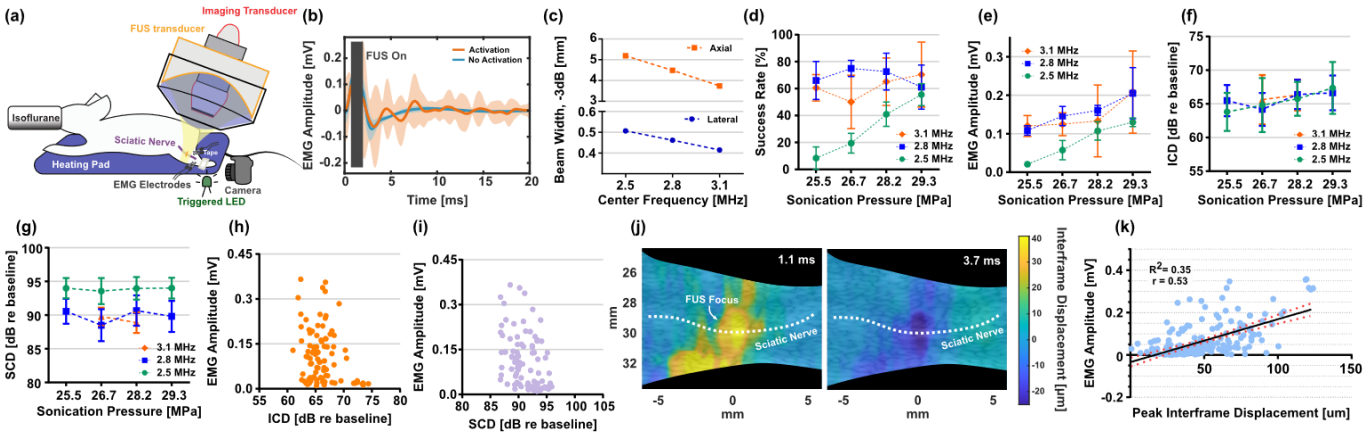
Abstract:

Introduction/Background:
Focused utrasound neuromodulation can non-invasively induce neural activity in the peripheral nervous system, making it a promising candidate for treating peripheral neuropathies. Further understanding, however, of its mechanisms is needed. Previous in vivo work has demonstrated a correlation between sciatc nerve displacement and compound muscle action potential (CMAP) generation. Ex vivo and simulation studies have proposed cavitation as a mechanism, but in vivo work is lacking. Additionally, the role of center frequency and focal size has been explored in central nervous system sonication, but not robustly in the periphery. This study, therefore, sought to investigate the relationship between peripheral nerve activation and both displacement and cavitation. The impact of center frequency and sonication pressure on activation were also explored.

Methods:
The sciatic nerves in both legs of mice (n = 9) were sonicated with single, 1 ms pulses to induce paw movement (Fig. 1a). Pressures from 25.5 to 29.3 MPa derated peak positive pressure and center frequencies from 2.5 to 3.1 MHz were used. Electromyography (EMG) electrodes were placed in the gastrocnemius and tibialis anterior muscles to record activation and videos of each sonication were taken to analze visible movement. Nerve activation was quantified by the presence CMAPs in the EMG (Fig. 1b). For each pulse, cavitation or interframe displacement were recorded with a coaxial 7.8 MHz imaging transducer. Cavitation was post-processed and passive cavitation images (PCI) and stable and inertial cavitation doses (SCD and ICD) were computed. Nerve displacement was estimated with 1D cross-correlation on reconstructed RF signals from plane wave imaging. Activtation success rates, CMAP amplitude, and ICD and SCD were computed across pressure for 2.5, 2.8, and 3.1 MHz. SCD and ICD were correlated with CMAP amplitude across all three frequencies, and interframe displacement was correlated with CMAP amplitude at 3.1 MHz.

Results/Disucssion:
Focal size increased with lower center frequency (Fig. 1c). Center frequency significantly affected activation success rate (Two-way ANOVA, $p < 0.0001$), with reduced success at 2.5 MHz (Fig. 1d). For all frequencies, EMG amplitude increased with pressure (Two-way ANOVA, $p = 0.037$) and was significantly impacted by frequency (Two-way ANOVA, $p = 0.026$), with lower amplitudes at 2.5 MHz (Fig. 1e). ICD was not significanty different across frequency, but did increase with pressure (Two-way ANOVA, $p < 0.01$) (Fig. 1f). In contrast, SCD was highest across all pressures at 2.5 MHz (Fig. 1g). ICD and SCD were not significantly different whether muscle activation was generated or not for any center frequency, and did not correlate with CMAP amplitude (Fig 1. h and i; graphs show combined dose across frequency). In contrast, peak interframe displacement on the nerve (Fig. 1j) at 3.1 MHz correlated with CMAP amplitude (Spearman ranked correlation, $r = 0.53$) (Fig. 1k). These results indicate that cavitation may not be a primary mechanism for peripheral neuromodulation, and that center frequency and focal size should be investigated as a factor for peripheral excitation. Future steps include analyzing nerve displacement at 2.5 and 2.8 MHz, as well as exploring center frequencies above 3.1 MHz.



Acknowledgments: Funding from the NIH (R01EB027576)

Conflicts of interest: None to report

Topic area: mechanisms **Preferred format:** oral

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

Title: ***Pulsed transcranial ultrasound depolarizes and paces neuronal membrane potentials in the awake mammal brain***

Authors: Emma Bortz, Erynne San Antonio, Jack Sherman, Hua-an Tseng, Laura Raiff, Xue Han

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Abstract:

Transcranial ultrasound neuromodulation exhibits exciting clinical potential as a noninvasive therapy. However, it remains unclear whether ultrasound can directly alter neuronal membrane voltage in the awake mammalian brain, and how ultrasound parameters impact its effect on neural circuits. Using cellular voltage imaging, we characterized the effect of 0.35 MHz transcranial ultrasound on the membrane potentials of individual cortical neurons in awake head-fixed mice. We discovered ultrasound delivered at pulse repetition rates of 10 Hz or 40 Hz evoked prominent membrane depolarization and increased spiking in many individual neurons, with a latency shorter than 18 milliseconds. Furthermore, pulsed ultrasound at 10 Hz and 40 Hz paced membrane voltage in many neurons, leading to prominent entrainment, supporting a direct cellular effect. These findings demonstrate that noninvasive ultrasound delivered to the brain at physiologically relevant frequencies robustly depolarizes membrane potentials of mammalian neurons, increases spike rate, and paces neural dynamics, highlighting its potential to entrain neural circuits in clinical applications.

Acknowledgments: **XH acknowledges funding from NSF (CBET-1848029 and CIF-1955981) and NIH R01NS109794. JS acknowledges NIH T32-GM008541. EB acknowledges NSF GRFP DGE-1840990 and NIH T32-EB006359. ES acknowledges NIH T32-GM008764. The authors acknowledged computational work done on the Shared Computing Cluster in Boston University's Research Computing Services.**

Conflicts of interest: None

Topic area: mechanisms **Preferred format:** oral

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

Title: Preliminary Results for Low Intensity Focused Ultrasound for Tobacco Use Disorder: High Resolution Targeting of the Human Insula

Authors: Evan Lindeman, Krystian Burum, Wynn Legon, Mary R. Lee

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Abstract:

Tobacco Use Disorder (TUD) is one of the leading causes of preventable death in the world. Most smokers have a strong desire to quit smoking, but most attempts at such fail within a week. Efficacy of current treatments for smoking cessation (pharmacotherapies and psychosocial interventions) is poor with most smokers relapsing within a year following treatment. Non-invasive neuromodulation of brain regions activated in response to smoking cue exposure offers a potential approach to understanding the neurocircuitry underlying TUD and may be a potential treatment for the latter. A key region activated in smoking cue exposure is the insula, specifically the anterior insular cortex (AI), which is a component of the salience network. Smokers with insular infarcts demonstrate a dramatic reduction in symptoms of nicotine addiction. The functional role of the insula in nicotine addiction can be probed using low intensity focused ultrasound (LIFU). We present preliminary results from an ongoing study, using LIFU to modulate the AI to determine its causal role in smoking cue-induced craving. We present results from n=7 participants with moderate-severe TUD who received LIFU to the left AI (Af= 500 Hz, PRF=1kHz, DC=36%, SD=500 ms). LIFU was well-tolerated; there were no adverse events. Mixed effects model was used to evaluate the effect of LIFU over TIME [Baseline, LIFU (0 W/cm2, 2 W/cm2, 4 W/cm2, and 6 W/cm2 and post-LIFU)] on blood pressure, heart rate, heart rate variability, galvanic skin response, respirations, smoking craving, and mood. There was no significant difference between these time periods for these measures. Participants completed the emotional Stroop task before and after LIFU stimulation. There was a main effect of LIFU on reaction time [$F(1,2070)=7.81$, $p=0.005$] where the mean reaction time significantly increased after LIFU compared to baseline (Before: mean = 956.24ms SD = 192.75ms, After: mean = 974.77ms SD = 213.56ms). Ongoing investigation of the effects of off-line LIFU vs Sham to AI on blood-oxygen-level-dependent (BOLD) to smoking vs neutral cue exposure will also be discussed as well as the effect of LIFU on temporal dynamics of large-scale networks associated with addiction.

Acknowledgments: Funded by Veterans Affairs Office of Research and Development, Clinical Sciences Research and Development Merit Award

Conflicts of interest: None

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

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

Title: Low-intensity focused ultrasound stimulation of motor cortex and internal globus pallidus in Parkinson's disease

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Abstract:

Parkinson's disease (PD) involves disruptions in the basal ganglia-thalamocortical circuitry, leading to a variety of motor dysfunctions. Transcranial ultrasound stimulation (TUS) is a safe and non-invasive technique for stimulating the cortical and subcortical brain nuclei with high spatial precision. This study aims to investigate the neuromodulatory effects of TUS on this circuitry to explore potential therapeutic applications. We employed a 2-channel transducer for primary motor cortex (M1) stimulation and a 4-channel transducer for internal globus pallidus (GPi) stimulation. We positioned both transducers over the corresponding M1 and GPi locations, simultaneously. Theta burst transcranial ultrasound stimulation (tbTUS) was then delivered in three separate sessions under different conditions: 1) real stimulation of M1 with sham GPi stimulation, 2) real stimulation of GPi with sham M1 stimulation, and 3) simultaneous dual-site sonication. Targeting was based individual MRI and the left and right hemispheres were targeted sequentially. Movement Disorders Society Unified Parkinson Disease Rating Scale (MDS-UPDRS) part III and transcranial magnetic stimulation (TMS) measurements were recorded before and after tbTUS. Presently, 6 participants (3 female, mean age 69.2, disease duration 7.8 years, and levodopa equivalent dose 575mg/day) have completed the study. Compared to baseline, motor-evoked potential (MEP) amplitude increased at 60 minutes post dual-site sonication (1.91x baseline, p= 0.049). Following real GPi/sham M1 sonication, the stimulation intensity needed to elicit 1 mV MEP was higher at 10 minutes post sonication compared to the intensity used at baseline (65.33 vs. 63.17 % maximal stimulation output, p= 0.01). There was a trend for increased MEP amplitude after real M1/sham GPi sonication whereas MEP amplitude decreased after real GPi/sham M1 sonication. Two-way ANOVA showed a significant sonication condition x time (baseline, post tbTUS 10, 45, 60 minutes) interaction (F (6, 30)= 2.752, p= 0.03) on MEP amplitude. MDS-UPDRS part III scores did not change after any of the three sonication conditions. The study is currently ongoing. We intend to present data from 12 PD patients at FUN24.

Acknowledgments: Funded by the Canadian Institutes of Health Research and the Natural Science and Engineering Research Council of Canada

Conflicts of interest: None

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

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

Title: TUS: Regulatory and Reimbursement Challenges and Opportunities in the USA

Authors: Mark Carol, M.D., Jeffery Aubrey, M.D., Emily White, M.D.

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Abstract:

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Therapeutic ultrasound has increasingly been applied to non-ablative neuromodulation (FUN). While ablative procedures traditionally have relied on capital equipment and "one time" treatments, transcranial neuromodulation (TUS) may benefit from multiple treatments using multiuse personalized technology. The regulatory path to FDA authorization can be the same for these devices as for capital equipment. However, such approaches may require a very different reimbursement path, with the equipment being classified as Durable Medical Equipment (DME).

The number of possible clinical applications of TUS is daunting; the regulatory and reimbursement burden can be just as daunting. Through blogs, papers, presentations, and webinars, the Focused Ultrasound Foundation (FUSF) has spent several years helping manufacturers get comfortable talking with clinicians and stockholders about traditional regulatory options and reimbursement processes. It is essential there exists the same deep knowledge of the different, specific pathways required for "wearable" devices, allowing rapid and less costly development of technology and providing comfort to investors, clinicians, and patients that the start-up "knows what it is doing."

The common goal of each stakeholder in the field is to get authorized and paid devices into the clinic in the shortest time possible so patients can benefit from the transformational approach that is FUN. A new field such as TUS can be expected to take many years, if not decades, to reach the point of an authorized, coded, and paid clinical standard of care. This process is further complicated by the issue of whether TUS and FUN specifically is classified a single field or rather characterized by dozens of related but regulatory and reimbursement distinct devices and applications. Must a single FUN device be authorized and paid separately for each of its specific clinical targets – depression, epilepsy, anxiety, PTSD, Alzheimer's, obesity - or can a single device be authorized and paid for all clinical applications at one time? Can/will multiple manufacturers each try to realize its own code for each clinical application or can/will multiple companies work together to realize a single code covering all devices for a given clinical use?

Because the field is so early in its development, there is an opportunity to reduce the burden on any one manufacturer by pooling resources between manufacturers. As examples, an organization such as ITRUSST might propose a set of guidelines and reporting criteria/structure that will allow better uniformity of reported results along with easier comparison of results from different clinical trials and devices. Adopting a set of common terms, tests, and reporting structures potentially may even simplify the regulatory review process. There are dozens of criteria used to assess evidence of neuromodulatory impact: Standardizing the criteria and scales used may speed up the review process for any single device or application due to a commonality of language. Manufacturers might also pool their data for submission to AMA or CMS when applying for new payment codes and payments rates. This would reduce the publishing requirements on any one manufacturer, speeding the time from clinical use to receipt of a CPT code and thereby allowing physicians and facilities or users of the technology to be paid earlier and patients to experience the benefits of the technology more quickly.

This presentation will outline some of the basic questions and options for TUS/FUN regulatory authorization and CMS payment and will discuss possible avenues of common exploration by consortiums of manufacturers and clinicians. It will also propose some possible next steps, including a FUSF-sponsored meeting at FUN that will occur this year, to explore the issue further among interested commercial and clinical partners.

Acknowledgments: The Focused Ultrasound Foundation (FUSF)

Conflicts of interest:	none		
Topic area:	clinical	**Preferred format:**	oral

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

Title: The effect of Transcranial Ultrasound Pulse Repetition Frequency on Sustained Inhibition in the Human Primary Motor Cortex: A Double-Blind, Sham-Controlled Study

Authors: Ali K. Zadeh(1,2), Hrishikesh Raghuram(3), Shirshak Shrestha(4), Mekale Kibreab(1,2), Iris Kathol(1,2), Davide Martino(1,2), G. Bruce Pike(1,2,3), Samuel Pichardo(1,2,3), Oury Monchi(1,2,3,5,6)
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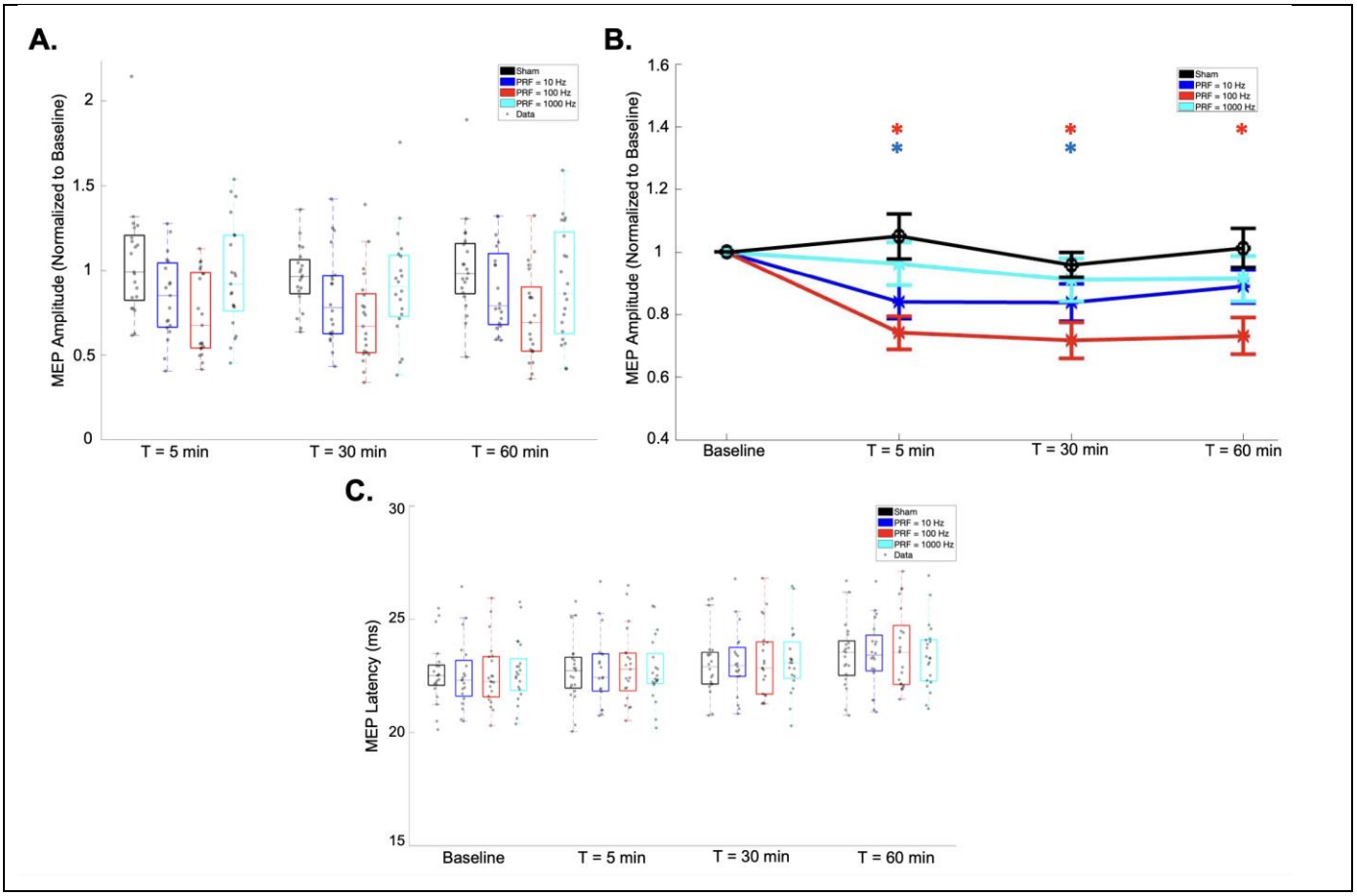
Abstract:

Background: Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) have shown promise for inducing brain plasticity but are limited by their precision in targeting deep brain areas. Transcranial Ultrasound Stimulation (TUS), known for its precise targeting capabilities, emerges as a potent alternative for modulating neurological and psychiatric disorders. Yet, its effectiveness and the impact of varying pulse repetition frequencies (PRF) on inducing long-lasting changes require further investigation.
Objective: This study aims to explore the enduring effects of different PRFs of TUS on motor corticospinal excitability and to determine the optimal PRF for modulating cortical excitability effectively.
Methods: High-resolution T1-, T2-weighted, and zero echo time (ZTE) magnetic resonance imaging (MRI) scans were obtained from 21 neurologically healthy participants. These scans facilitated the reconstruction of the skull for precise neuronavigation and transcranial ultrasound and thermal modelling (BabelBrain software). The study examined the effects of three distinct PRFs (10, 100, and 1000 Hz) of TUS, with a constant duty cycle of 10%, on the primary motor cortex's (M1) excitability. TMS-induced motor evoked potentials (MEPs) were recorded at intervals of 5, 30, and 60 minutes post-TUS to assess changes in excitability. Each PRF and sham condition was assessed on separate days. The ultrasound transducer used is a custom-made phased array device (250 kHz, 128 elements) with electronic steering capabilities.
Results: A linear mixed model (LMM) analysis confirmed the significant impact of PRF selection on MEP amplitudes. The study revealed significant decrease of MEP amplitudes with distinct PRFs, highlighting a notable decrease in excitability with PRFs of 10 Hz and 100 Hz, persistent for at least 30 and 60 minutes respectively, while no significant effects were observed with a PRF of 1000 Hz or under sham conditions.
Conclusions: The findings affirm the critical role of PRF in the efficacy of TUS for reducing corticospinal excitability, suggesting TUS's promising potential as a non-invasive brain stimulation technique for neurological and psychiatric applications.
Figure Caption: (A) Distribution of MEP amplitude of all four conditions, including pulse repetitive frequency (PRF) at 10 Hz, 100 Hz, 1000 Hz, and a sham. The MEPs are normalized to the mean value of the baseline at each session. (B) Average MEP changes for each condition during time. * Significantly different from baseline ($p<0.05$). Error bars represent the standard error of the mean. (C) Distribution of MEP latencies of all four conditions, including PRF at 10 Hz, 100 Hz, 1000 Hz, and a sham. Black colour represents the sham, blue represents the 10 Hz, red represents 1000 Hz, and cyan represents the 1000 Hz condition.



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Conflicts of interest: The authors declare no competing interests.

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

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

Title: TUS of rmPFC and precuneus differentially modulate decision making in private and social contexts

Authors: Mathilde Lojkiewiez 1,2, Jérôme Sallet 3,4, Siti Nurbaya Yaakub 1,2, Jamie Roberts 5, Elsa Fouragnan 1,2*, Nadège Bault 1,2*

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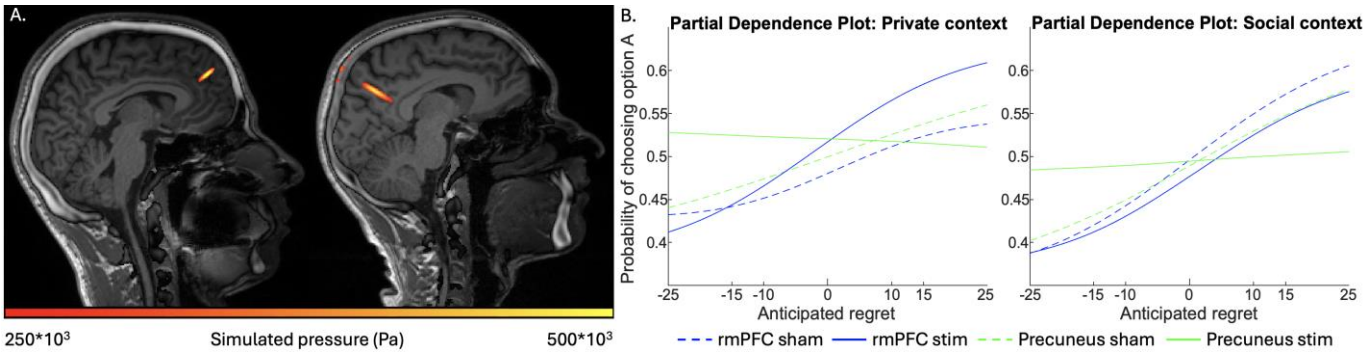
Abstract:

Many of our decisions are taken in a social context. The sole presence of a peer engaged in a similar task, as opposed to being alone (i.e., private context), has been shown to impact how we make decisions and perceive outcomes (Bault et al., 2009; 2011). These outcomes could be processed in multiple ways. In addition to the obtained outcome, we also evaluate the outcome of the alternative unchosen option (private counterfactual outcome) and, in a social context, the outcome obtained by a peer (social counterfactual outcome). While previous neuroimaging studies suggest that the rostromedial prefrontal cortex (rmPFC) and the precuneus both encode social counterfactual signals (Bault et al., 2011), their specific contribution and causal role into integrating those signals into the decision making process remains to be established.

In a double-blind sham-controlled study, an 80s 5Hz theta patterned transcranial ultrasound stimulation (TUS) was applied either to the rmPFC (N=40) or the precuneus (N=40) in two different groups of participants (Figure 1A). We used a probabilistic gambling task (Bault et al., 2011, 2019) coupled with fMRI to assess the offline effect of TUS on the behavioural and neural activity related to choices and counterfactual signals. In half of the trials, participants performed the task alone (private context), and in the other half, participants could observe the choices and outcomes of a peer (social context).

We first replicated previous findings on the effect of the private versus social context on behaviour. However, contrary to our prediction, stimulation of the rmPFC induced behavioural changes mainly in the private context, while stimulation of the precuneus induced effects in both the private and social contexts. These changes were observed mainly on how participants use counterfactual outcomes to guide their decision. Participants relied differently on the anticipated differences between outcomes of the chosen and counterfactual choices (i.e., regret) depending on the stimulation sites. Whereas regret aversion increased following the stimulation of the rmPFC, it decreased after stimulating the precuneus in the private context (Figure 1B). Stimulation of the precuneus but not the rmPFC impacted on anticipated regret in the social context. Ongoing analysis are investigating the effect of TUS on neural activity.

Figure 1. A. Simulated pressure map based on stimulations performed on the rmPFC (left) and the precuneus (right), single subject example. B. Effect of regret anticipation on choice in a private (left) and social (right) contexts in sham and active TUS trials. The probability of choosing option A is plotted against the anticipated regret associated with option B vs option A.



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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: Low-intensity focused ultrasound of the subthalamic nucleus: A preliminary evaluation of cognitive and motor effects

Authors: Fairbanks, T(1,2), Coreas, A(3), Naghizadeh, M(1), Raghuram, H(3), Shrestha, S(4), Li, S(3), Kam, J. W. Y(2,5), Pike, G. B(1,2,3), Pichardo, S.(1,2,3), Girgis, F(1,2).

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Abstract:

Low-intensity focused ultrasound (LIFU) is an emerging non-invasive neuromodulation technique. However, few studies have targeted subcortical structures and information on the impact of LIFU on cognitive and motor function is lacking. To address this gap, we administered LIFU to the subthalamic nucleus (STN), a target known to have both motor and cognitive involvement. Our primary aim is to assess the impact of LIFU stimulation of the STN on motor performance using a finger tapping task and cognitive performance using a Stroop task in healthy volunteers. We hypothesize that inhibition of the STN using LIFU would increase speed and error rates on motor and cognitive tasks. 10 healthy subjects were recruited and LIFU or sham stimulation was applied to the left STN in two sessions across two separate days in a double-blind manner. We used a 128-element transducer operating at 250 kHz (focal length 133 mm; diameter 135 mm) with a sonication duration of 120 s, 10 % duty cycle, 100 Hz PRF, Isppa = 10 W/cm2, Ispta = 1 W/cm2, MI ≤ 1, TI ≤ 2˚C. Frequency of finger tapping of the right index finger was measured using an accelerometer. Response time and error rate on congruent and incongruent trials in a Stroop task were recorded, and the Stroop effect (ie. a difference in response time between incongruent and congruent trials) was calculated. Results were normalized to baseline and analyzed as a change in movement and percent change in cognitive performance. Frequency of finger tapping decreased 0.085 Hz following sham and 0.165 Hz following LIFU. On the Stroop task, error rates increased a greater degree from baseline following sham than LIFU (congruent: sham 0.42 % vs. LIFU 0.35 %; incongruent: sham 0.90 % vs. LIFU 0.56 %). Response times decreased with LIFU compared to sham (congruent: sham 4.1 % vs. LIFU 6.3 %; incongruent: sham 2.3 % vs. LIFU 7.6 %) and the Stroop effect decreased following LIFU (39.8 %) but increased following sham (44.7 %). While none of these findings have reached statistical significance, likely due to a small sample size, the trends in response time and Stroop effect reflect the hypothesized results and are consistent with previous literature on non-LIFU STN stimulation. Here, we have demonstrated promising preliminary results for the ability of LIFU to transiently alter STN activity as predicted. Further testing with a larger sample size will assist in understanding its ability to modulate subcortical structures.

Acknowledgments: This work was supported in part by Hotchkiss Brain Institute CAPRI Grant, and Parkinson Association of Alberta Funding.

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

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

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

Title: A nudge in the 'right' direction: biasing eye movements with ultrasonic stimulation

Authors: Soha Farboud, Solenn Walstra, Benjamin Kop, Andrey Chetverikov, José Marques, Lennart Verhagen, Hanneke den Ouden

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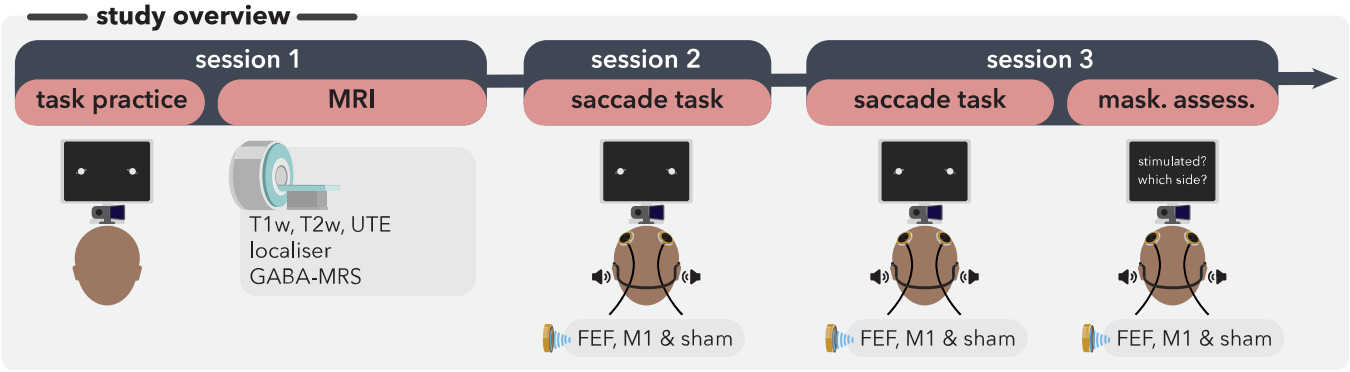
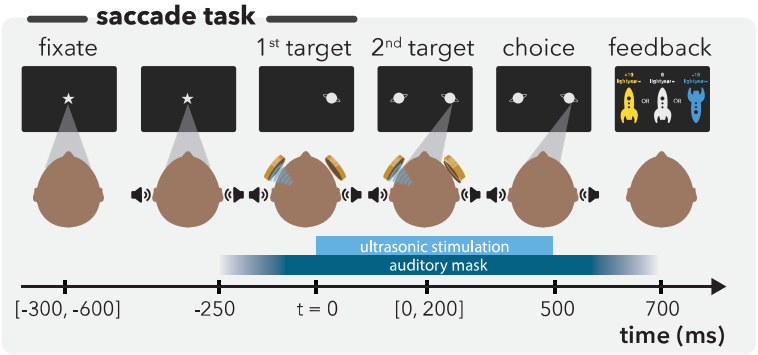
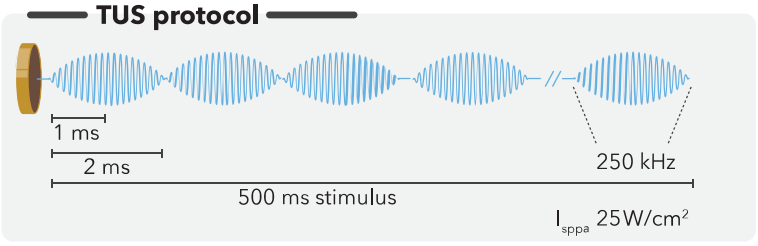
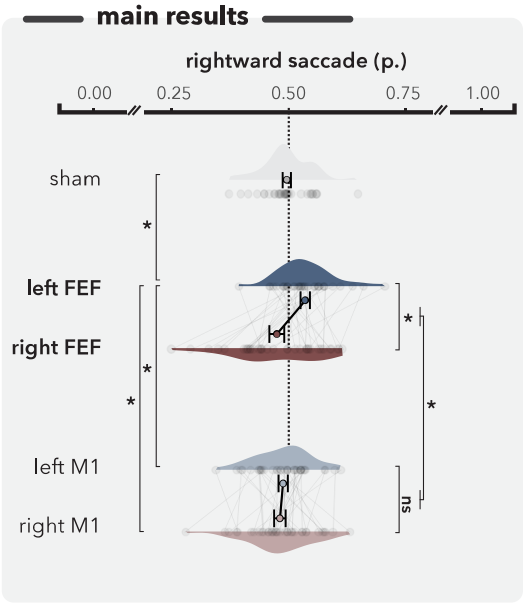
Abstract:

Transcranial Ultrasonic Stimulation (TUS) is well-established in animals, but evidence for robust neuromodulatory effects in humans is limited. Two critical questions are particularly urgent to answer: 1) are effects robust and target specific, tested in tightly controlled experimental conditions that account for confounding factors, and 2) can we predict the directionality of the effect, to distinguish putative inhibitory, excitatory, or perturbatory effects? We aim to establish an effective online TUS protocol in humans by adapting a validated non-human primate model (Kubanek et al., 2020), which demonstrates eye movement biasing following frontal eye field (FEF) stimulation. We selected this FEF paradigm for its translational potential, due to the well-defined link between FEF neural activity and eye movement control across species. The FEFs control voluntary contralateral eye movements, with excitation/inhibition driving contralateral/ipsilateral responses, respectively. To control for auditory and somatosensory confounds, we stimulated an active control area (primary hand motor cortex, M1), which is also lateralized but unrelated to eye movements. We show significant contralateral biasing of eye movement induced by FEF stimulation. Stimulation of M1 did not cause biasing changes of eye movements. This is suggestive of an excitatory TUS effect specific to FEF stimulation, replicating earlier macaque observations. This study embodies a crucial step to precisely validate, characterize, and quantify the effects of online TUS in humans.









Acknowledgments: This research was supported by the Radboud University and VIDI fellowships by the Dutch Research Council awarded to LV and HdO.

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)

Kai

Title: Dynamic changes in human brain connectivity following ultrasound neuromodulation

Authors: Cyril Atkinson-Clement, Mohammad Alkhawashki, Marilyn Gatica, James Ross, Marcus Kaiser

Email: Cyril.Atkinson-Clement@nottingham.ac.uk

Abstract:

Context: Non-invasive neuromodulation represents a major opportunity for brain and mental health interventions. Based on its ability to target deep-brain structures, transcranial focused ultrasound neuromodulation (FUS) is the most promising approach, destined to change clinical practice. However, some challenges prevent the community from fully understanding its outcomes and therefore moving to the next research step. Here we addressed one of them and unravelled the temporal dynamics of the ultrasound neuromodulation effects in humans.

Methods: In this study, 22 healthy individuals were recruited and divided into two groups of 11. One group received ultrasound stimulation to the right inferior frontal cortex (IFC), and the other to the right thalamus. We compared resting-state fMRI acquired before the stimulation to another one of ~40 minutes acquired right after. A dynamical approach was used to capture the dynamic of brain connectivity changes between the target (as a seed) and the rest of the brain. We also assessed behavioural changes during a cognitive task of reactive motor inhibition for which the inferior frontal cortex is known to be involved (the stop signal task).

Results: Our findings emphasise that: i) FUS effects are mainly time-constrained and connected to reduced functional connectivity with the parameters we used; ii) FUS causes connectivity alterations in the functional networks of the target, relating to the cerebello-thalamo-cortical network following Thalamus-FUS and to multiple networks changes after IFC-FUS; iii) IFC-FUS is directly associated with behavioural alterations through the acoustic pressure applied to the IFC and the IFC-post-central cortex disconnection.

Conclusion: Our study provides a detailed understanding of how ultrasound stimulation alters brain function over time. This is a first step towards the future prediction of the dynamic effects of ultrasound neuromodulation in terms of brain activity and behaviour, including both immediate (recorded during the stimulation) and long-term consequences (hours or days after the stimulation) of ultrasound neuromodulation.

Acknowledgments: M.K., C.A., and J.R. were supported by the Engineering and Physical Sciences Research Council (EP/W004488/1 and EP/X01925X/1). M.K. was also supported by the Guangci Professorship Program of Rui Jin Hospital (Shanghai Jiao Tong University).

Conflicts of interest: The authors declare no conflicts of interest

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

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

Title: Transcranial Ultrasonic Stimulation of the Human Amygdala to Modulate Threat Learning

Authors: Sjoerd Meijer, Eleonora Carpino, Benjamin Kop, Soha Farboud, Linda de Voogd, Karin Roelofs* & Lennart Verhagen*

Email: sjoerd.meijer@donders.ru.nl

Abstract:

Lesion studies in animals and human patients have identified a critical role of the basolateral amygdala (BLA) in associative threat learning during Pavlovian conditioning. However, our causal understanding of BLA functioning in neurotypical individuals is limited due to the lack of non-invasive deep brain interventions. Transcranial Ultrasonic Stimulation (TUS) is a novel non-invasive technique that can selectively modulate activity in deep brain structures by delivering mechanical energy. Here, we combined TUS with well-validated threat conditioning procedures for a causal test of BLA-dependent threat learning and subsequent extinction in healthy humans.

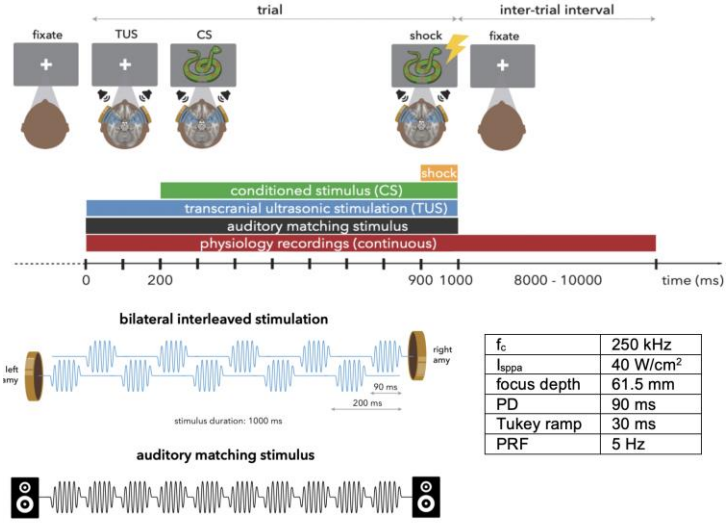
Two groups of healthy participants received TUS during threat conditioning (Fig. 1). The first group (n = 26) received bilateral TUS targeting BLA versus sham. The control group (n = 26) received bilateral TUS targeting the hippocampal tail (HPT) as an active control site, allowing us to assess the specificity of BLA-TUS effects on threat learning (preregistration: https://osf.io/ewkxm). Both active-TUS [Isppa = 40 W/cm2] and sham-TUS [Isppa = 0 W/cm2] were paired with an auditory matching stimulus. We measured the online and longer-term modulatory effects of TUS on conditioned responses to threat versus safety using robust physiological markers of threat memory strength, including skin-conductance and heart-rate responses.

Feasibility and safety of the stimulation protocol were assessed through individualized acoustic simulations, along with estimates of target exposure.

Our preliminary results suggest that TUS delivered during threat acquisition interacts with the learning dynamics, both during initial threat learning and after fear is reinstated following extinction. Specifically, we observe increased skin-conductance responses at the late stages of threat learning (Fig. 2). Critically, we also observe a diminished return of fear after re-activation (Fig. 3). This suggests the stronger response during learning reflects the formation of a threat memory trace that is more susceptible to extinction. This observation highlights the high selectivity of BLA computations to threat learning and subsequent extinction. Moreover, this study demonstrates that targeting specific sub-nuclei of the amygdala is possible by utilizing individualized estimates of target exposure based on acoustic simulations incorporating advanced pseudo-CT models (Fig. 4).

These findings contribute to our mechanistic understanding of BLA-dependent threat learning processes and demonstrate the potential of using TUS for selective modulation of deep brain structures, thereby paving the way for targeted non-invasive interventions of anxiety disorders.

We have recently completed data collection for both groups and plan to present the full study results during the conference.



f_c	250 kHz
I_{sppa}	40 W/cm²
focus depth	61.5 mm
PD	90 ms
Tukey ramp	30 ms
PRF	5 Hz

Fig 1. Stimulus timing and TUS protocol.

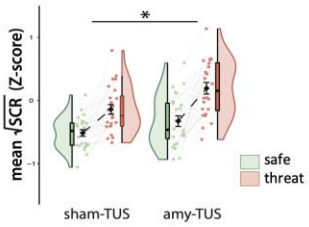


Fig. 2. BLA-TUS effect at the end of threat learning.

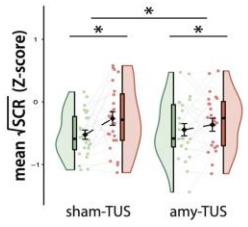


Fig. 3. BLA-TUS effect on reinstated fear following extinction.

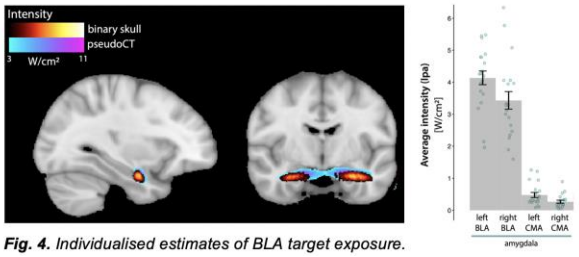


Fig. 4. Individualised estimates of BLA target exposure.

Acknowledgments: This work was supported by a consolidator grant DARE2APPROACH, from the European Research Council (ERC_CoG_772337) awarded to KR, and by a VIDI fellowship (#18919) by the Dutch Research Council awarded to LV.

Conflicts of interest: The authors declare that they have no competing interests.

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

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

Title: Reducing blood pressure with FUS neuromodulation: Investigating the role of inhibitory neurons

Authors: Neha Chauhan1, Harriet Lea-Banks1,2, Kullervo Hynynen1,3,4

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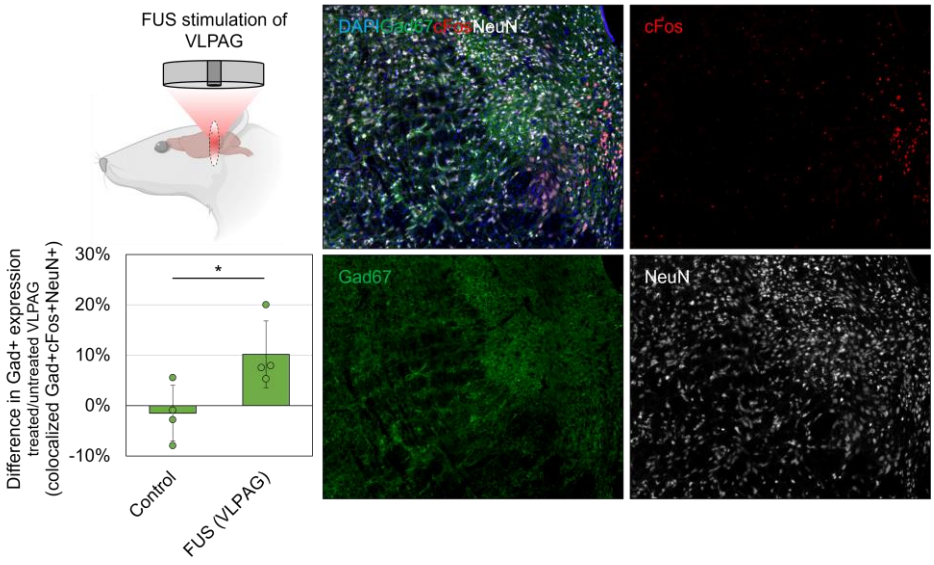
Abstract:

The ventrolateral periaqueductal grey (VLPAG) is a critical centre for blood pressure regulation. Previously we have shown that stimulating the VLPAG using focused ultrasound (FUS) can significantly reduce systolic and diastolic blood pressure in normotensive and hypertensive rats.

Here we investigate the influence of ultrasound pressure (0.275 – 2.100 MPa) and pulse length (1 – 100 ms) on blood pressure following FUS neuromodulation of the VLPAG, using a single element 540 kHz transducer (1 Hz PRF, 10 min duration). We map cFos expression 90 min following FUS, and use GAD67 staining as a specific marker of GABAergic neurons. Our results show that reduction in blood pressure following sonication of the VLPAG is pressure-dependent (-11 mmHg/MPa, p=0.02), and is driven by stimulating inhibitory neurons. Using cFos mapping we confirmed FUS stimulation of the VLPAG, whereby cFos expression was significantly elevated in the sonicated VLPAG (46.9%) following FUS, compared to control animals (-9.8%). Furthermore, increased neuronal activity was associated with inhibitory neurons, shown through higher colocalization of Gad67+ cFos+ and NeuN+ expression in FUS animals (10.2%) compared to controls (-1.5%).

Our results show that ultrasound-mediated blood pressure reduction is dose-dependent, but requires further work to investigate the influence of other ultrasound parameters, including ultrasound frequency and PRF.



Acknowledgments: The authors are grateful to veterinary technician Shawna Rideout-Gros, Onbee Kim for assistance with data analysis, and Jennifer Sun for processing histology. Funding was provided by the National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health (R01 EB003268), the Canadian Institutes for Health Research (FRN 119312), the Temerty Chair in Focused Ultrasound Research at Sunnybrook Health Sciences Centre, the Beamish Family Foundation and the Connor family.

Conflicts of interest: K.H. is a co-founder of FUS Instruments, a company that is commercializing the preclinical FUS system used in this work.

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

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

Title: Towards Physiological Guidance of Transcanial Ultrasound Neuromodulation

Authors: Taylor Webb, Carter Lybbert, Matthew Wilson, Henrik Odéen, Jan Kubanek

Email: taylor.webb@utah.edu

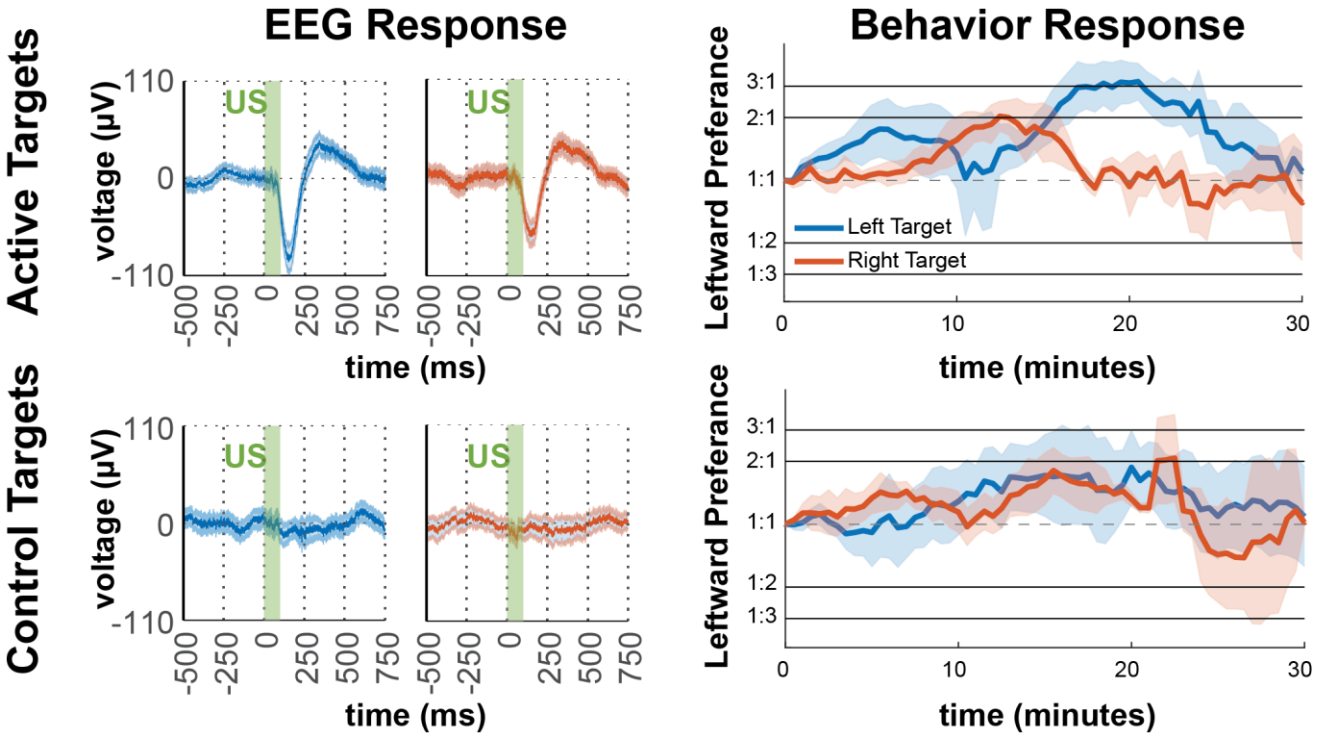
Abstract:

Background: Transcranial ultrasound neuromodulation (TUSN) treatments are limited by uncertainty in the intensity of the ultrasound energy delivered to target regions. In this abstract we explore the possibility of using neurological feedback to guide TUSN therapies. Specifically, we examine using electroencephalography (EEG) to measure ultrasound evoked neural activity. The goal is to guide TUSN therapies by determining the patient specific threshold at which TUSN elicits a neural response.

Methods: Using Remus—a deep brain neurological system capable of delivering TUSN to the brain of awake primates—we sonicated 24 neural targets in the deep brain of an awake nonhuman primate subject. The targets were organized in two grids surrounding the left and right lateral geniculate nucleus. Each sonication was 100 ms with a PRF of 200 Hz, a duty cycle of 50%, and an estimated in-situ pressure of 1 MPa. We hypothesized that the strength of the EEG response at each target would predict the strength with which TUSN modulated awake behavior. To test this hypothesis, we sonicated the targets with maximal (active) and minimal (control) EEG response during a visual behavior task and measured the resulting bias in the animal's behavior. The visual task and it's analysis have been described previously (Webb et al., Remus: System for Remote…, iScience, 2022).

Results: We found that ultrasound evoked an anatomically-specific voltage potential measurable with EEG electrodes placed in the approximate P3 and P4 10/20 EEG position (Figure 1; EEG Response). As hypothesized, sonication of the maximally responsive targets results in a strong behavioral bias, while sonication of unresponsive regions does not modulate awake behavior (Figure 1: Behavior Response).

This study provides preliminary evidence that EEG-based guidance of TUSN is feasible. Future work should identify whether neural targets relevant to disease also generate an EEG response.



Acknowledgments: *R00NS100986, RF1NS128569,221 S10OD026788, and F32MH123019*

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

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

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

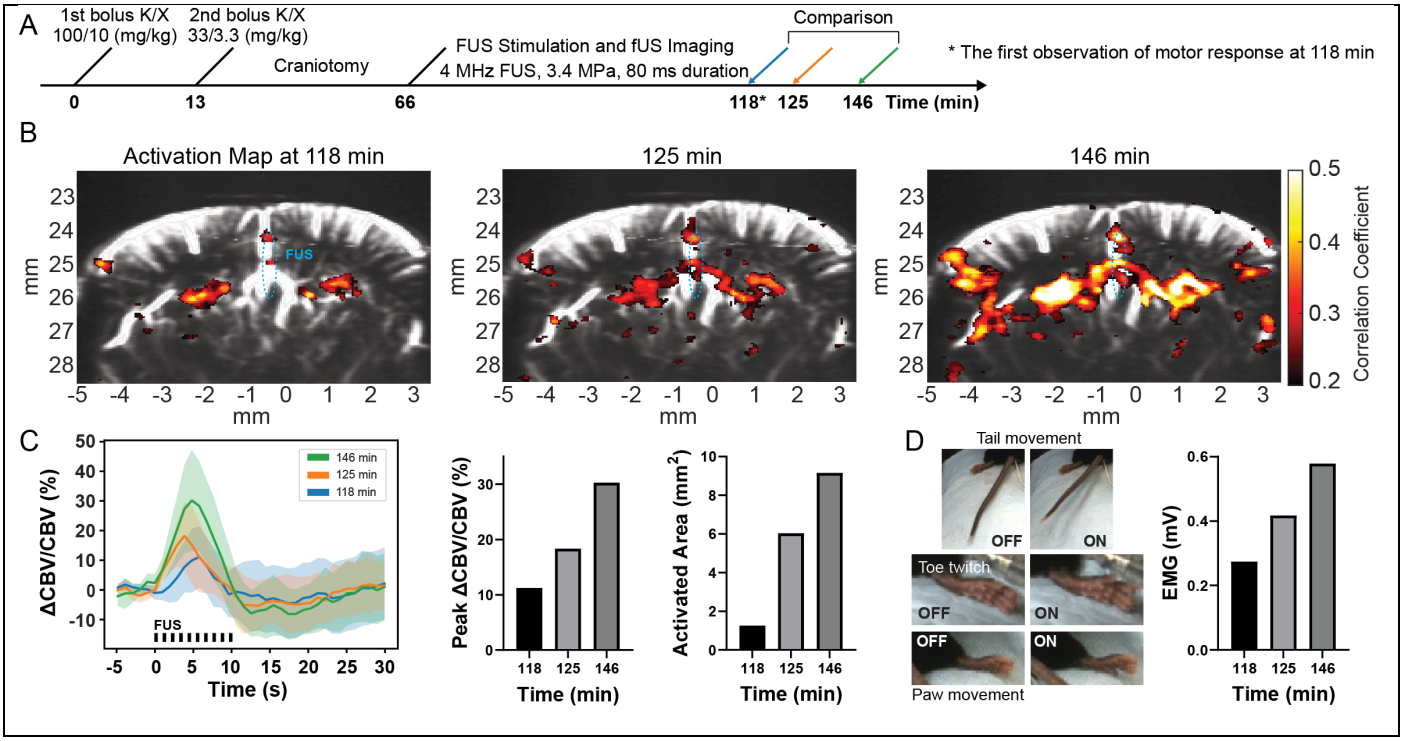
Title: Functional ultrasound (fUS) can detect the FUS-evoked neurovascular response to distinct depths of anesthesia

Authors: Seongyeon Kim [1], Jonas Bendig [1], and 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

Email: ek2191@columbia.edu

Abstract:

Background, Motivation and Objective. Focused ultrasound (FUS) can induce excitatory and inhibitory neurons in the central (CNS) and peripheral nervous system (PNS). Previous studies reported FUS evokes hemodynamic response characterized by the increase in cerebral blood volume (CBV). The anesthesia can affect neurovascular response, yet the effect of anesthesia on the FUS-evoked neurovascular response has not been studied at a length. We herein leveraged functional ultrasound (fUS) imaging to monitor neurovascular responses simultaneously with FUS targeting the sensorimotor cortex and subcortex at the pressure that can elicit behavioral responses in ketamine/xylazine(K/X)-anesthetized mice, and compare CBV responses at three different time points. The objectives of this study were to elucidate the FUS-induced neurovascular responses at the different depth of anesthesia (i.e. as the animal recovers from the anesthesia).
Statement of Contribution/Methods. To that end, we employed a 128-element linear imaging transducer (L22-14vXLF; Vermon) and an ultrasound research system (Vantage 256 HF; Verasonics) to perform fUS imaging. A single-element FUS transducer (H-215; 4 MHz, SonicConcepts) was used and axially aligned with the imaging transducer. A female C57BL/6J mouse ages 8-12 weeks was used and under anesthesia with intraperitoneal injection using ketamine/xylazine followed by craniotomy, imaging and FUS (Fig. A). During FUS modulation, electromyography (EMG) signals were collected to record FUS-elicited muscle activity from tibialis anterior muscle and tail. We targeted the sensorimotor cortex using FUS pulses at 3.4 MPa peak negative pressure with 80 ms duration. To induce CBV response to FUS, 10 FUS pulses with a pulse repetition frequency (PRF) of 1 Hz were applied. We acquired CBV signals at 118, 125, and 146 min post-anesthesia (Fig. A) and compared the CBV responses in order to investigate the effect of anesthesia depth on the FUS-evoked hemodynamic activation. Hemodynamic activation map was generated based on the Pearson's correlation between CBV signals and binary stimuli signals.
Results/Discussion. FUS evoked paw movement and/or toe twitches with tail movement (Fig D, left) at 3.4 MPa approximately 2 hours after the first bolus injection of K/X (the animal showed very mild paw twitches when pinched). In sharp contrast, sub-millimeter off-target FUS modulation resulted in no motor responses, indicating the observed motor responses are not due to confounding effect of FUS such unintended auditory and tactile stimuli from FUS as reported by others under light isoflurane anesthesia. Simultaneous fUS imaging revealed FUS-evoked hemodynamic activation (i.e. CBV increase peaks at 4~6 s post-FUS) at the part of hippocampus and the thalamus (Fig B). Interestingly, we observed CBV responses at thalamus which is not directly targeted but adjacent to FUS focus (dotted blue in Fig B), which may seem to shed light on the structural connectivity from the cortex to the subcortex along the midline. The FUS-elicited CBV and motor responses became stronger as the anesthesia waned. Peak CBV change, activation area, and peak EMG amplitude were 11.2 %, 1.71 mm^2, and 0.27 mV, respectively at 118 min and increased to 30.3 %, 8.4 mm^2, and 0.58 mV, respectively at 146 min post-anesthesia (Fig. C and D). In conclusion, we demonstrated fUS can successfully detect the changes in FUS-induced neurovascular response according to the anesthesia depth in mice. Our findings demonstrate brain imaging of anesthesia-dependent FUS-evoked neurovascular response.



Acknowledgments: This work was funded by National Institute of Health (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: Prospective planning of transcranial ultrasonic transducer placement – a fast and heuristic tool

Authors: Maximilian Lueckel [1,2], Suhas Vijayakumar [1], Til Ole Bergmann [1,2]; [1] Neuroimaging Center, Focus Program Translational Neurosciences, Johannes Gutenberg University Medical Center, Mainz, Germany; [2] Leibniz Institute for Resilience Research, Mainz, Germany

Email: mlueckel@uni-mainz.de

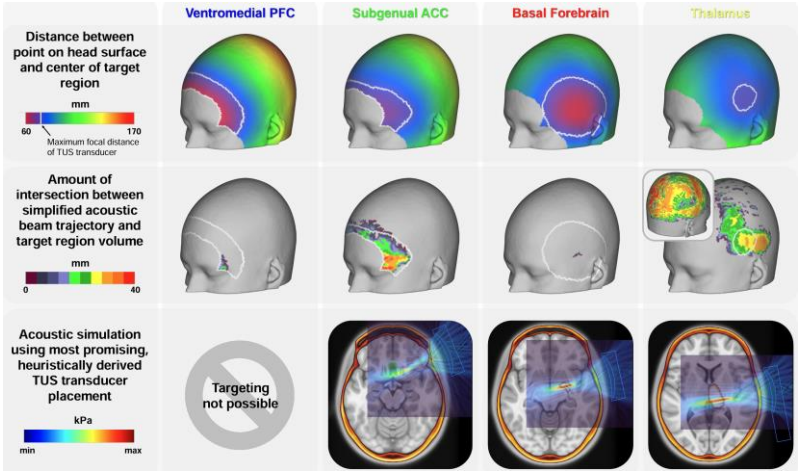
Abstract:

Introduction: The question of where to place an ultrasonic transducer on the scalp of an individual in order to optimally target a specific brain region is far from trivial – especially if one is constrained by properties of the equipment at hand (e.g., limited focal depth or steering capabilities of the transducer). The goldstandard for figuring out where the ultrasonic focus will (approximately) end up in the brain for a given transducer position is to run acoustic simulations based on individual skull bone information. However, these simulations are quite time-consuming, making, for example, grid search-like optimization procedures (i.e., running acoustic simulations for numerous potential transducer positions) hardly feasible. We therefore aimed to develop an approach that is used before running any acoustic simulation, and that quickly provides useful information to narrow down the number of potential transducer positions to the most promising ones. Eventually, these can then be used to run proper acoustic simulations in a feasible amount of time.

Methods: After generating a 3D head model from an individual's anatomical MRI scan, we compute and visualize several metrics for each potential transducer position (i.e., each point) on the head surface. These include, among others, the distance from the target region or the (extent of) intersection between the target area and an idealized ultrasound beam trajectory perpendicular to the head surface. The underlying code is fully based on open-source software and will be made publically available in the future. To evaluate the validity and usefulness of this approach for targeting different deeply located, clinically relevant brain regions (left basal forebrain (BF), left thalamus, subgenual anterior cingulate cortex (sgACC), and ventromedial prefrontal cortex (vmPFC)), we employed realistic acoustic simulations using the transducer positions derived from our heuristic approach.

Results: Using our fast and heuristic approach, we were able to easily identify and select transducer placements that resulted in good overlap between the simulated acoustic focus and both left BF and thalamus. Furthermore, our approach revealed that targeting sgACC and vmPFC would require transducer placements in or close to avoidance regions on the scalp (e.g., above air-filled cavities), rendering these regions hard and impossible to target, respectively, considering the constraints of our equipment (i.e., if the transducer is placed strictly tangential to the head surface and lateral steering of the ultrasonic focus is not possible).

Conclusion & Discussion: To conclude, we developed a heuristic tool that quickly provides a first indication of the most promising TUS transducer placements for targeting specific brain regions in a given individual. While it is fast and easy to use, our approach does not account for, e.g., aberrations of the ultrasound beam by the skull bone. Therefore, target engagement should always be validated using acoustic simulations.



Acknowledgments: -

Conflicts of interest: -

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

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

Title: A Time-Resolved Forward Model for MR-ARFI: Towards Acoustic Dosimetry for TUS

Authors: Kristen Zarcone1, Huiwen Luo2, Charles F. Caskey2, William A. Grissom1
1Case Western Reserve University Department of Biomedical Engineering, Nashville, TN, USA
2Vanderbilt University Institute of Imaging Science, Nashville, TN, USA

Email: kxz394@case.edu

Abstract:

Introduction: MR-Acoustic Radiation Force Imaging (MR-ARFI) provides maps of tissue displacement that are useful in determining the position of the acoustic focus in transcranial focused ultrasound applications. While MR-ARFI is a quantitative method, it presently is of limited use for TUS dosimetry since acoustic pressure plays a role in determining the level and type of neuromodulatory effect, but MR-ARFI measures tissue displacement which is coupled to pressure indirectly via unknown tissue mechanical properties. We report a forward model to calculate expected displacement measured by MR-ARFI, which will enable development of methods to recover acoustic intensity from imaged displacements, and subsequently make MR-ARFI a dosimetry method for TUS.

Methods: An 850kHz single element ultrasound transducer was simulated in k-Wave[1] (Figure 1) across a range of pressure levels from 0.27 - 2.70MPa. Average acoustic intensity and force density maps were calculated from each simulated pressure map. The force density maps were input to a finite element method (FEM) solver (LS-DYNA) to calculate displacements during MR-ARFI pulses[2]. FEM-based calculations were performed over a radially symmetric 2.0x2.0x2.5 cm3 slice around the focus with (100,100,150) nodes. Displacement was calculated using a Poisson's ratio of 0.49 a Young's modulus of 2000Pa and a timestep of 5x10-5s. The resulting average displacement maps were used to calculate simulated MR-ARFI displacement maps for a 4ms MEG.

The focal displacement FWHM's of MR-ARFI maps generated by a PSF-like Green's theorem steady state displacement calculation method[3] and the FEM-simulated ARFI maps were compared to phantom experiments performed in a 3T Philips Elition MR scanner with an agar-graphite phantom[4]. Because the stiffness of the phantom was unknown, all simulated displacements were normalized to the maximum observed displacement in the phantom, 2.5 µm.

Calculated MR-ARFI displacements from the PSF and FEM methods were used to generate a lookup table. The minimum, middle, and maximum displacements and corresponding intensities were used as source points in lookup table calculations to interpolate the 'unknown' intensities of the middle points, given their displacement. The predicted intensities were compared between PSF and FEM MR-ARFI maps.

Results & Discussion: The FWHM of coronal slices were 10mm for PSF, 2.7mm for FEM and 6.4mm for phantom measurements. The axial FWHM were 30.75mm for PSF, 23mm for FEM and 18.7mm for phantom measurements. While displacement and intensity varied linearly with the PSF method, it did not for the FEM method. Error was less than 3W/cm2 when using FEM source points to interpolate pressure from FEM displacement. When using the PSF method as a source and FEM displacement to calculate the intensity, the error between interpolated and known intensity was 29.07W/cm2, 14% of the true intensity for FEM with a 4ms MEG. This model will enable further development of inverse methods for MR-ARFI-based acoustic dosimetry in FUS neuromodulation.

References:
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[2] M. L. Palmeri, et al., "A finite-element method model of soft tissue response to impulsive acoustic radiation force," IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, 2005.
[3] A. Payne, et al., "A simulation technique for 3D MR-guided acoustic radiation force imaging," Medical Physics, 2015.
[4] H. Luo et al., "Reduced-field of view three-dimensional MR acoustic radiation force imaging with a low-rank reconstruction for targeting transcranial focused ultrasound," Magnetic Resonance in Medicine, 2022.

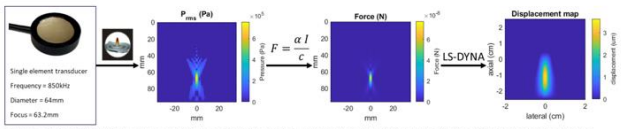

Figure 1: The MR-ARFI displacement map forward model. A transducer is simulated at a free-field pressure level in k-Wave, yielding pressure maps that are used to calculate acoustic intensity and force. The force field is input to an FEM solver (LS-DYNA) for the duration of the MR-ARFI MEG.

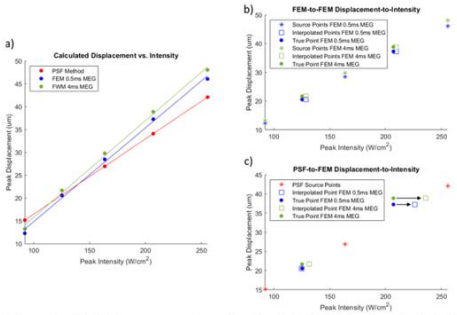

Figure 2: a) Displacement vs. Intensity for the PSF Method and FEM with 0.5 and 4 ms MEGs. b) The lowest, middle, and highest intensities and corresponding FEM displacement were used as source points to interpolate the intermediate FEM intensities from their modeled FEM displacements. c) The same calculations in (b) but using PSF-calculated displacements as source points in the lookup table calculation. Arrows mark displacements where the error between interpolated and known intensities were highest.

Acknowledgments: **NIH grants : 3T32EB007509-17S1, UG3 NS 135551**

Conflicts of interest: None

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

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

Title: Experimental validation of k-Wave simulations of ultrasound propagation through human skulls

Authors: Alisa Krokhmal, Department of Medical Physics and Biomedical Engineering, University College London, Ian Simcock, Department of Clinical Radiology, Great Ormond Street Hospital for Children, London, Bradley Treeby, Department of Medical Physics and Biomedical Engineering, University College London, Eleanor Martin, Department of Medical Physics and Biomedical Engineering, University College London, Wellcome/EPSRC Centre for Interventional and Surgical Sciences, University College London.

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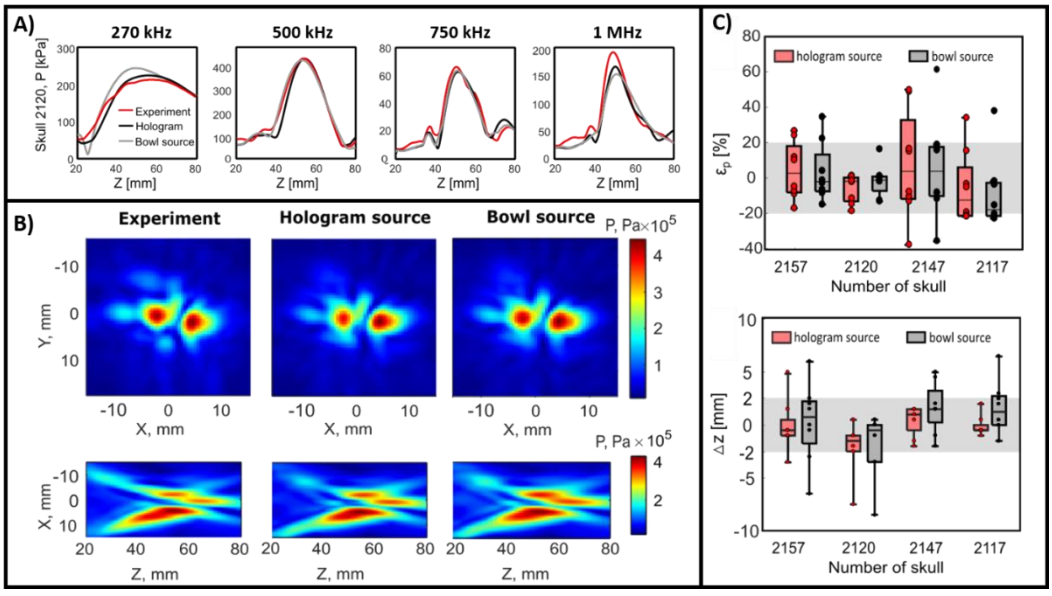
Abstract:

Transcranial ultrasound therapies, including neuromodulation, blood-brain barrier disruption, and high-intensity focused ultrasound, depend on accurately simulating ultrasound fields within the brain for effective and safe treatments. This study evaluates the accuracy of the k-Wave toolbox in simulating focused ultrasound propagation through cranial bones against measurements using two source models: one based on measured holograms and an equivalent bowl source with uniform amplitude and optimized curvature radius and aperture diameter. Unlike the complex measurements required for the hologram, defining the bowl source requires only two scans in axial and lateral directions, making it simpler and more accessible. We validated k-Wave simulations against hydrophone measurements using four ex-vivo human skulls, with fields generated by spherically focusing transducers with operating frequencies ranging from 270 kHz to 1 MHz, in both quasi-continuous and pulsed modes. Acoustic medium properties were mapped from calibrated CT scans of the skulls, registered with the transducer positions using CAD models of 3D printed holders. As shown in Fig. A , the simulated pressure profiles for both the hologram and bowl sources closely matched with experiment, accurately replicating the amplitude and beam shape at different frequencies. The spatial distribution of the simulated pressure fields matched very closely with the measured field, even where there was significant aberration, as seen in Fig B for a 500 kHz field. There was also good agreement close to the skull, in the near field regions where larger errors, particularly for the bowl source, might be expected. This replication of the field shape indicates that the mapping of sound speed and density from CT scans represents the properties of the skulls well. Errors in spatial-peak acoustic pressure amplitude were below 20% on average, but ranged from -40% to 60%, indicating that the skull absorption varies between skulls, and the constant with linear frequency dependence used was not suitable. In almost all cases, the median accuracy of the spatial peak pressure of the bowl source is comparable to that of the hologram source (Fig. C). The error in the axial position of the spatial pressure across all skulls is slightly higher for the bowl source, but remains under 2 mm, as shown in Fig. C. Our findings demonstrate that the k-Wave toolbox is a reliable tool for simulation of transcranial ultrasound propagation. However, the results indicate that better, more specific estimates of skull attenuation coefficients are needed to reduce errors in pressure amplitude. In terms of source definitions, both the hologram and equivalent bowl source resulted in comparable errors in pressure amplitude, focal position and focal size across skulls and frequencies, suggesting that the simpler bowl source is a practical alternative to more complex models.



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Conflicts of interest: No conflicts of interest

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

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

Title: A study of high temporal and spatial resolution noninvasive EEG acquisition methods based on transcranial focused ultrasound

Authors: Hao Zhang (Tianjin University), Yanqiu Zhang (Tianjin Medical University), Xue Wang (Tianjin University), Guowei Chen (Tianjin University), Xiqi Jian (Tianjin Medical University), Minpeng Xu (Tianjin University), Dong Ming (Tianjin University)

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Abstract:

Objective: The brain is the most important and complex organ in the human body, and exploring its functional activities is beneficial for humans to have a clear understanding of their state and to treat neurological disorders of the brain. Safe, accurate and non-invasive functional brain imaging is one of the key technologies for in-depth study of brain science. Traditional non-invasive neurofunctional imaging techniques are difficult to combine high temporal and spatial resolution, and cannot adequately meet the needs of scientific research and clinical practice. The acoustoelectric brain imaging (ABI) technique, which has emerged in recent years, combines the precise spatial localization properties of focused ultrasound with the rapid temporal response of electroencephalogram (EEG) signals. In view of this, this study designed an ABI experimental platform for transcranial dipole localization and decoding based on a self-developed 128-array ultrasound phased transducer, which achieves accurate dipole localization and high-precision waveform decoding under non-invasive conditions. Methods: In this study, real neuron discharges were simulated based on single/dual source dipoles, and real skulls were simulated using acrylic bone plates. Firstly, a numerical simulation model of transcranial focused ultrasound (tFUS), which was identical to the experimental setup, was established to explore the pre/post-transcranial acoustic field distribution of focused ultrasound (Fig.1). Then, phase and amplitude control algorithms were developed for the excitation signals of each array element of the ultrasound phased transducer to reduce the energy at the skull and increase the focal point energy under the premise of realizing accurate focusing on the set intracranial target point. Next, the optimal acquisition lead distribution was explored based on the acoustoelectric effect, and the dipole scanning localization strategy and source signal waveform decoding algorithm were further developed. Results: In terms of the acoustic field modulation results, the simulation-guided modulated focusing is significantly better than self-focusing, where the maximum acoustic pressure of self-focusing is 0.18 MPa and the maximum acoustic pressure of modulated focusing is 0.46 MPa. The self-focusing focal area is 4.09 mm2 and there is a large paraflap, while the modulated focusing focal area is 1.65 mm2, which is basically free of paraflap and can realize accurate modulated focusing in the direction of the acoustic axis (Fig.2). In terms of ABI results, accurate dipole localization and high-precision waveform decoding can be achieved, in which the maximum value of the acoustic-electric signal is 725.31 μV in the absence of cranial condition and 134.22 μV in the transcranial condition. The single-source dipole transcranial localization error is less than 0.4 mm and the decoding accuracy is greater than 0.93, while the dual-source dipole transcranial localization error is less than 0.2 mm and the decoding accuracy is greater than 0.89 (Fig.3). Conclusion: In this study, the effects of tFUS acoustic field modulation methods and dipole localization and decoding were investigated based on numerical simulations and experiments simulating the skull and imitating brain tissue phantoms. The results show that the proposed high spatiotemporal resolution noninvasive EEG acquisition method can achieve accurate transcranial acoustic field modulation focusing, localize the intracranial source signal location with high precision and decode the source signal time-domain waveform. This study addresses the influence of cranial bones on ABI from the source based on tFUS, and the related research results will provide a scientific basis and technical way for the further development of ABI.

Keywords: Acoustoelectric brain imaging, focused ultrasound, electroencephalogram, localization, decoding.

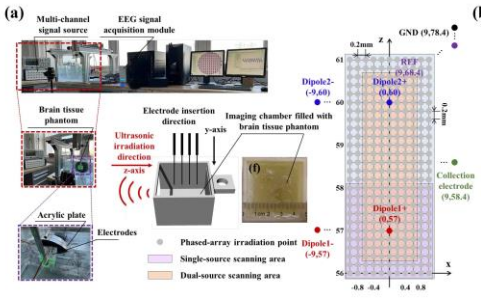

Fig. 1 ABI experimental platform.

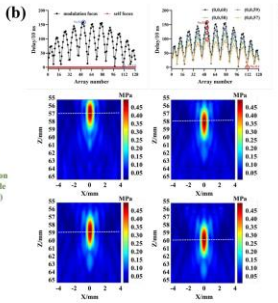

Fig. 2 Acoustic field modulation results.

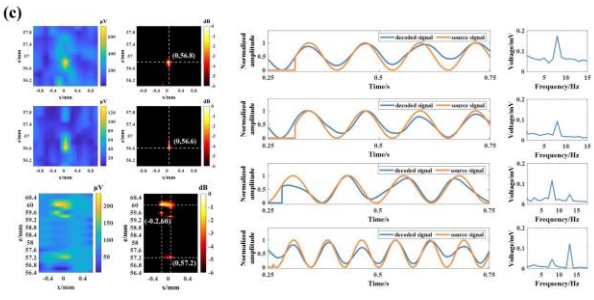

Fig. 3 Single/dual source localization decoding results.

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Conflicts of interest: The authors have no relevant financial or non-financial interests to disclose.

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

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

Title: Advancing Deep Brain Neuromodulation: An MR-Guided Transcranial Ultrasound System

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

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Abstract:

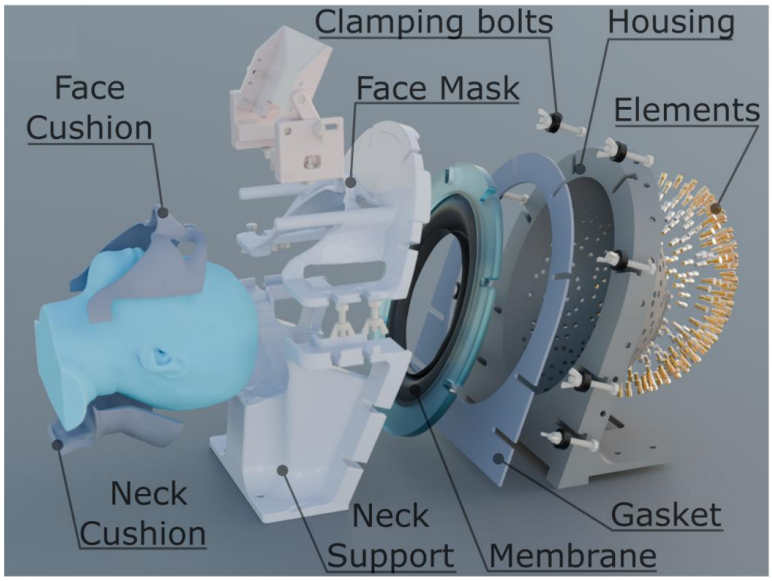
Modulating neural activity in deep brain structures with high spatial resolution and specificity is a key goal for both neuroscience research and clinical applications. However, existing neuromodulation techniques have limitations in targeting deep brain regions precisely. In this talk, we present a novel MR-guided transcranial ultrasound system designed to significantly improve the precision of deep brain neuromodulation.

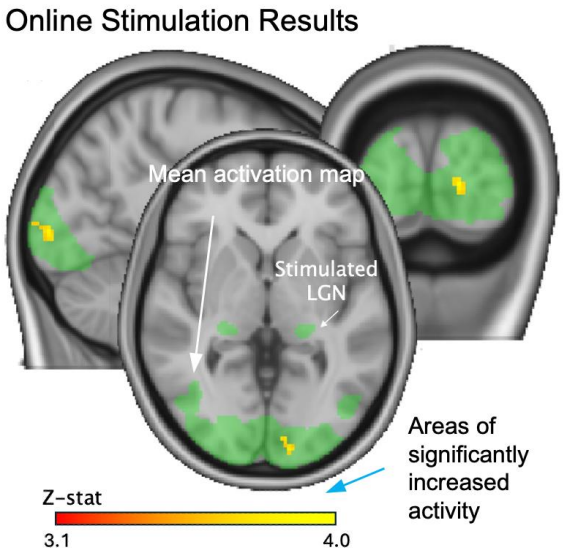
Our system features a 256-element, helmet-shaped transducer array operating at 555 kHz, integrated with a stereotactic positioning system, individualized treatment planning, and real-time monitoring using functional MRI. The transducer array's large aperture and sparse element distribution enable a small focal spot, allowing for highly selective targeting of thalamic nuclei compared to existing systems.

To characterize the system's performance, we conducted acoustic measurements and simulations across a wide steering range. The results demonstrate a -3 dB focal size of 1.3 mm laterally and 3.4 mm axially at the geometric focus, with a focal volume maintained across a broad range of target locations. Experimental validation using human skull caps confirmed the accuracy of the simulated focal parameters.

We evaluate the system's performance through two experiments targeting the lateral geniculate nucleus (LGN) in healthy humam participants. Our online stimulation paradigm shows modulation of visually-evoked activity in the primary visual cortex during concurrent ultrasound stimulation, indicating successful target engagement. Additionally, an offline theta-burst stimulation protocol demonstrates neuromodulatory effects lasting for at least 40 minutes post-stimulation, with decreased visual cortex activity. These effects are specific to the targeted LGN, as confirmed by control experiments.

The improved spatial resolution and prolonged neuromodulatory effects achieved by our system highlight its potential for studying the functional roles of deep brain structures and developing targeted, non-invasive therapies for neurological and psychiatric disorders. By enabling more selective modulation of deep brain regions, this technology offers a promising tool for investigating the relationships between neural activity and behavior, contributing to our understanding of the human brain.





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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:** oral

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