Title: Expanding the intramembrane cavitation model to morphologically realistic cortical cell models

Authors: Joaquín Gázquez Rodríguez (1), Thomas Tarnaud (1,2), Wout Joseph (1), Emmeric Tanghe (1)
(1) WAVES, Department of Information Technology (INTEC), Ghent University/IMEC, 9052 Ghent, Belgium
(2) 4BRAIN, Department of Head and Skin, Ghent University, 9000 Ghent, Belgium

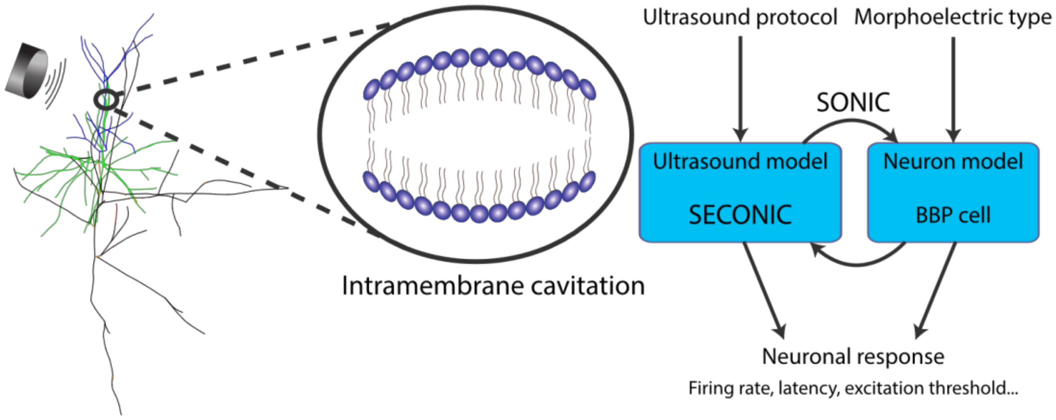
Email: Joaquin.GazRodriguez@UGent.be

Abstract:

Low-intensity ultrasound neuromodulation is a rapidly emerging technology due to its non-invasiveness and millimeter-scale precision. Although multiple experimental setups have shown that ultrasonic waves can modulate the neural activity in various brain regions, the coupling between the ultrasound source and the neuronal tissue is still not sufficiently understood. Multiple underlying mechanisms, such as mechanosensitivity, flexoelectricity, membrane displacement, and thermodynamic effects have already been proposed to explain in part the interaction between ultrasound and neurons. By understanding how the different mechanisms work, how they interact with each other and by quantifying their impact on the neuronal behavior, ultrasound neuromodulation therapy can be improved by optimizing the stimulation protocol in silico.

In this study, we concentrate on the predictions obtained by cortical cell models with the intramembrane cavitation mechanism, allowing us to determine if this mechanism can predict experimentally observed cell-type specificity and sensitivity to the ultrasonic protocol. Intramembrane cavitation is the mechanism where gas cavities form between the phospholipid membrane leaflets due to ultrasonic pressure waves, leading to capacitive displacement currents that induce membrane charge accumulation. This mechanism has been implemented in the neuronal intramembrane cavitation excitation (NICE) model. This model shows that action potentials can be generated due to oscillating hyperpolarizing currents when the bilayer sonophore is exposed to ultrasound. A multi-scale optimized (SONIC) model was also introduced that closely approximates the NICE model while reducing the computation time by more than a factor of 1000. However, this model has not yet been applied to multi-compartmental brain cells with potentially strong axial coupling (i.e., a limitation of the SONIC model). Previously, we introduced the SECONIC model, that accounts for Fourier overtones of the membrane charge, to enable multiscale optimized simulations of multi-compartmental cells with strong intercompartmental coupling.

Up to now, simulations have been conducted on models that have homogeneous membrane dynamics and don't have a branching morphology. The goal of this study is to predict for the first time the response to ultrasonic insonication of a selection of morphologically realistic Blue Brain Project cortical pyramidal cells and interneurons chosen across different layers and morphoelectric types. The optimized model further shows how the different ultrasound parameters, such as the frequency, the pressure amplitude and the sonophore radius, have an influence on cortical neuromodulation caused by the oscillating cavitation in the membrane.



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

Topic area: mechanisms **Preferred format:** poster

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

Title: Experimentally-validated computational pipeline for ultrasonic peripheral nerve stimulation

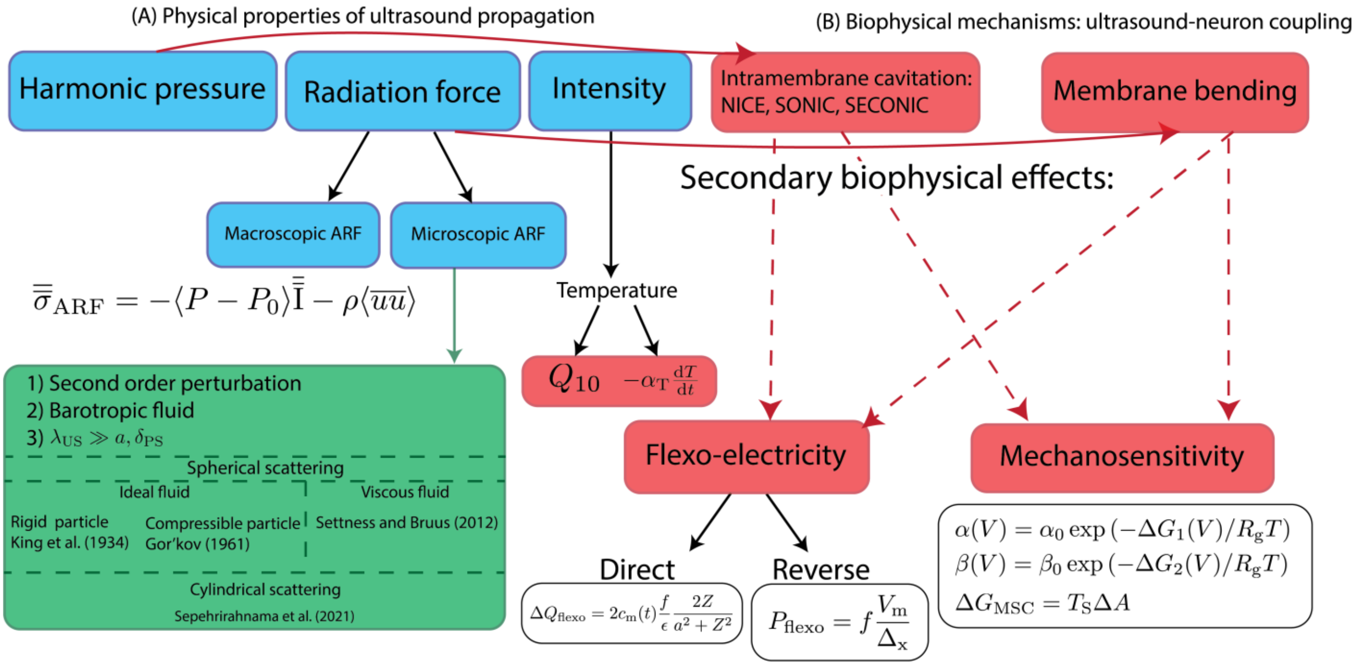
Authors: Thomas Tarnaud (1,2), Tom Plovie (1), Elena Vicari (3), Lucia Moya-Sans (4), Joaquín Gázquez Rodríguez (1), Ruben Schoeters (1,2), Pablo Benlloch Garcia (4), Esra Neufeld (4), Niels Kuster (4), Wout Joseph (1), Luc Martens (1), Silvestro Micera (3), Emmeric Tanghe (1)
(1) WAVES, Department of Information Technology, Ghent University/IMEC, 9052 Ghent, Belgium
(2) 4BRAIN, Department of Head and Skin, Ghent University, 9000 Ghent, Belgium
(3) TNE, École Polytecnique Fédérale de Lausanne, 1202, Lausanne, Switzerland
(4) Foundation for Research on Information Technologies in Society, 8004 Zurich, Switzerland

Email: thomas.tarnaud@ugent.be

Abstract:

Focused ultrasound is capable of modulating peripheral nerve activity non-invasively and with high spatial resolution. The goal of this project is to develop an open-source and experimentally validated computational pipeline, capable of predicting ultrasound-induced nerve modulation and resulting compound action potentials for a given protocol (waveform, transducer placement, and experimental set-up). The pipeline will be made available through the o2S2PARC-platform, and will be used to optimize ultrasonic protocols in silico. Furthermore, the simulations aim to improve our understanding of the underlying mechanisms of ultrasonic peripheral nerve stimulation. The pipeline starts from histological data, creates realistic and electrophysiologically functionalized nerve models, and automaticaly assigns acoustic parameters. For a given transducer placement, the pressure and displacement/velocity fields are simulated with finite difference time domain or pseudospectral methods. These fields are used to calculate the acoustic radiation force, which acts as a body force in subsequent viscoelastic and computational fluid dynamics simulations to determine the deformation and stress in the insonicated fascicles, as well as acoustic streaming in the surrounding fluid.

The obtained in-situ pressure, displacement and tension are used as input in a comprehensive computational axon dynamics model, that integrates various tentative underlying mechanisms of ultrasound-neuron coupling: i.e., membrane bending, intramembrane cavitation, thermomodulation of membrane capacity and ion channel dynamics, and flexoelectric effects. Working on a thermodynamical model of the TRAAK mechanosensitive ion channel is underway that leverages published suction clamp current data measured during insonication. This wide variety of tentative mechanisms are not only compared, but also, the potential interactions between them are investigated. The pipeline will be validated with ex vivo and in vivo experiments.



Acknowledgments: This research was funded by the FWO-projects G0A5623N and G019121N. T Tarnaud is a Postdoctoral Fellow of the FWO-V (Research Foundation Flanders, Belgium).

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

Topic area: mechanisms **Preferred format:** poster

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

Title: Elucidating the circuit mechanisms of cortical ultrasonic neuromodulation

Authors: Théo Lemaire [1], Yi Yuan [1], Amy LeMessurier [1], Junhyook Lee [1], Ben Stetler [1], Sarah R. Haiken [1], Robert C. Froemke [1], Justin P. Little [1], Shy Shoham [1]

[1] Tech4Health and Neuroscience Institutes, New York University Grossman School of Medicine, NY, USA

Email: theo.lemaire@nyulangone.org

Abstract:

Transcranial Ultrasound Stimulation (TUS) offers the unique ability to perturb brain circuits in a noninvasive, focal, and reversible manner. Yet, the mechanisms by which ultrasound interacts with heterogenous and interconnected neuronal populations to induce functional effects remain unclear. To elucidate these interactions, we applied TUS to the visual cortex of awake mice and monitored neural activity in three cortical subpopulations with two-photon calcium imaging. We show that TUS evokes focal and stereotypical population responses with cell-type-specific dose dependences. Through independent parametric variations, we demonstrate that evoked responses collectively scale with the time-average intensity of the stimulus. Finally, using a computational model we project that responses are actively modulated by local network inputs and require cell-type-specific intrinsic sensitivities to ultrasound. Our combined experimental and computational approach introduces a new framework to untangle direct vs network-mediated responses to TUS, thereby bringing crucial insight on the complex circuit mechanisms underlying ultrasonic neuromodulation and paving the way for its deployment in clinical settings.

Acknowledgments: NIH NINDS and BRAIN Initiative (grant 5R01NS109885-05), Swiss National Science Foundation (grant P500PB_211119)

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

Topic area: mechanisms **Preferred format:** poster

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

Title: Feasibility Assessment of Theta Burst Transcranial Ultrasound on Motor Cortex Function in Healthy Individuals: A Multimodal MRI Pilot Study

Authors: Maximilian Hasslberger, Theresa Faessler, Maximilian Lueckel, Berkhan Karsli, Genc Hasanaj, Kai-Yen Chang, Til Ole Bergmann, Daniel Keeser, Boris-Stephan Rauchmann

Email: max.hasslberger@tum.de

Abstract:

Introduction

Transcranial Focused Ultrasound Stimulation (TUS) offers the ability to noninvasively regulate neural activity in deep brain regions with high spatial accuracy. Despite its promise, the physiological processes through which focused ultrasound modulates brain activity remain unclear. Multimodal neuroimaging, integrating techniques such as arterial spin labeling (ASL), resting-state functional MRI (rsfMRI), and magnetic resonance spectroscopy (MRS) offers a comprehensive approach to elucidate some of the physiological effects of TUS on the motor cortex. ASL provides quantitative assessment of cerebral blood flow alterations, while rsfMRI reveals intrinsic brain connectivity changes. MRS allows for the characterization of neurochemical alterations underlying these effects.

Methods

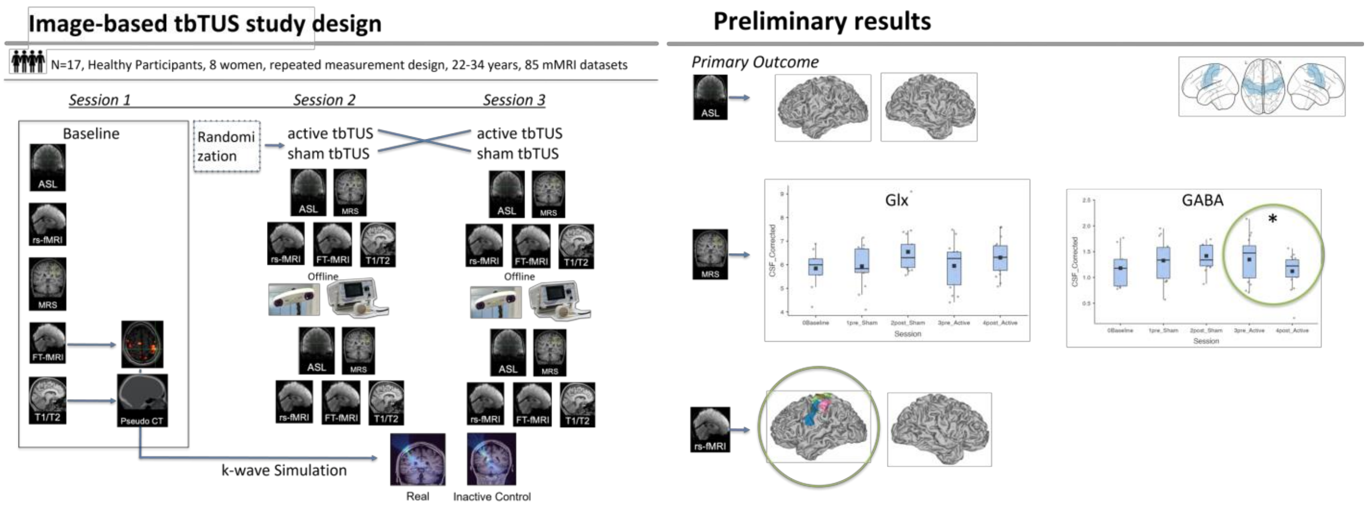
In this double-blind, sham-controlled crossover study, 17 healthy subjects (10 female, 7 male) were assessed. We utilized 80 seconds of theta burst transcranial ultrasound stimulation (tbTUS) targeted at the left human motor cortex, guided by the LOCALITE neuronavigation system. For each subject, we fixed the ultrasound transducer to one position in both active and inactive control tbTUS to yield equivalent auditory confounds. Thus, we merely adapted the focus depth and thickness of the ultrasound gel pad coupling the transducer to the skull. Furthermore, we adapted the hardware amplitude such that we yield an intracranial spatial-peak temporal average (ISPTA) below, but close to the FDA-approved limits based on individual acoustic simulations. Each subject underwent five MRI sessions to evaluate cerebral blood flow using ASL, rsfMRI, and MRS. ASL and rsfMRI analyses were conducted in a standardized atlas with selected regions of interest (ROIs): precentral gyrus (PrG), postcentral gyrus (PoG), and paracentral lobule (PCL). We measured the concentrations of glutamate + glutamine (Glx) and GABA using the Gannet MRS Toolbox.

Results

In our preliminary analysis, there were no significant effects on any ROIs for ASL. Within-seed-based analyses of rsfMRI revealed post-hoc effects of increased activated voxel for the left precentral gyrus (PrGL65, PrGL66) and postcentral gyrus (PoGL41, PoGL43) in comparison to baseline ($p<0.05$). For MRS tbTUS did not affect Glx but decreased GABA concentrations within the primary motor cortex significantly ($p<0.05$).

Conclusion

The preliminary results of this study indicate the capacity of tbTUS to modulate functional MRI connectivity and GABA concentrations, while no significant effects were observed in cerebral blood flow or glutamate levels. These findings suggest that tbTUS might selectively influence neural activity and neurochemical balance within targeted brain regions, demonstrating its potential for precisely exploring and modulating brain function.



Acknowledgments: The study is part of the MD thesis of Theresa Faessler

Conflicts of interest: -

Topic area: mechanisms **Preferred format:** poster

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

Title: Plasticity induction of theta burst transcranial ultrasound stimulation on motor cortex in Parkinson's disease – OFF and denovo PD patients.

Authors: Talyta Grippe , Yazan Shamli Oghli, Ghazaleh Darmani , Yi-Ying Lin,Tarun Arora, Can Sarica, Nasem Raies, Jean-François Nankoo, Francisco Cardoso, Robert Chen

Email: talyta.cortezgrippe@uhn.ca

Abstract:

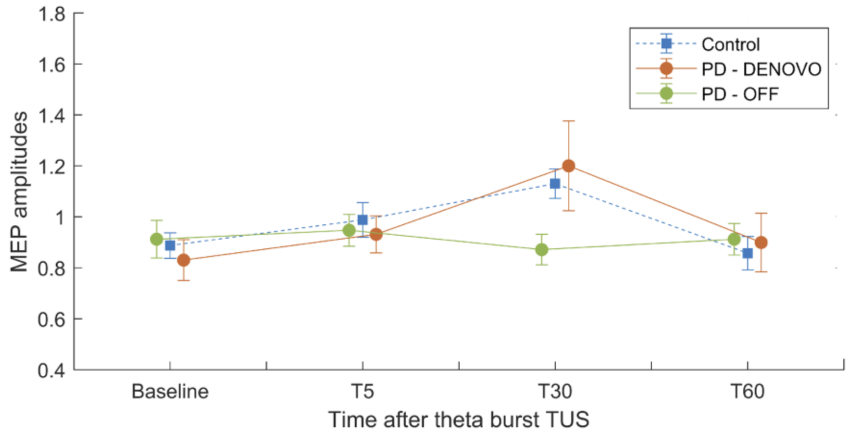
Objective
Evaluate the neurophysiological and clinical effects of low-intensity transcranial ultrasound stimulation (TUS) of motor cortex (M1) in patients with Parkinson's disease (PD) in different disease stages.

Background
TUS is a non-invasive neuromodulation technique, which in theta burst mode (tbTUS) can increase cortical excitability up to 30 minutes, likely due to LTP-plasticity, in PD patients while on dopaminergic medication, but not in the off medication state. The effects of tbTUS in denovo (untreated) PD patients is not known.

Methods
We studied 7 denovo PD patients (3F, 66.4 ± 8.7 years), 19 PD patients OFF dopaminergic medication (4F, 59.6 ± 8.2 years), and 17 controls (6F, 63.7±9.2 years). tbTUS was applied for 80 seconds at M1 at intensity of 20W/cm2. Motor evoked potential (MEP) from transcranial magnetic stimulation was recorded at baseline, at 5-minutes (T5), T30, and T60 after tbTUS. Motor (m)UPDRS was evaluated in PD at baseline and T60 and scored by two blinded raters.

Results
A linear mixed model on the squared roots of the MEP amplitudes comparing controls to PD-OFF and denovo PD showed a significant effect of time ($F=6.15$, $p<0.001$), interaction (group x time) ($F=2.49$, $p=0.026$), with no effect of group. Post-hoc analysis of time showed higher MEP amplitude at T30 compared to baseline ($p=0.001$) and at T30 compared to T60 ($p=0.002$). Post-hoc analysis showed higher MEP amplitudes at T30 compared to baseline in the control ($p=0.001$) and denovo PD groups ($p=0.002$), but not in the PD-OFF group ($P=0.524$) (Figure 1). There was a significant difference in mUPDRS bradykinesia score with lower values at T60 compared to baseline in denovo PD (Wilcoxon W, $p = 0.041$) but not in PD-OFF ($p= 0.779$). The total score and the other sub scores were not different when comparing baseline and T60 in denovo PD or PD-OFF.

Conclusion
The tbTUS induced motor cortical plasticity in older healthy controls and denovo PD patients, but not in OFF medication state. The denovo PD patients also showed mild improvement of the motor symptoms. These results highlight a similar behavior between denovo PD and PD ON medication state studied previously. Dopamine is probably necessary to mediate tbTUS plasticity in PD patients.



Acknowledgments: Enter acknowledgements

Conflicts of interest: None

Topic area: clinical **Preferred format:** Oral

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

Title: Cerebellar transcranial focused ultrasound in a patient with Spinocerebellar Ataxia 12

Authors: Sumayya Mustafa (1), Jean-François Nankoo (1), Nasem Raies (1), Amitabh Bhattacharya (1), Nika Sajadi Naeini (1), Marcus Callister (1, 2), Christopher Striemer (3, 4), Alfonso Fasano (1, 2, 5) & Robert Chen (1, 2, 5)
1 Krembil Brain Institute, University Health Network, Toronto ON, Canada
2 Edmond J Safra Program in Parkinson’s Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, University Health Network, Toronto ON, Canada
3 Department of Psychology, Macewan University, Edmonton AB, Canada
4 Neuroscience and Mental Health Institute, University of Alberta, Edmonton AB, Canada
5 Division of Neurology, University of Toronto, Toronto ON, Canada

Email: sumayya.mustafa@uhn.ca

Abstract:

Background: Spinocerebellar ataxia type 12 (SCA12) is a rare autosomal dominant neurodegenerative disorder characterized by cerebellar dysfunction, including gait ataxia, tremor, and other cerebellar signs. Neuropathological data shows cerebello-cortical degeneration with the loss of Purkinje cells in SCA12. Transcranial focused ultrasound (TUS) is a non-invasive neuromodulation technique that shows promise for use in SCA patients, as it can penetrate deep within the cerebellum to modulate the output nuclei while bypassing the dysfunctional Purkinje cell layer. However, no studies have investigated the use of TUS for neuromodulation in patients with spinocerebellar ataxia. We, therefore, present a case study assessing the safety and efficacy of TUS neuromodulation in a SCA12 patient. Specifically, we assessed the effects of theta burst TUS (tbTUS) on the dentate nuclei (DN), the primary cerebellar output nuclei projecting to the cerebral cortex.

Objective: This study assesses the safety and efficacy of transcranial focused ultrasound (TUS), a non-invasive neuromodulation technique, in modulating cerebellar output nuclei in a patient with SCA12.
Methods: We conducted a case study using theta burst TUS (tbTUS) targeting the dentate nuclei (DN), the main cerebellar output nuclei projecting to the cerebral cortex. The subject was a 62-year-old male with SCA12. We measured motor evoked potentials (MEPs) to evaluate the excitability of the cerebello-thalamo-cortical pathway. We also assessed performance on a prism adaptation task and compared clinical scores on the Scale for Assessment and Rating of Ataxia (SARA) and gait pre- and post-TUS.

Results: 5Hz DN TUS inhibited MEP, suggesting an inhibitory effect on the DN. Conversely, a 10Hz inhibitory protocol increased cortical excitability, indicating that inhibitory and excitatory protocols have opposite effects when stimulating the DN. No significant differences were observed in SARA and gait assessments pre- and post-TUS. In the prism adaptation task, bilateral DN TUS induced greater after-effects (compensation in the opposite direction) compared to unilateral stimulation and control participants.

Conclusion: TUS applied to the DN of the cerebellum can be safely and effectively used to modulate the cerebello-thalamo-cortical pathway in a SCA12 patient, influencing motor learning. These findings suggest that TUS should be further explored as a treatment modality for SCA12 and other spinocerebellar ataxias.

Acknowledgments:

Conflicts of interest: No financial or nonfinancial competing interests

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

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

Title: Exploring potential functional state dependency effects of human amygdala transcranial ultrasonic stimulation

Authors: Tim den Boer1,2 Johannes Algermissen2,3 Miruna Rascu2,3 Lilian Weber2,3 Elsa Fouragnan4,5 Miriam Klein-Flügge1,2,3

Email: tim.denboer@psych.ox.ac.uk

Abstract:

Endogenous activity in the neural circuitry targeted by transcranial focused ultrasonic stimulation (TUS) has been shown to influence its neuromodulation effects (Prieto et al., 2020). This phenomenon is known as ‘state dependency’. However, whether it is possible to change the magnitude of effects achieved with offline TUS by manipulating the functional state of the targeted brain circuit remains to be tested in humans.

In this study, we aimed to explore potential state dependency effects during sonication of the human amygdala. We assessed TUS-induced plasticity effects using a previously developed behavioral task involving social-emotional decision-making.

Participants (aim n=20, data collection ongoing) attended two TUS sessions. TUS sequentially targeted the amygdala in both hemispheres while participants viewed stimuli that either did or did not functionally engage the amygdala, respectively. The amygdala was engaged using a succession of face stimuli with negative emotional valence, which have previously been shown to significantly activate the amygdala, lasting for the duration of the sonication (80 seconds, theta-burst protocol as in Zeng et al., 2022, Yaakub et al., 2023). The control state was induced using a succession of emotionally neutral house stimuli presented for the same duration. After stimulation, participants performed a computerized cognitive task that measured social-emotional decision making, which our previous work (in prep) has shown recruits the amygdala.

We hypothesize that TUS effects observed when the unengaged amygdala is sonicated will be amplified during the functionally engaged amygdala condition. This would be supported by animal work, help us understand the biomechanisms underlying human TUS, and provide a foundation for making future clinical applications more effective.

Affiliations:
1 Department of Psychiatry, University of Oxford, Warneford Hospital, Warneford Lane, Oxford OX3 7JX, UK
2 Wellcome Centre for Integrative Neuroimaging (WIN), Centre for Functional MRI of the Brain (FMRIB), University of Oxford, Nuffield Department of Clinical Neurosciences, Level 6, West Wing, John Radcliffe Hospital, Oxford OX3 9DU, UK
3 Department of Experimental Psychology, Tinsley Building, Mansfield Road, Oxford OX1 3TA, University of Oxford, UK
4 Brain Research & Imaging Centre, Faculty of Health, University of Plymouth, Plymouth PL4 8BU, UK
5 School of Psychology, Faculty of Health, University of Plymouth, Plymouth PL4 8AA, UK

References:

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Acknowledgments: -

Conflicts of interest: -

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

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

Title: Simulation study of acoustic and electric field modes of action in transcranial magnetoacoustic stimulation for Parkinson's disease

Authors: Yanqiu Zhang (Tianjin medical university), Hao Zhang (Tianjin University), Tainya Xu (Tianjin medical university), Jiahe Liu (Tianjin medical university), Jiayang Mu (Tianjin medical university),Haixin Guo (Tianjin medical university), Xiqi Jian (Tianjin medical university)

Email: zhangyanqiu@tmu.edu.cn

Abstract:

Background: Parkinson's disease (PD) is a common degenerative neurological disorder in elderly people. Pathological enhancement of β-oscillations in the basal ganglia-thalamic (BG-Th) neural circuitry results in bradykinesia in PD patients. The subthalamic nucleus (STN) and the globus pallidus internal segment (GPi), which are located in the deep part of the brain, are the main target areas for clinical stimulation. Transcranial magnetoacoustic stimulation (TMAS) is a new therapeutic technique that utilizes the induced current generated by the coupling of the acoustic pressure field produced by transcranial focused ultrasound (TUS) and the static magnetic field to excite or inhibit neurons in the target area. This technology has the advantages of being non-invasive, high spatial and temporal resolution, and can be used for deep brain stimulation therapy for PD. Objective: To investigate the modulation methods of acoustic pressure field, static magnetic field and coupled electric field and their interaction modes during TMAS treatment of PD. Methods: A 3D digital skull was reconstructed based on the head CT reconstruction results of a 67-year-old male PD volunteer. Combining the structural parameters of the self-developed 128-array spherical coronal phased-array transducer with an inner surface radius of curvature of 90 mm and an opening diameter of 112 mm, the TMAS PD simulation model with the STN and GPi as the target points was established (Fig. 1 (a)), and the positions of the targets were determined based on the CT and MRI alignment maps (Fig. 1 (b)-(c)).The PD BG-Th neural network model containing STN and GPi neural nuclei clusters was constructed based on the Hodgkin-Huxle model, the Izhikevich model (Fig.1 (d)). The neuron models were stimulated using the acoustic pressure field and induced electric field of TMAS. And the mechanism of acoustic and induced electric field action in TMAS was evaluated by the neuronal discharge frequency, membrane potential amplitude and the amplitude of pathological β-oscillations of BG-Th neural network. Results: Fig.2 (a)-(d) show the transcranial focused acoustic pressure field, local magnification of acoustic pressure field, static magnetic field and induced electric field distribution, Fig.2 (e) shows the pathologic β -oscillation amplitude of each neuronal nucleus in the BG-Th neural network model after single-target and dual-target stimulation, and Fig.2 (f) shows the effects of ultrasound and induced electric and co-stimulation on the membrane potential of neuron. From Fig.2, it can be seen that TMAS can realize transcranial precise localization stimulation; TMAS-STN can simultaneously inhibit the β-band amplitude of GPi nuclei, while TMAS-GPi can not simultaneously inhibit STN. TMAS-STN&GPi can further reduce the amplitude of pathologic beta oscillations. Lower sound pressure ultrasound does not affect the firing state of neurons, but higher sound pressure ultrasound may promote or inhibit the stimulatory effect of induced currents. Conclusions: TMAS multinuclear stimulation with appropriate ultrasound intensity was the most effective in suppressing the amplitude of pathological β oscillations in PD.
Keywords: Transcranial magnetoacoustic stimulation, parkinson's disease, transcranial focused ultrasound

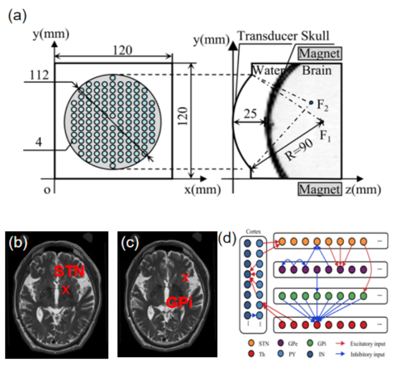


Fig. 1 Multi-physics field simulation model and neural network model.

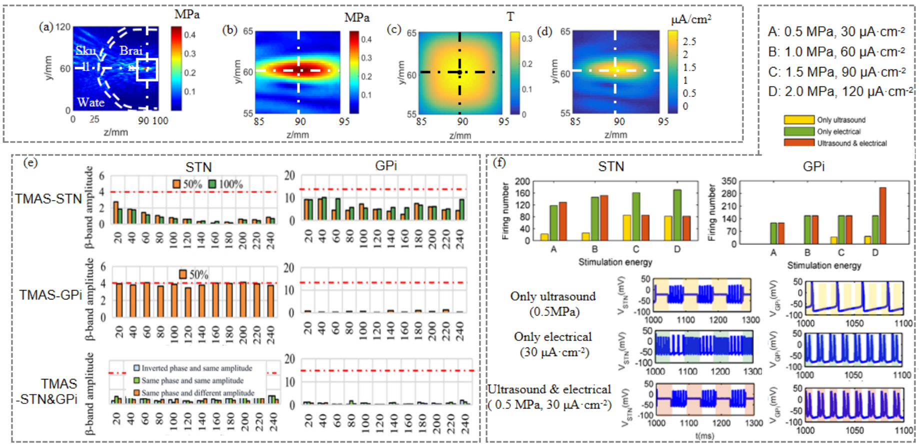


Fig.2 Numerical simulation results based on multiphysics field numerical simulation model and neural network.

Acknowledgments: This work was partially funded by the National Natural Science Foundation of China (Grant No. 81272495 and No. 82272125), the Natural Science Foundation of Tianjin (Grant No. 16JC2DJC32200).

Conflicts of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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

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

Title: Robot-navigated transcranial ultrasonic stimulation of the human basal forebrain and simultaneous electroencephalography

Authors: Maximilian Lueckel [1,2], Saman Seifpour [1,2], Dorina Laurila-Epe [1], Jennifer Weinberg [1], 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 basal forebrain (BF) is a major cholinergic source region of the brain that is involved in different cognitive processes and affected in aging-related neurodegenerative diseases like Alzheimer's. Given its small size and deep location in the brain, the BF is a well-suited target for transcranial ultrasonic stimulation (TUS). However, to provide proof of successful BF stimulation, TUS needs to be combined with readouts of neuronal activity. Here, we thus aimed to develop an experimental setup that combines TUS with simultaneous electroencephalography (TUS-EEG), hypothesizing that TUS-induced increases in cholinergic BF signaling would lead to a widespread desynchronization of cortical neuronal activity, reflected in reduced EEG alpha activity.

Methods: Using a modified 64-channel EEG cap that had electrodes and fabric removed over the temporal window to make space for the TUS transducer, we tested different solutions for (1) holding the transducer in place (manual vs. custom-designed, 3D-printed holders vs. robotic arm), (2) coupling (gel pads vs. silicone pads), and (3) mitigation of auditory confounds (auditory masking vs. pulse ramping). TUS transducer placement and targeting were individually planned and monitored using MRI scans as well as acoustic simulations and neuronavigation, respectively. To test both acute ("online") and prolonged ("offline") effects of TUS, all experimental piloting sessions consisted of two resting-state EEG (rsEEG) runs, interleaved by a simultaneous TUS-EEG run. Offline TUS effects were analyzed as changes in the (alpha) frequency content of the post- vs. pre-TUS rsEEG. Online TUS effects were examined using a time-frequency analysis of the TUS-EEG data.

Results: The modified EEG cap allowed proper placement and coupling of the TUS transducer over the temporal window. While fixating the transducer manually or using 3D-printed holders was suboptimal, robot-navigated transducer placement allowed for a high level of stability and precision across the entire duration of the experimental session (~30 min). Custom-molded silicone pads proved practically superior to gel pads for transducer coupling, and auditory confounds could be effectively reduced using a stimulation protocol with ramped pulses. For offline TUS effects, we found a reduction in posterior alpha power and an increase in fronto-central theta power, while for online TUS effects, we observed difficult to interpret bursts across several frequency bands.

Conclusion & Outlook: In conclusion, we developed a functioning experimental setup for simultaneous BF-targeted TUS and EEG acquisitions. However, the preliminary pilot data needs to be interpreted with caution. Future extensions of this setup will also include stimulation of an active control site (e.g., insula) as well as pupil size and heart rate measurements (as additional indicators of cholinergic tone).

Acknowledgments: -

Conflicts of interest: -

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

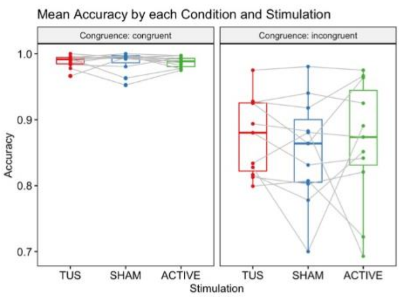
☒ Are you an early career researcher? (trainee, student, post-doc, etc)

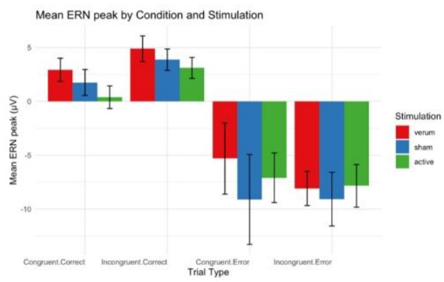
Title:	*Monitoring errors under the influence of transcranial ultrasound stimulation: Behavioural and electrophysiological correlates in humans*

Authors:	*Camila S. Agostino1, Izel Avci1, Markus Ullsperger1,* *1 Otto-von-Guericke Universität, Magdeburg, Germany*
Email:	*camila.agostino@ovgu.de*

Abstract:

Performance monitoring is critical for survival, as it allows individuals to adapt their behaviour in response to environmental demands. A key component of performance monitoring is error monitoring, which is essential for cognitive control. In this study, we investigate the effects of transcranial ultrasound stimulation (TUS) on error monitoring processes. Eleven participants (age:26.6, ±3.1, one female) joined four sessions in which they performed a flanker task. In the first session, functional MRI (fMRI) was used to functionally localise the individual anterior midcingulate cortex (aMCC). In the subsequent three sessions, participants received, bilaterally, either verum TUS over the aMCC, sham, or verum TUS over the posterior cingulate cortex (PCC), chosen as an active control region. We used a fundamental frequency of 250kHz (4 element transducer) in a 5 Hz protocol (SD: 120s; 1/PRF: 0.2s; PD: 0.03s ramp) with ISPPA of 30W/cm^2, ISPTA 4.5W/cm^2. Simulations were performed to determine the individual focus and to ensure that the applied intensity was within safety limits. Neural activity was monitored by EEG approximately 16 minutes after the stimulation (a reduced set-up of 16 electrodes from an equidistant EEG cap (Easycap) was used). For the behavioural analysis, we adopted a linear mixed model to investigate the effect of congruence (congruent vs. incongruent) and stimulation (verum, sham and active control) on performance accuracy and reaction time (RT). In the latter case, we included also correctness (error vs. correct) as a fixed factor. To account for individual variability, we included subject as a random effect in both models. For the preliminary EEG analysis, response-locked epochs were extracted and the interval 250 to 150 ms prior to response onset was used as baseline. Thereafter, we compared the peak amplitude of the ERN (0-100ms time window) at FCz channel between all congruent and incongruent correct and incorrect trials for the three different stimulations conditions; using a repeated measures ANOVA. The accuracy model results revealed significant main effects of congruence (F(2, 22386)=1311.53, p<0.001), stimulation (F(2, 22386)=3.51, p=0.03) and a significant interaction between both factors (F(2, 22386)=3.62, p=0.027). Post hoc comparisons showed that in the incongruent conditions, accuracy was significantly lower in the sham condition compared to both verum (t=-3.684, p=0.0007) and active control (t=-2.544, p=0.033) conditions (left figure). For RT, main effect of congruence (F(2, 22386)=5287.45, p<0.001), stimulation (F(2, 22386)=7.27, p<0.001) and correctness (F(2, 22386)=2492.97, p<0.001) were observed. Additionally, results indicated a marginally significant interaction between correctness and stimulation (F(1, 22386)=2.42, p=0.088), with error differences between verum and active in the congruent condition (t=-5.40, p<0.0001) and in the incongruent condition (t=-3.08, p=0.03). Our preliminary EEG results (right figure) revealed only a significant main effect of correctness (F(1, 20.887), p=0.003), indicating that the peak ERN amplitude differed significantly between correct and incorrect trials, as expected. Further single-trial regression analysis will be performed in order to obtain more conclusive results. In summary, our preliminary results suggest that TUS in both aMCC and PCC might influence accuracy during an interference task and the peak ERN amplitude in FCz was primarily influenced by the correctness of the trial, rather than the stimulation or congruence.





Acknowledgments:	*This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement No 101018805)*

Conflicts of interest:	*We declare no conflict of interest*		
Topic area:	*Cognitive Control, Brain Stimulation*	**Preferred format:**	*Poster presentation*

☐ Are you an early career researcher? Post-doc.

Title: Mapping the brain circuit of pain modulation with transcranial ultrasound stimulation (TUS)

Authors: Dr Sophie Clarke [1,2], Samuel Mugglestone [1], Dr Sam Hughes [2], Dr Elsa Fouragnan [1]
1. University of Plymouth, 2. University of Exeter

Email: Sophie.clarke@plymouth.ac.uk

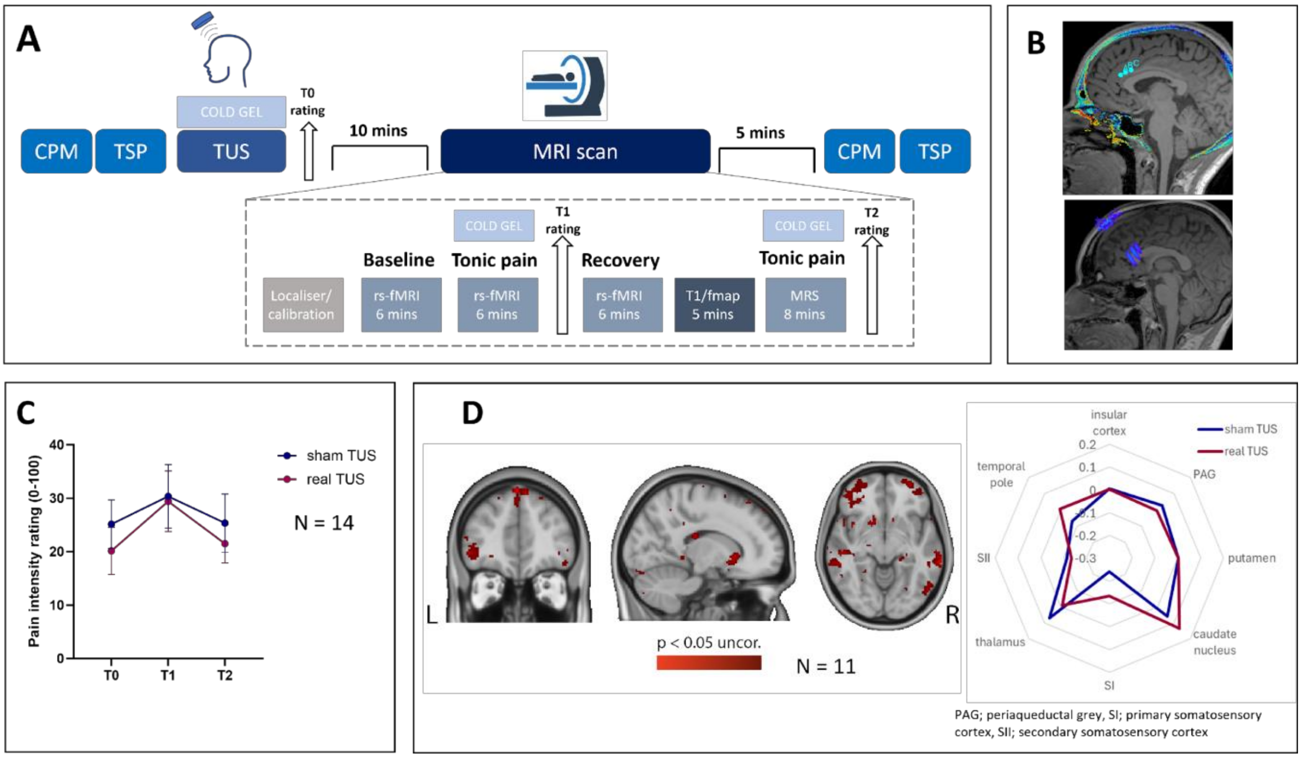
Abstract:

Background: The dorsal anterior cingulate cortex (dACC) integrates sensory input from ascending pain pathways and modulates pain perception through descending pathways, influencing both the perception of pain intensity and the emotional response to pain. This study aims to investigate the effects of TUS of the dACC; a) on functional connectivity between pain-related brain regions during a tonic cold pain stiumulus using functional magnetic resonance imaging (fMRI), and b) on conditioned pain modulation (CPM) and temporal summation of pain (TSP) paradigms. Overall it aims to further our understanding of the role of the dACC in pain modulation.

Methods: Healthy participants attended 3 sessions; one to acquire T1-weighted, T2-weighted and PETRA images for acoustic simulations, followed by two main TUS-fMRI sessions with either TUS or sham (double-blind, randomised). Study protocol is shown in fig.A; first pre-TUS CPM and TSP assessments are conducted using cuff-algometry, then TUS is applied to the dACC, followed by the MRI scan, and post-TUS CPM and TSP assessments. TUS was applied to three sites in the dACC consecutively (fig.B) with the following protocol; ff=500kHz, prf=10Hz, DC=10%, ISPPA in water=54w/cm2, duration=80s. Tonic pain was induced using a modified cold pressor test with gelled water (temp range: 3.8+/-2.3oC).

Results: Interim analysis has been conducted (N=14, N=11 for rs-fMRI). For pain ratings provided during tonic cold (fig.C), we found no significant main effect of condition (real/sham-TUS), $F(1, 66) = 2.108$, $p=0.1513$, but did find significant effects of gel temperature and subject, $F(1, 66) = 6.775$, $p=0.0114$ and $F(13, 66) = 5.791$, $p<0.0001$, respectively. Seed-based functional connectivity analysis (fig.D) showed altered connectivity between the dACC (seed region) and pain related brain regions, increasing with the caudate nucleus, primary somatosensory cortex and temporal pole, and decreasing with the PAG and thalamus, following real-TUS compared to sham-TUS. Analysis of CPM/TSP data and further imaging data, and data collection, is ongoing.

Discussion: This interim analysis shows TUS of the dACC has resulted in altered functional connectivity in brain regions associated with pain perception. As additional datasets are included, analysis from this ongoing study will provide further insights into modulation of the neural correlates of pain processing by TUS, enhancing our understanding of the role of the dACC in pain perception and modulation. Overall, the study will provide insight into the potential of TUS as an analgesic strategy for chronic pain.



Acknowledgments: None

Conflicts of interest: None

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

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

Title: Temporal patterning effects of low-intensity focused ultrasound (LIFU) for human neuromodulation

Authors: Andrew Strohman, Gabriel Issac, Yunruo Ni, Wynn Legon

Email: andrewstrohman@vt.edu

Abstract:

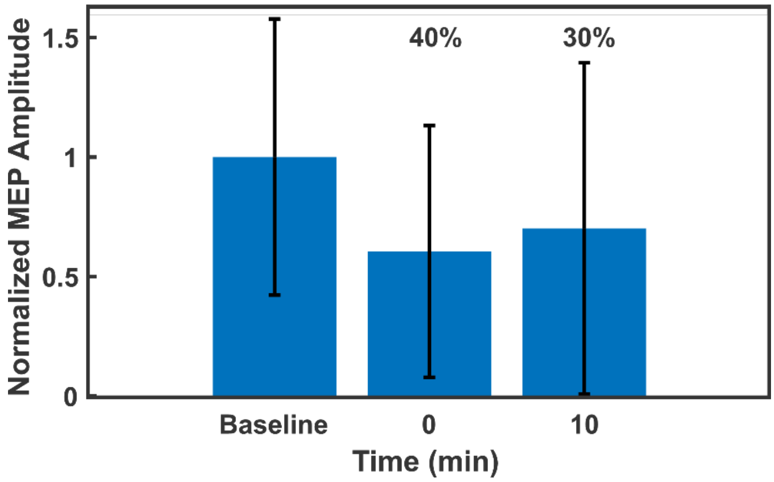
Background. While a large number of studies have been conducted in humans, the parameters used to deliver low-intensity focused ultrasound (LIFU) are variable and there is no current consensus on what LIFU parameters lead to robust excitatory or inhibitory effects that last long enough to be considered clinically meaningful.

Methods. We stereotaxically targeted LIFU to the left primary motor cortex (M1) at the right first dorsal interosseous (FDI) muscle hotspot identified using single-pulse transcranial magnetic stimulation (TMS) on four separate days in a pre/post design. Single-pulse TMS was then used to elicit 20 motor-evoked potentials (MEPs) at an average baseline peak-to-peak amplitude of 1 millivolt from the right FDI muscle before and after LIFU application. Each day consisted of a different parameter set, matched on the total time of active LIFU (8 seconds) and intracranial intensity (5 W/cm2 Isppa), plus an inactive sham. The parameters included: theta burst transcranial ultrasonic stimulation ("tbTUS") based on prior literature (10% duty cycle (DC), 5 Hz pulse repetition frequency (PRF), 80 sec duration), a "standard LIFU" stimulation pattern (5% DC, 50 Hz PRF, 160 sec duration), and a "novel pattern" of LIFU stimulation consisting of a different distribution of pulses over time. Continuous auditory masking was applied across all conditions to mask the participant. MEPs were measured at baseline and at 0 and 10 minutes post LIFU or Sham application. Data are reported normalized to the pre-LIFU baseline.

Results. Preliminary results (N=3) demonstrate the novel pattern of LIFU led to reductions in normalized MEP amplitudes of 40% and 30% compared to baseline at 0 and 10 minutes post LIFU, respectively. Continued work will directly compare tbTUS, standard LIFU, and the novel pattern with Sham in 16 subjects for an extended time window at 0, 15, 30, 45, and 60 minutes post LIFU.

Conclusions. Our findings point to the importance of how LIFU is delivered with regards to the temporal patterning of energy across time while holding the total amount of energy constant. These results have implications for future studies on the identification of long-lasting, robust LIFU parameters that could translate to clinical therapeutic applications.

Figure Caption. Group (N=3) mean +/- SEM normalized MEP amplitudes at baseline (pre LIFU) and at 0 and 10 minutes post LIFU for the novel LIFU pattern only. X-axis is time and y-axis is normalized MEP amplitudes. Percentages represent the percent reductions compared to baseline.



Acknowledgments: Thank you to Jessica Florig and Brighton Payne for assistance with data collection.

Conflicts of interest: No conflicts of interest

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

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

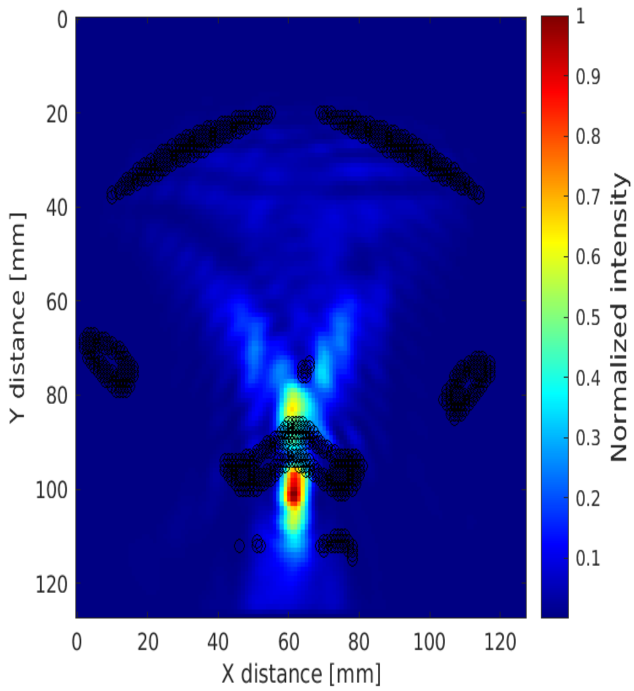
Title: Desing and developement of a FUS device for the stimulation of the spinal cord

Authors: Agustin Conesa-Celdran, Jordi Garcia-Ojalvo, Pablo Villoslada.

Email: agustinfernando.conesa@upf.edu, jordi.g.ojalvo@upf.edu, pvilloslada@researchmar.net

Abstract:

Focused Ultrasounds (FUS) is a promising technology for treating the Central Nervous System. FUS can be also applied to the spinal cord as part of the CNS to adress spinal cord injuries, chronic pain syndromes, and slow degenerative diseases progression through low intensity neuromodulation paradigms. This work is focused on the design and developement of a FUS device optimized to target the spinal cord, and an adaptable therapy pipeline. By conducting ultrasound simulations using k-Wave software, we have studied the performance of our designs on a variety of scenarios, and over several parameter ranges to asses the characteristics of the beamform, bone penetration capabilities, security limits, and optimized thus the device desing. The FUS device is based on a double concave transducer approach, adapted to be placed on the back of the patient, each containing 32 elements with a fundamental frequency of 250-350-kHz. The transducer curvature radii can be oriented to target the interior of the spinal canal, and the beams of each intersect inside it, improving the spatial resolution. We have chosen a transvertebral approach to deliver the beam into the spinal canal trought the two laminae to ensure lower variability due to spine changes with aging compared woth other approaches (e.g. inter-spinous protuberance or through the conjunction whole of the vertebrates). We modelled FUS stimulation of the spinal cord within the following ranges: ISPTA: 0.1-1 W/cm2; maximum pressures: 0.1-1MPa; and MI<1.9. By applying aberration correction techniques based on simulating backward US propagation, we obtained adequate bone penetration and focusing capabilities. This approach avoids several drawback from intervertebral trageting shuch as shadowing of the beam, and is more robust to off target displacements. To overcome the limitations of state-of-the-art technologies regarding the correct, robust and efficient positioning of the devices with respect to the patients anatomy, we designed an adjustable stretcher. The strecher allows keeping the patient's position fixed with respect to the spinal region treatment and the device, a crucial step considering the significant variability that can occur due to factors like vertebral rotations or lateral tilts. In summary, our integrated approach, combining multi-array FUS, optimized stimulation parameters ontroling for bone aberrations, and patient positioning solutions, holds promise for advancing spinal cord treatment and improving outcomes for individuals with neurological disorders.



Acknowledgments: Grant from Pompeu Fabra University: 2022 UPF INNOValora programme

Conflicts of interest: PV has received consultancy fees and hold stocks or stock-options from Bionure, Accure Therapeutics, Adhera Health, Attune Neurosciences, QMENTA, CLight, Nimbus Therapeutics, Clarity Thecnologies, NeuroPrex, Oculis, Stimusil and Spiral Therapeutics

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

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

Title:

Development of a Wearable Ultrasonic Auricular Vagus Nerve Stimulator

Authors: Stanley Stephenson, Andrew Slegaitis, Jon Hacker

Email: hacker@neurgear.com

Abstract:

This paper discusses the design and development of a wearable and portable ultrasound auricular nerve stimulator. The device is in the form of a headset that presses against the Cymba Concha depression in the ear and stimulates the auricular vagus nerve with ultrasound energy. This paper reviews the development, design, and material structures for such a system, including the characterization of the working prototypes. The devices are being supplied to various organizations and universities for clinical trials in which effectiveness will be assessed. The device is light, compact, and an effective neurostimulator to induce calm. To the best of the author's knowledge the device is the first fully-built ultrasonic auricular nerve stimulator in the world.

paper can be found on IEEE: https://ieeexplore.ieee.org/document/10363217

Acknowledgments: We would like to thank Dr. Izzy Kohler for her efforts as the CSO of NeurGear and validating our approach. Further, wewould like to acknowledge the contribution of Kyle Legg todeveloping and refining this circuit. Further, we would like to thank Dana Wolcott, Project Advisor of the Simone Center forInnovation at Rochester Institute of Technology, for hismentorship of this startup. Additionally, we would like to thank Dr. Marcus Kaiser at the University of Nottingham for his continuing work in characterizing test devices and advising the work. Last but not least, we would like to acknowledge Sterling Cooley of VagusHub and Berkley Ultrasound for his guidance andassistance.

Conflicts of interest: Work funded by NeurGear, Jon Hacker is NeurGear’s CEO, Stanley Stephenson is NeurGear’s CTO, and Andrew Slegaitis is NeurGear’s COO.

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

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

Title: **Report on improvements to BabelBrain planning software for Transcranial Ultrasound Stimulation experimentation: The first year and half experience.**

Authors: Samuel Pichardo 1,2, Alan Coreas 1,2, Bruce Pike 1,2
1 – Cumming School of Medicine, Radiology, University of Calgary
2 – Hotchkiss Brain Institute

Email: samuel.pichardo@ucalgary.ca

Abstract:

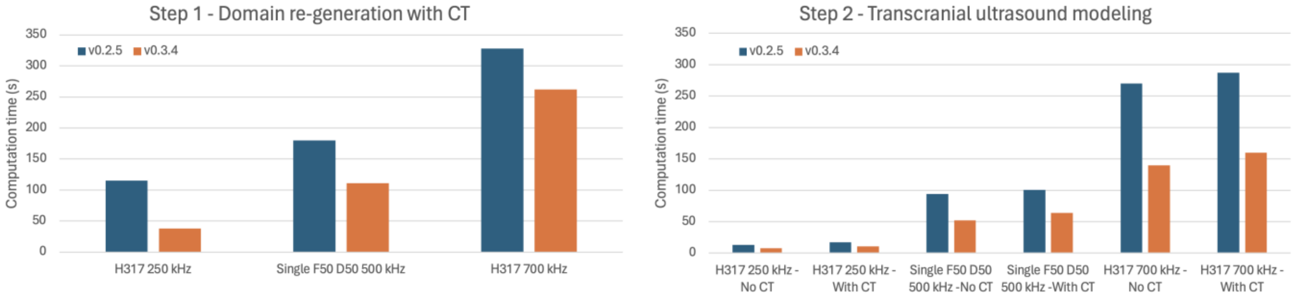
Background. The tool BabelBrain for planning Transcranial Ultrasound Stimulation (TUS) experimentation was released as an open-source project in January 2023. To the best of our knowledge, this tool is being utilized at least in a dozen studies in multiple centers to perform prospective planning and retrospective analysis of human TUS experiments. The tool's operation consists primarily of three steps: 1) creating a simulation domain, 2) simulating transcranial ultrasound, and 3) simulating thermal effects and losses introduced by the skull bone. This communication summarizes some of the most important improvements to the tool since its initial release.

Methods. The development of new features for the BabelBrain tool has been primarily driven by user feedback, both internal and external to our group. This feedback has been instrumental in shaping the tool's evolution, leading to the implementation of additions and corrections to GPU processing, as well as more efficient handling of intermediate files. The modelling of acoustic sources in the tool has also undergone significant revamping to enhance the speed of calculations in step 2.

Results. Nine releases have been published since the initial publication. The accumulated changes to the current version of the tool (v0.3.4) include four new transducers (three of them phased arrays) for a total of eight. The tool can now fully integrate with the neuronavigation software Brainsight (v2.5.3, Rogue Research). Computational costs in reprocessing domains with computed tomography input in Step 1 were reduced by around 20 to 80%. The modelling of acoustic sources was improved, translating into a reduction of computational costs in Step 2 by around 33 to 48%. Export of thermal simulation results in Nifti format was added. Examples of batch processing were added. Multiple usability improvements in the graphic user interface were implemented.

Conclusions. BabelBrain has greatly improved thanks to user feedback. External users' testimonials highlight the ease of use, good documentation, and speed of calculations. This tool will continue to be improved in the future, with the continuous mission of supporting researchers from different disciplines in the planning of their TUS experiments.

Figure caption: Representative examples of computing performance when reprocessing CT input data and in calculations of transcranial ultrasound modelling before and after the latest release (0.3.4) of BabelBrain. Tests were performed with a phased array (H317, Sonicconcepts) operating at 250 and 700 kHz and a single-element transducer with a focal and diameter of 50 mm operating at 500 kHz. The target location was 25 mm from the scalp surface through the parietal bone.



Acknowledgments: Canada Foundation for Innovation, NSERC, INOVAIT, Cumming School of Medicine Fund.

Conflicts of interest: None

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

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

Title: The effect of skull porous microstructure on ultrasonic attenuation

Authors: Fei Shen 1,2, Elly Martin 1, Bradley Treeby 1
1 Department of Medical Physics and Biomedical Engineering, University College London, United Kingdom; 2 School of Biological Science and Medical Engineering, Beihang University, China

Email: fei.shen@ucl.ac.uk

Abstract:

Background: Transcranial ultrasound has emerged as a promising modality of neuromodulation for brain disorders. While the advancements in aberration correction techniques promote safe delivery of ultrasonic energy, treatment effects vary among individuals because of natural differences in skull properties. Many application scenarios can benefit from better fundamental understanding of the mechanisms of interaction between skull and ultrasound. This work aims to investigate the influence of skull porous microstructure on ultrasonic attenuation.
Method: Skull-mimicking simulation models were generated using a finite element method framework with a typical three-layer structure, where spherical pores of red marrow were randomly distributed in the middle layer representing the diploë (Fig. 1). The acoustic properties of skull and pores were defined respectively as cortical bone and water. Sound absorption in the skull was set to zero, so the only factor contributing to attenuation was scattering from the porous microstructure. A plane wave was propagated across the bone in the direction perpendicular to the layered structure. In all simulations, both ends of the skull in the direction of wave propagation were configured with a perfectly matched layer to eliminate reflection. The other four surfaces of the skull were assumed to be periodic to avoid boundary effects. The attenuation was calculated from the pressure and particle velocity recorded at the bottom surface of the skull. The dependence of attenuation on porosity, pore size, and thickness of diploë was investigated.
Results: The relationship between attenuation and porosity varies with ultrasound frequency. For a given pore size and diploe thickness, at lower frequencies, attenuation increases with average porosity with a power law dependence. At higher frequencies, this dependence holds only at low average porosity, beyond which the dependence becomes irregular (Fig. 2). In general at a given frequency, attenuation coefficient increases with pore size, but this relationship is less well defined as average porosity increases above 5% (Fig 3). For a given pore size and high porosity, the relationship between frequency and attenuation exhibits a minimum spanning a range of a few hundred kHz in the mid kHz frequency range. The central position of this minimum shifts to higher frequencies as the thickness of the diploe is reduced (Fig. 4).
Discussion: Ultrasound attenuation caused by the skull trabeculae is heavily dependent on the microstructure of the pores. The overall relationships between attenuation and porosity, pore size, and thickness of trabecular bone appear complex, but suggest that attenuation due to scattering within skull bone is highly dependent on skull internal structure. Further investigation will improve understanding of the mechanisms of attenuation of ultrasound in skull bone and may lead to new techniques for mapping of skull attenuation coefficients from structural images of the skull.

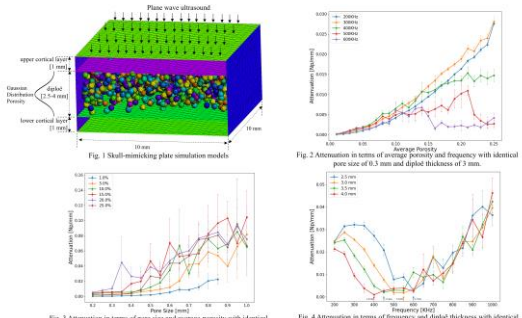


Fig. 1 Skull-mimicking plate simulation models
Fig. 2 Attenuation in terms of average porosity and frequency with identical pore size of 0.3 mm and diploë thickness of 3 mm.
Fig. 3 Attenuation in terms of pore size and average porosity with identical ultrasound frequency of 500KHz and diploë thickness of 3 mm.
Fig. 4 Attenuation in terms of frequency and diploë thickness with identical pore size of 0.3 mm and average porosity of 25%.

Acknowledgments: The research is supported by international joint doctoral education fund of Beihang University.

Conflicts of interest: No conflict of interest statement

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

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

Title: Computational investigation of impact of gyral geometry on low-intensity transcranial focused ultrasound neuromodulation for a standardized target in the left dorsolateral prefrontal cortex

Authors: Parsa Tadayon 1,2, Annika MacKenzie 2, Elizabeth Gregory 2, Hengameh Marzbani 1,2, Samuel Pichardo 3, Fidel Vila-Rodriguez 1,2,4

1.School of Biomedical Engineering, Faculty of Applied Science, Faculty of Medicine, University of British Columbia. 2.Department of Psychiatry, Faculty of Medicine, University of British Columbia. 3.Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary. 4.Djavad Mowafaghian Centre for Brain Health, University of British Columbia.

Email: parsatad@student.ubc.ca

Abstract:

Research Objectives:
There are limited studies with the purpose of quantifying the precision of LIFU for cortical targets, and the challenges of such a focal technique to aim at complex geometric structures such as the cerebral cortex. Our objective was to address this gap by investigating the impact of gyral geometry on the energy distribution of LIFU for a standardized target within the left dorsolateral prefrontal cortex.

Methods:
20 individualized head models were created from T1w and T2w MRI using the charm pipeline in SimNIBS software. Cortical parcellation was performed using FreeSurfer software. Standardized target coordinates in the DLPFC were identified using ANTs software. Acoustic fields were calculated using BabelBrain simulation software. The volumetric measurements were taken for left middle frontal gyrus and sulcus and LIFU beam at 3 different thresholds of above-30%, -50% and -70% of the maximum acoustic intensity.

Results:
A mean of 29.3%, 38.1% and 46.2% of the LIFU beam is delivered to middle frontal gyrus at 3 different thresholds of above-30%, -50% and -70% of peak acoustic intensity respectively. For middle frontal sulcus, a mean of 13.2%, 10.4% and 7.6% was delivered at the same thresholds respectively. A mean of 0.86%, 0.47% and 0.20% of the middle frontal gyrus was targeted by the LIFU beam at 3 different thresholds of above-30%, -50% and -70% of peak respectively. Meanwhile, a mean of 2.33%, 0.79% and 0.22% of the middle frontal sulcus was targeted by the LIFU beam at same thresholds respectively.

Conclusions:
The results demonstrate that LIFU is capable of focalizing energy to a precise target. Furthermore, the results showcase the capability of LIFU to stimulate specific cortical regions with high accuracy. There is a high level of variability in results between different subjects which can be attributed to individual differences in the neuroanatomy of the cerebral cortex, particularly the gyral geometry.

Acknowledgments: Enter acknowledgements

Conflicts of interest: Enter disclosures or conflicts of interest

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

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

Title: Refocusing ultrasound with skull-specific properties for Transcranial Focused Ultrasound Neurostimulation

Authors: Shirshak Shrestha; Samuel Pichardo

Email: shirshak.shrestha@ucalgary.ca

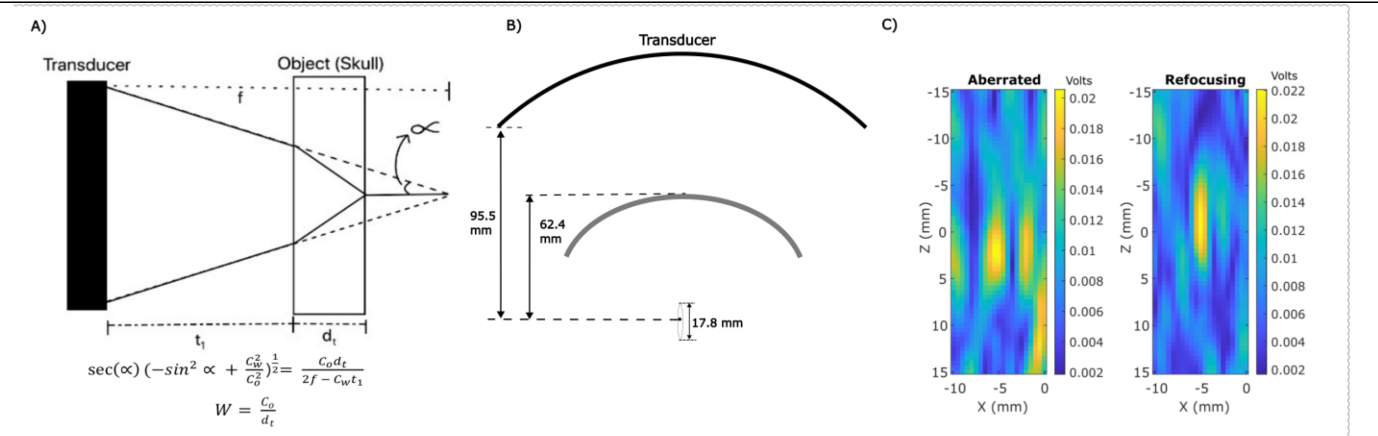
Abstract:

Background and objective: Transcranial Focused Ultrasound Neurostimulation (TUS) has shown its capabilities in inducing transient and reversible modulation of brain activity in humans (Tufail et al., 2010; Cain et al., 2021). Skull aberration correction has been identified as a significant step when targeting deeper subcortical structures of the brain with high precision. The current method for the aberration correction, used in ablative surgeries, makes use of computed tomography (CT) and empirical data to estimate the skull properties which are simulated, and a correction applied with phased-array transducers (Hynynen et al., 2006; Elias et al., 2013). This method uses generalization formulas to map CT data to acoustic properties, limiting the potential true skull bone acoustic properties of a subject. Furthermore, neurostimulation studies involving healthy volunteers often have limited access to CT data, forcing to use constant values of the acoustic properties. Here, we demonstrate a method of imaging the skull using ultrasound to obtain the necessary participant-specific skull properties which is used for correcting the aberrations.

Methods: Two human calvaria (Univ. of Calgary Anatomy lab) were imaged using 1-MHz, 32-element linear array (IP-111; SonicConcepts) to validate the new imaging method by focusing on the inner surface of the skull to estimate the acoustic characteristics (Wydra et al., 2013). The transducer and the skull, attached to a 3-axis rotational frame, was placed in an acoustic tank (UMS3; Precision Acoustics) filled with deionized (<2µS) and degassed (<5ppm) water. The skull was rotated to have surface orthogonal to transducer. The transducer was moved 18 mm away from the skull to ensure minimize the losses and the US reflections at the transducer's surface. Ultrasound (US) was focused 5 mm within the skull (starting at 23 mm) while the input voltage and time gain control were adjusted for greater than 2 dB gain between echo of the further signal and closer surface. US focus was electronically traversed further away from the transducer (ending at 48 mm). An algorithm was developed in python to identify the focus distance where the US was focused at the inner surface of the skull, indicated by a highest echo observed. The skull characteristics (speed of sound and thickness) was estimated using transducer aperture, the focus distance and time of flight of echoes from the two skull surfaces described in figure A. The transducer was driven using Vantage system (Verasonics). The estimations were compared to thickness and speed of sound calculated using CT and needle hydrophone (SN: 2869; Precision Acoustics) measurements.
The skull speed of sound was used with the TUS planning software BabelBrain (Pichardo, 2023) to simulate the ultrasound propagation passing through the skull. The phases differences calculated with the software was applied with 128-element spherical phased array (H-317; SonicConcepts) operating at 825 kHz to refocus the ultrasound to the target. Acoustic maps with and without the refocusing were obtained using the needle hydrophone to validate the new method using the setup described in the provided figure B. The hydrophone measurements were obtained in the acoustic tank with degassed and deionized water.

Results: The errors for the skull speed of sound were calculated to be -157 m/s and 375 m/s for each skull respectively while thickness was calculated to be -0.6 mm and -0.22 mm. The acoustic maps showing the uncorrected and refocused acoustic fields can be found in the figure C. Plots of refocusing indicate that the measured ultrasound speed of sound is sufficient to ensure correct refocusing of ultrasound.

Conclusions: The new method of estimating the skull properties can be effectively applied with existing ultrasound simulations to calculate the phase differences required for refocusing. This method can allow for improvements in precise targeting of the ultrasound accounting for patient-specific speed of sound of the skull.



A) Estimation of Skull properties with IP-111 Transducer

B) Acoustic Tank Setup with H-317 Transducer

C) Acoustic Maps

Acknowledgments: NSERC Discovery Grant; Canada Foundation for Innovation; Cumming School of Medicine Research Fund

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

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

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

Title: Optimising Transcranial Focused Ultrasound Stimulation:An Open-Source Tool for Precise Targeting

Authors: Cyril Atkinson-Clement, Marcus Kaiser

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

Abstract:

Context: Focused ultrasound stimulation (FUS) is a recent and under-development non-invasive neuromodulation technique. Its unique capability to safely penetrate deep targets with notable spatial accuracy underscores its significance. However, this spatial accuracy also implies careful preparation to deliver the right energy to the selected target. Two aspects have to be considered to successfully perform FUS: (i) The skull density, which absorbs a large part of the acoustic power and requires therefore to adapt the FUS parameters. (ii) The angle between the scalp and the TUS transducer, since it could deviate the acoustic field. If tooles are available to address the first point, one is still missing for the second. The angle plays a critical role in FUS and is frequently selected manually, inducing a lack of precision and a decrease in intra and inter-studies reliability. we introduce here a novel open-source tool specifically designed for TUS studies. Its main objective is to determine, at an individual-level basis, the optimal transducer position over subjects' scalps.

Details: The code found the best transducer position over the head by minimising the transducer-scalp angle through the following steps: (i) Target centroid determination. (ii) Distance selection. (iii) Decrease spatial resolution. (iv) Angle estimation. (v) Exact positioning calculation..
Notably, this code is flexible and could be adapted to many research protocols, allowing it to be useful for many researchers in the field. First, all the characteristics of the transducer could be modified to match those of other devices. Second, users could provide an exclusion area to avoid the acoustic fields going through (such as a brain region), or to avoid putting the transducer in a specific location (by avoiding impossible entry through the eyes or ears for example, or to be adapted to concomitant EEG recordings). In addition, it provides multiple outputs which could be useful for other research steps or to report details about the FUS procedure.

Validation: This code is commonly used for FUS research at the University of Nottingham, and was assessed on 40 healthy subjects, each for 5 different targets with different characteristics: the right thalamus (deep), the medial anterior cingulate cortex (in the optimal depth, medial and frequently targeted), the right insula (on the side), the medial primary motor cortex (close to the surface) and the right middle temporal cortex (behind the ear). The results showed: (i) A high inter-subject and inter-target spatial variability, highlighting the need to use an individual-based approach when selecting the best transducer position. (ii) A high relation between the angle estimation (quick to estimate [<1sec/item]) and the real volume (longer to calculate [~7sec/item]) between the scalp and the transducer ($R2=0.869$, $p<0.0001$)

Acknowledgments: M.K. and C.A., 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: technical **Preferred format:** poster

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

Title: Cross-beam validation of 3D steerable TUS system

Authors: C. Windischberger1, H. Hewener2, A. Arbabi3, B. Campilho1, C. Risser2, J. Marques3, S. Grosshagauer1, C. Degel2, D. van den Heuvel3, L. Nohava1, S. Hodono3, E. Laistler1, S. Tretbar2, D. Norris3 1 Medical University of Vienna, Austria; 2 Fraunhofer IBMT, Germany; 3 Donders Institute, Radboud University, Netherlands

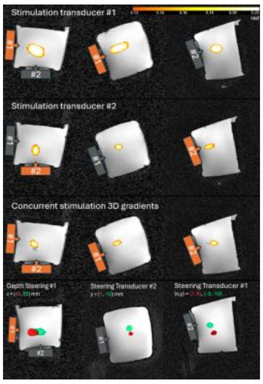
Email: christian.windischberger@meduniwien.ac.at

Abstract:

Even with the latest developments in aberration correction software packages like k-Wave, the main challenge for TUS application is appropriate validation of the sonication target. This validation is achievable with Magnetic Resonance Acoustic Radiation Force Imaging (MR-ARFI), as it can assess tissue displacement from sonication at the submillimetre level (Darmani et al., 2022) with minimal temperature elevation (Pauly, 2015). Along with validation arises the need for modifying the sonication target without changing the transducer setup. This can be achieved with steerable multi-element transducers where the target can be modified solely by changing sonication parameters.

In the CITRUS project, we have develope a novel TUS-MRI system employing two 256-element transducers arranged in a cross-beam configuration. Validation of the focus position for each of the MR-compatible, steerable transducers was achieved using a HASTE-based MR-ARFI sequence (van den Heuvel, 2023). In addition to high-resolution FLASH-based images ($0.7x0.7x2mm^3$) to assess phantom geometry, we have acquired ARFI data ($2x2x5mm^3$, NA=6, TE/TR=78/1000ms) with and without sonication (283kHz, 19ms). The differences in ARFI image phases represent displacements and thereby reveal sonication effects. A custom-made soft tofu phantom was used to simulate brain tissue. Transducers were mounted in orthogonal fashion to study the effects for both single and combined transducer sonication (see figure).

The results show clear acoustic foci at the intended target can be seen when each transducer is individually activated (shown in orange), as well as when both are simultaneously sonicating. Furthermore, the 3D steering capabilities of the implemented setup are validated. Overall, these results show the feasibility of using a steerable cross-beam TUS MR-ARFI setup to ensure precise, validated sonication.



Acknowledgments: This work was supported by the European Innovation Council.

Conflicts of interest: All authors declare that they have no conflicts of interest.

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

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

Title: Effective mitigation of oscillatory axial hydrophone reflection interference in low-intensity focused ultrasound transducer metrology: A single-case study.

Authors: Stein Fekkes, Margely Cornelissen, Erik Dumont, Jan Menssen, Eleanor Martin, Lennart Verhagen

Email: Stein.fekkes@ru.nl

Abstract:

Introduction: Transcranial Ultrasonic Stimulation (TUS) utilizes single-frequency transducers to generate low-intensity focused ultrasound for neuro modulation. Accurate spatial and absolute deposition of ultrasound energy necessitates prior knowledge of the specific acoustic field shape and pressures. Particularly in the near-field, pressure field characteristics can lead to pressure hotspots in the scalp and skull, potentially causing thermal effects to adjacent tissue and exacerbating auditory and somatosensory confounds. To address this concern, field measurements are obtained can suffer from interference from reflections between the transducer and hydrophone when ring-up times are long. Here we propose a method to acquire unbiased estimates by exploiting the spatial regularities of ultrasound in free water.

Methods: A four-channel TUS transducer (CTX500-026, Sonic Concepts, WA, USA) was driven by a Transducer Power Output (TPO) (105-010, Sonic Concepts, WA, USA) with a pulse duration of 250 μs at a center frequency of 500 kHz and 2.5 W per channel without ramping. 7 subsequent center-axial pressure profiles (focal distance range = 39 mm - 80 mm) - were acquired using a novel metrology setup* with a spatial resolution of 0.5 mm and a length of 140 mm. The transducer-specific ring-up time (Fig. 1a) was determined by averaging all normalized pulse envelopes. In-house developed post-processing uses an FFT-based method to acquire a single average amplitude reading for each recorded pulse. Two distinct pulse window selections were used. Firstly, a small window (aka pre-reflection) of 2 periods before three times the transducer-to-hydrophone time of flight. Secondly, a window (aka reflection) in between the pulse ring-up time and pulse end. A spatial FIR Butterworth low pass filter with a cutoff frequency of 0.2 mm^{-1} was applied to the amplitude profile using the latter window to remove oscillating interference caused by the hydrophone reflections (aka filtered reflection, Fig. 1b). The mean +/- std least squares differences (RMSE) between the ISPPA profiles provided by the manufacturer and for all acquired measurements were used as a comparison metric.

Results/conclusion: The ring-up time was estimated at 90 μs at which a steady-state amplitude level was reached. The RMSE for the ring-up period (0-70 mm) between manufacturer and the pre-reflection, reflection, and filtered reflection ISPPA profiles were, 1.6 ± 0.8, 2.6 ± 0.4, 1.3 ± 0.5 respectively. For post ring-up period (70-140 mm), the RMSE 0.4 ± 0.4, 0.5 ± 0.5, 0.4 ± 0.5, respectively indicating best resemblance using the filtered approach. Differences between the during- and post-ring-up periods is likely due to combination of underestimation of the amplitude and reflection interference being the most dominant in the focal region. In conclusion, accurate measurements of US should avoid ring-up and reflection periods. When this cannot be avoided such as in the near field and focal spot, we show that unbiased estimates can be obtained by spatial filtering approaches.

*Abstract FUN24: A novel scanning platform for cost-effective, open-source, high quality FUS metrology

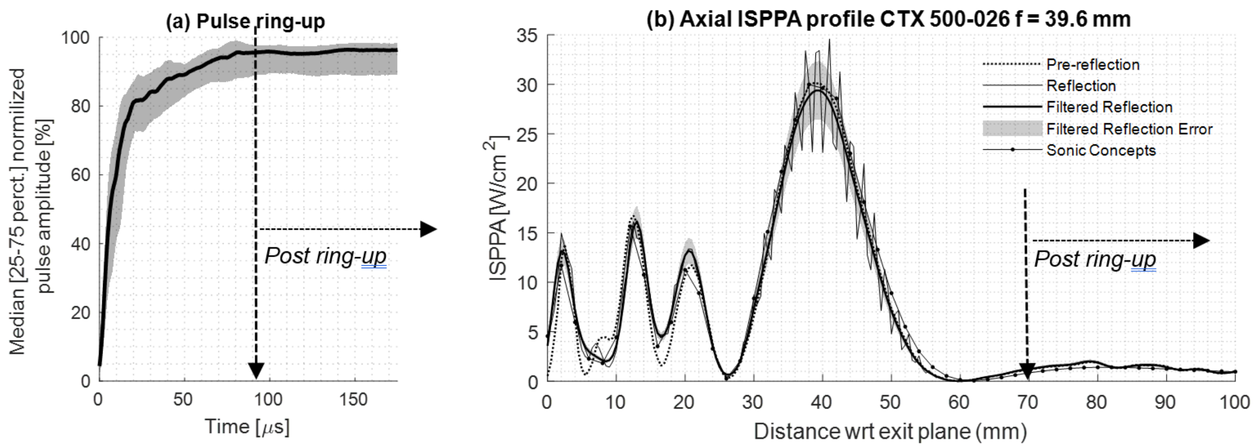


Figure 1 ***(a)*** *The median pulse ring-up characteristic showing amplitude stabilization after 90 μs.* ***(b)*** *A single center-axial ISPPA profile (f = 39.6 mm) depicts the effective mitigation of oscillatory reflection interference and underestimation of the ISPPA.*

Acknowledgments: -

Conflicts of interest: -

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

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

Title: A novel scanning platform for cost-effective, open-source, high quality FUS metrology

Authors: Stein Fekkes, Erik Dumont, Margely Cornelissen, Twan de Bruin, Sibrecht Bouwstra, Norbert Hermesdorf, Lennart Verhagen

Email: Stein.fekkes@ru.nl

Abstract:

Introduction:Transcranial Ultrasonic Stimulation (TUS) utilizes single-frequency transducers to generate Low-Intensity Focused Ultrasound (LIFU) for neuromodulation. Accurate and standardized US metrology is essential, both for all individual TUS research labs, and for the field in general, to collaborate and replicate. However, current metrology systems are geared for engineering use-cases, and their expense, size, and required know-how prohibits field-wide adoption by researchers. Here we aim to develop an open-source affordable US metrology platform that achieves the same standards of accuracy and reproducibility.

Methods: An independent metrology setup (Fig. 1) enables accurate positioning (dx,y,z = 5 μm) of the hydrophone (HGL 0200, Onda corp., Sunnyvale, USA) in front of the transducer submerged in degassed, filtered and deionized water at ambient temperature. Pulses can be acquired using a PicoScope 5244D (Pico Technology, UK) at a sample frequency of 25 MHz using a custom-developed, user-friendly, open-source, and integrated closed-loop control program triggered by any pulse-driving system. The modular software enables easy integration of signal generators using simple python drivers. The orthogonal alignment of the transducer with respect to the hydrophone XYZ-movement is assured by the aluminum fixed references on the base plate while keeping the assembly modular for mobility ease. A specific probe holder enabled accurate and reproducible mounting for easy, fast, and reliable pressure acquisition and comparison over time. Finally, cost and assembly effort are roughly estimated to be <10 k€ and a few hours, respectively.

Results/conclusion: Figure 1 shows a render of the setup excluding the water degassing and filtering pump system. Quick assembly of the base plate, motor stage, and the water tank – all within a desktop footprint (60 x 60 cm)-empowers research teams to perform state-of-the-art transducer characterizations and start their own quality assurance.

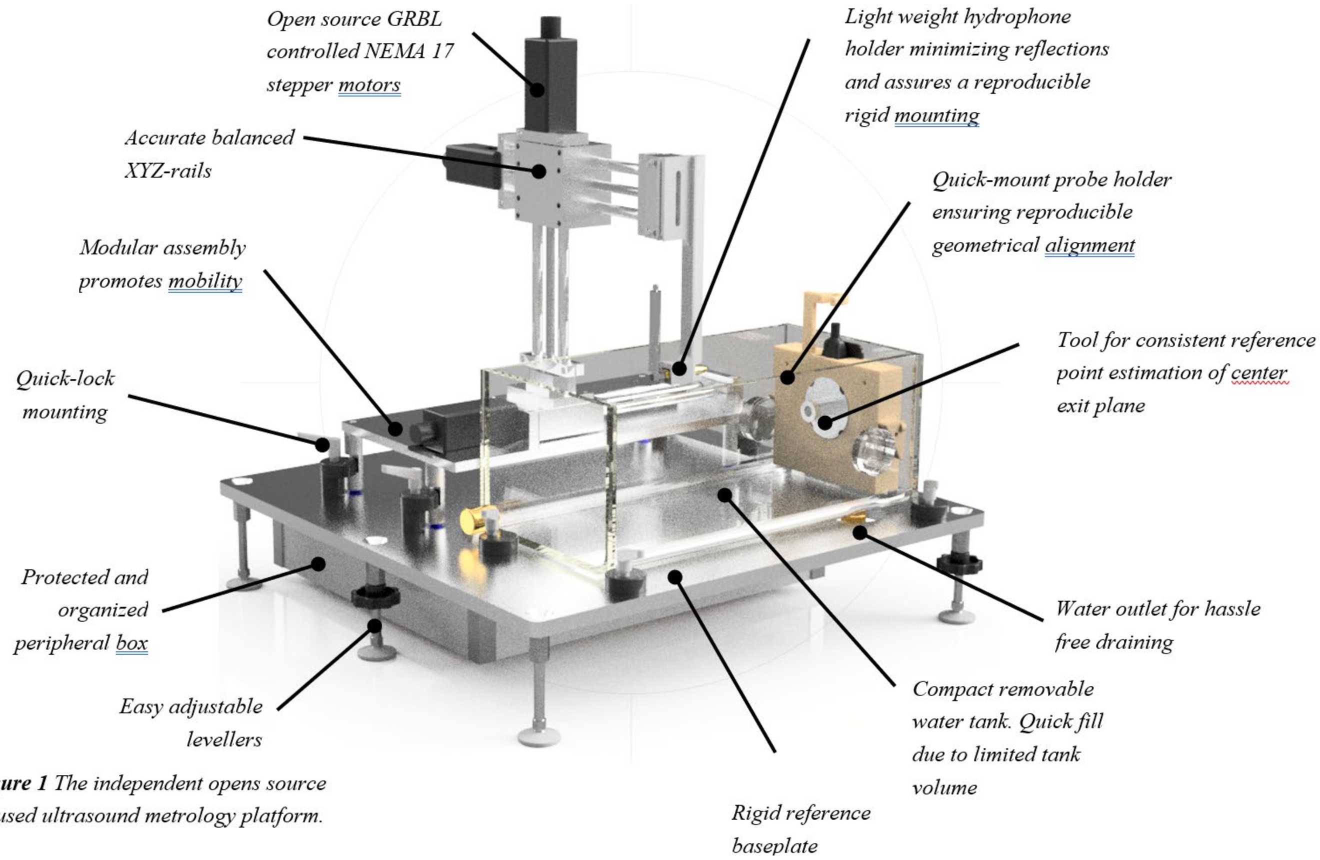


***Figure 1** The independent opens source focused ultrasound metrology platform.*

Acknowledgments: -

Conflicts of interest: -

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

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

Title: Comparative Analysis of Computed Tomography- and SimNIBS' Charm-Derived Skull Masks in Transcranial Ultrasound Stimulation

Authors: Ali K. Zadeh (1,2), Oula Puonti(3,4), Björn Sigurðsson(3,5), Axel Thielscher(3,5), Oury Monchi(1,2,6,7,8), Samuel Pichardo(1,2,6)
Affiliations: (1) Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada (2) Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada (3) Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital - Amager and Hvidovre, Copenhagen, Denmark (4) Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, MA, USA (5) Section for Magnetic Resonance, DTU Health Tech, Technical University of Denmark, Kgs Lyngby, Denmark (6) Department of Radiology, University of Calgary, Calgary, AB, Canada (7) Department of Radiology, Radio-oncology and Nuclear Medicine, Université de Montreal, QC, Canada (8) Centre de Recherche, Institut Universitaire de Gériatrie de Montréal, Montreal, QC, Canada

Email: Ali.khosroshahizadeh@ucalgary.ca

Abstract:

Background: In Transcranial Ultrasound Stimulation (TUS), ultrasound wave transmission through the skull poses significant challenges due to potential aberration and attenuation, which may impact studies' outcomes. Planning strategies incorporating 3D computed tomography (CT) scans have been developed to mitigate distortions caused by the skull's complex structure. Nevertheless, the reliance on CT imaging raises ethical concerns, especially in studies involving healthy participants. A solution involves generating skull masks from participants' 3D isotropic 1mm resolution T1- and T2-weighted scans using the charm segmentation tool of SimNIBS.

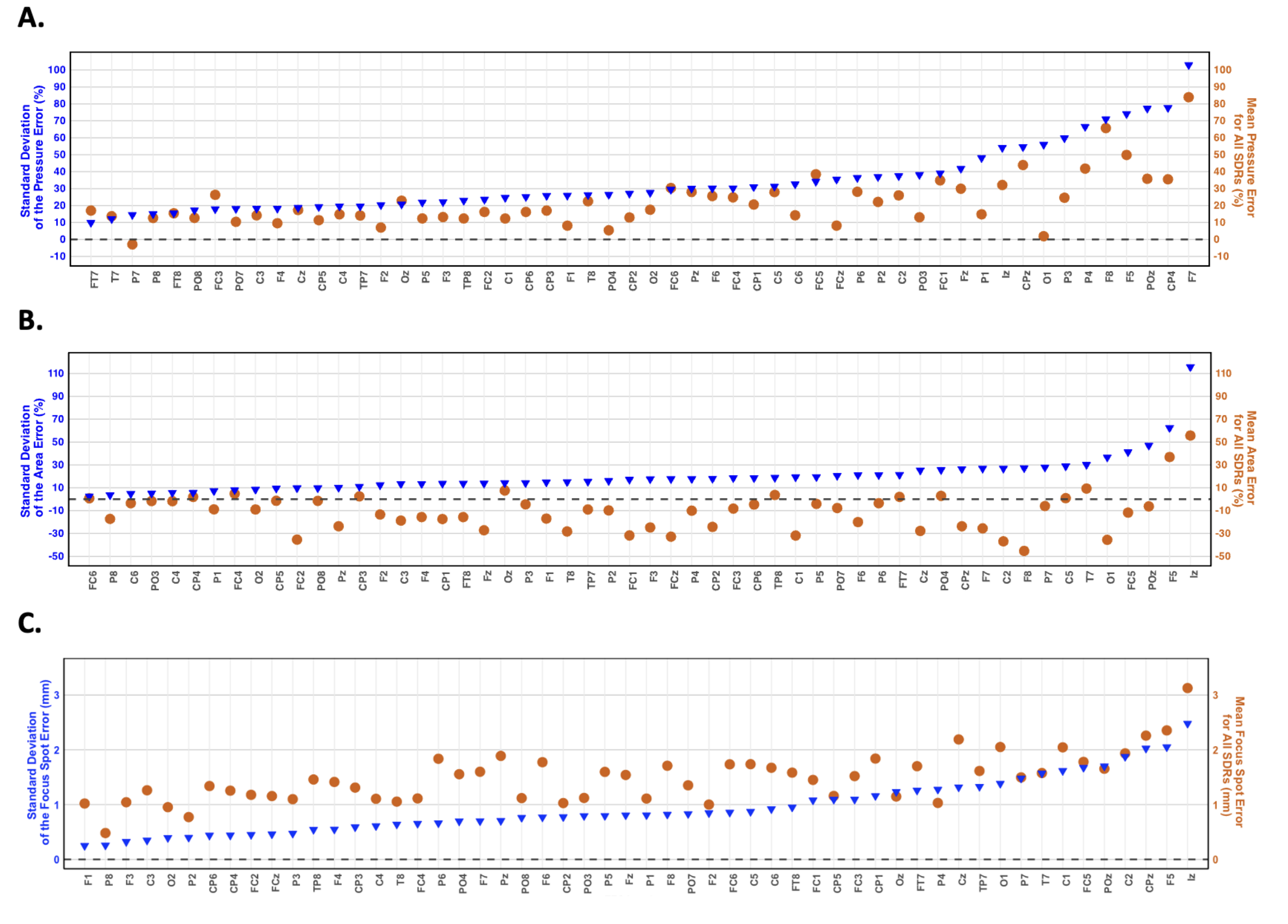
Objective: This study aimed to compare ultrasound predictions between CT-derived and charm-derived skull masks.

Method: In this study, a range of skull density ratios (SDRs) at values of 0.31, 0.42, 0.55, 0.67, and 0.79 were selected (public dataset: DOI:10.5281/zenodo.7894431), for which both CT and MRI scans were available. The ultrasound simulation was performed using the BabelBrain (DOI: 10.1109/TUFFC.2023.3274046, v0.2.9) software employing a simple focusing single-element transducer at 500 kHz. For the CT-derived masks, a threshold of 300 HU was applied to produce the mask and the mapping from HU to density, speed of sound, and attenuation. 1-mm isotropic T1- and T2-weighted scans were processed using charm with standard settings (SimNIBS v4.0.0). For charm-derived masks, the skull was modelled as consisting of three layers – cortical (10%), trabecular (80%), and cortical (10%) again. The methodology included adjustments to target ultrasound 30 mm below the skull's surface at the 54 electroencephalogram (EEG) locations.

Result: The deviations in maximum pressure, focal area size and focus spot location between simulations based on CT- and charm-derived skull masks were assessed for the different EEG sites and subjects. The error ranges for maximum pressure and area size differed across EEG locations, with standard deviations ranging from 9.93% to 103% and 2.57% to 116%, respectively. Furthermore, the standard deviation in the focus spot location error varied between 0.25mm and 2.48mm.

Conclusion: The findings indicate that charm-derived skull masks can already achieve satisfactory accuracy at many EEG sites. However, the significant errors occurring at certain locations necessitate careful consideration of stimulation location when choosing between CT- and charm-derived skull modelling. Our ongoing research aims to enhance the performance of charm-derived masks to achieve uniformly satisfactory accuracy across all locations.

Figure Caption: The standard deviation and mean of the (A) maximum pressure error (B) area size error and (C) focus spot error at different EEG locations.



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Conflicts of interest:	The authors declare no competing interests.

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

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

Title: Optimization of Intracranial Multi-Target Sonication to Limit Off-Target Pressures using Orthogonal Phased Array Ultrasound Transducers

Authors: Maximilian Hasslberger, Kasra Naftchi-Ardebili, Morteza Mohammadjavadi, Alexander Helmut Paulus, Kim Butts Pauly

Email: maxhb@stanford.edu

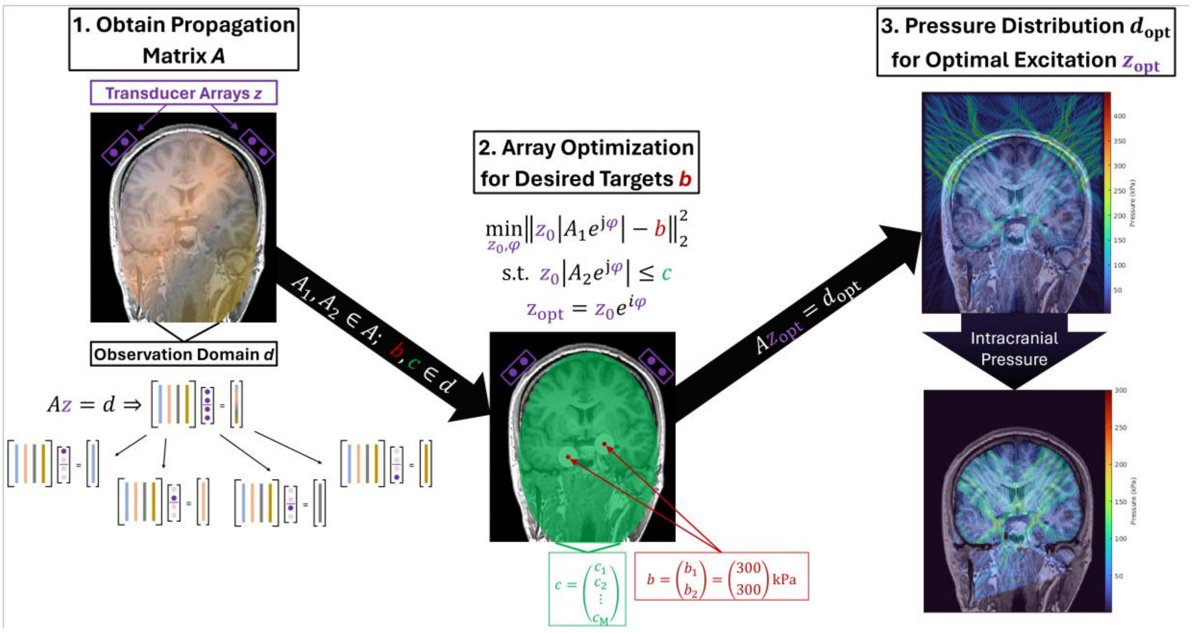
Abstract:

Introduction
Focused Ultrasound (FUS) is an advanced modality for precise and non-invasive neuromodulation, capable of targeting deep brain regions. However, demonstrating and reproducing the physiological effects of FUS remains challenging. A key source of uncertainty is the potential inadvertent modulation of adjacent brain areas caused by the typical cigar-shaped intracranial focal beams, which can result in significant off-target pressure values. In scenarios involving multiple targets and transducers, unintended circuits may be activated due to the constructive interference of acoustic waves.

Methods
In our method, we can define sonication volumes of any shape and reduce intracranial off-target pressures to below a specified tolerance value by solving a constrained optimization problem. We carry out 3D acoustic k-wave simulations to obtain a propagation matrix, which establishes a linear relationship between the excitation of each phased array element and the acoustic profile in the observation domain, thereby accounting for phase aberrations introduced by the skull. We then formulate and solve a phase retrieval problem to determine the optimal excitations, including phase values. Depending on the available hardware, the array amplitude can be treated as an additional degree of freedom or restricted to a single element value.

Results
Array parameters were optimized for different target areas and skull slices in an orthogonal setup of transducers. We simulated various configurations with up to three transducers in different alignments and up to four focal volumes in anatomically relevant regions. Target amplitudes at the intended foci could be yielded with a maximum error of 0.4 % per target while maintaining intracranial pressures below the constrained off-target limit and cranial pressure values below the FDA-approved limits.

Conclusions
Our interface allows flexible and precise planning for therapeutic ultrasound applications involving both multiple targets and transducers. Although the offline computation time for determining the propagation matrix is substantial, once the setup of the skull and transducer positions is fixed, optimization for arbitrary targets can be performed efficiently. After obtaining the optimal transducer coefficients, the acoustic pressure distribution can be plotted straight away using the propagation matrix.



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Conflicts of interest: -

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

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