FOCUSED ULTRASOUND NEUROMODULATION CONFERENCE

FUN26

PARIS · 22–24 JULY 2026

99 Poster Presentations · 24 Oral Presentations · 7 Topic Areas

COMPILED FROM THE OFFICIAL FUN26 ACCEPTED-SUBMISSIONS RECORD

WELCOME MESSAGE

On behalf of the organizing committee, I am delighted to welcome you to the 7th Focused Ultrasound Neuromodulation (FUN26) Conference, taking place from July 22 to 24, 2026, at PariSanté Campus, Paris. The conference is co-organized with ITRUSST, the International Transcranial Ultrasonic Stimulation Safety and Standards Consortium.

Paris is famously known as the *City of Light* but it is also the *City of Ultrasound* thanks to the groundbreaking work of renown researchers. The piezoelectric effect was discovered here by Pierre and Jacques Curie in 1880, and in 1917, Paul Langevin and Constantin Chilowsky filed the patent for the first directive emission and reception of ultrasonic waves using thin quartz crystals. Their pioneering contributions laid the foundation for biomedical ultrasound and their innovative spirit continues to inspire us today.

FUN26 will be held in a hybrid format, allowing for both in-person and remote participation via live Zoom access. This format ensures an engaging exchange of ideas and advancements in the field of ultrasound neuromodulation. Given the booming interest in ultrasound stimulation, FUN26 is fully booked. We thank you for contributing to this outstanding participation. To accommodate as many on-site attendees as possible, we have expanded the capacity, and the auditorium sessions will be streamed live to two duplex rooms.

We are deeply grateful to all the exhibitors supporting our conference. This year, we have the highest number of companies and organizations contributing to a FUN meeting. Their financial support is essential for organizing the technical and social events, while their presence provides valuable insight about the latest commercial technologies in our field.

I am extremely thankful to the organizing committee for their hard work, the very pleasant collaborative atmosphere, and the exceptional technical and social program we have created together to make this meeting a success. We hope all participants will fully engage in live discussions, collaborative opportunities, and networking events during the conference and during the highly anticipated dinner cruise on the Seine River.

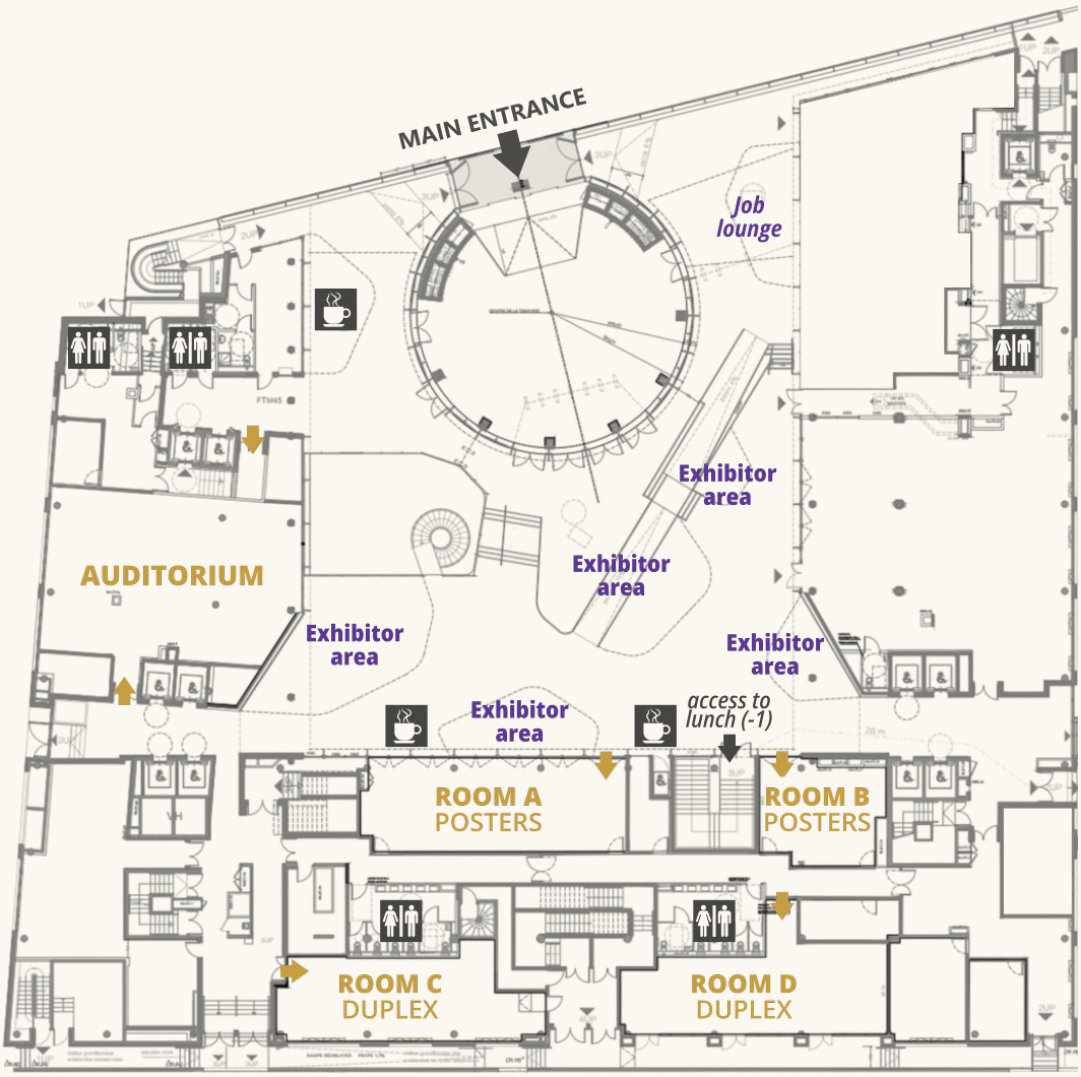
I sincerely wish you an exciting and productive time in Paris. I have no doubt that all the FUN will be yours during these three memorable days of learning, sharing, and advancing the field of Focused Ultrasound Neuromodulation.

Jean-François Aubry,
Research Director at Physics for Medicine Paris,
Chair of FUN26

FLOOR MAP

FUN26 takes place at PariSanté Campus, located **2-10 rue d'Oradour-sur-Glane, 75015 Paris, France**. It is accessible through various **public transportation options**: metro line 8 Balard, metro line 12 Porte de Versailles, tram T2 Porte d'Issy, tram T3a Desnouettes.

Please note that all visitors undergo security checks at the entrance of the building, including bag inspection. Therefore, please avoid bringing large suitcases, especially on the first day (backpacks and handbags are allowed).



REGISTRATION

Registration is open every day, but we encourage you to come and register on July 21 between 3 pm and 7 pm to avoid long waiting time on July 22.

The default lanyard is black. If you do not want to be photographed, please ask for a red lanyard at the registration desk.

LUNCHES

Lunch will be served at the restaurant downstairs. To avoid long wait times, participants will be divided into two groups each day.

On July 22:

- **Group A** (last names A–K) will have lunch at **13:15**.
- **Group B** (last names L–Z) will have lunch at **12:30**.

On July 23:

- **Group A** (last names A–K) will have lunch at **12:30**.
- **Group B** (last names L–Z) will have lunch at **13:15**.

In the restaurant, take a tray at the entrance, choose a starter, a main course, a dessert and a drink (water or soda) and then hand your **meal voucher** to the cashier. You may sit anywhere in the restaurant, but you will find a dedicated area on your left. Meal vouchers are in your badge holder. Coffee will be available after lunch, upstairs in the exhibition area.

Depending on your dietary restrictions, do not hesitate to ask for meat, fish, or a vegetable selection.

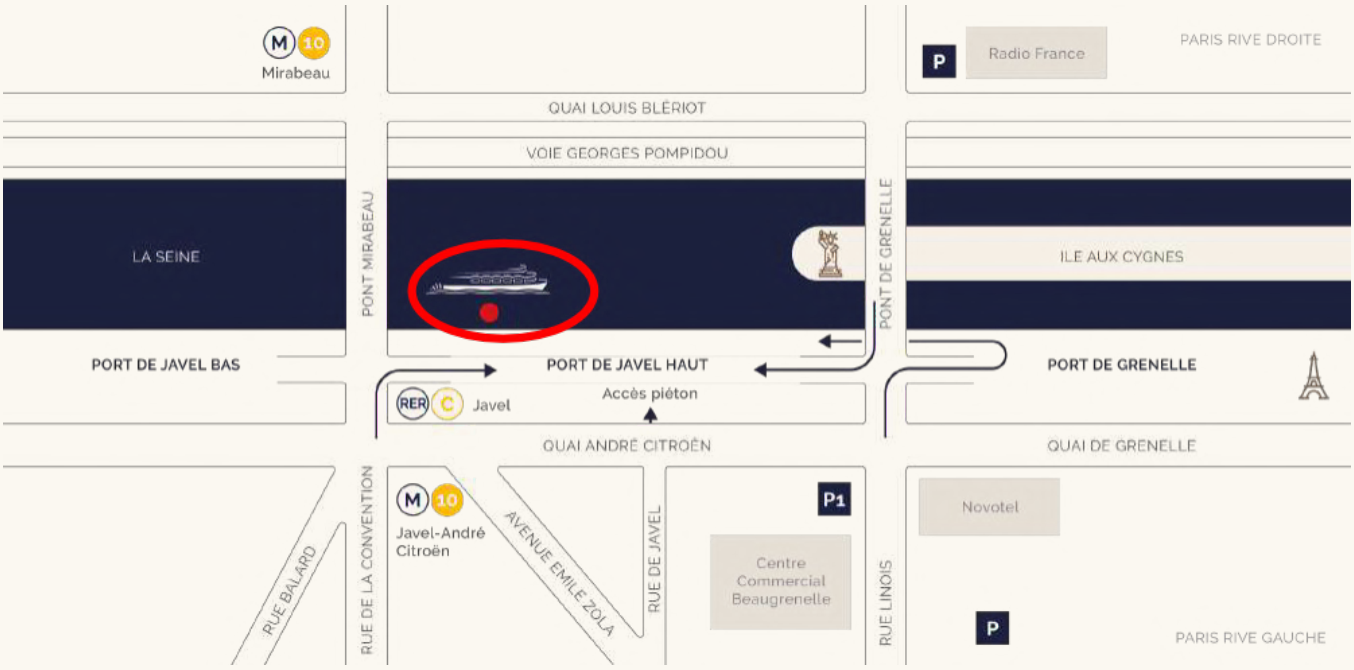
REFRESHMENT BREAKS

Refreshments will be served in the exhibitor area at the times specified in the programme. Coffee will also be served in the exhibitor area after lunch.

JOB LOUNGE

Participants who are either offering a job or seeking a job are welcome to meet in person in the Job Lounge. A job board is available to post messages. ITRUSST members will soon be offered the possibility to share online job offers, so stay tuned.

DINNER CRUISE ACCESS



The gala dinner is held on a boat, cruising along the Seine River to enjoy Parisian scenery from a unique perspective! The cruise will last approximately 2 hours, starting from 20:00, and the boat will return to the dock around 22:30 for us to enjoy the rest of the evening until midnight.

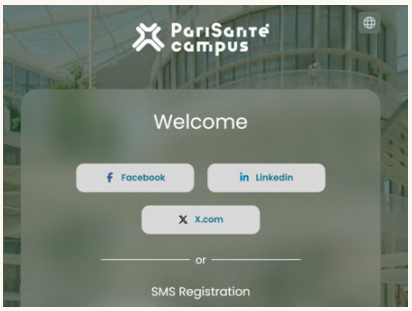
The gala dinner is fully booked. Make sure to bring with you the gala dinner voucher inserted in the badge holder that was given to you at registration. No admission will be allowed without the voucher.

The dress code for the gala dinner is casual chic. We understand that you may adjust according to a possible heat wave, so sandals and Bermuda shorts will be authorized.

Boarding is at the "Port de Javel Haut" starting from 19:00 and no later than 19:30. The Port is a 30-min walk from the conference venue. Public transportation options include: metro line 10 Javel-André Citroën, RER C Javel, or bus line 30.

Get directions

WI-FI



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Program Overview

DAY BY DAY

WEDNESDAY, JULY 22, 2026

08:30	*Coffee & registration*
08:45	Welcome

HUMAN TECHNICAL ADVANCES

Chairs: Lennart Verhagen · Carter Lybbert

09:00	**Helen Mayberg, MD:** Decoding Multimodal Recovery Signals to Optimize Deep Brain Stimulation for Depression
09:30	**Suhas Vijayakumar:** Protocol Optimization and Neural Target Engagement of the Human sgACC Using Online TUS-fMRI with the CITRUS System
09:45	**Benjamin R. Kop:** MR-ARFI-quantified dose-response effects of TUS on the visual system
10:00	**Elena Brunet:** Cell-Specific Effects of Transcranial Ultrasound Stimulation (TUS) in the Human Brain: A Pilot Diffusion Magnetic Resonance Spectroscopy (dMRS)
10:15	*Discussion*
10:30	*Coffee*

BEYOND LOCAL EFFECTS

Chairs: Hartwig Siebner · Martin Wimmers

11:00	**Antoine Jérusalem, PhD:** Neuromodulation, when the why matters; from cellular experiments to organ-scale model prediction
11:30	**Xue Han:** Transcranial ultrasound stimulation modulates neuronal membrane potentials in the awake mammalian brain
11:45	**Héctor Estrada:** Evidence of vascular and blood flow effects of ultrasound stimulation observed in mice
12:00	**Vivek Sharma:** Ultrasound stimulation of a deep thalamic nucleus modulates large-scale neural synchrony in humans
12:15	*Discussion*

LUNCH (STAGGERED) AND EXHIBITION

12:30	***Group A** starts in auditorium ITRUSST Acoustic properties **Julian Kosciessa** & **Samuel Pichardo** then Lunch* ***Group B** starts at the lunch venue*

VOLUNTARY ACTION AND DECISION MAKING

Chairs: Robert Chen · Erynne San Antonio

14:00	**Vera A. Khokhlova, PhD:** In Memoriam: The Pioneering Legacy of Dr. Leonid R. Gavrilov in Ultrasound Neuroscience
14:30	**Isla Barnard:** Effects of focused ultrasound thermal neuromodulation of the mediodorsal thalamus on value-based decision making
14:45	**Maja Friedemann:** Investigating the role of human pgACC in cost-benefit decision-making using transcranial ultrasound stimulation (TUS)
15:00	**Joshua Kosnoff:** Enhancing the discriminative power of voluntary motor signals with transcranial focused ultrasound
15:15	*Discussion*
15:30	*Coffee*

POSTERS AND EXHIBITION

Chairs: Hyungmin Kim · Anastasia Grigoreva

16:00	Poster pitches
16:30	Parallel sessions: Posters / Industry Exhibition
18:30	*Walk to Gala dinner*
19:00	*Gala dinner with cruise on the Seine*

THURSDAY, JULY 23, 2026

08:30	*Coffee*

SKULL / PLANNING

Chairs: Markus Kaiser · Vanshika Sharma

09:00	**Kim Butts Pauly, PhD:** MR-ARFI as an Experimental Measure of Dose in Human Transcranial Ultrasound Stimulation
09:30	**Samuel Pichardo:** Measurement of ultrasound-induced thermal effects in skull bone using 3D thermometry with X-ray Computed Tomography: Preliminary Results
09:45	**Jonas Kielmann:** Fast Geometric Re-planning Compensates for Small Transducer Placement Offsets in Transcranial Ultrasound Stimulation
10:00	**Justin Rameau:** Ray-Tracing based automated workflow for fast skull aberration correction, in-situ pressure level estimation and 3D pressure field display
10:15	*Discussion*
10:30	*Coffee*

HUMAN CLINICAL TUS APPLICATIONS

Chairs: David Attali · Charlotte Smets

11:00	**Joline Fan, MD:** Toward Focused Ultrasound for Treatment and Presurgical Mapping in Epilepsy
11:30	**Amanda R. Arulpragasam:** Low Intensity Focused Ultrasound Modulates Amygdala Activity and Resting State Connectivity in Depressed Patients
11:45	**Regina Annirood:** Behavioral effects of 5 Hz vs 10 Hz transcranial ultrasound stimulation of the globus pallidus internus in Parkinson's disease
12:00	**Molly Acord:** Low Intensity Focused Ultrasound for Tobacco Use Disorder: High Resolution Targeting of the Human Insula
12:15	*Discussion*

LUNCH (STAGGERED) AND EXHIBITION

12:30	***Group A** starts at the lunch venue* ***Group B** starts in auditorium ITRUSST Acoustic properties **Julian Kosciessa** & **Samuel Pichardo** then Lunch*

TOWARDS NOVEL INDICATIONS

Chairs: Miriam Klein-Flügge · Julian Q. Kosciessa

14:00	**Quanxiang (Salvia) Xian, PhD:** Precision sonogenetic neuromodulation and its therapeutic potential
14:30	**Vinay Parameshwarappa:** High-Frequency Focused Ultrasound targeting the Midbrain in the Guinea Pig Induces Activation and Plasticity of the Efferent System, and Protection Against Noise-Induced Hearing Loss
14:45	**Haorun Huang:** Transcranial Focused Ultrasound Neuromodulation in Cerebellar Circuits: Dissecting Central and Peripheral Contributions
15:00	**Qiu Zhihai:** Focused ultrasound neuromodulation of the hypothalamic preoptic area promotes NREM sleep and reduces brown adipose tissue temperature in mice
15:15	*Discussion*
15:30	*Coffee*

POSTERS AND EXHIBITION

Chairs: Pengfei Song · Guillaume Coudriet

16:00	Poster pitches
16:30	Parallel sessions: Posters / Industry Exhibition
18:30	*End of the day*

FRIDAY, JULY 24, 2026

08:30 *Coffee*

NEUROTRANSMITTERS / NEUROCHEMICALS

Chairs: Elsa Fouragnan · Emma Lescrauwaet

09:00 **Daniel Whitcomb, PhD:** Cellular and molecular effects of ultrasound neuromodulation of the hippocampus

09:30 **Samuel Winiarski:** Ultrasound-mediated serotonin delivery causally modulates motivation in primates

09:45 **Jonas Bendig:** Region and pulse repetition frequency dependent bidirectional modulation of dopamine release by focused ultrasound (FUS)

10:00 **Tom Aubier:** In Vivo Characterization of Localized Neurochemical Responses in the Rat Striatum to Focused Ultrasound Neurostimulation

10:15 *Discussion*

10:30 *Coffee*

FROM PRECLINICAL TO CLINICAL

Chairs: Charles Caskey · Bartol Bartulovic

11:00 **Axel Thielscher, PhD:** Controlling the dose in transcranial brain stimulation

11:30 **Sarina Grewal:** Parameter-dependent focused ultrasound modulates neuroinflammation and delays early Alzheimer's pathology

11:45 **Tayeb Pourebrahim:** Real-Time Intracranial Pressure Field Prediction in tFUS Using a Physics-Informed Fourier Neural Operator

12:00 **Yunruo Ni:** Personalized Low-Intensity Focused Ultrasound to Medial Temporal Lobe for Human Episodic Memory Enhancement

12:15 *Discussion*

LUNCH STAGGERED

12:30 ***Group A*** *Auditorium ITRUSST MR-TUS* ***Kristen Zarcone*** *&* ***Morteza Mohammadjavadi*** *-- Group B Lunch*

13:15 *Group A Lunch --* ***Group B*** *Auditorium ITRUSST MR-TUS* ***Kristen Zarcone*** *&* ***Morteza Mohammadjavadi***

CLOSING SESSION

Chairs: Elly Martin · Madison Lees

14:00 FUN closing ceremony & ITRUSST future

14:30 TUS community tool pitches

15:00 **Parallel Sessions (free rotation possible):**

Meet the Builders & Experts
In-depth discussions & demos with creators of open TUS tools (speed-dating format).

Physics for Medicine Paris Lab Visits
Guided tours of the Physics for Medicine Paris laboratory, a designated Focused Ultrasound Center of Excellence (multiple rounds).

ITRUSST Collaborative Community & Working Groups

Safety & Standards: Reporting, Biophysical Safety, Physiological Safety, Acoustic Properties, Uncertainty & Sensitivity Analysis, MR-TUS.

Clinical Translation: Clinical Trial Guidance, Practical Guide, Mental Health & Psychiatry, Neurology & Neurosurgery.

Education & Dissemination: Open Community Tools, Reference Databases, Education & Certification.

New Ideas: Brainstorming and discussion on proposals for new working groups.

16:00 *Final closure & goodbye*

Organizing Committee

FUN26 · PARIS 2026

FUN26 ORGANIZING COMMITTEE

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Thu-Mai Nguyen

Miriam Klein-Flügge

Martin Wimmers

Benjamin Robert Kop

Elsa Fouragnan

Elly Martin

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PLATINUM SPONSOR

Gestala

Gestala is building a next-generation ultrasound brain--computer interface platform designed for whole-brain reading, writing, and analysis. By combining focused ultrasound, functional ultrasound imaging, artificial intelligence, and neuroscience, we aim to unlock scalable, non-invasive access to brain function at an unprecedented level.

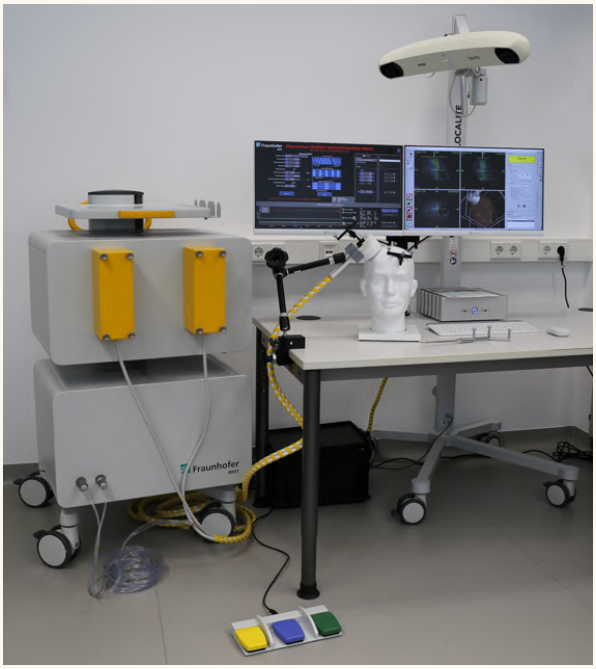
Our mission is twofold: to develop transformative therapies for neurological and psychiatric disorders, and to advance a deeper understanding of how the brain generates cognition, emotion, and intelligence. We believe the future of brain--computer interfaces will be defined not only by hardware innovation, but also by the integration of large-scale neural data, AI foundation models, and adaptive closed-loop systems.

At Gestala, we view neuroscience and artificial intelligence as two sides of the same coin. Through our efforts to build next-generation NeuroAI models, we hope to accelerate both clinical translation and fundamental discoveries about the human brain. As a Platinum Sponsor of FUN26, we look forward to engaging with researchers, clinicians, engineers, and industry leaders from around the world to advance the future of ultrasound neuromodulation and brain--computer interfaces together.

PLATINUM SPONSOR

Localite & Fraunhofer IBMT

Localite GmbH and Fraunhofer IBMT collaborate in research projects to advance precise, image-guided workflows for transcranial ultrasound stimulation. Combining Localite's expertise in neuronavigation with Fraunhofer IBMT's focused ultrasound know-how, the joint work aims to translate research results into future application-oriented TUS solutions. Localite and Fraunhofer IBMT are proud to support FUN26 as Platinum Sponsors and to present their newest joint developments.



PLATINUM SPONSOR

Sonomind

Sonomind is developing a personalized, non-invasive therapy for treatment-resistant depression based on low-intensity focused ultrasound. Building on more than 25 years of pioneering research in therapeutic ultrasound at Physics for Medicine, the company combines patient-specific acoustic lenses and precision neuromodulation to target deep brain circuits involved in neuropsychiatric disorders.

As a Platinum Sponsor of FUN26, Sonomind joins the international focused ultrasound community in advancing the clinical translation of transcranial ultrasound stimulation and exploring its potential to transform the treatment of brain disorders.

Brainbox

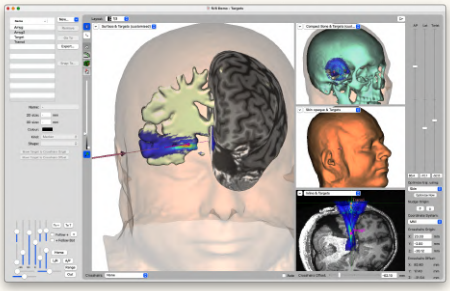
Brainbox supports cutting-edge neuroscience research through integrated hardware, software, and technical expertise, working at the centre of the neuromodulation community. At FUN26, explore the NeuroFUS 3D planning and neuronavigation software running on Brainbox's platform, alongside a broader portfolio spanning TMS, tES, EEG, and neuronavigation that helps research teams build and refine experimental workflows.

Openwater

Openwater's Low Intensity Focused Ultrasound (LIFU) platform for research is flexible, easy to use, and can deliver LIFU to targets located nearly anywhere in the head or body. Open-LIFU 2.0 is ready to use out of the box, while its open-source design supports customization across diverse applications --- bridging proof-of-concept research and manufacturable, regulated medical devices.

Rogue Research

As developers of the Brainsight® family of neuronavigation systems, Rogue Research has made non-invasive brain stimulation more accurate and effective for almost 25 years, in both humans and animals. Brainsight® NIBS continues to evolve with guided focused ultrasound, including a new robotic arm for human research, while Brainsight® Vet supports robotic workflows for large and small animal models.



Soterix Medical

Soterix Medical is a global leader in non-invasive brain stimulation, with a portfolio spanning transcranial electrical stimulation (tES), transcranial magnetic stimulation (TMS), and emerging focused ultrasound modalities. BrainSonix pioneered Low-Intensity Focused Ultrasound Pulsation (LIFUP); Soterix Medical is now a collaborative partner in developing, manufacturing, and distributing BrainSonix systems for safe, reproducible, and scalable TUS delivery.

Verasonics

For 25 years, Verasonics has been the leader in programmable ultrasound research systems, trusted by researchers, engineers, and commercial partners worldwide. Its platforms let researchers design custom transmit sequences, build real-time processing pipelines, and implement advanced closed-loop protocols. The Vantage NXT supports interleaved imaging and a wide output range, making it a preferred platform for focused ultrasound neuromodulation.

Vermon

For more than 40 years, Vermon has designed and manufactured advanced ultrasound transducers for medical, industrial, and scientific applications. Its expertise covers the full acoustic chain --- piezoelectric materials, 1D and 2D arrays, and phased-array probes. Vermon's 2D and phased-array technologies, with centre frequencies from approximately 500 kHz to 15 MHz, are well suited to focused ultrasound neuromodulation.

Brain Research & Imaging Centre (BRIC)

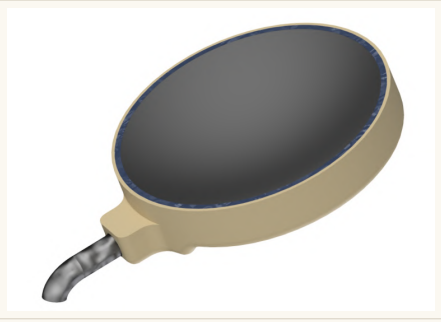
The Brain Research & Imaging Centre (BRIC) at the University of Plymouth advances understanding of the human brain through cutting-edge imaging and non-invasive brain stimulation, spanning cognitive neuroscience and clinical neuroimaging.

Focused Ultrasound Foundation

The Focused Ultrasound Foundation is the leading philanthropic organisation accelerating the development and adoption of focused ultrasound as a transformative medical therapy --- funding research and engaging clinical and regulatory stakeholders worldwide.

Imasonic

With over 30 years of experience in therapeutic ultrasound, IMASONIC designs and manufactures advanced transducer solutions tailored for neuromodulation. Its customized products, built on a unique piezocomposite technology, offer unmatched performance, reproducibility, and predictability.

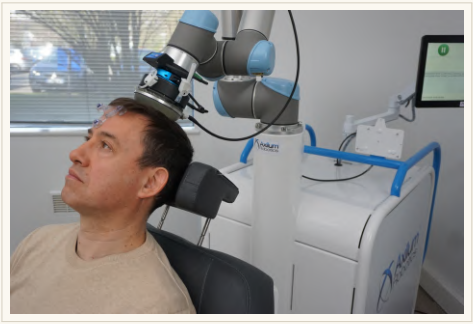


Sanmai

Sanmai is a neurotechnology company developing non-invasive ultrasound neurotherapeutics for mental health and neurological disorders, combining transcranial ultrasound stimulation with AI-driven software to deliver safe and effective treatments.

Axilum Robotics & IGT

Axilum Robotics, a French medical robotics company, has designed a navigated robotic platform to improve the delivery of Transcranial Ultrasound (TUS), building on its expertise in Transcranial Magnetic Stimulation. Image Guided Therapy (IGT) develops sophisticated phased-array focused ultrasound systems with a particular emphasis on TUS.



Tianqiao & Chrissy Chen Institute

The Tianqiao and Chrissy Chen Institute is a philanthropic organisation dedicated to advancing brain science for the benefit of humanity. We fund bold, interdisciplinary research at the frontier of neuroscience, including focused ultrasound neuromodulation, which holds tremendous promise for understanding and treating brain disorders. By supporting and convening the global research community, we aim to accelerate the translation of discoveries into meaningful impact for patients worldwide. We are honoured to support FUN26 and the community it represents.

Sonic Concepts

This year, Sonic Concepts will debut NeuroFUS 3D, their latest innovation in transcranial focused ultrasound technology. Attendees can connect with the team to learn more about how this new platform is advancing neuroscience research and therapeutic ultrasound applications.

Invited Speakers

FUN26 KEYNOTE & INVITED LECTURES

INVITED SPEAKER

Helen Mayberg

MD

Decoding Multimodal Recovery Signals to Optimize Deep Brain Stimulation for Depression

ABSTRACT

It is now 20 years since the first proof-of-principle case of Deep Brain Stimulation (DBS) for treatment resistant depression. Initial studies were catalyzed by critical clinical need, informed by converging findings from imaging studies of depression pathophysiology and antidepressant treatment, and operationalized using established standards for movement disorder surgery. As subcallosal cingulate DBS has evolved and matured, neuroimaging continues to play a crucial role, with implementation of refined multimodal imaging techniques for surgical targeting, and emerging clues as to which patients are most likely to benefit. Additional perspectives on trajectory, time-course, and sustainability of DBS circuit effects have been advanced by engineering device innovations and animal models that address mechanisms at the neural level. Further, availability of brain sensing systems combined with computer vision and other machine learning strategies now enables neural and behavioral monitoring during ongoing treatment, providing new tools for DBS treatment optimization. Such studies link first-person experiences to changes in brain state towards a comprehensive but nuanced understanding of illness and recovery. These observations and insights now also inform testing and refinement of next-generation, non-surgical neuromodulation alternatives, including focused ultrasound.

BIOGRAPHY

Helen Mayberg MD, is a neurologist known for her neuroimaging studies of brain circuits in depression and their translation to the development of Deep Brain Stimulation as a novel therapy for treatment-resistant patients. She is Professor of Neurology, Neurosurgery, Psychiatry, & Neuroscience and founding Director of the Nash Family Center for Advanced Circuit Therapeutics at The Icahn School of Medicine at Mount Sinai in New York, where she leads a transdisciplinary research team advancing precision surgical treatments for complex neuropsychiatric disorders. She is a member of the US National Academies of Sciences and National Academy of Medicine, as well as the National Academy of Inventors, and the American Academy of Arts and Sciences.

INVITED SPEAKER

Kim Butts Pauly

PhD

MR-ARFI as an Experimental Measure of Dose in Human Transcranial Ultrasound Stimulation

ABSTRACT

Transcranial ultrasound stimulation (TUS) studies typically estimate in situ exposure and target location using acoustic simulations. However, these simulations are subject to multiple sources of uncertainty, including skull acoustic properties and acoustic coupling. Planning simulations can be complemented by an experimental measure of acoustic radiation force displacement obtained with MRI (MR-ARFI). Because MR-ARFI displacement reflects not only acoustic intensity but also the interaction of the ultrasound beam with tissue mechanical properties, we propose that it may serve as a surrogate measure of absorbed dose.

In a cohort of 24 human subjects, we measured the fMRI response of the lateral geniculate nucleus (LGN) to a visual stimulus during TUS and compared it with TUS delivered to a control location in the temporal lobe. MR-ARFI displacement was significantly correlated with the magnitude of the fMRI response and demonstrated a stronger association than simulated acoustic intensity.

Our findings also suggest several refinements to MR-ARFI acquisition and analysis. First, accurate localization of the acoustic focus will likely require shorter ultrasound pulses, as displacement spreads laterally during the excitation. Second, the observed displacement patterns provide evidence of shear wave generation, consistent with predictions from elastography. Given that it remains unclear whether neuromodulatory effects are more closely related to normal strain or shear strain, future studies should quantify both. Such measurements could improve TUS dose estimation while also providing insight into the underlying mechanisms of neuromodulation and informing more precise targeting strategies.

BIOGRAPHY

Kim Butts Pauly received a B.S. degree in physics from Duke University and a Ph.D. degree in biophysical sciences from the Mayo Graduate School. After postdoctoral training at both Mayo and Stanford, she joined the Department of Radiology at Stanford University. She is currently a Tenured Professor of Radiology at Stanford University, where she is also the Interim Vice Chair for Research and with a courtesy appointment in Electrical Engineering. She has a broad background in MRI and ultrasound physics and has specialized in MRI-guided focused ultrasound for the treatment of cancer, noncancer neurological disorders, and neuromodulation. Dr. Butts Pauly is a fellow of the International Society of Magnetic Resonance in Medicine (ISMRM), a Distinguished Investigator of the Academy of Radiology Research, and a member of the American Institute for Medical and Biological Engineering (AIMBE)'s College of Fellows.

INVITED SPEAKER

Antoine Jérusalem

PhD

Neuromodulation, when the why matters; from cellular experiments to organ-scale model prediction

ABSTRACT

Ultrasound neuromodulation is rising to be the most promising non-invasive neuromodulation technique of its generation. It is effective, does not require a surgical intervention and can be as local as the underlying technology allows it to be. Paradoxically, and not unlike anaesthetics in the mid-19th century, its translation to practice seems to bypass altogether the need for an understanding of the underlying mechanisms leading in the first place to the modulation of individual neurons and neuronal networks. While this gap in the knowledge does not necessarily preclude advances in the field (and luckily so in the case of anaesthesia!), it constrains these to rely mostly on trial-and-error instead of mechanistic predictions of what inputs are required to lead to a given modulatory effect. In this talk, we show how some of our recent experimental results at the cellular scale --- both in anaesthesia and ultrasound neuromodulation --- can provide some insights into the potential mechanisms at play. We then present a novel thermodynamics-based theoretical framework able to upscale our predictions to the organ and eventually functional scales.

BIOGRAPHY

Professor Antoine Jérusalem graduated in 2004 with a double degree from the Ecole Nationale Supérieure de l'Aéronautique et de l'Espace with a Diplôme d'Ingénieur, and from the Massachusetts Institute of Technology with a Master of Science in Aeronautics and Astronautics. In 2007, he obtained his Ph.D. in Computational Mechanics of Materials from MIT, where he stayed as a Postdoctoral Associate for an additional year.

Professor Jérusalem was the group leader of the Computational Mechanics of Materials Group in Madrid's Advanced Studies Institute of Materials (IMDEA Materials) from 2008 to 2012, after which he moved to the University of Oxford where he is currently a Professor of Mechanical Engineering. His research activities focus on the computational modelling of many types of materials and structures, ranging from metals to composite materials with a major interest in brain mechanics with bioclinical applications ranging from traumatic brain injury, to neuromodulation, foetal brain health and shunt design. His modelling activities involve the development and use of state-of-the-art advanced numerical techniques with a focus on novel design optimisation methods and AI-mechanical coupling. Professor Jérusalem has active collaborations with many institutes and universities around the world.

INVITED SPEAKER

Vera A. Khokhlova

PhD

In Memoriam: The Pioneering Legacy of Dr. Leonid R. Gavrilov in Ultrasound Neuroscience

ABSTRACT

This presentation is dedicated to the memory of Dr. Leonid Gavrilov, whose visionary research and long-term international collaborations starting in the 1970s have provided important contributions for today's ultrasound-based neuromodulation clinical studies. Four major distinct contributions should be listed: feasibility and mechanisms of neurostimulation, the feasibility of focusing through intact skull, the establishment of thresholds for thermal and mechanical brain damage, and development of randomized multi-element therapeutic arrays that can be used for safe and effective focus steering and aberration correction. Long before transcranial neuromodulation, brain barrier opening, and HIFU ablation became global ``hot topics,'' Leonid Gavrilov pioneered the use of focused ultrasound to interact directly with the peripheral nervous system. He was the first to demonstrate that short, high-intensity pulses could non-invasively generate a broad spectrum of sensory perceptions --- tactile, thermal, and pain --- by targeting peripheral neural structures. He proved that ultrasound could be effectively focused through the intact skull. His seminal research in the early 1970s also provided quantitative measurements of cavitation thresholds in living brain tissue, establishing the critical distinction between thermal and mechanical ablation mechanisms. As the technology evolved, his focus shifted to the engineering challenges of ultrasound skull penetration: his original concept of randomized two-dimensional phased arrays mitigated the critical problem of grating lobes, and this work eventually led to sophisticated, fully populated mosaic array designs developed in collaboration with Lomonosov Moscow State University and international partners. Dr. Gavrilov's legacy is an inspiring example that bridges the gap between 20th-century discoveries and 21st-century clinical reality.

BIOGRAPHY

Vera A. Khokhlova received the M.S. degree in physics, and the Ph.D. and D.Sc. degrees in acoustics from Moscow State University (MSU), Moscow, Russia, in 1986, 1991, and 2012, respectively. She is currently an Associate Professor with the Department of Acoustics of the Physics Faculty and a Co-Head of the Laboratory for Industrial and Medical Ultrasound of MSU. Since 1995, she has been with the Center for Industrial and Medical Ultrasound of the University of Washington (UW) in Seattle, USA. Dr. Khokhlova has served as a member of the Executive Council of the Acoustical Society of America (2012–2015), as a member of the Board of the International Society for Therapeutic Ultrasound (2004--2008 and 2011–2014), and a Vice-President of the Russian Acoustical Society (since 2024), co-organized international conferences and schools on therapeutic ultrasound. Her major research interests are to better understand fundamental acoustic wave phenomena and to use them in developing new ultrasound medical technologies. She has been leading teams at UW and MSU working on projects aimed to use nonlinear waves for improving High Intensity Focused Ultrasound (HIFU) therapy, to develop simulation and measurement tools for characterization of HIFU devices, design compact therapeutic arrays, understand bioeffects, facilitate regulatory oversight, and enhance safety and efficacy of HIFU treatment. While working on these projects, a novel method of ``boiling histotripsy'' (BH) to mechanically ablate tissue using pulsed HIFU was discovered. This technology has gained momentum and already is being explored for various clinical applications.

INVITED SPEAKER

Joline Fan

MD

Toward Focused Ultrasound for Treatment and Presurgical Mapping in Epilepsy

ABSTRACT

Drug-resistant epilepsy affects more than 20 million people worldwide, and while surgical resection and implantable neurostimulation can be highly effective, their success depends on accurately identifying the epileptogenic network through an extensive presurgical evaluation. Despite advances in neuroimaging and electrophysiology, current approaches remain limited in their ability to causally interrogate brain networks before invasive intervention. Low-intensity transcranial ultrasound stimulation (TUS) offers a unique opportunity to address this challenge through noninvasive, millimeter-scale modulation of deep brain structures. In this talk, I will review the current landscape of epilepsy surgery and discuss how TUS may complement existing diagnostic and therapeutic approaches. I will then present our studies in healthy participants demonstrating the feasibility of targeting epilepsy-relevant deep brain structures, including the anterior nucleus of the thalamus, followed by our ongoing efforts translating TUS to individuals with drug-resistant epilepsy. In the context of the comprehensive presurgical evaluation, we will discuss our development of a stimulation mapping framework that uses focused ultrasound as a causal network perturbation tool to characterize individualized network responses and identify potential targets across heterogeneous epilepsy networks. Finally, I will discuss emerging biological considerations for ultrasound neuromodulation, highlighting how regional differences in spatial transcriptomic architecture may contribute to variability in stimulation responses. Together, these studies position focused ultrasound as a precision tool for personalized network mapping to advance diagnosis, surgical planning, and targeted neuromodulation in epilepsy.

BIOGRAPHY

Joline Fan, MD, MS, is an Assistant Professor at UCSF in the Departments of Neurology (Division of Epilepsy) and Psychiatry & Behavioral Sciences. Her research focuses on developing innovative neurostimulation technologies for epilepsy and neuropsychiatric disorders, as well as exploring the complex relationship between sleep and epilepsy through multimodal neuroimaging. As an epileptologist, Dr. Fan specializes in invasive recording methods, including intracranial responsive neurostimulation and stimulation mapping. Furthermore, she is passionate about developing and translating personalized, non-invasive, low-intensity focused ultrasound methods for treating neuropsychiatric disorders like depression and epilepsy. Dr. Fan earned her bachelor's degree in Chemical Engineering from Princeton University and her master's in Bioengineering from Stanford University. She completed her medical education, neurology residency, and epilepsy fellowship at UCSF. Her work has garnered numerous early-career investigator awards, including the NIH K23 Career Development Award, American Epilepsy Society Young Investigator Award, NARSAD Brain Behavior Research Foundation, Doris-Duke Physician Scientist Fellowship, and the Chen Scholars Junior Award.

INVITED SPEAKER

Quanxiang Xian

PhD

Precision sonogenetic neuromodulation and its therapeutic potential

ABSTRACT

Sonogenetics couples focused ultrasound with genetically encoded actuators to enable noninvasive, cell-type-specific neuromodulation. However, ultrasound neuromodulation remains constrained by incomplete mechanistic understanding and diffraction-limited spatial resolution. Here, we establish a sonogenetics framework that resolves both challenges. First, we identify specific mechanosensitive proteins as key mediators of ultrasound sensitivity. Leveraging this insight, we develop a strategy that overcomes spatial diffraction limits, enabling cell-type-specific and spatially targeted modulation of deep-brain circuits. We further demonstrate therapeutic efficacy in preclinical models of neurological and psychiatric disorders, validating a mechanism-driven sonogenetics platform. By bridging fundamental biophysics with circuit neuroscience, this work positions sonogenetics as a foundational strategy for interrogating dysfunctional brain circuits and enabling a new class of non-invasive, cell-type-specific precision therapies.

BIOGRAPHY

Dr. Quanxiang Xian received her PhD in Biomedical Engineering from The Hong Kong Polytechnic University in 2021 under the supervision of Prof. Lei Sun, following an M.Sc. in neuroscience from Jinan University. She is currently a Research Assistant Professor in the Department of Biomedical Engineering at The Hong Kong Polytechnic University. Her research focuses on developing and refining non-invasive sonogenetic technologies for precise modulation of deep brain circuits, with therapeutic applications in rodent models of neurological and psychiatric disorders. She is also conducting comprehensive studies on the mechanisms underlying ultrasound neuromodulation and advancing its potential for clinical translation. Dr. Xian's research has been published in high-profile journals, including PNAS, Molecular Psychiatry, Advanced Science, and Cell Reports.

INVITED SPEAKER

Daniel Whitcomb

PhD

Cellular and molecular effects of ultrasound neuromodulation of the hippocampus

ABSTRACT

Focused ultrasound stimulation (FUS) is now established as a major non-invasive neuromodulator for experimental and therapeutic purposes. But how exactly does FUS exert its effects? Our work centres on understanding the cellular and molecular mechanisms that underpin neuromodulation by ultrasound. We previously reported how transient ultrasound stimulation of rodent cortical neurons leads to rapid and persistent increases in intrinsic excitability, effects that are initiated by synaptic activity (Clennell et al., 2021, Brain Stimul. 14(2):217--225; 2023, Brain Stimul. 16(2):540--552). Building on this, we have also shown how transcranial ultrasound stimulation directed to the hippocampus strengthens the synaptic circuitry within this brain region and, importantly, conditions the network for elevated function many hours following stimulation (Brain Stimul. 2025, 18(5):1587--1599). In our most recent unpublished work, we have found evidence of specific molecular pathways responsible for these effects, with our data now indicating that the basal state of the neural circuit is a significant determinant of the specific effects of ultrasound stimulation. These findings may have important implications for the use of FUS as a research tool and in therapeutic interventions.

BIOGRAPHY

Daniel Whitcomb is a Senior Lecturer in Translational Neuroscience (School of Psychology and Neuroscience, University of Bristol, UK). Having completed a PhD in Neuroscience determining mechanisms of aberrant synaptic plasticity in Alzheimer's disease pathology (Cell 141 (5), 859--871; Nature Neuroscience 14 (5), 545--547), Daniel went on to characterise cellular and molecular processes underlying synapse loss in the disease during a Post-Doctoral Research Associate position (Wellcome Trust/Medical Research Council Neurodegenerative Initiative Program) (Journal of Neuroscience 35 (12), 4804--4812; Brain 135 (7), 2103--2114). Using a range of electrophysiological and molecular biology techniques, Daniel's research now centres on understanding the molecular mechanisms that underpin neuromodulation by ultrasound, and how these effects can be leveraged for therapeutic benefit (Brain Stimulation 14 (2), 217--225; Brain Stimulation 18 (5), 1587--1599).

INVITED SPEAKER

Axel Thielscher

PhD

Controlling the dose in transcranial brain stimulation

ABSTRACT

The primary focus of the talk will be on personalized dose control in transcranial electrical and electromagnetic stimulation, but will also include ultrasound stimulation. It will begin by proposing a working definition of ``stimulation dose,'' followed by a discussion of why quantifying the dose is important for both basic research and clinical applications, and how accurately it needs to be known to support reliable interpretation and optimization of stimulation effects and safety assessments. After briefly outlining the current status of in vivo dose measurements in humans, the main part of the talk will focus on personalized dose calculations, addressing: the dependence of the calculated stimulation dose on technical factors and biophysical tissue properties; quantifying and managing uncertainties in dose calculations; and strategies to improve the accuracy and robustness of personalized dose modeling. Overall, the talk will highlight conceptual, methodological, and practical considerations relevant to the application of dose calculations in basic and clinical research.

BIOGRAPHY

Axel Thielscher received doctoral degrees in Electrical Engineering and Biomedical Sciences, both with highest honors, from the University of Ulm, Germany. He subsequently completed a postdoctoral fellowship at Brown University (Providence, RI, USA) and worked as research group leader at the Max Planck Institute for Biological Cybernetics in Tübingen, Germany. In 2012, he moved to Denmark to take up a shared position as Associate Professor at the Technical University of Denmark (DTU) and Senior Researcher at the Danish Research Centre for Magnetic Resonance (Copenhagen University Hospital Amager & Hvidovre). In 2021, he was promoted to Full Professor, and in 2022 he took over the role as Head of Section for Magnetic Resonance at DTU. Axel Thielscher's research interfaces engineering with neuroscience and clinical neuropsychiatric research. His work focuses on the integration of non-invasive brain stimulation techniques with advanced brain imaging, as well as the development of computational dosimetry methods for brain stimulation. A central theme of his research is the investigation of the fundamental biophysical mechanisms underlying non-invasive brain stimulation, with the aim of translating this knowledge into more effective and precise stimulation protocols. He is the founder of the SimNIBS project (Simulation of Non-Invasive Brain Stimulation), which pioneered the first open-source software pipeline enabling individualized finite element method (FEM) simulations of brain stimulation based on MRI data. SimNIBS is now widely used by the international research community and has been incorporated into several clinical trials in Denmark and internationally.

Conference Abstracts

ORAL PRESENTATIONS

Oral presentations will be delivered in the Auditorium. To meet demand for attendance, there will be two additional rooms (Room C and Room D) to seat delegates. Both rooms are linked to the hall by live video with two-way audio, so wherever you are seated, you can follow the full program, put questions to the speakers, and take part in the discussion alongside everyone across the rooms.

POSTER PRESENTATIONS

Posters are separated into two sessions, one on Wednesday, one on Thursday. These will begin with a poster pitch session in the Auditorium, during which each of the presenters allocated a slot on that day will have the opportunity to present a 1 minute pitch with a single slide. This must be uploaded in advance of the conference.

Following the poster pitches, there will be a poster session held in Rooms A and B, running in parallel with the industry exhibition.

Posters are numbered in the format [Day]-[Category]-[Sequence number] as follows:

Day:

W- Wednesday poster session

T- Thursday poster session

Subject category:

1. Biomechanisms
2. Clinical
3. Cognitive Neuroscience
4. Other Ultrasound Applications
5. Preclinical
6. Technical/Engineering
7. Early Stage

Posters may be displayed on the day of presentation only, materials for hanging will be provided.

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BIOMECHANISMS

CLINICAL

COGNITIVE NEUROSCIENCE

OTHER ULTRASOUND APPLICATIONS

PRECLINICAL

TECHNICAL/ENGINEERING

Biomechanisms

SECTION 01 / 06 · 6 ORAL PRESENTATIONS · 19 POSTERS

Cell-Specific Effects of Transcranial Ultrasound Stimulation (TUS) in the Human Brain: A Pilot Diffusion Magnetic Resonance Spectroscopy (dMRS)

Elena Brunet[1], *Kadir Şimşek*[2], *Jessica Cleverly*[2], *Lewis Kitchingman*[2], *David McGonigle*[2], *Marco Palombo*[2], *Mara Cercignani*[2], *Elsa Fouragnan*[1]

1 Brain Research Imaging Centre (BRIC), Faculty of Health, University of Plymouth, Plymouth, UK
2 Cardiff University Brain Research Imaging Centre (CUBRIC), Cardiff University, Cardiff, UK

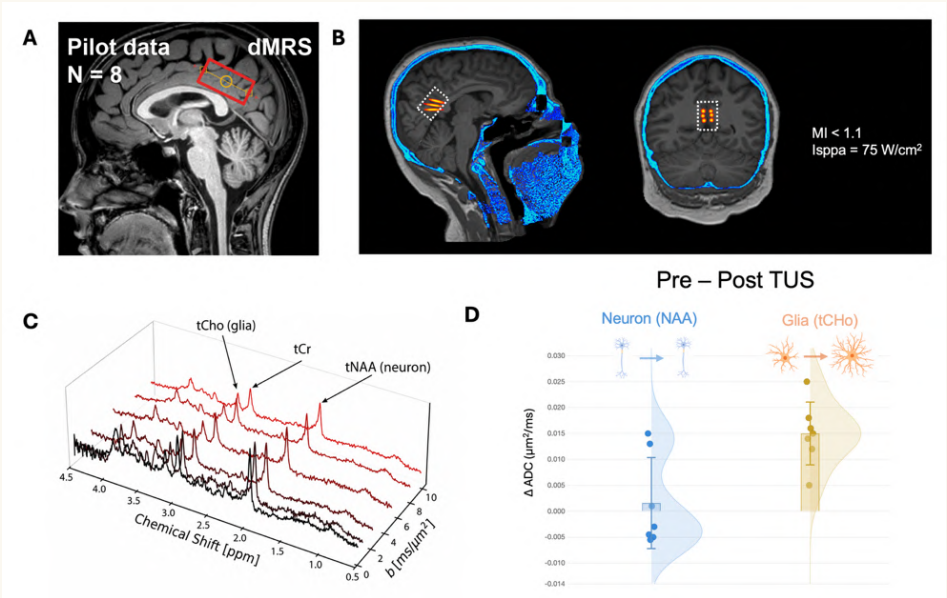
Background, Motivation and Objective: Transcranial ultrasound stimulation (TUS) is a non-invasive neuromodulation technique enabling precise targeting of deep brain structures (Tufail et al., 2011; Folloni et al., 2019; Yaakub et al., 2023). However, the differential cellular impact on neurons and glial cells remain poorly understood (Oh et al., 2019). While conventional diffusion MRI lacks cellular specificity due to ubiquitous water diffusion (Ronen et al., 2014), diffusion-weighted magnetic resonance spectroscopy (dMRS) probes cell-specific microstructural alterations in vivo (Ligneul et al., 2019; Palombo et al., 2018). Specifically, total N-acetylaspartate (tNAA) and total choline (tCho) serve as exclusive markers for neuronal and glial compartments, respectively (Urenjak et al., 1993; Choi et al., 2007).

Methods: To capture cell-specific microstructural changes, dMRS data were acquired in the high diffusion-weighting regime on a high-performance Connectome gradient system scanner, immediately before and after a single session of multi-focal TUS to the bilateral posterior cingulate cortex (3 targets per hemisphere) (Figures A and B). Metabolite apparent diffusion coefficients (ADC) for tNAA and tCho were calculated via a standard monoexponential decay model:

$$ln\left(\frac{S_b}{S_0}\right) = -b.ADC,$$

where S_b and S_0 represent the diffusion and non-diffusion-weighted signals, and b is the diffusion-weighting factor $(ms/\mu m^2)$. Data preprocessing and modeling were performed as described in Ligneul et al. (2023) (Figure C). Changes in ADC (ΔADC) were evaluated using statistical comparisons between pre and post TUS (Figure D).

Results/Discussion: Preliminary data from N=8 revealed distinct cell-type responses post-TUS. Glial tCho exhibited an increase and wider variance in diffusion, indicating an acute glial-specific structural or metabolic reaction to ultrasound (Figure D). By contrast, and as hypothesized, tNAA showed no significant microstructural or diffusion alterations, suggesting that transcranial ultrasound does not compromise neuronal integrity. These results validate dMRS feasibility for tracking human cell-specific neuromodulation in vivo. Taken together, our preliminary findings suggest that low-intensity TUS preferentially alters glial microstructure or intracellular dynamics within the PCC and provides a better understanding of the cellular mechanisms of TUS in humans.



Evidence of vascular and blood flow effects of ultrasound stimulation observed in mice

Héctor Estrada[1,2], *Yitong Li*[1,2], *Lukas Glandorf*[1,2], *Paul Wrede*[1,2], *Justine Robin*[1,2,3], *Quanyu Zhou*[1,2], *Ali Özbek*[1,2], *Zhenyue Chen*[4], *Shy Shoham*[5], *Daniel Razansky*[1,2].

1 Institute of Pharmacology and Toxicology and Institute for Biomedical Engineering, Faculty of Medicine, University of Zurich, Switzerland
2 Institute for Biomedical Engineering, Department of Information Technology and Electrical Engineering, ETH Zurich, Switzerland
3 Physics for Medicine Paris, INSERM U1273, ESPCI Paris, PSL University, CNRS, Paris, France
4 Institute of Precision Optical Engineering, School of Physics Science and Engineering, Tongji University, Shanghai, China
5 Department of Ophthalmology and Tech4Health and Neuroscience Institutes, NYU Langone Health, New York, USA

Research into transcranial ultrasound neurostimulation (TUS) has traditionally focused on neuronal response, yet in-vitro studies often overlook the vascular complexities present in-vivo[1]. Because ultrasound is inherently cell-agnostic, it likely impacts the entire neurovascular unit, as evidenced by reports of astrocyte activation[2], vasodilation[3], and red-blood-cell (RBC) manipulation[4]. Using an integrated imaging platform[5,6], we demonstrate three specific vascular effects induced by TUS. First, we applied holographic TUS to the mouse cortex (3 MHz, 1.2 MPa, 3 foci, 15 s, 40% duty cycle, 100 ms pulse duration, 4 Hz) and observed the expected local hemodynamic response. Beyond the focus, however, we detected significant oxygenated hemoglobin responses 3.5 mm deeper than the target and deoxygenated hemoglobin moving from the stimulated region toward the superior sagittal sinus (SSS). To further investigate how the ultrasound field affects RBCs, we targeted a pial vessel while imaging Calcium dynamics in GCamp6f mice (single focus, 0.6 MPa). We observed a sharp increase in fluorescence inside the vessel during the 150 ms sonication, which then moved downstream toward the SSS after stimulation. Finally, we explored ARF effects in the absence of blood flow by imaging transcranial brain tissue displacement using ex-vivo optical coherence tomography. With the same spherical array and single focus at 2.8 MPa, we observed a maximum displacement of 2 µm in the vicinity of a vessel, extending up to 0.7 mm - much further than the 350 µm focal size. Collectively, these results underscore that TUS is not merely neuron-centric, necessitating further research into how these vascular and blood flow interactions scale to the human brain.

References: 1. Lemaire, T. et al. Microscopic deconstruction of cortical circuit stimulation by transcranial ultrasound. 2024.10.10.617091 Preprint at https://doi.org/10.1101/2024.10.10.617091 (2024).
2. Oh, S.-J. et al. Ultrasonic Neuromodulation via Astrocytic TRPA1. Current Biology 30, 948 (2020).
3. Shen, Y. et al. Label free, capillary-scale blood flow mapping in vivo reveals that low intensity focused ultrasound evokes persistent dilation in cortical microvasculature. 2024.02.08.579513 Preprint at https://doi.org/10.1101/2024.02.08.579513 (2024).
4. Dyson, M., Woodward, B. & Pond, J. B. Flow of Red Blood Cells stopped by Ultrasound. Nature 232, 572–573 (1971).
5. Estrada, H. et al. Holographic transcranial ultrasound neuromodulation enhances stimulation efficacy by cooperatively recruiting distributed brain circuits. Nat. Biomed. Eng 1–10 (2025) doi:10.1038/s41551-025-01449-x
6. Estrada, H. et al. Brain-wide hemodynamic responses to precise transcranial ultrasound neuromodulation. Brain Stimulation 19, 102978 (2026)

Region and pulse repetition frequency dependent bidirectional modulation of dopamine release by focused ultrasound (FUS)

Jonas Bendig[1,2], *David Sulzer*[2] *and Elisa Konofagou*[1,3,4]

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2 Department of Psychiatry, Columbia University Irving Medical Center, New York, NY, USA
3 Department of Radiology, Columbia University Irving Medical Center, New York, NY, USA
4 Department of Neurosurgery, Columbia University Irving Medical Center, New York, NY, USA

Transcranial focused ultrasound (FUS) can modulate targets deep in the brain in a non-invasive manner, but it is not well understood whether it acts on neuronal cell bodies, dendrites or axonal projections. We addressed this open question by using fiber photometry with the genetically encoded dopamine sensor GRAB-DA3m to measure striatal dopamine release in awake, freely moving mice during transcranial FUS (550 kHz, 5-s pulse trains, 20% duty cycle, 0.76 MPa peak negative pressure, PhoCUS system) targeting either the substantia nigra pars compacta (SNc, n = 5 animals) or the dorsal striatum (n = 4 animals). To localize the cellular site of FUS action, SNc and striatal stimulation were compared at pulse repetition frequencies of (PRF) 2.5 and 10 Hz. SNc FUS at 2.5 Hz produced a significant increase in dopamine release during FUS (mean Z-score = 0.72 ± 0.20, p = 0.0234) while striatal modulation did not (mean Z-score = 0.28 ± 0.44, p = 0.5748, panel B). Similarly, for 10 Hz FUS we found a significant decrease of dopamine release when targeting the SNc (mean Z-score = -1.17 ± 0.28, p = 0.0131) but not when targeting the striatum (mean Z-score = -0.30 ± 0.13, p = 0.0997, Panel C).To further characterize PRF-dependent effects at the SNc, six stimulation frequencies were tested (1, 2.5, 5, 10, 20, and 100 Hz). PRF strongly determined response polarity across animals (Friedman χ^2 = 19.97, p = 0.0013; panel C). Low PRFs (1–2.5 Hz) evoked positive dopamine release, whereas medium-to-high PRFs (10–20 Hz) produced sustained suppression. The 2.5 Hz condition yielded the largest excitatory peak; mean responses across the stimulation epoch by PRF are shown in panel D. In addition, Post-FUS spontaneous dopamine transients at 2.5 Hz showed increased amplitude (pre 6.6 vs. post 9.4% ΔF/F, p = 0.035), prolonged duration (333 vs. 433 ms, p = 0.016), and a concurrent reduction in event rate (0.48 vs. 0.38 events/s, p = 0.023), indicating circuit-level effects that outlast the stimulation window. Together, these findings show that FUS modulates dopamine dynamics through action at the cell bodies or dendrites but not axons and that the magnitude of dopamine release can be modulated via the PRF of the FUS signal.

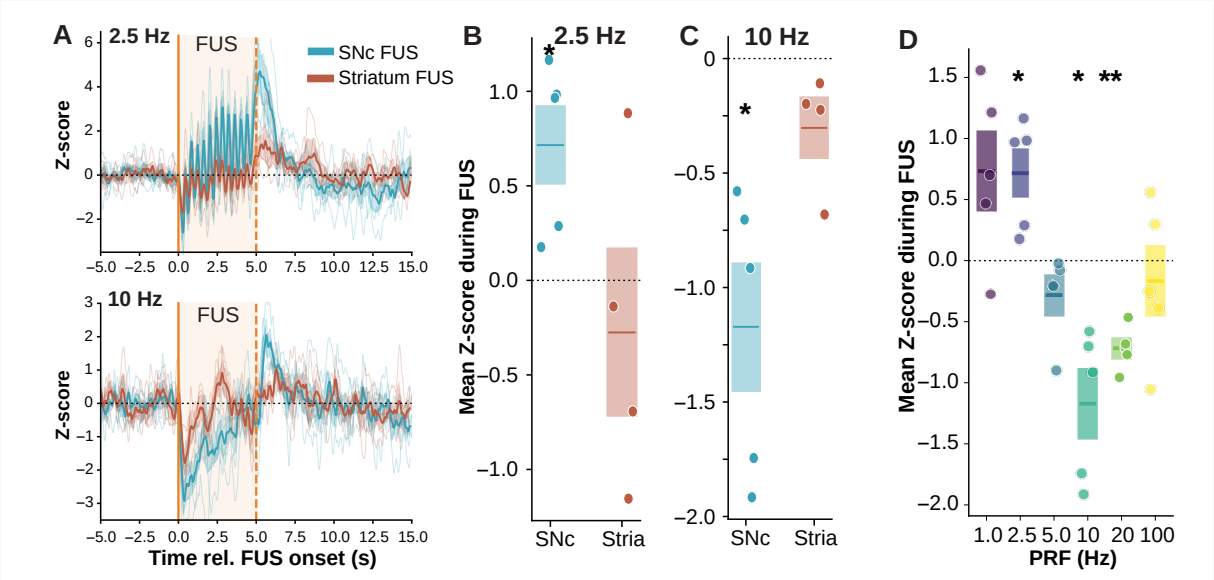


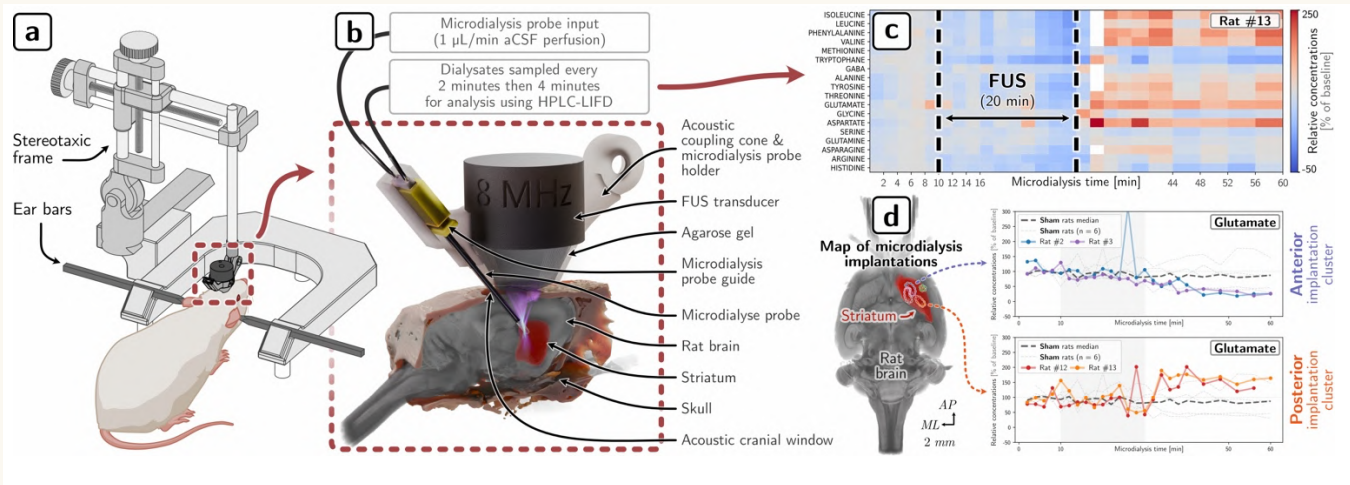
Figure 1: Region and frequency dependent effects of FUS on dopamine release. A Z-scored traces of GrabDa3m signal in the SNc and striatum at PRFs of 2.5 and 10 Hz. B/C Mean Z-scores during FUS targeting the SNc (blue) or striatum (orange) with a PRF of 2.5 Hz (B) and 10 Hz (C). D Mean Z-scores during FUS targeting the SNc for different PRFs. Curves and bar graphs show mean (line) and SEM (shaded areas/bars), One-sample t tests against 0 $*$: $<$0.05; $**$: $<$0.01.

In Vivo Characterization of Localized Neurochemical Responses in the Rat Striatum to Focused Ultrasound Neurostimulation

Tom Aubier[1], *Sandrine Parrot*[2], *Jorge Torres*[1], *Alexandre Carpentier*[3], *Ivan Suarez-Castellanos*[1], *W. Apoutou N'Djin*[1]

1 LabTAU, INSERM, Centre Léon Bérard, Université Claude Bernard Lyon 1, F-69003, Lyon, France
2 INSERM, Centre de Recherche en Neurosciences de Lyon CRNL U1028 UMR5292, F-69500 Bron, France
3 Sorbonne Université, AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, Service de Neurochirurgie, Paris, France

Focused ultrasound (FUS) neurostimulation is a promising non-invasive approach for modulating brain activity with high spatial specificity, yet its underlying neurochemical mechanisms remain poorly understood. In this preliminary study, we investigated the effects of prolonged lowintensity FUS exposure on the biochemical microenvironment of the rat striatum using in vivo microdialysis. Female rats anesthetized with ketamine/xylazine were exposed to a 20-minute FUS sequence composed of 500 µs pulses delivered at 100 Hz and a central frequency of 8.24 MHz. The concentrations of 18 amino acids were monitored online within the FUS-targeted striatal region through continuous collection of microdialysates for subsequent neurochemical analysis via high-performance liquid chromatography coupled to a laser-induced fluorescence detector (HPLC-LIFD). Positioning of the FUS transducer and the microdialysis probe using a stereotaxic frame, post-mortem reconstruction of the probe localization, together with numerical modeling of focal pressure distribution ($p < 0.8$ MPa) and max local heating, was performed using the open-source software CoperniFUS (Fig. a and b). Compared with the sham group composed of 6 animals, substantial alterations – predominantly occurring after the end of the sonication period – were observed in the local neurochemical microenvironment of the 7 FUS-stimulated subjects (Fig. c). Indeed, the stimulation protocol altered the extracellular concentrations of several amino acids known to play key roles in local neural activity (Glutamate, GABA, Leucine, Tyrosine, among others, Fig. c and d). Significant inter-individual variability was also observed, potentially linked to differences in probe positioning, regional heterogeneity of the striatum, and tissue sensitivity to stimulation (Fig. d). Numerical simulations performed within CoperniFUS using k-Wave confirmed that the applied FUS protocol remained within the safety margins recommended by the ITRUSST Consortium (MI < 0.3 and tissue heating < 0.1°C). These preliminary findings suggest that prolonged low-intensity FUS neurostimulation can induce marked neurochemical perturbations within targeted brain tissue with potential region-dependent effects at a millimeter scale. Further work is required to further describe the mechanisms, reproducibility, spatial specificity, and safety of these effects. Project support: French National Research Agency (ANR16-TERC0017, ANR-21-CE19-0007 & ANR-21-CE19-0030), the Focused Ultrasound Foundation (Centers of Excellence).



Ultrasound stimulation of a deep thalamic nucleus modulates large-scale neural synchrony in humans

Vivek Sharma[1], *Martin Wimmers*[1,2], *Sjoerd Meijer*[1], *Debby Klooster*[2,3,4], *Paul Tiesinga*[1], *Lennart Verhagen*[1]

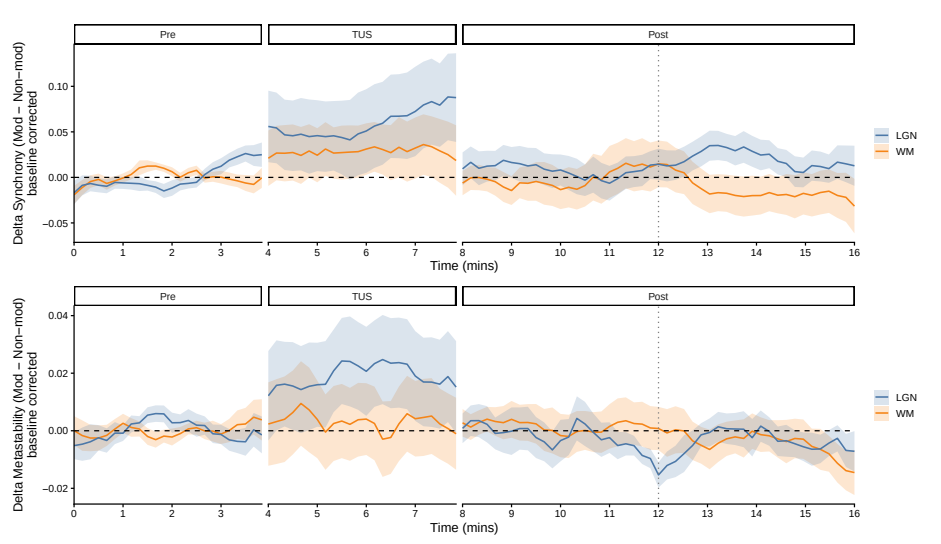
1 Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, Netherlands
2 Electromagnetics for Care+Cure Lab, Electromagnetics Group, Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands
3 Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, Netherlands
4 Academic Center for Epileptology, Maastricht University Medical Center and Kempenhaeghe, Heeze, the Netherlands

Introduction: Low-intensity transcranial ultrasound stimulation (TUS) can non-invasively reach deep brain structures with millimetre precision, but evidence for reliable and functionally specific effects in humans remains limited (Sarica et al., 2022). Here, we asked whether TUS targeted to the lateral geniculate nucleus (LGN), a thalamic relay in the visual system, can selectively alter large-scale neural dynamics (Ash et al., 2025).

Methods: Twenty-four healthy participants took part in two experiments: a preregistered cohort (n = 12) and an independent replication (n = 12). Simultaneous 6 and 7.5 Hz visual flicker frequency-tagged the pathway through the stimulated LGN ("modulated") and the contralateral pathway ("non-modulated") (Norcia et al., 2015). TUS (500 kHz) was delivered to the LGN or to a nearby white-matter control site while synchrony and metastability were quantified from EEG using the weighted Kuramoto order parameter (Cabral et al., 2014), and steady state visual evoked potential (SSVEP) amplitude was estimated using Rhythmic Entrainment Source Separation (Cohen & Gulbinaite, 2016).

Results: TUS selectively modulated synchrony and metastability at the tagged frequency associated with the stimulated pathway. In the preregistered experiment, significant Timepoint × Modulation interactions were observed for synchrony ($F = 9.82$, $p = 0.0018$) and metastability ($F = 10.14$, $p = 0.0015$). These effects were independently replicated for synchrony ($F = 11.08$, $p < 0.0001$) and metastability ($F = 6.77$, $p = 0.0001$). In the replication, metastability showed a significant Timepoint × Modulation × Target interaction ($F = 3.21$, $p = 0.022$), while synchrony showed a similar trend ($F = 2.15$, $p = 0.091$). By contrast, SSVEP amplitude was unaffected.

Conclusion: LGN-targeted TUS selectively modulated synchrony and metastability within the stimulated thalamo-cortical pathway, indicating that ultrasound can non-invasively reshape large-scale dynamics in deep human brain circuits.



Acknowledgements: Supported by the European Union Horizon Europe programmes AISN (101057655) and eBRAIN-Health (101058516).

Transcranial ultrasound stimulation modulates neuronal membrane potentials across broad timescales in the awake mammalian brain

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Transcranial ultrasound stimulation (TUS) offers noninvasive neuromodulation with high spatiotemporal precision, but its cellular-level effects in the awake brain remain poorly understood. Using the genetically encoded voltage indicator SomArchon, we performed highspeed kilohertz voltage imaging in awake head-fixed mice. TUS was delivered with a 0.35 MHz transducer at 10 or 40 Hz pulse repetition frequency, at intensities below the estimated threshold for auditory brainstem activation. We analyzed changes in membrane potentials (Vm), spiking, and coordination across simultaneously recorded neurons. We found that TUS evoked rapid (<10 ms) Vm depolarizations in 42.8 % of neurons, while only increasing spiking in 20.5 % of neurons, highlighting a direct effect of TUS on modulating synaptic inputs. Many neurons were entrained at both PRFs (20.8 % at 10 Hz; 12.7 % at 40 Hz) with Vm exhibiting significant phaselocking to individual TUS pulses. Vm entrainment was accompanied by increased temporal coordination across neurons and reset network synchrony. Furthermore, TUS-evoked cellular responses adapted over time, often transitioning from membrane depolarization to hyperpolarization upon repeated exposures, demonstrating prominent response depression. By resolving single-neuron responses in the awake mammalian brain, our results demonstrate that TUS directly activates individual cortical neurons with latencies often shorter than 10 ms. TUS pulsed at physiologically relevant frequencies of 10 and 40 Hz robustly entrains neural dynamics, alters network coordination and evokes neuronal plasticity. These results highlight the therapeutic potential of designing TUS pulsing patterns to target desired neural dynamics and plasticity features.

Predicting which neurons fire and how: an open-source framework mapping transcranial focused ultrasound from acoustic field to single-neuron spike raster

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Background: Transcranial focused ultrasound (tFUS) is a non-invasive neuromodulation modality with millimetre resolution and access to deep brain structures, yet its biophysical mechanism remains unresolved. Exposure is conventionally specified by transducer surface or derated focal pressure, quantities only indirectly related to what ultimately matters for therapy, namely which neurons fire and through which pathway they are recruited. No published tool carries an exposure prescription through to a per-voxel statement of firing, so competing mechanistic hypotheses cannot be compared on a common field. We present an open-source, end-to-end framework that maps a transcranial acoustic field to per-voxel neural firing maps registered to anatomy, with six interchangeable mechanism modules evaluated on one shared multi-compartment Hodgkin-Huxley neuron.

Methods: The pipeline (Fig. 1a) couples heterogeneous nonlinear full-wave acoustic propagation (Fullwave) through a micro-CT human-skull specimen, a radiation-force-driven viscoelastic shear-FDTD solve giving tissue displacement and strain, and a Pennes bioheat solve giving temperature rise. The mechanical pathway converts local tissue strain into an effective lipid-bilayer membrane tension, $T = K_a \cdot \alpha \cdot \varepsilon_{eq}$, where ε_{eq} is the von Mises equivalent strain, K_a is the bilayer area-expansion modulus, and α is a dimensionless multi-scale coupling factor relating far-field tissue strain to local membrane area change. This tension gates two-state Boltzmann mechanosensitive channels, a depolarising Piezo1 and a hyperpolarising TREK-1, on a dendrite-soma-AIS Hodgkin-Huxley neuron that also carries intramembrane-cavitation, Ca^{2+}/SK, thermosensitive (TRP), astrocytic (TRPA1 to glutamate to NMDA), and mechanosensitive-synaptic pathways. The product $K_a \cdot \alpha$ is the single operative calibration knob and is treated as a literature-bracketed modelling parameter. Every numerical parameter is classified by source and bracketed by a ±25% sensitivity sweep. We demonstrate the framework on the Yaakub theta-burst protocol (500 kHz CTX-500 array, 20 ms bursts at 5 Hz, 10% duty, 80 s session) delivered through the Halle micro-CT skull with the bowl auto-aimed at the left dorsal anterior cingulate cortex (dACC). The surface drive is calibrated to reproduce Yaakub's reported 0.5 MPa transcranial focal pressure.

Results: At the calibrated exposure (focal PNP 0.50 MPa, MI 0.71, I_SPPA 8.1 W/cm², the acoustic metrics remaining within ITRUSST consensus safety envelopes), the focal membrane tension reaches about 6.5 mN/m, roughly 2.4 times the Piezo1 half-activation tension, and the strain-driven Piezo1/TREK-1 pathway alone produces firing at 5,468 brain voxels at up to 300 Hz. The resulting iso-25% firing volume is 8,523 mm^3, substantially larger than the acoustic -6 dB focal volume (116 mm^3) and elongated along the beam axis by the focal aspect ratio (Fig. 1c). Focal heating is modest, with a focal ΔT of 233 mK and a skull-bone peak of 0.94 K. A real-field mechanism sweep (six strain levels by five scenarios) shows the dendrite-heavy three-compartment geometry is necessary for firing at the working point, where the single-compartment baseline stays subthreshold, while the Piezo1-inactivation/Ca2+/SK pathway suppresses firing by about 30 to 33% (up to about 58% at saturation). Sensitivity analysis identifies the Piezo1 half-activation tension and the strain-to-tension product $K_a \cdot \alpha$ as the dominant uncertainties. End-to-end runtime is about 17 min per scenario on a single workstation for the fully volumetric, heterogeneous head model of roughly 28 million voxels over the 130 by 80 by 80 mm volume. By linking acoustic exposure to cellular firing, the framework is released open-source as a starting point for discriminating tFUS mechanisms against experimental recordings.

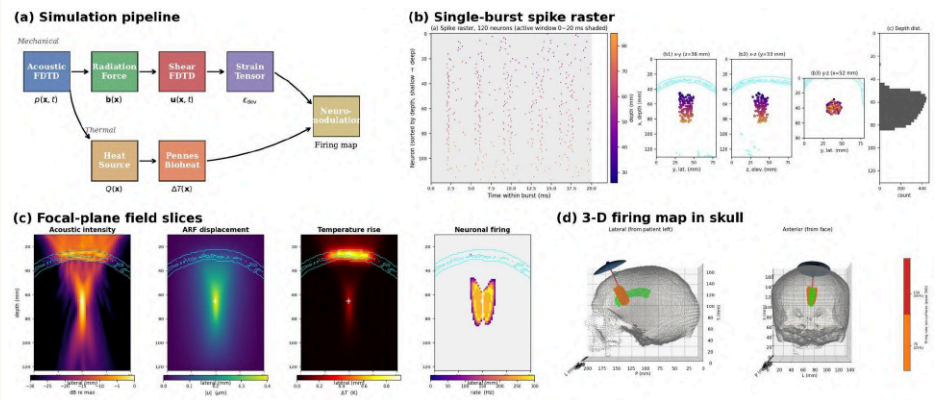

Figure 1: End-to-end prediction for the Yaakub theta-burst sonication through the Halle micro-CT human skull, aimed at the left dACC. (a) Simulation pipeline, in which the acoustic FDTD pressure field branches into a radiation-force and shear-FDTD mechanical path (strain) and an absorption and Pennes thermal path (ΔT), both converging on the multi-pathway Hodgkin-Huxley neuromodulation block. (b) Single-burst spike raster across 120 firing voxels sorted by depth, with co-registered ROI slices and a depth histogram. (c) Co-registered depth and lateral slices through the focal plane for acoustic intensity, radiation-force displacement, temperature rise, and neuronal firing rate, with the skull outline in cyan and the focus marked. (d) Three-dimensional iso-surfaces of the per-voxel firing rate (50% and 25% of peak) within the skull, viewed in lateral and anterior projections. Predicted, 5,468 firing voxels, iso-25% firing volume 8,523 mm^3, focal ΔT 233 mK.

From high-throughput transcranial ultrasound parameter discovery in non-human primates to translational challenges in humans

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Introduction: Transcranial Ultrasound Stimulation (TUS) is an attractive non-invasive brain stimulation (NIBS) technique, as it combines the ability to focus an ultrasound wave at millimeter-scale resolution [1]. Most TUS studies adopt stimulation parameters that have been previously shown to induce neural modulation in pre-clinical models and apply them in behavioural tasks [2, 3]. However, even though robust neural changes have been reported [1, 4, 5], there is no clear consensus on which parameters are best to elicit a specific neuromodulatory outcome. In the present study, our objective was to address these challenges through a high-throughput parameter mapping in non-human primates (NHP) to identify a set of inhibitory parameters capable of producing neuromodulatory effects and translate them to a healthy human cohort.

Methods: In the NHP work, two adult cynomolgus macaques (female Macaca fascicularis) were used. A two-step optimization framework consisting of a reach-and-pull task and electrophysiological readouts was used to scan a 109-space of candidate parameters across Pulse Repetition Frequency, Duty Cycle, and Power while targeting the primary motor cortex (M1) using a 250 kHz transducer (NeuroFUS Pro). The optimal inhibitory set of parameters extracted was translated to fifteen healthy participants by accounting for the difference between humans and NHPs in intensity delivered after skull absorption. Motor evoked potential (MEP) changes from single-pulse TMS before and after sonication of either the M1 or the superior parietal lobule (SPL). Several factors to explain the variability sources in the outcomes, such as baseline MEP levels, bone thickness, session order, and demographic variables, were then explored using Aligned Rank Transform (ART) for nonparametric factorial analysis ANOVAs and stepwise regression analyses.

Results: A framework to test TUS parameters was successfully developed and allowed rapid identification of a large number of parameters. An optimal parameter that showed the highest inhibitory effect was identified as eliciting both behavioural and electrophysiological changes in NHP. In humans, our group-level analysis revealed a facilitatory effect after TUSSPL, whereas no inhibitory effect was observed after TUSM1. Although we did not observe an inhibitory effect at the group level after TUSM1, baseline MEP levels and cumulated energy levels in M1 appeared to be good predictors of MEP changes post-TUS.

Conclusion: This study establishes a high-throughput, translational framework to systematically identify TUS parameters inducing reliable neuromodulation. Duration and intensity emerged as critical modulators, with longer sonication enhancing suppression and higher intensities shifting effects from inhibition to excitation. Translation to humans confirmed region-dependent neuromodulatory effects. Importantly, individual factors such as spatial precision, skull attenuation, and level of target engagement seem to be strong drivers of inter-individual variability, underscoring the need for multi-modal validation (e.g., TMS-EEG, fMRI) and personalized dosing to optimize TUS for clinical applications. We believe that this unique combination of model and techniques will help to identify safe and effective stimulation parameters and provide future translational guidelines for targeted circuit interrogation and therapeutic interventions.

The Influence of Endogenous Activity State on Offline Transcranial Ultrasound Stimulation Effects in the Human Motor Cortex

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Background: State dependency (whereby stimulation effects are contingent upon the ongoing activity state of the targeted region) has been observed across multiple brain stimulation modalities but remains largely unexplored in transcranial ultrasound stimulation (TUS). Understanding how endogenous neural activity during sonication shapes TUS' offline effects is critical both for optimizing future experimental designs and for informing therapeutic applications. Unlike transcranial magnetic stimulation, TUS does not appear to induce action potentials directly in humans, suggesting it acts through sub-threshold modulation of membrane potentials. If so, the presence or absence of endogenous activity may be a key determinant of whether TUS can meaningfully alter neural output. Here, we present preliminary data from an ongoing study systematically investigating state dependency of offline TUS effects in the human primary motor cortex (M1).

Methods: In a within-subject, two-by-two design, healthy right-handed participants (aged 18–35; planned N=24, data presented from N=6) receive TUS to either the left M1 or a control target (anterior ventricular horn/white matter), while M1 is either endogenously activated through a pinchforce task or at rest (watching a nature video). The M1 target is individually defined via task-fMRI functional localisation of the right first dorsal interosseous (FDI) muscle representation. TUS is delivered using a Neurofus Pro 250 kHz transducer (PRF: 100 Hz, DC: 10%, SD: 120 s (Zadeh et al., 2024)), with intensity optimized per participant using prospective acoustic simulations based on pseudo-CT skull models. Participants attend one planning MRI session and four TUS sessions (one condition per session, randomized, $\geq$72 h apart). Pre- and post-TUS (~5 and ~45 min) outcome measures include single-pulse TMS motor evoked potentials (MEPs), paired-pulse TMS (short-interval cortical inhibition, intracortical facilitation, long-interval cortical inhibition), and a pinchforce sequence learning task probing both force modulation and motoric sequence learning.

Results: Data collection is ongoing and will progress prior to poster submission. Preliminary data from six participants show a trend for M1-TUS to decrease MEP amplitude relative to control-TUS independent of activity state, with a numerically larger effect at ~45 minutes post-sonication than at ~5 minutes. No clear state dependency effects are yet evident in the neurophysiological measures. However, behavioral data from the force tracking task show a potential state dependency pattern: Active-M1-TUS was associated with a relative decrease in tracking error compared to Active-Control-TUS, while Rest-M1-TUS was associated with an increase relative to Rest-Control-TUS. No clear differential patterns in sequence learning between conditions emerged.

Conclusions: While neurophysiological markers of state dependency remain inconclusive at this early stage, the behavioural force tracking data offer an encouraging signal that the endogenous activity state during sonication may shape TUS' offline effects. Data collection is ongoing towards the full sample.

Focused ultrasound neuromodulation of calcium activity in glioblastome cell cultures: Preliminary characterisation of spatiotemporal properties and exploration of underlying mechanisms

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Introduction: The diverse biological effects of ultrasound have enabled the development of a broad range of therapeutic strategies for the treatment of numerous pathologies[1]. Among these applications, the neuromodulatory effects of focused ultrasound (FUS) have gained increasing attention for the treatment of neurological disorders and the improvement of patient quality of life[2,3,4]. Brain tumors, whose management typically relies on multimodal therapeutic approaches, may also benefit from the modulatory effects of FUS[5]. However, the impact of ultrasound stimulation on brain tumor cells remains poorly understood. In this preliminary study, we investigated FUS-induced calcium responses in glioblastoma cell cultures to assess their sensitivity to mechanical stimulation and explore the cellular mechanisms potentially involved. Understanding these responses may help evaluate the potential of FUS neuromodulation as an additional ultrasound-based tool for glioblastoma treatment.
Method: Calcium activity in glioblastoma cells was monitored using Fluo-4 fluorescence imaging. Cellular responses were quantified from normalized fluorescence variations ($\Delta F/F_0$) measured in individually segmented cells. Ultrasound stimulation was delivered as single pulses at 8.09 MHz. Different pulse durations (100 µs and 400 µs), selected based on previous studies in neuronal cultures, were evaluated. An input-voltage dose-escalation approach was used to gradually increase the acoustic stimulation intensity and identify activation thresholds in tumor cells. To distinguish ultrasound-evoked responses from spontaneous calcium activity, a classification algorithm was developed to identify responding cells and quantify activation rates. The effects of repeated stimulations were investigated, together with the spatiotemporal characteristics of calcium signaling. Perfusion experiments were performed to assess the contribution of extracellular signaling pathways to response propagation. The involvement of mechanosensitive channels was explored using Ruthenium Red pharmacological blockade. Finally, cell viability and mitochondrial integrity were assessed using CellEvent and MitoTracker staining before and after ultrasound exposure.
Results: Focused ultrasound elicited detectable calcium responses in glioblastoma cells (Fig. 1b) above a defined activation threshold (f = 8.09 MHz, pulse duration = 100 µs, acoustic energy = 460 µJ). A reduced response amplitude was observed when two stimulations were delivered less than 10 minutes apart (Fig. 1c), suggesting the presence of adaptation mechanisms or incomplete recovery of the underlying cellular processes. In contrast to previous observations in neuronal cultures, calcium responses remained spatially confined to the stimulated region, with no clear evidence of intercellular propagation. Perfusion experiments did not reveal extracellular signaling mechanisms capable of mediating calcium wave propagation. Furthermore, pharmacological inhibition with Ruthenium Red, tested at multiple concentrations, did not abolish ultrasound-induced responses. MitoTracker imaging did not reveal obvious changes in mitochondrial activity under the stimulation conditions investigated. The CellEvent data are still under analysis.
Discussion: These findings demonstrate that focused ultrasound can trigger localized calcium responses in glioblastoma cells and reveal both activation threshold and temporal adaptation properties. The absence of detectable intercellular propagation and the persistence of responses following Ruthenium Red treatment suggest that mechanisms distinct from those previously reported in neuronal cultures may be involved. This work provides a first step toward understanding the cellular pathways underlying ultrasound sensitivity in glioblastoma and evaluating the potential of focused ultrasound as a tool for modulating brain tumor cell activity.

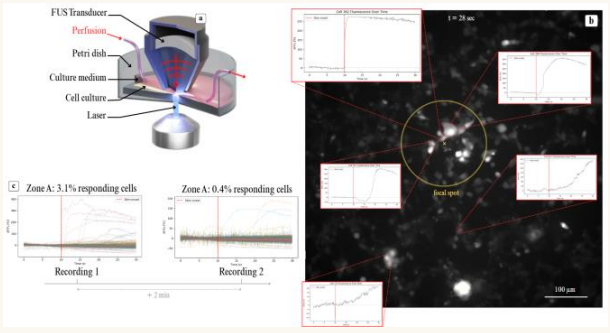

Figure 1: (a) Experimental setup. (b) Examples of fluorescence dynamics ($\Delta F/F_0$) in responding cells (focal spot) and non-responding cells. (c) $\Delta F/F_0$ in the same region of interest for the first and second ultrasound pulses

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Acknowledgments: This work was supported by the following projects and organizations: ANR-16-TERC0017, ANR-21-CE19-0007 and ANR-21-CE19-0030, INSERM First Step, INSERM 2021-2030 Cancer Control Strategy and the Focused Ultrasound Foundation.

A Miniature tFUS Device for Neuromodulation: From Cellular Mechanisms to Proof-of-Concept Applications

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Introduction: Transcranial focused ultrasound stimulation (tFUS) is an emerging, noninvasive technique with high spatial and temporal resolution. Despite this potential, the underlying mechanisms, the safety profile, and the full spectrum applications require further investigation. This study aims to advance the field by designing and testing a miniature US device for use in pre-clinical studies, with a focus on both cellular and systems-level effects.

Methods: We developed a custom ultrasound device and conducted both in vitro and in silico studies to assess its cellular effects. In laboratory experiments using hippocampal cell cultures, current-clamp recordings were obtained from synaptically isolated neurons. Neuronal voltage responses to current steps were measured before and after brief ultrasound stimulation and compared with sham stimulation. In parallel, computational models based on the Hodgkin-Huxley formalism were used to simulate the potential mechanisms underlying the observed changes. We also validated the device in vivo in anesthetized rats by eliciting evoked potentials and motor responses. **Results:** Electrophysiological recordings revealed that brief ultrasound exposure caused long-term changes in membrane properties, including increased voltage noise and resting membrane potential, as well as decreased spike latency and action potential amplitude. In silico modeling supported the hypothesis that these electrical changes may result from altered membrane permeability or capacitance. In vivo experiments showed a robust ultrasound-evoked potential in anesthetized animals, along with a more variable motor response.

Conclusions: Our results demonstrate the feasibility of miniaturized tFUS for basic research, and provide evidence that besides the acute modulation of ion channel activity, longer-term and subtler effects by modulating membrane properties also emerge following transient US stimulation. In future studies, we plan to use closed-loop stimulation triggered by sleep spindle detection in animal models with cognitive deficits to investigate effects on learning and memory.

Bidirectional modulation of cortical activity by PRF-controlled focused ultrasound in mice

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Focused ultrasound (FUS) is a promising tool for non-invasive neuromodulation, but how stimulation parameters shape neural circuit responses remains unclear. Here, we investigated the effects of tFUS parameters such as pulse repetition frequency (PRF) and duty cycle (DC) on neural activity in the primary somatosensory cortex (S1) in a group of 10 mice. Using a 128-channel random phased-array transducer with sub-mm spatial resolution, we delivered spatially precise ultrasound stimulation while recording multi-unit activity and local field potentials (LFPs). We found that PRF primarily determines the selective manipulation of distinct neuronal subtypes at 60% duty cycle. High-PRF stimulation (3 kHz) induced excitatory responses in regular-spiking units (RSUs), which exhibited both time-locked (0 – 0.1s) and delayed firing (0.2 – 0.5s). In contrast, low-PRF stimulation (40 Hz) produced inhibitory effects, engaging fast-spiking units (FSUs) that exhibited delayed responses and pronounced low-gamma oscillations, frequency range within 30-50Hz (Figure 1a-b). To investigate the underlying mechanisms, we applied pharmacological blockers targeting excitatory and inhibitory synaptic transmission. Blockade of glutamatergic receptors (AP5 + CNQX) largely abolished RSU responses to 3 kHz stimulation, indicating that excitatory effects are mediated by glutamatergic signaling compared to control treated with PBS (Veh; vehicle). In contrast, GABAA receptor blockade (SR95531) suppressed FSU responses to 40 Hz stimulation and significantly reduced gamma oscillations, suggesting a key role of GABAergic circuits in inhibitory modulation (Figure 1c-d). Together, these results demonstrate that PRF can selectively recruit distinct neuronal subpopulations, enabling bidirectional control of cortical activity. Our findings provide insight into the circuit-level mechanisms of ultrasound neuromodulation and highlight its potential for precise and flexible control of brain activity.

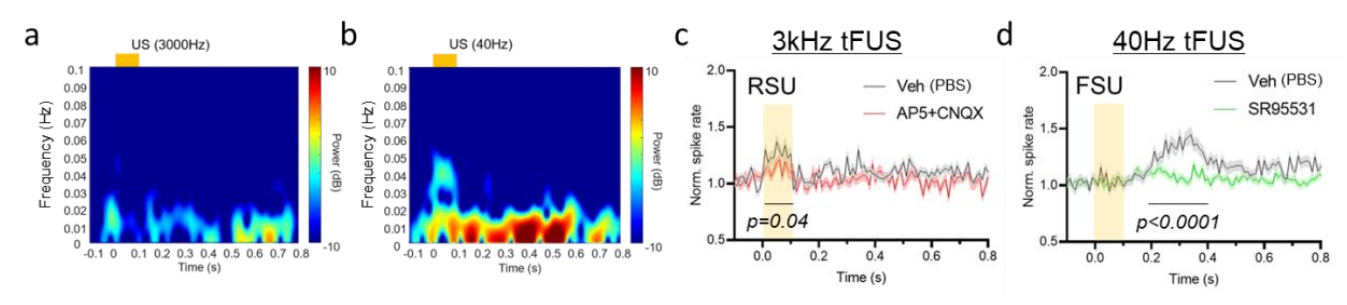

Figure 1: (a-b) LFP spectrograms show gamma oscillations at 40Hz tFUS but not 3 kHz tFUS. (c) RSU spike responses to 3 kHz tFUS are reduced by application of glutamate receptor blocker. (d) FSU spike responses to 40 Hz tFUS showed delayed pattern and suppressed by treatment of GABAA receptor blocker. Yellow shaded region indicates stimulation period.

Acknowledgments: NIH grants NS124564 (PI: B.H.), NS131069 (PI: B.H.).

Ultrasonic Inhibitory Neuromodulator (UIN) Activates PV Neurons in a Parameter-Dependent Manner

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Background and Objective: Transcranial ultrasound neuromodulation has emerged as a promising neurotechnological approach owing to its high spatial resolution, ability to access deep brain regions, and non-invasive nature. Previous studies have shown that ultrasound stimulation can induce bidirectional neural effects, including excitation and inhibition. In particular, inhibitory ultrasound neuromodulation has been investigated for decades; however, its cell-type-specific response profiles remain largely unresolved. It is generally recognized that ultrasound parameters play a critical role in determining whether stimulation produces excitatory or inhibitory effects. Nevertheless, how distinct neuronal populations sense and respond to specific ultrasound parameters, and how these cell-type-specific responses are translated into network-level excitation or inhibition, remain insufficiently understood. In addition, achieving long-term, stable, and reproducible ultrasound stimulation in freely moving animals, while simultaneously monitoring local and remote neural effects, remains technically challenging. In this study, we developed a platform for ultrasound stimulation and multimodal neural recording in freely moving mice. Using this platform, we systematically investigated inhibitory ultrasound neuromodulation through an integrated framework encompassing technological development, parameter-dependent effect characterization, cell-type-specific response profiling, and disease-model application.

Methods: We established the Freely-moving Ultrasound Stimulation and Integrated Observation of Neural effects (FUSION) Platform. This platform enables stable and reproducible ultrasound stimulation in freely moving mice, while simultaneously integrating fiber photometry recordings at the stimulation site, electroencephalography recordings from remote brain regions, and in vivo electrophysiological recordings at the stimulation site, including local field potentials and unit spiking activity. Thus, FUSION allows long-term and multiscale monitoring of ultrasound-evoked neural effects. Using the FUSION platform, we first examined the relationship between ultrasound stimulation parameters and the firing rates of excitatory neurons in the hippocampal dentate gyrus through in vivo electrophysiological recordings. Gaussian process regression was then applied to map neural activation and inhibition across the ultrasound parameter space. Next, fiber photometry was used to compare the responses of CaMKII-, PV-, and SST-expressing neurons to different ultrasound parameters, thereby identifying the cell-type-specific basis of ultrasound-induced network inhibition. Finally, the therapeutic potential of inhibitory ultrasound parameters was assessed in PTZ- and KA-induced mouse seizure models, as well as in brain slices derived from patients with epilepsy.

Results: In vivo electrophysiological recordings revealed that ultrasound stimulation of the hippocampal dentate gyrus induced bidirectional modulation of excitatory neuronal firing rates. Gaussian process regression, firing-rate raster plots, and statistical analyses consistently demonstrated that distinct ultrasound parameters produced either significant neural excitation or inhibition. Based on these parameter-dependent bidirectional effects, we defined the parameters that induced excitation as the ultrasonic excitatory neuromodulator (UEN), and those that induced inhibition as the ultrasonic inhibitory neuromodulator (UIN). These findings first established that ultrasound stimulation can achieve opposite directions of neural modulation through specific parameter configurations at the network-output level. To determine how UIN produces network inhibition, we next examined the responses of distinct neuronal populations to ultrasound stimulation. Fiber photometry recordings showed that the overall activity of CaMKII, PV, and SST neurons increased with ultrasound intensity, indicating a clear parameter dependence of ultrasound-evoked neuronal responses. Notably, under UIN parameters, PV neurons were preferentially activated, whereas CaMKII and SST neurons showed no evident activation. Because calcium photometry has a limited dynamic range for detecting reductions in neuronal activity, no clear calcium-signal suppression was observed under this condition. To further validate this cell-type-specific response, we expressed PV-neuron-specific GCaMP8s and CaMKII-neuron-specific jRGECO1a in PV-Cre mice and performed dual-channel fiber photometry. The results showed that, under UIN conditions, PV neurons were significantly activated, whereas CaMKII neurons exhibited no obvious response. In contrast, under UEN conditions, both PV and CaMKII neurons were activated. These findings indicate that PV neurons exhibit selective hypersensitivity to inhibitory ultrasound parameters, suggesting that UIN may suppress local excitatory neuronal activity and network excitability by preferentially activating PV inhibitory interneurons. This identifies a cell-level mechanism underlying the action of UIN. Based on the finding that UIN preferentially activates PV neurons and reduces network excitability, we further evaluated its potential for controlling epileptiform activity. In PTZ- and KA-induced mouse seizure models, UIN stimulation rapidly and significantly suppressed abnormal epileptiform EEG activity; meanwhile, we also observed an improvement in seizure-related behavioral manifestations following UIN stimulation. Furthermore, in ex vivo cultured brain slices derived from patients with epilepsy, extracellular electrophysiological recordings demonstrated that UIN also suppressed abnormal electrical activity in human epileptic brain tissue. These results suggest that inhibitory ultrasound neuromodulation not only ameliorates abnormal EEG activity and seizure-related behaviors in mouse seizure models, but may also be conserved in human pathological neural tissue, highlighting its potential translational value for epilepsy treatment.

Conclusion: In this study, we established the FUSION platform, which enables stable long-term integration of ultrasound stimulation with multimodal neural activity monitoring in freely moving mice. Using this platform, we systematically characterized parameter-dependent excitatory and inhibitory neural effects of ultrasound stimulation and identified that the inhibitory ultrasound parameter UIN preferentially activates PV inhibitory interneurons, thereby suppressing local network excitability. Furthermore, UIN effectively alleviated abnormal epileptiform activity in both mouse seizure models and human epileptic brain slices. Together, these findings establish a coherent research framework linking technological development, parameter-dependent neuromodulatory effects, cell-type-specific mechanisms, and disease-model application. This work provides a new experimental platform and mechanistic basis for understanding cell-type-specific ultrasound neuromodulation, and suggests a potential non-invasive therapeutic strategy for epilepsy and related neurological disorders.

Ultrasound-driven mechanical stimulation of dorsal root ganglion neurons

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Background, Motivation and Objective: Dorsal root ganglion (DRG) neurons have a wide range of functions, including sensing touch, pain and itch. These neurons have recently emerged as promising targets for non-invasive focused ultrasound (FUS) neurostimulation. Despite growing interest in FUS neurostimulation, the biophysical mechanisms by which acoustic waves trigger neuronal activation remain poorly understood. The aim of the present study is to explore FUS stimulation of cell bodies of DRG neurons in vitro and to quantitatively analyze the mechanical forces responsible for FUS-induced activation.

Statement of Contribution/Methods: FUS stimulation at 20 MHz was combined with calcium imaging to monitor neuronal activity of FUSsensitive DRG neurons, and with high-speed optical imaging to monitor the cell deformation (Fig. 1A). Two distinct mechanical components are involved in our in-vitro set-up: (i) the acoustic radiation force, exerting mainly a compressive stress, and (ii) the hydrodynamic force arising from acoustic streaming, resulting mainly in shear stress along the neuronal membrane. The scattering-driven radiation force exerted on the cell was analytically derived from the radiation stress tensor from the field scattered by the cell. Acoustic streaming was characterized experimentally using tracer-particle velocimetry coupled to high-speed imaging, enabling estimation of local flow velocities and associated hydrodynamic forces. In order to assess the predominant physical mechanism involved, an acoustically transparent plastic film was inserted above the cells within the focus beam, reducing streaming by more than five orders of magnitude.

Results/Discussion: DRG neurons were activated for acoustic pressures 4-5 MPa and stimulus durations 0.1-1 ms at 20 MHz (Fig. 1B). FUS stimuli (5 MPa, 1 ms) activated around 52% of DRG neurons (N=192), with higher prevalence in GINIP-expressing neurons. FUS activation was found to be concomitant with cellmembrane deformation at large scale (Fig. 1B). This supports the hypothesis that FUS stimulation of DRG neurons is driven by cell deformation as a result of the FUS-induced mechanical forces. FUS parameters [20 MHz, 5 MPa, 1 ms] exerted on neurons of 20-µm diameter induced radiation forces and hydrodynamic forces of similar amplitudes (≈25 nN) (Fig. 1C), whereas the axial radiation force F_z was found to be predominant over the transverse radiation force F_r and the hydrodynamic forces for neurons larger than 20 μ m in diameter (Fig. 1C). Interestingly, suppression of acoustic streaming reduced the proportion of FUS-responsive neurons from 52% to below 1% (N=132), demonstrating that shear stresses generated by acoustic streaming constitute the primary mechanism underlying DRG activation under these stimulation conditions. Ongoing work aims to determine whether increasing acoustic intensity can recruit DRG neurons through direct radiation-force-driven axial compression in the absence of streaming.

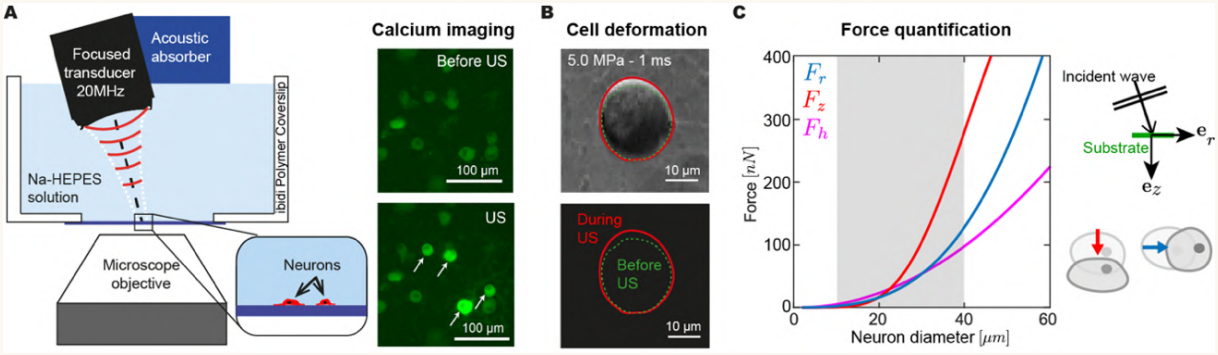

Figure 1: (A) Schematic of the experimental set-up combining FUS stimulation and calcium imaging, along with examples of calcium imaging of isolated DRG neurons. (B) Example of cell deformation during FUS stimulation monitored by a high-speed camera, showing that FUS activation is concomitant with cell-membrane deformation. (C) Comparison of axial (F_z) and transverse (F_r) radiation forces, and hydrodynamic forces (F_h) within the focus region as a function of neuron diameter.

Integrating electrophysiology and two-photon imaging for multi-scale investigation of transcranial ultrasound stimulation in awake head-fixed mice

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Transcranial ultrasound stimulation (TUS) in a non-invasive neuromodulation technique capable of targeting superficial and deep brain regions with high spatial precision, making it a promising tool for therapeutic applications in humans. Despite this potential, preclinical studies have reported conflicting findings regarding the optimal parameters, the mechanism of action, and the direction of neural effects (inhibition vs excitation). In particular, contradictory results have been described for the pulse repetition frequency (PRF), with some studies reporting excitation at high PRFs and others at low PRFs. However, these studies often differ substantially in their recording modalities and targeted brain regions, complicating direct comparisons. To systematically investigate these discrepancies and the effects of TUS, we developed a dual-modality platform that combines electrophysiology and two-photon calcium imaging in awake head-fixed mice. This platform integrates a flexible implanted probe with a chronic optical window, enabling simultaneous recordings of neuronal electrical activity and calcium dynamics during TUS. The flexible probe allows monitoring of both action potentials and local oscillatory activity across cortical and subcortical regions, while two-photon imaging provides cellular-resolution measurements of calcium signaling. This combined approach enables us to determine whether TUS has an effect and whether possible TUS-induced changes in calcium activity are accompanied by alterations in neuronal spiking and network oscillations. Importantly, the implanted probe spans multiple brain regions, enabling simultaneous investigation of superficial cortical areas and deeper structures. This may help explain inconsistencies in the literature, as different brain regions could exhibit distinct sensitivities or response profiles to TUS. To enable the integration of ultrasound stimulation with two-photon imaging, we developed a custom ring-shaped ultrasound transducer with a large inner aperture that preserves optical access for the imaging. In addition, a dedicated headplate was designed to support stable head fixation while accommodating electrophysiology, TUS delivery, and optical imaging. Using this platform, we aim to systematically characterize the effects of TUS across neuronal activity levels, brain regions, stimulation parameters, and recording modalities, providing a more comprehensive understanding of the mechanisms underlying ultrasound neuromodulation.

Developing an integrated in vitro platform for exploring multi-modal interaction of low-intensity focused ultrasound and electrical stimulation

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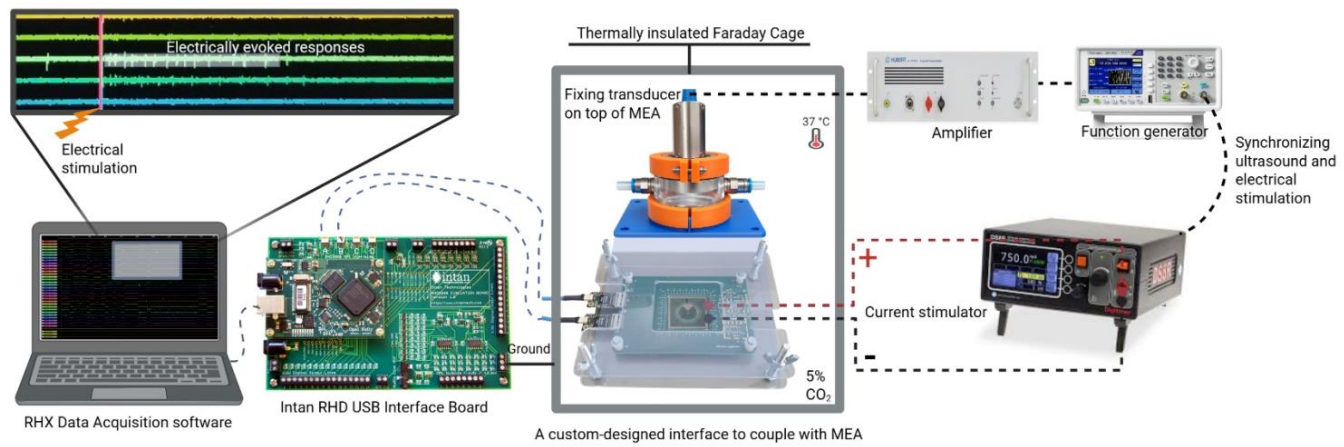
Background, motivation, and objective: Low-intensity focused ultrasound (LIFUS) has become a promising approach in neuromodulation. However, the source of variability across studies and underlying ultrasound neuromodulation mechanisms remain unclear. In contrast, electrical stimulation is a well-established technique for neuromodulation. Our goal is to develop a reproducible in vitro platform that performs electrical and ultrasound stimulations both separately and combined to better understand the interaction between ultrasound and neural tissue and have better insight into sources of variabilities in ultrasound findings.

Statement of contribution / methods: We used a commercial setup to acquire electrophysiological signals (Intan Technologies, see Fig a). Primary cortical neurons were cultured at E16.5 dropwise on the center of micro-electrode arrays (MEA) with 60 gold electrodes. A custom-designed interface was developed to effectively connect the MEA devices to the recording hardware which supports up to 60 recording channels . Spikes were recorded from DIV12 till DIV18 at a sampling frequency of 20 kHz and filtered using low-pass filter with a cut-off frequency of 3 kHz and high-pass filter with cut-off frequency of 300 Hz. During the recordings we provided a stable condition for MEA in a faraday cage, 5% CO2 and 95% O2 and 37 °C temperature. For electrical stimulation we used a biphasic pulse from a current stimulator (DS8R) with and used the MEA electrodes for stimulation. We used a single element transducer with a frequency of 1 MHz from precision acoustics for ultrasound stimulation. A rigid structure was designed to keep the transducer at the focal spot. Ongoing work is focused on optimizing the stimulation parameters to improve the reproducibility of the neurons' evoked responses to electrical, ultrasonic and combined pulses.

Results / Discussion: Spontaneous neural activity and electrically evoked responses were successfully recorded with our setup with a low noise level. Preliminary findings showed that CO2 and temperature play a significant role when detecting neural activity. Electrical stimulation was successfully measured but further parameter optimization is currently investigated. An ultrasound probe has now been integrated into our setup, enabling upcoming experiments using ultrasound stimulation.



Transcranial ultrasonic stimulation targeted to the locus coeruleus induces parameter-dependent changes in hippocampal noradrenaline levels

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The locus coeruleus (LC) is a small pontine nucleus and the primary source of noradrenaline (NA) in the central nervous system. It regulates cognitive processes and is implicated in the pathophysiology of various neurological disorders, making it an attractive target for neuromodulation-based interventions. In this study, we targeted the LC using TUS in freely moving awake mice (n = 14) using different sets of stimulation parameters. Using fiber photometry and genetically encoded biosensors, effects of LC-targeted TUS on local Ca^{2+} and NA levels and hippocampal NA levels were investigated. Using positron emission tomography (PET), we investigated effects of LC-targeted TUS on glucose uptake in the brain and body. Short trains (5 s) of LC-targeted TUS resulted in significant and sustained increases in LC Ca^{2+} levels. The increased Ca^{2+} levels were accompanied by a brief increase in hippocampal NA levels, followed by a longer lasting and significant decrease. When a longer pulse train (30 s) was used with lower pulse repetition frequencies, sustained hippocampal NA increases throughout the stimulation period were found. PET imaging revealed widespread decrease in glucose uptake in the brain and increased glucose uptake in brown adipose tissue, suggesting that LC-targeted TUS exerts both central and systemic effects. With this study we demonstrated for the first time that LC-targeted TUS can be used to modulate the LC-NA system in a parameter-dependent manner in awake mice.

Microsecond ultrasound pulses drive rapid membrane-voltage responses in awake mice

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Boston University, Department of Biomedical Engineering

Focused transcranial ultrasound stimulation (TUS) is a promising noninvasive neuromodulation approach, yet its effects on neuronal membrane voltage in the awake mammalian brain remain poorly understood. In clinical settings, constraints on tissue heating limit total acoustic energy delivery, motivating the use of brief pulses rather than prolonged sonication. A recent clinical study showed that bursts of pallidal TUS delivered at 130 Hz, with each pulse lasting 90 µs, suppressed pathological basal ganglia beta oscillations in Parkinson's disease patients (Eraifei et al., Nature Communications, 2026). However, how such short pulses of TUS shape neuronal responses remains unclear. Here, we investigate this by performing kilohertz voltage imaging of cholinergic interneurons in the striatum, a key basal ganglia structure important for motor control, in awake mice voluntarily locomoting. TUS was applied with a 0.475 MHz transducer positioned on the side of the head to sonicate a forebrain region encompassing the striatum and the overlying cortex. Stimulation consisted of 90 µs pulses delivered as a single-pulse or as 800 ms long pulse trains at 5 or 130 Hz. Across all conditions, neurons exhibited rapid, stimuluslocked depolarizations, indicating that even brief ultrasound pulses are sufficient to evoke membrane voltage responses. The evoked response during repeated pulses was augmented over time, with 130 Hz TUS producing the strongest responses. Interestingly, single-pulse and 5 Hz stimulation produced comparable effects, suggesting that pulse repetition frequency is a critical consideration in overall response augmentation. Together, these findings demonstrate that ultra-brief, 90 µs TUS is sufficient to drive rapid membrane-voltage changes in the awake mammalian brain, with the pulse repetition pattern shaping the magnitude and persistence of responses. Critically, these robust neuronal effects achieved under energy-limited conditions highlight the potential to improve therapeutic benefits through temporal patterning rather than increasing exposure, thereby minimizing total delivered energy, consistent with clinical safety considerations regarding heating.

Non-invasive in vivo acoustoelectric neuromodulation and its contribution to ultrasound stimulation

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Non-invasive brain stimulation offers therapeutic potential without the risks of surgery, yet current electrical approaches lack spatial precision and depth due to the long wavelengths of electric fields. Here we demonstrate that the acoustoelectric interaction—the nonlinear coupling between applied acoustic and electric fields—can overcome these limitations to achieve spatially focused, non-invasive neuromodulation. Using in vitro and in vivo rodent electrophysiology, we show motor-evoked potentials that depend on both the amplitude and frequency of the acoustoelectric field, with artefactual controls excluding purely acoustic or electrical origins. We further identify an acoustoelectric contribution to conventional ultrasound stimulation, arising from the interaction between ultrasound-induced electrical signals and propagating acoustic waves. These findings establish acoustoelectric neuromodulation as a distinct mechanism of neural activation and a significant contributor to how ultrasound stimulation influences brain activity, opening new directions for precise, non-invasive neuromodulation and neurotherapeutic development.

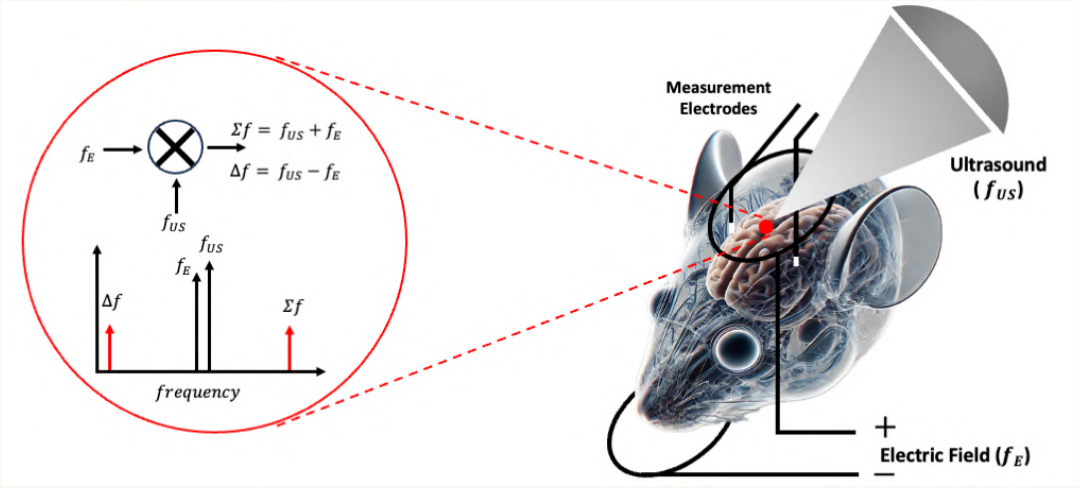

Figure 1: Acoustoelectric neuromodulation and its contribution to ultrasound neuromodulation. A focal acoustic field $P(f_{US})$ and a non-focal electric field $E(F_E)$ mix via the acoustoelectric interaction, producing electrical signals at the difference frequency $f_{US} - f_E$ and at the sum frequency $f_{US} + f_E$. If the difference frequency Δf is in the range to induce electrophysiological responses, then neuromodulation is possible.

RELEVANT PUBLICATIONS:

1. Rintoul, J. L., Butler, C., Cleveland, R. O. & Grossman, N. Non-invasive in vivo acoustoelectric neuromodulation and its contribution to ultrasound stimulation. bioRxiv 2025.11.02.685597 (2025) doi:10.1101/2025.11.02.685597.
2. Rintoul, J. L., Neufeld, E., Butler, C., Cleveland, R. O. & Grossman, N. Remote focused encoding and decoding of electric fields through acoustoelectric heterodyning. Communications Physics 2023 6:1 6, 1–11 (2023). doi: 10.1038/s42005-023-01198-w

Ultrasound Meets Memory: Transcranial Ultrasound Stimulation Induces Long-Term Depression In Vivo and Suggests Non-Canonical Plasticity Mechanisms

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Transcranial ultrasound stimulation (TUS) is an emerging neuromodulation technique that offers non-invasive access to deep brain structures with high spatial precision. Although in vitro studies suggest that TUS can modulate synaptic plasticity, its in vivo mechanisms remain poorly understood. Importantly, neuroplasticity is not limited to synaptic potentiation but includes bidirectional processes such as long-term potentiation (LTP) and long-term depression (LTD), both of which are essential for adaptive information processing and memory function. Cognitive processes such as working memory and memory formation rely on the coordinated activity of the hippocampal (HPC)–medial prefrontal cortex (mPFC) circuit. Synaptic plasticity within this pathway is dynamically regulated, and disruptions are implicated in neuropsychiatric and neurodegenerative disorders, including schizophrenia, depression, anxiety, and Alzheimer's disease. Here, we propose a novel in vivo framework to investigate how TUS modulates bidirectional synaptic plasticity within the HPC–mPFC pathway. Using a rodent model, we examine synaptic transmission between the ventral hippocampal CA1 region and the prelimbic (PrL) or infralimbic (IL) cortex. Preliminary findings demonstrate that TUS can directly induce robust LTD in vivo in the absence of conventional electrical stimulation. This LTD was consistently observed across 6 adult anesthetized Sprague-Dawley rats received TUS (500 kHz, 200 µs pulse duration, 250 Hz pulse repetition frequency, 1.32 MPa peak pressure). It was characterized by sustained reductions in fEPSP slope and amplitude relative to baseline. Notably, the ability of TUS to induce LTD without patterned electrical input raises the possibility that it engages non-canonical mechanisms of synaptic plasticity. Given the known sensitivity of mechanosensitive and ion channel-mediated processes to ultrasound, TUS may modulate synaptic efficacy through direct biophysical interactions with neuronal and glial elements, rather than solely through activity-driven synaptic depolarization. These findings position TUS not merely as an alternative stimulation modality, but as a potential tool to probe previously inaccessible mechanisms of synaptic plasticity. Ongoing work aims to determine whether TUS-induced LTD shares canonical molecular dependencies (e.g., NMDA receptor signaling) or represents a distinct pathway involving mechanosensitive ion channels and neurochemical modulation.

A Viscoelastic Theory for Ultrasound-Induced Intracellular Streaming

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While ultrasound neuromodulation is a fast-developing field, showing promising results both in vitro and in vivo, the underlying physical mechanisms remain incompletely understood. Often the ultrasound excitation is treated as a black-box stimulus. However, to fully unlock the potential of ultrasound neuromodulation as a non-invasive method with high spatiotemporal control, a more complete and predictive understanding of the excitation process is crucial. To this end theoretical descriptions of all physical effects, including radiation forces, streaming, cavitation, and local heating are needed. Among these mechanisms, we focus on intracellular acoustic microstreaming, which might induce organelle movement or alter gene expression. As a model for the viscoelastic nature of cells and their surroundings, we use the Oldroyd-B model, which is known from polymer physics and adds new terms to the stress tensor. Building on existing work, we calculate the streaming flows inside and outside of a sphere sonicated with a plane wave. The streaming is treated as a secondorder perturbation expansion of the Navier-Stokes equations. The resulting equations are solved separately for both media and combined using suitable boundary conditions. Using our model, we predict the strength and overall field shape of intracellular streaming induced in suspended biological cells depending on ultrasound frequency and crowder concentration.

Low-Intensity Focused Ultrasound Modulates Hippocampal Neurogenesis and Attenuates Neuroinflammation in a Kainic Acid-Induced Epilepsy Model

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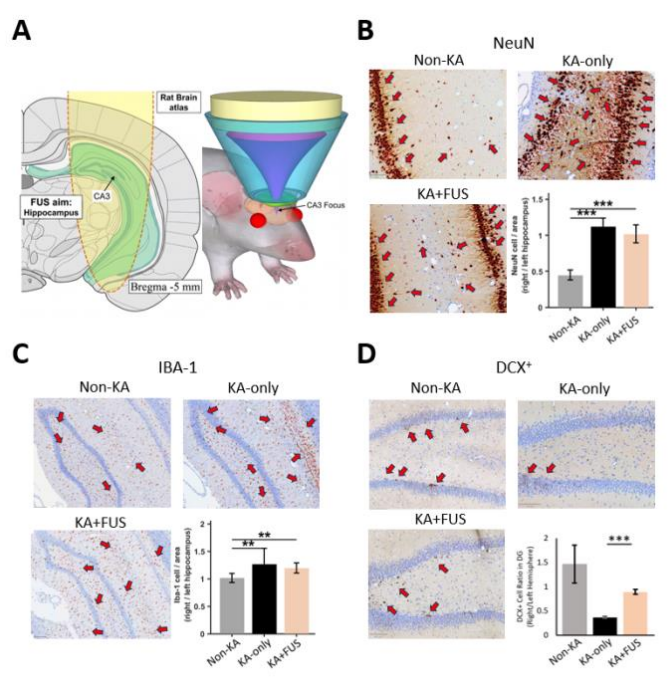
Background, Motivation and Objective: Epilepsy is characterized by aberrant neuronal activity, chronic neuroinflammation, and impaired neurogenesis within the hippocampus. Low-intensity focused ultrasound (FUS) has emerged as a promising non-invasive neuromodulation tool for treating neurological disorders. This study aims to investigate the therapeutic potential of FUS in modulating the hippocampal microenvironment, specifically focusing on its ability to suppress seizure-related pathological markers and restore neurogenesis in a kainic acid (KA)-induced epilepsy rat model.

Methods: Nine rats were categorized into Non-KA control, KA-only, and KA+FUS groups. FUS was targeted at the hippocampus with a 0.25 Mechanical Index (MI) and a 30% duty cycle, delivered in three 10-minute sessions per day for a total of six sessions over two weeks (Fig. 1A). To evaluate the therapeutic effects, histological analysis was performed to quantify NeuN expression for seizure-related neuronal activity, IBA-1 for microglial-mediated neuroinflammation, and Doublecortin (DCX) for the rate of hippocampal neurogenesis within the targeted region.

Results/Discussion: Histological analysis indicated that FUS application altered the pathological state of the hippocampus. NeuN-positive signaling, which reflects seizure-related neuronal activity, reached 1.12 ± 0.12 in the KA-only group and was 1.02 ± 0.12 in the KA+FUS group (Fig. 1B). Regarding neuroinflammation, the expression of IBA-1, a marker for microglial activation, measured 1.27 ± 0.29 in the KA-only group and 1.20 ± 0.09 in the KA+FUS group (Fig. 1C). Assessment of the neurogenic niche showed that KA administration reduced DCX levels to 0.37 ± 0.03, while FUS treatment resulted in an increase to 0.89 ± 0.18 (Fig. 1D). These data show that repeated FUS stimulation modifies epileptic circuits by reducing inflammatory responses and supporting the survival of immature neurons. The recovery of DCX-positive cells indicates that FUS promotes a regenerative environment within the targeted hippocampal region. Consequently, FUS serves as a method for restoring neural homeostasis, suggesting its potential in the long-term management of epilepsy-related brain pathology.



Quantification of Transcranial Focused Ultrasound Stimulation using functional PET

Godbersen, G.M.[1,2,#], Lückel, M.[3,4], Milz, C.[1,2], Falb, P.[1,2], Harouak, A.[1,2], Vijayakumar, S.[3], Stöhrmann, P.[1,2], Al Barede, K.[1,2], Dörl, G.[1,2], Reed, M.B.[1,2], Rasul, S.[5], Hacker, M.[5], Rujescu, D.[1,2], Bergmann, T.O.[3,4], Hahn, A.[1,2], Lanzenberger, R.[1,2,#]

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Background: Objective quantification of transcranial focused ultrasound stimulation (TUS) is essential for biologically informed optimization of sonication parameters. Currently available outcome measures are limited by objectivity, insufficient temporal or spatial resolution, or reliance in indirect outcome parameters. Functional positron emission tomography (fPET) has recently emerged as a method to quantify stimulation-induced changes in cerebral glucose metabolism [1,2]. Here, we combine TUS with fPET to assess whether sonication-induced metabolic changes can be quantified in order to support future stimulation parameter optimization, as well as for planning and monitoring of interventions. The posterior cingulate cortex (PCC), a metabolically relevant hub of the default mode network [3], was selected as a proof-of-principle target region for this pilot study.

Methods: Seven healthy participants (3 females; mean age 26.1 ± 3.6 years) underwent online TUS, sham, and auditory stimulation during a 45-minute [18F]FDG (5.1 MBq/kg) bolus-plus-constant-infusion fPET scan on a long axial field-of-view PET/CT (Biograph Vision Quadra). Following a 10min baseline (BL), participants received pseudorandomized 30s stimulations comprising: 440 Hz bone-conducted reference tone, a sham mimicking TUS acoustics, and verum TUS, each followed by a 30s BL; an additional 5 min BL was acquired in the end of the scan. Neuronavigated TUS was applied to the PCC (MNI coordinates: -5, -35, 35) using a NeuroFUS® Pro system and a CTX-500-4 transducer. Each of the 10 TUS paradigms consisted of 30 s sonication (i.e., 5 min total). 500 kHz TUS pulses without ramping had a pulse width of 5 ms, delivered at 10 Hz, i.e., pulse repetition interval of 100 ms, and duty cycle of 5% (free-field I_{SPPA} : 30 W/cm²; simulated in-situ I_{SPPA} at target: 4.29 ± 0.46 W/cm²). Individual acoustic simulations were performed in k-Plan based on T1-derived pseudo-CTs; exposure estimates remained within ITRUSST-recommended safety limits [4]. Auditory stimuli were delivered bilaterally via BHM BC-1 audiometric bone conductors positioned over both mastoid processes. Percent signal change (PSC) in cerebral glucose metabolism was computed using the fPET toolbox [4]. Stimulus-related PSC for the three conditions relative to baseline was analyzed whole-brain and region-wise (a 5 mm PCC sphere) using one-sample t-tests.

Results: The PCC region-of-interest analysis revealed a significant metabolic increase during TUS (mean PSC = 8.96 ± 8.31%; $p = 0.029$). In contrast, neither the bone-conducted 440 Hz nor the sham stimulus elicited significant changes (both $p > 0.9$). Whole-brain analyses did not reveal significant effects.

Discussion & Conclusion: These proof-of-principle data suggest that fPET may provide an objective readout of TUS-induced effects in humans. The absence of significant whole-brain effects highlights the preliminary nature of these findings and warrants replication in larger, well-powered studies. Interindividual variability (as indicated by the large PSC standard-deviation) may reflect differences in transducer coupling quality, a potentially relevant methodological challenge in initial online TUS-imaging studies. Concurrent PET/MR protocols combining fPET with MR-ARFI [5] could help verify adequate coupling while simultaneously quantifying stimulation-induced cerebral metabolic changes.

Towards a multiscale model of TUS: A thermodynamically consistent variational model of neuronal multiphysics

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Transcranial ultrasound stimulation (TUS) offers a promising non-invasive approach to modulating neuronal activity, yet its precise biophysical mechanisms remain poorly understood. Classical electrophysiological models, such as the Hodgkin-Huxley (HH) model and Cable Theory (CT), have long underpinned our understanding of neuronal excitability. However, they remain phenomenological in nature and do not account for the mechanical dimension of neuronal function. Since TUS acts primarily through mechanical perturbation of neural tissue, these models are fundamentally ill-equipped to explain how acoustic stimuli translate into changes in membrane potential, ion channel gating, or network-level activity. While existing multiphysics extensions of HH and CT incorporate some mechanical effects, they remain fragmented in scope and lack a unified, thermodynamically consistent treatment of coupled mechanical, electrophysiological, and biochemical dynamics. Critically, by construction, they cannot provide a clear pathway from subcellular membrane mechanics to larger-scale brain dynamics.

To address this gap, we apply Onsager's variational principle to the neuronal membrane, deriving a thermodynamically consistent multiphysics model that couples ionic electrodiffusion, membrane mechanics and deformation, ion channel gating dynamics, and chemical binding kinetics. This energetic framework is particularly well-suited to TUS, as it provides a physically grounded basis for capturing how ultrasound mechanically perturbs membrane state and ionic transport. We then validate our framework with patch-clamp simulations of transmembrane voltage, demonstrating bidirectional coupling between membrane mechanics and electrophysiology. The model reproduces classical action potential dynamics and captures mechanically driven modulation of excitability. Though validated here for a 1D problem, the approach is extendable to 3D neuronal geometries, spatially distributed acoustic profiles, and brain-scale dynamics.

This work offers a principled approach to understanding how ultrasound modulates neuronal firing, advancing mechanism-based modelling and laying the groundwork for computational tools to optimise TUS parameters for therapeutic and research applications.

Direct modulation of axonal activity by focused ultrasound

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Focused Ultrasound Stimulation (FUS) shows promise to modulate the nervous system non-invasively. However, the direct neurophysiological impact of ultrasound on axonal structures, a primary target for both central and peripheral neuromodulation, remain unclear. To isolate these direct effects from the influence of surrounding mechanosensitive structures, we developed a microfabricated nerve-on-a-chip platform enabling controlled focused sonication and multi-site recordings from isolated nerve fascicles.

We found that single FUS pulses directly activate peripheral axons in a dose-dependent manner, and identified an optimal FUS regime that reliably evokes compound action potentials and sustained firing during pulsed stimulation. Extending these findings in vivo, we show that pulsed sonication of motor fascicles in the rat hindlimb induces robust neural and muscular activity, which can be modulated in real-time with dynamically adjusted FUS protocols.

Together, these findings show that FUS can directly excite and modulate axonal activity, establishing a mechanistic foundation for targeted ultrasound neuromodulation of neural pathways.

Clinical

SECTION 02 / 06 · 4 ORAL PRESENTATIONS · 16 POSTERS

Low Intensity Focused Ultrasound Modulates Amygdala Activity and Resting State Connectivity in Depressed Patients

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5 University of Georgia

Background: Low intensity focused ultrasound (FUS) delivers acoustic energy to non-invasively modulate deep brain regions. In September 2021, we launched a first-in-human clinical trial of FUS to modulate the amygdala in patients with depression (NCT 05147142). This study examined safety and MRI-metrics of target-engagement of amygdala-targeted FUS.

Methods: Study procedures were performed under FDA IDEG200146 and VA Providence IRB approval. This describes the first n=10 a priori-defined cohort where participants with depression (with or without anxiety) received MRI-guided FUS targeting the amygdala (target) or primary somatosensory cortex (S1; active control) in a randomized, crossover design. Neuroimaging (including 12-minute resting-state and arterial spin labeling) was acquired at each FUS session and at 24-hours and 1-week. FUS was delivered in two 10-minute applications using a 10Hz pulse repetition frequency and ISPTA.3 of 719 mW/cm2. ASL data was preprocessed using the FSL-BASIL GUI. Resting state data were preprocessed using the fMRIprep standard preprocessing pipeline. Major steps include: 1) realignment, 2) slice time correction, 3) registration to MNI-152 volumetric and FreeSurfer spaces, and 4) spatial smoothing with a 5 mm full-width half-max (FWHM) Gaussian kernel using SPM25. rsFC data were analyzed using CONN. Seed-to-voxel analyses were performed with the basolateral amygdala (BLA) as an a priori seed.

Results: Ten patients with depression (Nfemale = 2) completed the study. There were no serious adverse events; common adverse effects were sedation and headache (p =.002, more following amygdala FUS). One participant demonstrated acute clinical worsening and required study-defined monitoring over 1-month. Significant ASL changes were observed in the amygdala vs. S1 (t=6.02, p<.001) and in the amygdala vs. ipsilateral hippocampal head and (t=5.62, p<.001). ASL changes following amygdala sonication were correlated with symptom changes in depression (r = 0.79, p =0.007) and PTSD (r =0.85; p =0.002). Compared to baseline, FUS to the amygdala was associated with decreased connectivity between the right BLA and left postcentral gyrus (x = -22, y = -28, z = 88, pFDR = 0.001), right precentral gyrus (x = 48, y = -4, z = 42, pFDR = 0.036), and left supplementary motor cortex (x = -6, y = -10, z = 56, pFDR = 0.026). There were no changes to connectivity between right BLA and any other brain regions following S1 sonication compared to baseline. Decreased rsFC between right BLA and postcentral gryus following amygdala sonication were significantly correlated with improvements in depression (r = 0.73, p =0.017) and PTSD symptoms (r = 0.71, p =0.021). Decreased rsFC between right BLA and precentral gryus following amygdala sonication were significantly correlated with improvements in depression (r = 0.70, p =0.025) Spontaneous reports heavily favored the amygdala target (p<.001).

Conclusions: This study provides early compelling evidence that MRI-guided FUS to the amygdala is safe and able to with amygdala in a spatially specific way. Spontaneous reports indicate benefit even after a single FUS administration. In sum, these findings underscore the promise for FUS as a near-term precision neuroscience tool with high potential for therapeutic use.

Effects of focused ultrasound thermal neuromodulation of the mediodorsal thalamus on value-based decision making.

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Background: Previous work indicates modulation of the mediodorsal (MD) thalamic nucleus alters human choice stochasticity in reinforcement learning tasks[a]. The mechanism of MRgFUS neurosurgery is targeted tissue ablation - however low-temperature sonications are routinely used to reversibly neuromodulate motor structures to guide lesion prior to tissue ablation. We conducted an intra-operative feasibility study in patients undergoing MR-guided focused ultrasound (MRgFUS) for essential tremor to assess if low-temperature sonication[b] directed at MD thalamus produces measurable effects on exploration–exploitation behaviour.

Methods: The four-armed restless bandit task[c] (adapted for periprocedural use) is delivered pre-operatively and again after a brief non-ablative thermal exposure to the MD region. Sonications are delivered below ablative thresholds, with real-time MR thermometry confirming peak temperature elevations remain below routine thresholds. This approach allows direct, real-time assessment of thalamic contributions to decision making behaviour while avoiding tissue damage. To characterise the neuromodulatory dose, planar MR thermography maps are extracted postoperatively. These are used to validate subject-specific volumetric acoustic and thermal fields computed using in silico models, enabling estimation of volumetric low-dose energy deposition and extent in the thalamus during the initial sonication. Behavioural data are fitted using reinforcement learning models to quantify changes in choice stochasticity, reliance on learnt value estimates, and exploration–exploitation balance.

Results: In this pilot study, patients receiving MD sonication (n = 13), the proportion of exploitative choices increased from 0.63 to 0.71, with corresponding reductions in directed exploration (0.13 to 0.09) and random exploration (0.24 to 0.20), relative to pre-operative baseline. Patients receiving VIM sonication (n = 13) showed no comparable shift (exploit: 0.68 pre, 0.68 intra). Hierarchical Bayesian modelling of a Kalman plus softmax-with-exploration-and-perseveration (SMEP) model revealed a statistically significant increase in the group-level reward sensitivity parameter (β) following MD sonication (posterior mean 0.14 0.20), with non-overlapping credible intervals between pre and intra(MD) conditions. VIM posteriors remained consistent with baseline (posterior mean 0.14 0.15, overlapping credible intervals). No credible shifts were observed in directed exploration or perseveration parameters for either target. Intraoperative monitoring indicates that exposures remain within a narrow spatial and thermal window confined the target nucleus and are within established ablative cumulative equivalent minutes at 43°C (CEM43) thresholds. Ongoing recruitment and dose–response analysis aim to determine how behavioural shifts scale with focal thermal exposure and spatial dose distribution. This study demonstrates the feasibility of performing intra-procedural cognitive assessment as part of a routine clinical procedure. Thermal neuromodulation produced measurable effects which parallel those previously observed in this task caused by delayed postoperative oedema within the MD. Further data collection is needed to understand dose- response relationship in greater detail, and with this further refinement thermal neuromodulation could be used to map thalamic function at sub-nuclear resolution using the clinical MRgFUS system.

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

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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. Noninvasive 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 TUD. The functional role of the insula in TUD can be probed using low intensity focused ultrasound (LIFU). We present results from an ongoing study in individuals with current TUD (moderate-severe), using LIFU to modulate the dorsal AI to determine the blood-oxygen-level-dependent (BOLD) response to smoking vs neutral cue-exposure as well as assessments of cigarette craving. We present results from n=17 participants who received 1 session of LIFU (NeuroFUS, CTX-500 transducer) to the left dorsal AI (Af= 500 kHz, PRF=100Hz, DC=10%, SD=120 seconds) and one session of sham stimulation (sessions were separated by > 7 days). Immediately before and after LIFU/sham participants underwent the smoking cue exposure task during fMRI scanning. Resting state functional connectivity was also conducted before the smoking cue task. LIFU was welltolerated and there were no serious adverse events. LIFU compared to sham significantly reduced BOLD response to smoking vs neutral cues in the left insula, precuneus and cingulate gyrus. There were no significant changes in state measures of smoking craving for LIFU compared to sham. LIFU versus sham effects on resting state functional connectivity between key nodes of the default mode network (the medial prefrontal cortex (mPFC) and the posterior cingulate cortex (PCC)) and salience network (the anterior cingulate cortex (ACC) and the AI), and their correlations with smoking cue-reactivity will also be discussed.

Behavioral effects of 5 Hz vs 10 Hz transcranial ultrasound stimulation of the globus pallidus internus in Parkinson's disease

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Background: There is a critical need for effective non-invasive treatment options for Parkinson's disease (PD), which affects both motor and cognitive function. Recent preclinical studies, including work from our group, suggest that GPi-targeted transcranial ultrasound stimulation (TUS) induces frequencydependent neuromodulatory effects in PD and can disrupt response inhibition in healthy individuals, highlighting the critical role of the GPi in this behaviour[1]. However, it remains unclear whether GPiTUS modulates behavior in PD and if effects are stimulation frequency-dependent. The goal of this pilot study is to evaluate the effects of two TUS protocols to the GPi 5 Hz theta burst (tbTUS) and 10 Hz stimulation, on task performance in PD.

Methods: This randomized, sham-controlled, within-subject study will be conducted in 15 PD patients (currently n = 5). Each patient undergoes four sessions, beginning with MRI-guided neuronavigation to target the GPi. Study sessions include 5 Hz tbTUS (2 minutes of bilateral sequential stimulation), compared to 10Hz-TUS (40 seconds of bilateral sequential stimulation). Sham stimulation is performed in a separate session which targets the Brodmann area 19 (~30 mm minimum sonication depth in bilateral sequential stimulation using tbTUS protocol) to mimic TUS sensations without activating motor circuits. Each session includes baseline and post-sonication assessments with Unified Parkinsons Disease Rating Scale (MDS-UPDRS III) (video recorded) and finger accelerometry. Response inhibition is assessed via a stop-signal task at baseline and at two subsequent time points (post1 and post2) following sonication. We used BabelBrain to optimize sonication trajectories and ensure safe acoustic and thermal levels to account for skull attenuation.

Results Preliminary results in 5 PD patients showed that stimulation at 5Hz TUS significantly increased both Go trial RTs from 560.4 ± 58.2 ms a baseline to 587.3 ± 61.0 ms post stimulation ($p = 0.048$) and failed stop RTs (sRT) froom 541.7 ±44.5 ms to 567.9 ± 47.8 ms ($p = 0.013$), suggesting slowed motor execution. There was a trend toward reduced stop signal reaction time (SSRT) with 5Hz TUS from 286.9 ± 51.6 ms at baseline ($p = 0.074$), indicating potential improvement in inhibition. In contrast, 10Hz TUS did not produce significant changes in SSRT, stop reaction time (sRT), Go RT, or accuracy. Sham stimulation did not yield significant changes in any metric.

Conclusion Preliminary results suggest that 5Hz GPi-TUS may slow motor execution while potentially enhance inhibitory control, as indicated by shorter SSRT. This pattern may reflect differential basal ganglia pathway engagement—slower reactions linked to reduced direct pathway activity, and improved inhibition to increased indirect pathway activation—both converging on the GPi. Given the small sample size (n = 5), findings are preliminary and should be interpreted cautiously.

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Targeting Effort and Reward Valuation in Depression: a combined Mental Imagery and Transcranial Ultrasound Neuromodulation Study

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Motivational anhedonia – reduced reward anticipation, valuation, and willingness to exert effort – is a core but poorly targeted component of depression. Mental imagery interventions employed as components of innovative cognitive-behavioural therapies can enhance anticipatory pleasure and motivate engagement in rewarding activities, yet their efficacy is constrained by blunted reward responsiveness. Transcranial ultrasound stimulation (TUS) offers a novel means of modulating deep reward circuitry, including the Nucleus Accumbens (NAcc), with high spatial precision. This pre-registered study combined neurocomputational and cognitive approaches to test whether NAcc-targeted TUS with reward imagery intervention can modulate reward and effort-based decision-making in depressed individuals.

Participants with moderate-to-severe depressive symptoms (PHQ-8 $>$ 10) received either bilateral NAcc-TUS (n=30) or Sham stimulation (n=30) before a brief, structured rewardbased imagery intervention. They subsequently engaged with the Apple Gathering task (AGT) – an effort for reward decision-making task – to extract subject-specific computational sensitivity parameters. We recorded self-reported anticipatory and experienced pleasure following the reward imagery, and two weeks of behavioural sampling reporting day-by-day engagement in selected activities. Data were analysed using logistic and linear mixed effects regression models.

Participants' willingness to exert effort for reward was significantly impacted by task variables (effort level, stake and probability of success) whereby acceptance decreased with lower rewards and higher effort. Overall acceptance rates decreased in Session 2 versus baseline for all participants, with exploratory within-group analyses showing TUS-NAcc decreased acceptance significantly while Sham did not. Importantly, these effects appeared to be specifically observable near individuals' value indifference point, where choice uncertainty is maximal. Application of computational modelling of subjective value to our data showed that a model with a parabolic cost function integrating effort (β_E) and reward (β_R) sensitivity parameters with a time modulation parameter (β_{Time}) and an acceptance bias term (α) fitted best to people's choices (lower BIC values).

Our brief reward imagery intervention succeeded to elicit the experience of positive emotions across dysphoric individuals, and self-ratings revealed a significant association between positive anticipated pleasure and subsequent emotional impact of imagery. Imagery quality (vividness and immersion) drove emotional change and experience of positive emotions specifically, during reward imagery in both experimental groups.

We observed significantly higher real-world engagement in the imagined activity compared to the non-imagined activity, yet overall engagement did not differ between groups. Importantly, engagement in the imagined activity was predicted by reward imagery quality in the TUS-NAcc group only. It suggests TUS-NAcc could be influencing how imagery quality translated into behavioural change.

All together, these results open new understanding of whether NAcc-TUS can modulate reward and effort valuation in the context of mood disorders, and whether it could be used to enhance reward sensitivity to target reward activities when combined with brief reward imagery training.

Theta-burst TUS of salience network nodes, implicated in psychoses, modulates working memory and theta connectivity in healthy adults

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Background: Cognitive dysfunction is among the most disabling and therapeutically refractory features of psychoses. Convergent evidence implicates aberrant salience-network function anchored cortically in the dorsal anterior cingulate cortex (dACC) and anterior insula (aINS) and extended subcortically, through cortico-striatal-thalamic loop circuits, to the mediodorsal nuclei of the thalamus (Thal). Transcranial ultrasound stimulation (TUS) enables non-invasive modulation of cortical and subcortical targets with high spatial precision, yet whether stimulation of salience network nodes can modulate cognition and its electrophysiological signatures remains unexplored. We tested whether theta-burst TUS of the dACC, aINS and Thal modulates visual working memory and task-related EEG functional connectivity in healthy adults.

Methods: Twenty-four healthy adults completed a within-subjects crossover study comprising one MRI visit and four weekly stimulation sessions. Theta-burst TUS (500 kHz; 5 Hz pulse repetition frequency; 10% duty cycle; 5-minute sonication) targeted the left dACC, right aINS, left Thal, or left lateral ventricle, which served as a sham target. In-water intensity was individually calibrated to maintain a constant in-situ dose of ~5 W/cm² ISPPA across participants and targets. Each session included pre- (baseline), on-, and 30-minute post-stimulation blocks of a visuospatial working memory task previously shown to detect specific feature recall and binding deficits in patients with psychoses. Mixed-effects models assessed target-specific pre-to-post outcome change (trial-level accuracy, reaction time and spatial-binding error types) and baseline-dependent post-stimulation effects. Poststimulation task-EEG was analysed using debiased squared weighted phase-lag index connectivity ($wPLI^2$) across theta, alpha and beta bands, complemented by weighted graph theory network analysis.

Results: Although target effects on mean pre-to-post behavioural change were not significant, post-stimulation accuracy showed a robust target × baseline-performance interaction ($\chi^2(3) = 39.51$, Bonferroni-adjusted $p < .001$). Relative to sham, Thal and dACC stimulation predicted higher poststimulation accuracy among lower-performing participants and lower post-stimulation accuracy among higher-performing participants, whereas aINS did not significantly differ from sham. EEG analyses revealed higher post-stimulation global theta $wPLI^2$ after Thal compared to sham ($r = 0.69$, Bonferroniadjusted $p = .010$). Intra-regional parietal and inter-regional fronto-parietal and centro-parietal theta connectivity increased after both Thal and aINS stimulation. Weighted graph theory metrics showed higher global theta mean node strength and mean clustering coefficient after Thal stimulation compared to sham (both Bonferroni-adjusted $p = .010$).

Conclusion: Theta-burst TUS produced target-specific modulation of theta connectivity and baseline-dependent modulation of working-memory accuracy under individually calibrated dosing. Thal stimulation modulated both behaviour and connectivity, whereas dACC selectively modulated behaviour, and aINS selectively modulated connectivity. Behavioural effects were baseline-dependent, improving accuracy in lower-performing participants while attenuating accuracy in higher-performing participants relative to sham. These findings identify baseline performance as a determinant of response direction and magnitude, illustrate that theta-burst TUS can engage cortical and subcortical salience network nodes to modulate visual working memory and its electrophysiological signatures and inform future circuit-specific protocols for trials on cognitive dysfunction in psychoses.

Low Intensity Focused Ultrasound for Chronic Pain: High Resolution Targeting of The Human Insula

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Chronic pain, i.e., pain that persists or recurs for 3 months or more, is a major public health problem. An estimated 100 million Americans have experienced chronic pain producing significant economic and social burden. Chronic pain is associated with disability, cognitive impairment, cardiovascular disease as well as psychiatric/substance use disorders and is more prevalent among Veterans compared to non-Veterans, with the most common site as the back. Analgesic pharmacologic treatment approaches have limited efficacy, including opiates which are associated with increased risk of substance use disorder, overdose and death. Nonpharmacologic treatments for chronic pain also have limited efficacy. Chronic pain affects neurocircuitry associated with nociceptive processing, mood, and self-referential processing. The insula is an integral part of the pain connectome and part of the salience network. The posterior subregion of the insula (PI) receives nociceptive input from spinothalamic tracts, relays it to the anterior insula which integrates expectation, awareness, and emotion to form the overall experience of pain. Our preliminary data indicate that LIFU to PI reduces laboratory measures of central sensitization and evoked pain in healthy controls but there was no such effect of LIFU to anterior insula. We utilized the spatial specificity and depth penetration of low intensity focused ultrasound (LIFU) to target the PI in participants with chronic back pain (CBP) and assessed the neural response to evoked (thermal) pain during fMRI scanning. The Medoc TSA-2 thermode was used for the evoked pain task. A calibration procedure was done before scanning to determine the temperature that each individual rated as 'warm'[3/10, numeric pain rating scale (NRS)] and near the limit of pain tolerance 'hot' (8/10 NRS), with a cap at 48°C. fMRI images were acquired during 36 trials: 18 'hot' and 18 'warm'. At the start of each task trial, the words 'warm' or 'hot' appeared on the screen for 3 s. Following a 7-13 s jittered anticipation interval, the thermal stimulus (hot/warm) was delivered. The thermal stimulus was delivered for 10 s then participants were prompted to rate the intensity of the pain stimulus using a visual scale (0-10). The first 10 s of the cue and jitter periods were used as the 'rest' condition. We present preliminary results from N=15 participants in an on-going study who received one session each of LIFU (Af = 500 kHz, PRF = 100 Hz, DC = 10%, SD = 120 s) and sham (sessions separated by >7 days) to the PI bilaterally (sequentially administered to right and left PI counterbalanced) using the NeuroFUS CTX-500. Immediately before and after LIFU/sham sessions, participants underwent the evoked pain task during fMRI scanning. Resting state functional connectivity scan was also performed prior to the task. LIFU was well-tolerated and there were no serious adverse events. There was significant activation in blood-oxygen dependent (BOLD) response to 'hot' cues versus the 'warm' and rest periods in regions such as the right and left insula, precentral and postcentral gyri, and left and right opercula. The effect of LIFU versus sham on BOLD response to these conditions will be discussed. The effect of resting state tonic pain signature and neurologic pain signature during the task will also be discussed as well as their correlation with BOLD response to the evoked pain task.

Investigating ultrasound neuromodulation of pain responses during central sensitisation.

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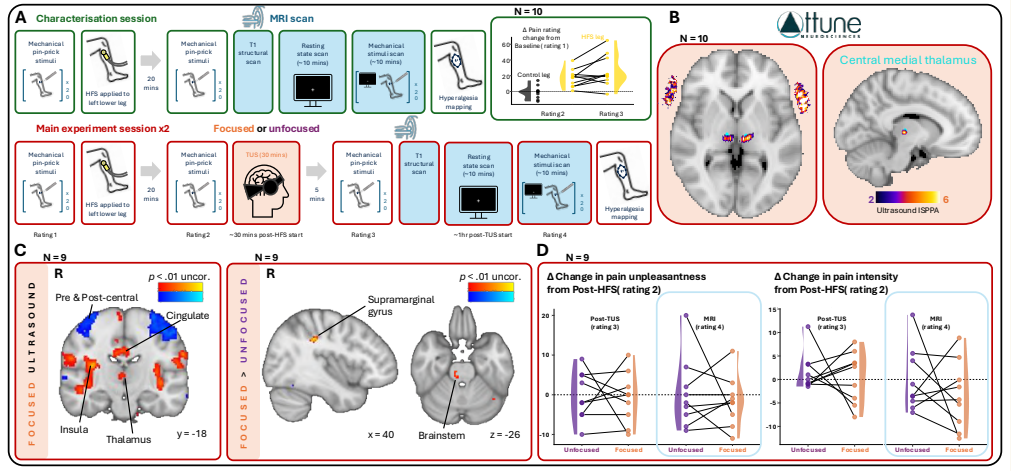
Background: High-frequency stimulation applied to peripheral nociceptors can induce secondary hyperalgesia (SHA), reflecting the amplification of ascending pain signals within the central nervous system which emulates a dysfunctional state of nociplastic chronic pain. The centromedian nucleus of the thalamus (CMT) is critical for the propagation of this noxious sensory information to the cortex, interacting with the somato-cognitive action network (SCAN). Therefore, this study aims to investigate the effects of transcranial ultrasound stimulation (TUS) of the CMT on functional connectivity between pain-related brain regions using functional magnetic resonance imaging (fMRI) alongside behavioural readouts of SHA. We have previously demonstrated that TUS can alter functional connectivity within the SCAN and modify sensory encoding (Clark et al., 2026, Nat Comms). This demonstrates the effectiveness of engaging with the SCAN for manipulating the perception of noxious stimuli. Therefore, we aim to further investigate the differential neural processing of pain dependent upon the state of induced sensitivity by applying TUS following the induction of SHA.
Methods: Healthy participants (current N = 10) attend 3 sessions (Fig. A). Firstly, to acquire T1-weighted and PETRA images for acoustic simulations, alongside characterising the HFS development time course to screen for non-responders. This demonstrated the robust development of SHA within 9 out of 10 participants. Two main TUS-fMRI sessions (double-blind, randomised) with either active (focused) or sham (unfocused) stimulation conduct the same pre- and post-HFS assessments (ratings 1-2 respectively), followed by a postTUS pain assessment (rating 3), MRI scan (rating 4), and post-MRI SHA mapping. TUS targeting is shown in Fig. B: (ff=500kHz, PRF=1Hz, DC=4% interleaved between left and right targets, 75V/pulse, duration=40s on/20s off repeated for 30 minutes total). Individualised segmentations of thalamic nuclei were used to identify the CMT (Saranathen et al., 2025, HBM). Outside of the scanner, pinprick testing was applied to the left (test) and right (control) legs (ratings 1-3). Within-MRI pinprick testing blocks (rating 4) included the left (test) leg only. Collection of data is ongoing; the planned final sample size is N = 30.
Results: Interim analyses have been conducted (N = 9). BOLD signal time locked to pinprick stimulus onset (Fig. C) demonstrated altered hemodynamic activity ($p < .01$ uncor.) including the pre- and post-central gyri, cingulate cortex, insula, and right-thalamus. A contrast between focused and unfocused conditions ($p < .01$ uncor.) suggests altered activity within the supramarginal gyrus and brainstem. Mean mechanical pinprick sensitivity (MPS) was lower following focused rather than unfocused ultrasound for ratings 3 and 4 respectively when normalised to individual post-HFS scores, although no consistent change was evident across participants. Pain unpleasantness ratings were similar for across conditions and rating time points.
Discussion: This interim analysis demonstrates that the post-HFS MRI pinprick task evokes activity within relevant areas of the SCAN network and suggests that TUS of the CMT may alter sensory processing within the supramarginal gyrus and brainstem. As additional datasets are included, analyses will provide further insights into the modulation of SCAN nodes and neural correlates of pain sensitivity by TUS. Overall, this study will provide insight into the potential of TUS as an analgesic strategy for chronic pain by precisely modulating the CMT within a clinically relevant and mechanistically specific sensitised pain state.



Cerebellar TUS for Modulating Physiological Tremor in Healthy Volunteers: A Pilot Study

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Background: The dentate nucleus (DN), located in the cerebellum, is a critical node in the cerebello-thalamo-cortical tract (CTC tract), the main neural pathway involved in motor control and tremor generation. Transcranial ultrasound stimulation (TUS) offers millimeter-scale spatial precision sufficient to target deep cerebellar nuclei non-invasively, making it a perfect candidate for tremor neuromodulation. Despite growing interest in cerebellar TUS, its online effects on motor output and associated cortical dynamics remain poorly characterized.

Objective: To assess whether TUS directed at the dentate nucleus modulates physiological postural finger tremor in healthy participants, and to establish the recording and analysis pipeline necessary for subsequent application in essential tremor (ET).

Methods: Participants maintained a tremor-inducing postural position (wrist rested, fingers splayed) while three-axis finger accelerometry and 128-channel EEG were recorded simultaneously with TUS delivery to the dentate nucleus. Each trial consisted of a 60-second prestimulation baseline followed by 60 seconds of TUS and a 60-second post-stimulation period. The ultrasound trigger was simultaneously recorded as an auxiliary channel. Different TUS parameters were tested following an I-optimal Design of Experiments. Tremor was characterized via three analyses applied to the raw accelerometry vector magnitude: (1) Welch power spectral density compared across baseline, early TUS (first 30 s), and late TUS (last 30 s) epochs; (2) shorttime Fourier transform spectrogram baseline-normalised to the pre-stimulation period; and (3) a Rayleigh-based entrainment analysis testing whether the instantaneous tremor phase at each pulse onset was non-uniformly distributed.

Preliminary results: Data collection and analysis are ongoing. Initial observations are mixed, with TUS influencing tremor-band oscillatory activity in a parameter-dependent manner and effects appearing to evolve over the course of the stimulation period rather than emerging immediately at onset. Entrainment and cortical analyses are currently underway and will be reported in full.

Discussion: These preliminary results suggest that TUS directed at the DN can modulate physiological tremor in healthy participants in a parameter-dependent way. The addition of the full 128-channel EEG into the analysis pipeline will allow examination of cortico-kinematic coherence between EEG electrodes and finger acceleration, event-related spectral perturbation, and pulse-triggered cortical evoked responses as a readout of CTC tract engagement. Source localization will further confirm that TUS-induced cortical effects are spatially consistent with the known dentate projection topography. Once stimulation parameters and analysis pipelines have been optimized in healthy participants, the protocol will be translated to a clinical cohort of individuals with essential tremor.

Modulating Performance Monitoring and Decision Making via Transcranial Ultrasound Stimulation in Patients with Obsessive-Compulsive Disorder

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Obsessive-Compulsive Disorder (OCD) is characterized by disturbances in performance monitoring and uncertainty tolerance in decision contexts. Imbalance in the cortico-striatal-thalamic-cortical loop was suggested to underlie such functional restrictions. Correspondingly, electrophysiological recordings show increased error-related negativity (ERN) in OCD patients[1]. Further, central beta-power lateralization can serve as an index of decision formation in two-alternative forced choice paradigms[2,3]. It was previously shown, that decision drift rates and thresholds are compromised in OCD patients[4]. Thus, we ask whether transcranial focused ultrasound stimulation (TUS) of the cortico-striatalthalamic-cortical loop has different effects on decision making and performance monitoring, as well as their neural correlates, in patients compared with healthy individuals . Twenty patients with OCD and twenty healthy participants (18-50 years, matched on age, gender and education) will complete two tasks during EEG recordings after eighty seconds of bilateral (theta-burst) stimulation[5] of the ventral striatum, the posterior medial frontal cortex and the lateral ventricles (control) in three separate sessions. We will implement an incentivized performance-monitoring (flanker-) task to infer modulatory effects on error- and reward processing and a perceptual decision-making (Random Dot Motion-) task with varying levels of uncertainty to explore stimulation-based modulations of evidence accumulation and decision threshold. Specifically, we expect modulations of post-error slowing, decision speed and speed-accuracy tradeoff after posterior medial frontal cortex stimulation in patients compared to healthy participants. We hypothesize that ventral striatal stimulation leads to reward-related behavioral adaptations in both cohorts. We expect TUS-induced modulations of the ERN indexing enhanced or diminished error processing, as well as modulations of the trajectory (peak Ime and drift rate) of beta power lateralization. The present study aims to explore causal relationships and dissociations between stimulation sites to indicate different functionalities. Moreover, we will add to foundations for investigating therapeutic potentials of TUS. Non-invasive and functionally focused treatment of OCD (lifetime prevalence of 4%[6] will be a milestone on the road to individualized therapeutic opportunities. The study is currently being planned and piloted. Preliminary findings will be presented at the conference.

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Transcranial ultrasonic (TUS) modulation of the right inferior frontal gyrus to improve inhibitory control and emotion regulation: a proof-of-principle study in healthy subjects

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Introduction: Deficits in emotion regulation and cognitive control are commonly found in patients with externalizing psychopathology (e.g. ADHD, BPD), prevalent in violent offending populations. Mechanistically, the right inferior frontal gyrus (rIFG) is a critical hub in the inhibition of emotional interference of cognitive processing, functionally and spatially segregated for emotional and cognitive processing across its subdivisions via a/b-band oscillations.

Objectives: Here, we present the experimental design and methodology to interfere with emotional and cognitive processing via modulation of the rIFG. By leveraging the millimetre spatial precision of low-intensity focused transcranial ultrasonic stimulation (TUS) we aim to selectively engage the anatomically segregated subdivisions of the rIFG, and thus to specifically modulate emotional or cognitive processing, or emotioncognition interaction.

Materials and Methods: In this proof-of-principle study, healthy volunteers (N = 5), expected recruited from the local university community, will receive three TUS sessions, following individualized safety simulations, selectively targeting the pars orbitalis, pars opercularis, pars triangularis, and an off-target control region in a single-blinded, randomized fashion. We will collect concurrent, neuro-navigated high-density EEG during an emotional Flanker task. Behavioural trends will be evaluated using mixed-effects models, while EEG data will be analysed by time-frequency analysis with cluster-based permutation testing.

Results: We expect target-specific TUS to selectively modulate rIFG subdivisions, evidenced by localized shifts in a-/b-band power and correlated behavioral alterations in the emotional Flanker task compared to baseline. Conclusions: TUS modulation of the rIFG may prove an interventional approach to precisely target and modulate brain networks involved in emotional regulation and cognitive control, opening new ways for neuroscience-informed interventions to reduce aggression in patients in forensic psychiatry.

Suppression of pathological oscillations with transcranial focused ultrasound in Parkinson's disease

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Transcranial ultrasound stimulation (TUS) is an emerging method for non-invasive neuromodulation of deep brain structures. However, to date, there is no evidence that TUS can directly modulate disease-related pathological oscillations in the same direction as known therapies. Inspired by clinical deep brain stimulation, in this randomised controlled cross-over study we probed the effects of pallidal TUS pulsed at 130 Hz on subthalamic beta-band activity, a biomarker in Parkinson's Disease (PD) in four male participants with PD. Beta-band power reduced in the ipsilateral subthalamic nucleus (STN) by 10.34% (95% CI: 3.81% to 16.87%, $p<0.05$, false discovery rate (FDR) adjusted). Beta power reduction was correlated between the ipsilateral ($R^2=0.980$, $p<0.05$, FDR adjusted), but not contralateral, STN and primary motor cortex. Bradykinesia, as measured by change in reaction time, was also reduced by 17.70% (95% CI: 8.95% to 26.41%, $p<0.05$, FDR adjusted). In this proof of concept study, we demonstrate that TUS can suppress pathological oscillations, potentially opening the door for therapeutic TUS (NCT06932185).

The effects of bilateral globus pallidus internus 10 Hz and theta-burst TUS on interference control in Parkinson's disease and healthy older adults

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Background: Cognitive decline is a common feature in Parkinson's disease (PD) patients and is associated with a worse prognosis. PD patients commit more errors when completing tasks that involve rapid decision-making in the presence of conflicting stimuli or interference control. A common test to measure interference control is the Flanker task; the performance of which depends on structures in the basal ganglia (BG) network. The BG network, crucial for volitional movement, is affected in PD. The globus pallidus internus (GPi) is the main output nucleus of the BG and is crucial for cognitive processing during movement. This structure is a therapeutic target for deep-brain stimulation in PD. Transcranial ultrasound stimulation (TUS) can noninvasively reach the GPi in humans. Two protocols, 10 Hz and 5 Hz or theta-burst (tb) TUS, have shown opposing neuromodulatory effects when applied to the motor cortex in healthy young adults. Our group applied tbTUS to the bilateral GPi of PD patients and observed improvement in motor signs; we also observed increased inhibitory reaction time (RT) in healthy young adults. However, the effects of GPi TUS on interference control have not been investigated.

Aims: To examine the effects of bilateral GPi 10Hz and tbTUS in 20 PD patients and 20 age-matched healthy controls (HCs) on Flanker task reaction time (RT, primary outcome measure) and accuracy (secondary outcome measure). Hypothesis: 1. Bilateral GPi tbTUS will increase RT In 'incongruent' Flanker trials. 2. Since 10 Hz TUS has opposing neuromodulatory effects, bilateral GPi 10 Hz TUS will decrease RT on 'incongruent' Flanker trials. Methods: Participants complete up to 4 visits (minimum 1 week washout period). We collected anatomical MRI during their first visit for individualized sonication. Visits 2-4 involved: (1) baseline computerized Flanker task (306 trials), (2) bilateral, neuronavigation-guided GPi TUS (randomized to 10 Hz, tbTUS, or Sham [tbTUS protocol; inactive sham]), (3) post-sonication Flanker task. We analyzed preliminary data from 5 HCs (2 female) and 6 PD patients (2 female). We analyzed RT using a linear mixed model (LM), and accuracy was analyzed using a binary generalized LM.

Preliminary Results: TUS did not affect RT or accuracy in HC. In the PD cohort, Estimated Marginal Means (EMM) showed that RT for incongruent trials post-TUS differed depending on condition (Sham: 881 ms ± 42 ms; 10 Hz: 993 ms ± 42 ms; tbTUS: 962 ± 41 ms). Post-hoc, pairwise comparisons (Bonferroni-corrected) indicate significant differences ($p < 0.0001$) between protocols in incongruent post-TUS trials. Sham vs. tbTUS (100 ms ± 17 ms faster); Sham vs. 10 Hz TUS (145 ms ± 18 ms faster). Furthermore, the 10 Hz protocol decreased accuracy ($p = 0.01$) for incongruent trials from baseline (EMM accuracy: 85% ± 8%) to post-TUS (EMM accuracy: 79% ± 9%). Follow-up pairwise comparisons (Bonferronicorrected) between TUS protocols show PD patients were less likely to respond correctly on incongruent trials post-10 Hz TUS compared to post-tbTUS (EMM accuracy: 96.2% ± 2 %; odds-ratio = 0.15, $p < 0.0001$). This was also true for post-Sham TUS incongruent trials (EMM accuracy: 91.5% ± 4 %; odds-ratio = 0.35, $p = 0.0002$). Conclusions: These results suggest 10 Hz and tbTUS have distinct effects on interference control in PD. Though both active interventions increased incongruent trial RT, 10 Hz TUS had the worst accuracy and the slowest RT among the protocols. We did not observe these effects in HCs, suggesting neuromodulation of the BG network on interference control is more noticeable in PD. Overall, our results demonstrate that GPi 10 Hz and tbTUS differentially modulate interference control in PD. We are collecting more data to determine whether our results remain in a larger sample.

Transcranial Focused Ultrasound of the Globus Pallidus Internus in Dystonia Patients with Deep Brain Stimulation

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Introduction: Dystonia is a debilitating hyperkinetic movement disorder associated with dysregulated synaptic plasticity and increased low-frequency (LF) activity in the globus pallidus internus (GPi), a basal ganglia structure crucial for movement. While deep brain stimulation (DBS) can be an effective therapy for dystonia, there are several limitations. Transcranial focused ultrasound (TUS) offers an innovative solution, however, it remains a newer field in dystonia research. A previous study by Darmani et al. applied TUS to the GPi in a DBS movement disorder cohort (with one dystonia patient) and recorded local field potentials (LFPs) to assess target engagement and neuromodulatory effects, with promising results. Here, we propose a methodology to expand on these prior findings in a dystonia GPi-DBS cohort using novel, adapted versions of the TUS protocols. We aim to assess the neuromodulatory effects of GPi TUS in dystonia using LFPs from GPi-DBS leads, as well as the clinical benefits using rating scales and intramuscular coherence via electromyography (EMG) recordings.

Methods: In this study, 5-10 dystonia patients with GPi-DBS using the Medtronic Percept device will be recruited for a total of four study visits. The first visit involves an anatomical MRI scan for acoustic field modelling to guide precise ultrasound targeting of the GPi. The following three sessions will each involve one randomly assigned accelerated sonication protocol (theta burst TUS (tbTUS) (a plasticity-associated protocol), 130 Hz TUS (a typical DBS frequency) or active sham), which will be repeated three times within the session with white noise auditory masking. The active sham protocol will consist of sonicating a non-motor region (the occipital cortex) using tbTUS. Each sonication visit will begin with assessment of the clinical rating scale and surface EMG. For cervical dystonia, EMG will be recorded from the bilateral splenius capitis and sternocleidomastoid muscles. For other subtypes, EMG will be recorded from the biceps, triceps, and wrist flexor and extensor muscles on the body side with more severe dystonic symptoms. For either setup, participants will perform a short series of postural and movement tasks. The DBS device will then be turned off, and 5 mins of LFPs will be recorded from the DBS leads. After a 30 min washout period, baseline assessments will be performed, including a clinical rating scale, 5 mins of LFP recordings and surface EMG. These outcome assessments will be repeated after the final sonication of each visit. LFPs will also be recorded for the duration of the sonications and for 5 mins between blocks. Following the outcome assessments, the DBS device will be turned on and returned to its initial settings, with a neurologist present for verification.

Significance: This study will provide preliminary evidence of the effects of GPi TUS in modulating LF activity in dystonia patients. It will also elucidate the impact of TUS on dystonia symptoms. This study will help to plan future longer-term studies to investigate TUS as a novel, non-invasive treatment for dystonia.

Transcranial Ultrasound Stimulation of the Pedunculopontine Nucleus to Address Freezing of Gait in Parkinson's Disease

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Background: Freezing of gait (FOG) is a disabling axial symptom of Parkinson's disease (PD). It is characterized by brief halts or marked slowing of forward foot movement despite the intention to walk, increasing the risk of falls, hospitalization, reduced quality of life, and loss of independence. Treatment options remain limited. Dopaminergic medications show limited benefit, and the effects of conventional deep brain stimulation (DBS) targets such as the subthalamic nucleus and globus pallidus internus have been inconsistent. The pedunculopontine nucleus (PPN), a brainstem structure within the mesencephalic locomotor region, is a promising neuromodulation target because of its role in gait, posture, and locomotor control. Although PD patients who underwent PPN-DBS studies showed improvements in falls, gait, and postural stability, its invasiveness, cost, and potential surgical complications limit widespread use. Transcranial ultrasound stimulation (TUS) may offer a non-invasive alternative for precise modulation of the PPN and its connected locomotor networks. Functional imaging markers such as resting-state functional connectivity (rsfMRI) and arterial spin labelling (ASL) cerebral blood flow can help assess target engagement and network-level effects of PPN-TUS.

Objective: To assess the feasibility and effects of PPN-TUS on gait, motor function, and functional imaging markers in PD-FOG patients.

Methods: Seven PD-FOG patients completed four study visits. Visit 1 included an anatomical MRI scan for individualized BabelBrain acoustic modelling and precision PPN targeting. During Visits 2-4, participants received 5 Hz, 100 Hz, or sham PPN-TUS in the on-medication state. Each stimulation visit included three repeated applications of the assigned protocol. Safety, adherence, gait measures, Movement Disorder Society-Unified Parkinson's Disease Rating Scale motor part III (MDS-UPDRS III) scores, rsfMRI and ASL, were assessed before and after stimulation. Sham stimulation was delivered by flipping the transducer away from the scalp while maintaining similar auditory and tactile cues.

Results: 100 Hz PPN-TUS produced the most prominent gait and motor effects. All seven PD-FOG patients reported gait improvement lasting approximately 24 hours after 100 Hz stimulation, which was not observed after 5 Hz or sham stimulation. Quantitative gait analysis showed that 100 Hz PPN-TUS increased gait velocity by +5.21 cm/s, exceeding the minimal clinically important difference, with a large paired effect size (d = 0.97). Step length increased by +2.51 cm, stride length increased by +5.29 cm, and double-limb support time decreased, consistent with improved gait efficiency and dynamic stability. MDS-UPDRS III scores improved from 43.1 ± 15.9 to 41.0 ± 14.8, with improvement in the gait item from 1.38 ± 0.80 to 1.10 ± 0.94. Neuroimaging showed frequency-specific effects: 100 Hz PPN-TUS preferentially engaged locomotor-related networks, whereas 5 Hz produced cortical-cerebellar connectivity changes. No significant gait or clinical improvements were observed after 5 Hz or sham stimulation.

Conclusion: PPN-TUS is a feasible and safe non-invasive approach for modulating locomotor networks in PD-FOG patients. The preliminary findings suggest that 100 Hz PPN-TUS produces the most promising effects, with clinically meaningful improvement in gait velocity, improved motor scores, and engagement of locomotor-related functional networks. These results support further investigation of 100 Hz PPN-TUS as a potential therapeutic strategy for PD-FOG.

Investigating Sustained sgACC Network Modulation Following Offline TUS Using the CITRUS System

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Introduction: Transcranial ultrasound stimulation (TUS) is emerging as a promising non-invasive neuromodulatory technique capable of focally targeting deep brain structures inaccessible to conventional electromagnetic approaches. The subgenual anterior cingulate cortex (sgACC; Brodmann Area 25) represents a compelling translational target due to its central role in affective networks and its established dysfunction in major depressive disorder 1. Importantly, offline TUS protocols may induce sustained post-stimulation alterations in neural activity and functional connectivity 2, making them particularly relevant for therapeutic neuromodulation applications.

Methods: We investigated neural target engagement of the sgACC in healthy human participants in an ongoing randomized, within-subject, sham-controlled crossover design offline TUS-fMRI study (n=5 completed). Experimental condition delivered focused low-intensity transcranial ultrasound targeting the sgACC bilaterally, and control condition used defocused stimulation where element phases were randomized to prevent focal intracranial convergence yet stimulator output matched to experimental condition. Sessions were counterbalanced across participants, as was hemispheric stimulation order (left-first versus right-first). High-resolution (0.8 mm iso) T1-weighted and PETRA images were acquired for subject-specific target localization, skull density modelling (SimNIBS; petra2density), and acoustic simulation (k-Plan). Five candidate transducer positions were sampled per hemisphere, and individualized k-Plan simulations were used to identify trajectories maximizing intracranial ultrasound transmission while remaining within ITRUSST safety limits. Ultrasound was delivered using the 256-element phased-array CITRUS transducer operating at 286kHz and positioned using an optical neuronavigation system (Localite). The offline stimulation protocol used a 5Hz pulse repetition frequency 3 (PD = 25ms (5ms ramp), PRI = 200ms, DC = 10%, and 80s total sonication duration, yielding 400 pulses per hemisphere). Each TUS session included four resting-state fMRI acquisitions using a multiband multi-echo sequence (MB3ME4; TR = 1.5s, 400 volumes, 10min duration): one baseline scan acquired prior to stimulation (preTUS15), followed by three post-stimulation scans acquired approximately 15min (postTUS15), 30min (postTUS30), and 45min (postTUS45) following TUS. Transducer positions were continuously recorded during stimulation to enable post-hoc verification of transducer stability and targeting accuracy.

Hypothesis & Outlook: We hypothesize that focused offline TUS targeting the sgACC will induce temporally dynamic and spatially selective changes in sgACC functional connectivity relative to the defocused control condition, thereby providing evidence of sustained neural target engagement. Demonstrating reproducible modulation of sgACC network dynamics using individualized focused ultrasound would represent an important step toward precision non-invasive neuromodulation for treatment-resistant depression.

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Electrophysiological effects of Transcranial Ultrasound Stimulation (TUS) of the motor cortex in epilepsy

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Background: Transcranial Ultrasound Stimulation (TUS) is a non-invasive neuromodulation technique under investigation as a treatment for neurological diseases. We evaluated the feasibility of electrophysiological recordings before and after TUS targeting the primary motor cortex in patients with drug-resistant epilepsy to explore its mechanism of action and neurophysiological effects.

Methods: We report on the first two adult patients with epilepsy (PwE) included in a prospective, single-blind study using TUS (NeuroFUS Pro, Brainbox) targeting the left-sided cortical hand region, localized on MRI. Treatment planning was performed using K-Plan and neuronavigation. Patients received 4 randomized sessions: two active TUS sessions, one white-matter TUS session (targeted deeper than the primary motor cortex) and one inactive sham session. Stimulation parameters expected to induce inhibition were selected (Nakajima et al.). A flexible water balloon and ultrasound gel ensured efficient transducer-scalp coupling. White noise via bone-conducting headphones and ramping provided auditory masking. 75 baseline motor evoked potentials (MEPs), 25 post-TUS MEPs at 10, 30, 60, and 90 minutes along with pre- and post-resting-state electroencephalography (EEG) were recorded to investigate excitability changes. Median MEP amplitudes were normalized to baseline (100%).

Results: The water balloon, ultrasound gel and auditory masking provided a feasible setup for motor cortex targeting based on MRI localization in PwE. MEPs and EEG were successfully recorded. In patient 1, the first active TUS session resulted in absent MEPs at 10 and 30 min (0%), facilitation at 60 min (133%), and suppression (78%) at 90 min. The second active session showed suppression at 10 min (16%), normalization at 30 min (102%), and suppression at 60 min (31%) and 90 min (30%). Whitematter TUS showed absent or inconsistent MEPs at 10-60 min and facilitation at 90 min (160%), while inactive sham responses fluctuated between 102–175%. In patient 2 the first active TUS session resulted in suppression at 10 min (60%), absent MEPs at 30 min (0%), 43% at 60 min and 44% 90 min. Following the second active TUS session, MEP amplitudes were 63%, 65%, 52% and 63% at 10, 30, 60 and 90 min, respectively. White-matter TUS resulted in MEP amplitudes of 105% at 10 min, 119% at 30 min, 135% at 60 min and 101% at 90 min relative to baseline. Inactive sham showed responses of 126% at 10 min, 115% at 30 min, 142% at 60 min and 114% at 90 min.

Clinical significance: These preliminary findings demonstrate the feasibility of MRI-guided TUS and electrophysiological measurements in PwE and support further evaluation of TUS-related modulation of cortical excitability in the full cohort.

Cerebellar Transcranial Focused Ultrasound for Primary Orthostatic Tremor

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Background: Primary orthostatic tremor (POT) is a rare movement disorder marked by high frequency (13–18 Hz) tremor in the lower limbs upon standing, frequently accompanied by a pronounced and debilitating sense of imbalance. Accumulating evidence suggests that cerebellar dysfunction plays a key role in the pathophysiology of POT. Transcranial focused ultrasound stimulation (TUS), a novel noninvasive brain stimulation technique, enables precise targeting of deep brain structures with superior spatial resolution compared to established methods such as transcranial magnetic stimulation (TMS). Owing to its capacity for selective cerebellar modulation, TUS presents a promising therapeutic approach for POT. This study investigates the effects of low-intensity TUS targeting the dentate nucleus (DN) on the clinical manifestations of POT. Purpose/Hypothesis: To evaluate the therapeutic potential of MRI-guided bilateral cerebellar TUS in POT and to characterize associated changes in neural circuitry. We hypothesize that theta-burst TUS (tbTUS) of the DN will improve tremor in the weight-bearing limbs.

Methods: We studied 16 patients with POT. In the first visit, anatomical MRI scans were acquired to enable MRI-guided TUS and acoustic modeling of the ultrasound beam. During the second and third visits, baseline assessments included the Orthostatic Tremor Severity Scale, surface electromyography (EMG), TMS motor-evoked potentials (MEPs), and cerebellar inhibition (CBI). Patients then received 120 seconds of excitatory theta burst TUS or sham stimulation to each hemisphere while seated. Outcomes were measured at 5-, 15-, and 30-minutes post-stimulation and included the patient's Global Impression of Severity. Tremor frequency was derived from EMG using power spectral analysis, and amplitude changes were measured by power at the peak frequency.

Results: Preliminary analysis suggests that DN tbTUS results in greater cerebellar inhibition of M1 compared to sham stimulation. Tremor power decreased in the tbTUS condition. However, the response was heterogeneous and occurs on top of a non-specific sham-related reduction in tremor. These findings suggest that tbTUS applied to the DN may influence cerebellar circuitry to alter cerebellar-M1 inhibitory connectivity and tremor amplitude. Data analyses are ongoing.

Conclusion: This study serves as a proof-of-concept study for the safe and effective application of TUS in POT and for improving our understanding of cerebellar involvement in POT.

Non-Invasive Transcranial Ultrasound Stimulation of the Uncinate Fasciculus as a Treatment for Freezing of Gait in Parkinson's Disease

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Background & Rationale: Freezing of gait (FOG) is one of the most debilitating and treatment-resistant symptoms in Parkinson's disease (PD), affecting up to 50% of patients and severely impairing quality of life. Current pharmacological and surgical approaches offer limited relief. The uncinate fasciculus (UF), a white matter tract connecting orbitofrontal and anterior temporal regions implicated in limbic-motor integration, represents a compelling but unexplored target for neuromodulation. Transcranial ultrasound stimulation (TUS) uniquely enables non-invasive, focal modulation of deep structures such as the UF, which are inaccessible to conventional non-invasive stimulation techniques.

Objectives: This study aims to: (1) evaluate the safety, tolerability, and efficacy of UF-targeted TUS (UF-TUS) for reducing FOG in PD; (2) characterize TUS-induced changes in cortical oscillations (EEG beta and theta activity) and local field potentials (LFPs) from deep brain stimulation (DBS) implants; and (3) assess effects on mood and patient-reported outcomes.

Methods: Twenty PD patients with FOG will be enrolled in a randomized, double-blind, sham-controlled crossover design: 10 without DBS and 10 with a Medtronic Percept DBS device (enabling simultaneous LFP recording). Visit 1 comprises anatomical and diffusion MRI; TUS neuronavigation planning will be performed using BabelBrain software with individual skull modelling (targets: bilateral UF at MNI X=±10, Y=20, Z=−12). Visits 2–4 will each deliver three rounds of bilateral UF-TUS (ISPPA 30 W/cm² in water) in one of three conditions: excitatory (tbTUS: 5 Hz PRF, 200 ms tone bursts, 10% duty cycle, 120 s), inhibitory (pulsed 500 kHz, 30 ms bursts at 100 Hz, 10% duty cycle, 120 s), or sham (transducer fliped). Visits are separated by ≥1 week washout. Outcome measures will be collected pre-stimulation, immediately post, and 30 minutes post and include: Ziegler FOG test (3 conditions, video-scored by blinded neurologists), MDS-UPDRSIII, Zeno™ Walkway gait analysis, EEG, wireless EMG, auditory Stroop dual-task, and State-Trait Anxiety Inventory. LFPs are simultaneously recorded from DBS Percept devices. A static auditory mask will be applied to mask participants to transducer noise.

Hypotheses & Expected Outcomes: We hypothesize that UF-TUS will transiently reduce FOG severity, normalize pathological beta oscillations, and attenuate frontal theta activity. In DBS patients, LFP recordings are expected to show decreased theta power during non-motor tasks and reduced beta power during motor tasks following active TUS. Improvement in mood scores is anticipated as a secondary outcome reflecting FOG reduction. Data will be analyzed using within-subjects linear mixed models (intervention × time) with appropriate post-hoc corrections.

Significance: To our knowledge, this is the first study targeting the uncinate fasciculus with TUS for FOG in PD. Concurrent LFP recordings from Percept DBS devices will provide a unique mechanistic window into the neural underpinnings of UFTUS. If successful, this study will establish proof-of-concept for a novel, non-invasive neuromodulation strategy for one of PD's most refractory motor symptoms and will inform the design of larger clinical trials.

Keywords: transcranial ultrasound stimulation, freezing of gait, Parkinson's disease, uncinate fasciculus, deep brain stimulation, EEG, local field potentials

Effects of low intensity focused ultrasound stimulation combined with functional electrical stimulation on upper extremity motor symptoms in Parkinson's disease

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Background: Low-intensity focused transcranial ultrasound stimulation (TUS) delivered at theta frequency (tbTUS) has shown to increase cortical excitability in Parkinson's disease (PD) patients in the on-medication state, suggesting that tbTUS can induce plasticity in PD. The objective of the current study was to examine the effects of combining tbTUS of bilateral motor cortex (M1) with functional electrical stimulation (FES) of the hand muscles on corticospinal excitability and PD motor signs.

Method: 17 individuals with PD attended 3 study visits in a random order. The visits consisted of 1) Real tbTUS (120 s train of 20 ms ultrasound bursts, repeated every 200ms) followed by Real FES (bilateral stimulation of the opponens pollicis brevis (OP) and first dorsal interossei (FDI) muscles during execution of functional tasks involving a pinch grip), 2) Real tbTUS+ Sham FES or 3) Sham tbTUS+ Real FES. Corticospinal excitability was measured using transcranial magnetic stimulation with motor-evoked potentials (MEP) recorded from bilateral FDI, OP and abductor digiti minimi (ADM) muscles at baseline (BL), immediately after tbTUS (T0), after 30 min of FES training (T30) and at 30 mins (T60) post FES. PD motor signs were measured using MDS-UPDRS-III scores and finger accelerometry. This study was recently completed, and we are in the process of analyzing the data.

Result: Corticospinal excitability as measured by MEP amplitude in the FDI and OP muscles increased at T30 and T60 compared to BL in both the FDI and OP muscles in both arms in all study conditions. Finger accelerometry data and MDS-UPDRS-III data need to be analyzed to understand effects of these changes on motor function.

Conclusion: Real tbTUS, real FES and their combination resulted in an immediate increase in corticospinal excitability that persisted at T60, suggesting that all three excitatory protocols may produce LTP-like changes in PD. The effect of these changes on motor function will be analyzed and shared at the meeting.

Cognitive Neuroscience

SECTION 03 / 06 · 6 ORAL PRESENTATIONS · 27 POSTERS

MR-ARFI-quantified dose-response effects of TUS on the visual system

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Transcranial ultrasonic stimulation (TUS) would strongly benefit from in vivo verification of target exposure. Acoustic simulations provide an estimate of dose delivery location and magnitude, yet do not fully account for real-world confounds such as coupling quality, transmission through hair, or subject-specific skull acoustics. Recent work has demonstrated that magnetic resonance acoustic radiation force imaging (MR-ARFI) can capture the tissue displacement produced by TUS in humans, providing an in vivo, in-situ verification approach. Here, we present the first study to leverage MR-ARFI as an integral component of a TUS protocol, using it to achieve individualized targeting and dosimetry of the lateral geniculate nucleus (LGN), a canonical relay within the retinotopically organized, lateralized visual pathway. By empirically quantifying individualized dose, we are uniquely positioned to establish veridical dose-response relationships and better explain inter-individual variability in TUS outcomes. We use concurrent TUS-fMRI to capture online effects of LGN-TUS on local and network-level BOLD responses in a within-subject, double-blind design. We simultaneously measure behavioral performance on a contrast-detection task to investigate whether perception of individualized threshold-level stimuli can be biased by TUS. For both neuroimaging and behavioral outcomes, we investigate MR-ARFI-quantified dose-response effects. Our results demonstrate significant and spatially specific online effects of TUS on BOLD. We find lateralized effects in the targeted left LGN, but not in the right LGN. In addition, we show effects on left LGN only when it is stimulated, and not when TUS is applied to an active control site (i.e., the left temporal lobe grey matter). Explicit quantification of blinding efficacy confirmed that participants could not distinguish between TUS conditions. We also show that greater MR-ARFI-quantified in-situ displacement is indeed associated with higher magnitude neural responses. Additional analyses, including on network-level effects, will be complete prior to the conference. This study represents the first implementation of MR-ARFI in a TUS neuroscience protocol and offers an unprecedented opportunity to empirically characterize the full dose-to-brain-to-behavior pathway in human ultrasonic neuromodulation.

Enhancing the discriminative power of voluntary motor signals with transcranial focused ultrasound

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Transcranial focused ultrasound (tFUS) is an emerging neuromodulation technique with high spatiotemporal specificity, but its effects on upper-limb voluntary motor signals relevant to brain-computer interfaces (BCIs) remain unknown. In this study, we investigated whether tFUS targeted at the motor cortex can enhance movement-related cortical potentials (MRCPs) and improve the discriminability of hand grasp signals in eighteen healthy human participants. Participants performed visually-cued left and right hand grasps while simultaneous electroencephalography (EEG) and electromyography (EMG) were recorded. The experiment consisted of three condition types: left motor cortex-targeted tFUS, right prefrontal cortex-targeted tFUS (spatial sham), and a non-modulated baseline. Pulse trains were delivered time-locked to movement cues. The influence of ultrasound parameter choices was also investigated, using pulse repetition frequencies (PRFs) of 30 and 3000 Hz and duty cycles of 30% and 60%. EEG data were aligned to EMG onset and averaged across trials. To capture the contralaterally distributed MRCP, Laplacian-filtered C3 data were extracted for right hand grasp trials, and Laplacian-filtered C4 data were extracted for left hand grasp trials. Offline BCI analysis was conducted with a shrinkage linear discriminant analysis (sLDA) classifier to predict whether each trial was a left or right hand grasp. For each subject and each condition, trials were 70/30 chronically segmented into training/testing sets. Left motor cortex-targeted tFUS significantly amplified the left hemisphere MRCP amplitude (1.97 ± 1.12 uV) relative to both spatial sham (1.04 ± 0.54 uV; $p < 0.01$) and non-modulated conditions (1.43 ± 0.73 uV; $p < 0.05$). The right hand MRCP amplitude was unchanged across conditions ($p > 0.05$, log10(Bayes Factor) < 0). Left hemisphere MRCP modulation was not found to be a function of tFUS PRF ($p > 0.05$, log10(Bayes Factor) < -0.5) or duty cycle ($p > 0.05$; log10(Bayes Factor) < -0.5). Offline BCI classification was significantly increased for left motor cortex-targeted tFUS (75.4 ± 9.8%) compared to the spatial sham (63.8 ± 8.4%; $p < 0.01$) and non-modulated (64.7 ± 14.4%; $p < 0.01$) conditions. BCI accuracy improvement was not found to be a function of tFUS PRF ($p > 0.05$, log10(Bayes Factor) < 0) or duty cycle ($p > 0.05$, log10(Bayes Factor) < -0.5). These findings are the first, to our knowledge, that demonstrate tFUS can selectively enhance upper-body voluntary motor cortical signals and improve motor EEG-based BCI performance.

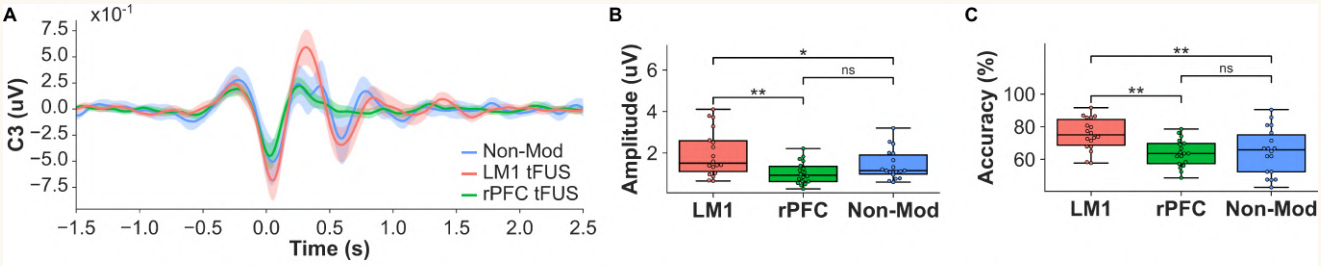

Figure 1: Targeted voluntary motor signals are significantly enhanced from focused ultrasound neuromodulation. (A) The grand average left hemisphere movement related cortical potential (MRCP) is presented for all 18 subjects across the three ultrasound condition types. The plotted waveforms are the mean ± 95% confidence interval. (B) Comparisons of subject MRCP peak-to-peak amplitudes. (C) Data discriminability were assessed in an offline brain-computer interface (BCI). Resultant BCI accuracies are plotted for each condition. Boxplot key: Boxplots mark the data median (center line), 1st and 3rd quartiles (edges of box), and 1.5 * interquartile range (whiskers). Individual data points, one for each subject's average value for that condition, are overlaid. Statistics key: False discovery multiple comparison correction was applied. ns $p > 0.05$, * $p < 0.05$. ** $p < 0.01$

Acknowledgments: This work was supported in part by NIH grants NS124564 (PI: B.H.), NS131069 (PI: B.H.), NS127849 (PI: B.H.), NS096761 (PI: B.H.), and EB029365 (J.K.; PI: B.H.). J.K.'s work was partially supported by NSF Graduate Research Fellowship DGE2140739.

Conflicts of interest: B.H. and J.K. are co-inventors of pending patent applications for brain-computer interfaces and neuromodulation.

Investigating the role of human pgACC in cost-benefit decision-making using transcranial ultrasound stimulation (TUS)

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Balancing costs and benefits is a fundamental aspect of adaptive decision-making. The pregenual anterior cingulate cortex (pgACC) has been implicated in integrating costs and benefits to guide approach and avoidance behaviours (Amemori & Graybiel, 2012; Kable & Glimcher, 2007; Friedman et al., 2015). However, causal evidence for its role in human cost-benefit arbitration remains limited, despite the clear relevance of this process for people with apathy or anhedonia. Here, we investigated whether transcranial ultrasound stimulation (TUS) of the pgACC modulates reward-effort trade-offs in humans. Twenty-four participants performed a reward-effort decision-making task following TUS applied either to the pgACC or to a pgACC-unrelated white-matter control site in a within-subjects design. We employed a 5Hz-patterned TUS protocol delivering an 80-second pulse train with 20-millisecond pulse duration and a pulse repetition interval of 200 milliseconds (Algermissen et al, 2026; Zeng et al., 2022; Yaakub et al., 2023). This protocol has been shown to induce neuromodulatory effects lasting up to an hour. During the task, participants decided on each trial whether to exert physical effort via a handheld dynamometer to gain rewards (approach blocks) or to avoid losses (avoidance blocks). Reward or loss magnitude and required effort were varied trial-wise to assess cost-benefit trade-offs. Participants' choices were sensitive to both effort cost and outcome magnitude, with higher acceptance for larger outcomes and lower effort demands. Compared with control stimulation, pgACC TUS significantly reduced acceptance rates, indicating a reduced willingness to exert effort to obtain rewards or avoid losses. This effect scaled with decision conflict and was strongest for high-conflict trials near participants' indifference boundaries, where preferences are most malleable. pgACC TUS also increased reaction times to accept offers, consistent with increased deliberation or reduced motivational drive. These findings suggest that TUS to the human pgACC can influence cost-benefit decision-making. The reduction in acceptance rates, particularly for high-conflict choices, indicates that pgACC stimulation may shift how effort costs and outcome benefits are integrated during action selection. This provides a framework for using TUS to investigate motivational circuits with potential relevance to apathy and anhedonia.

Ultrasound-mediated focal serotonin delivery causally modulates motivation in primates

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Serotonin is thought to regulate behavioural state and motivation, yet causal investigation of serotonergic function has been limited by the lack of methods that are both spatially precise and translatable across species. Here, we use ultrasound-mediated blood-brain barrier opening to focally and non-invasively deliver serotonin to the perigenual anterior cingulate cortex (pgACC) of awake macaques, enabling circuit-specific causal interrogation of serotonergic modulation of motivated behaviour. Previously (at FUN25), we demonstrated the use of low-intensity transcranial ultrasound combined with microbubbles to transiently open the blood-brain barrier at the pgACC and deliver serotonin. We targeted the pgACC because it receives dense serotonergic projections from the dorsal raphe nucleus, the principal source of serotonin in the brain, and is implicated in integrating reward context with motivational state to guide behaviour. We showed that focal serotonin delivery to the pgACC reduced local glutamatergic metabolite signal and altered functional connectivity between pgACC and anatomically connected frontal regions, confirming central circuit-level effects of focal serotonin delivery. Following this work, we next asked if we could use ultrasound-mediated serotonin delivery to the pgACC to manipulate motivated behaviour. Animals performed a sequential decision-making task in which reward opportunities were encountered within environments varying in overall reward richness. Behaviour was analysed using computational modelling to infer latent motivational states, while pupillometry was used to assess neural and physiological effects of focal serotonin delivery. Under baseline conditions, animals adjusted reward pursuit according to both the expected value of the current offer and the richness of the recent reward environment. Richer environments increased occupancy of a high-motivation state characterised by an increased likelihood of pursuing reward opportunities. Focal serotonin delivery to pgACC selectively reduced the influence of environment richness on reward pursuit and motivational state occupancy, while leaving sensitivity to the immediate value of the current offer unchanged. Serotonin delivery also biased animals out of the high-motivation state by increasing transitions from high- to low-motivation states, reducing overall occupancy of the high-motivation state. Together, these findings suggest that serotonin in pgACC regulates how environmental reward statistics are translated into sustained motivational engagement and behaviour, rather than altering immediate offer valuation itself. Further, focal serotonin delivery altered pupil-linked state dynamics, providing a separate confirmation of central circuit-level effects of focal serotonin delivery. These findings identify pgACC serotonin as a causal regulator of context-dependent motivational state and establish ultrasound-mediated neuromodulator delivery as a non-invasive and spatially precise approach for causal neuropharmacology in awake behaving primates, bridging the gap between systemic pharmacology and invasive circuit manipulation methods.

Protocol Optimization and Neural Target Engagement of the Human sgACC Using Online TUS-fMRI with the CITRUS System

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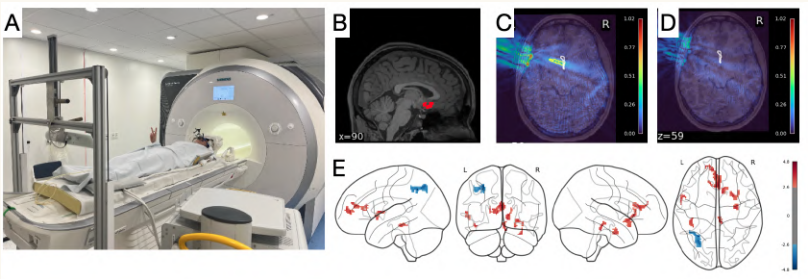
Introduction: Demonstrating acute neural target engagement during transcranial ultrasound stimulation (TUS) remains a major challenge for deep brain neuromodulation. Online TUS-fMRI enables direct measurement of stimulation-induced neural modulation during sonication and provides a framework for optimizing stimulation parameters in vivo. This is particularly relevant for the subgenual anterior cingulate cortex (sgACC; Brodmann Area 25), a ventromedial limbic region implicated in major depressive disorder (MDD)1,2, where modulation is complicated by limited acoustic access, skull variability, MRI-related artifacts, and a large multidimensional TUS parameter space. We report preliminary findings from an ongoing study evaluating protocol-dependent online engagement of sgACC circuitry.

Methods: The CITRUS (Closed-loop Individualised image-guided Transcranial Ultrasonic Stimulation) project developed a fully MR-compatible TUS-fMRI device integrating a 256-element phased-array ultrasound system, custom 16-channel MR head coil, and Localite neuronavigation for individualized targeting (Fig A). Structural MRI ((Fig B) and PETRA acquisitions were used for skull density modelling (SimNIBS petra2density) and individualized acoustic simulations in k-Plan, enabling phase-corrected 3D beam steering toward the sgACC target. To improve targeting precision, an online geometric replanning feature in Localite recalculated phase corrections immediately prior to sonication to compensate for minor transducer repositioning inaccuracies; this workflow was validated in gelatin phantom experiments using MR thermometry. Four healthy participants completed a within-subject study comprising focused (experimental; Fig C) and defocused (control; Fig D) stimulation conditions during the pilot phase, and the finalized study is ongoing (n=10 completed). Four stimulation protocols systematically varied pulse duration, pulse repetition frequency, and duty cycle while maintaining constant total ultrasound "on" time of 40 ms pulse duration. TUS was delivered interleaved with multiband multi-echo sequence using alternating 10-ON/10-OFF blocks (18 s). Analyses are descriptive given the pilot sample size.

Results: Acoustic simulations confirmed focal sgACC targeting in the focused condition, with reduced intracranial convergence in the defocused control. Preliminary analyses demonstrated protocol-dependent modulation of sgACC-associated circuitry during stimulation. One protocol produced the clearest engagement, with "experimental > control" contrasts revealing modulation within pregenual anterior cingulate and thalamic regions (Fig E). Other protocols preferentially engaged lateral frontal and parietal networks. Local sgACC signal changes were modest, whereas distributed medial frontal-thalamic effects were more evident. Millimeter-scale deviations between planned and recorded transducer positions during sonication produced meaningful differences in target dose based on post-hoc acoustic simulations, supporting the importance of online geometric replanning which has been implemented in the finalized study workflow.

Discussion & Conclusion: These preliminary findings demonstrate the feasibility of detecting acute modulation of sgACC-centered networks during interleaved TUS-fMRI. Neuromodulatory effects were protocol-dependent and expressed primarily at the distributed circuit level rather than as large local sgACC BOLD responses, underscoring the importance of parameter optimization for deep medial targets.



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Personalized Low-Intensity Focused Ultrasound to Medial Temporal Lobe for Human Episodic Memory Enhancement

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Introduction: Episodic memory impairment is a growing public health concern, particularly in aging and neurodegenerative disorders. Current neuromodulation methods are either invasive or lack the depth and precision to reach the medial temporal lobe (MTL), a critical hub for episodic memory. Low-intensity focused ultrasound (LIFU) uniquely offers noninvasive, millimeter-scale precision with deep brain access. Here we propose personalized MTL stimulation using task-based fMRI to define functional targets, with LIFU delivered concurrently during encoding in a face-name associative task. We evaluate effects on both task-specific recall and broader fluid cognition, and integrate participant-specific diffusion tractography to test whether individual variation in beam–tract overlap accounts for memory response variability.

Methods: Twenty healthy adults (12 male; mean age = 32.2 ± 13.6 years) completed a three-visit study. In Session 1, participants underwent CT, T1-weighted MRI, diffusion kurtosis imaging (DKI), and task-based fMRI during a face–name associative exam (FNAE) to define individualized MTL targets. In Sessions 2 and 3 (order randomized), participants received either LIFU (pulse duration = 1 s, f_0 = 500 kHz, PRF = 10 Hz, DC = 30%, I = 6.17 W/cm^2, total sonication duration = 96 s) or active sham delivered concurrently with the FNAE SPPA encoding phase. Immediately following encoding, participants completed an immediate recall test, then a tabletbased NIH Toolbox Cognition Battery. A delayed recall test was administered 30 minutes after immediate recall.

Results: Behavioral analysis of the FNAE task showed a trend toward higher accuracy for LIFU compared to sham. Immediate recall was 54.9% ± 11.8 for LIFU versus 51.4% ± 11.5 for sham (paired t = 1.71, dz = 0.38, p = 0.10; n = 20), and delayed recall was 47.4% ± 13.7 for LIFU versus 44.0% ± 11.7 for sham (t = 1.29, dz = 0.29, p = 0.21; n = 20; Fig 1.A). On the NIH Toolbox Fluid Cognition Composite, LIFU produced a significant improvement: composite scores were 559.9 ± 21.9 for LIFU versus 553.0 ± 20.5 for sham (mean LIFU - Sham changes= +6.9; 95% CI: [+2.5, +11.3]; dz = 0.71; t(20) = 3.26, p = 0.004; Fig. 1A). To examine whether individual variation in beam–tract targeting accounted for variability in memory change, we computed 1) FWHM beam total pressure overlap with, and 2) peak ultrasound beam voxel distance to, four pre-specified memory-relevant whitematter tracts (Fig 1.B). For delayed recall (n = 13), greater overlap with the uncinate fasciculus predicted greater LIFU-induced improvement (standardized β = 0.57, p = 0.044, r^2 = 0.32).

Conclusion: Personalized MTL-targeted LIFU produced a significant improvement on fluid cognition and trends toward improved recall accuracy overall. Greater uncinate fasciculus beam overlap predicted delayed recall improvement, suggesting white matter maybe a promising target for LIFU.

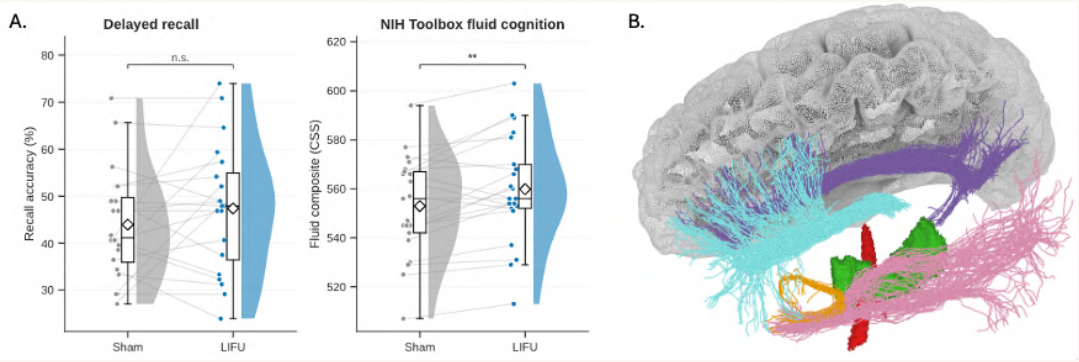

Figure 1: (A) Group (N = 20) FNAE delayed recall and NIH Toolbox Fluid Cognition Composite for Sham vs. LIFU; ** = p<0.01 (B) Personalized LIFU pressure field (red, FWHM beam); hippocampus in green and four memory-relevant white-matter tracts in left hemisphere (blue, anterior thalamic; purple, cingulum cingulate; pink, inferior longitudinal; orange, uncinate)

Causal dissociation of aversive and appetitive learning in human subcortex with TUS

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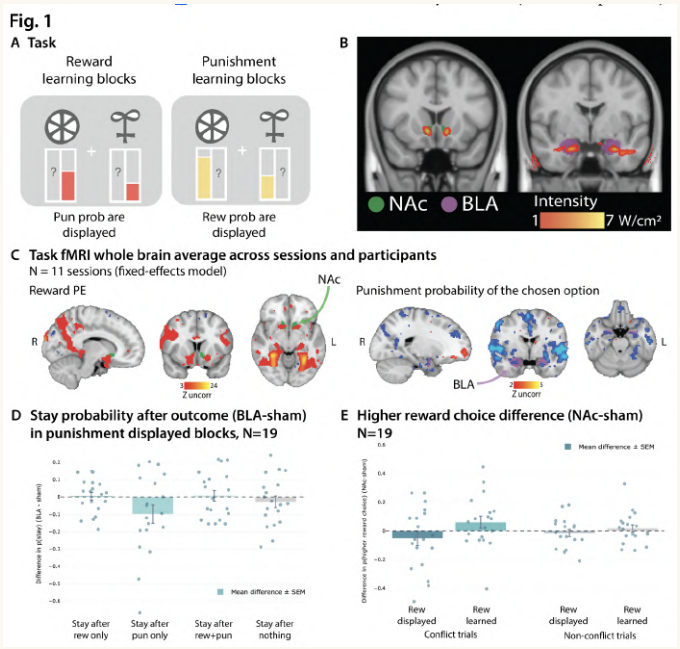
Integrating costs and benefits is fundamental for adaptive decision-making. Lesion work in animals and correlational work in humans points to an important role of several small subcortical nuclei in learning and valence processing, in particular the nucleus accumbens (NAc) (Cox & Witten, 2019; Costa et al., 2016; O'Doherty et al., 2003; Rutledge et al., 2010) and basolateral amygdala (BLA) (Malvaez et al., 2019; Wassum et al., 2011; West et al., 2012). Here, we asked whether these two regions have distinct roles in cost-benefit choices when participants' learning focuses on aversive or appetitive outcomes. We designed a task where participants made choices between options associated with both probabilistic reward and punishment. In one block type, reward had to be inferred, in the other punishments were learned (Fig. 1A). We employed TUS and subsequent fMRI (3T) to selectively and bilaterally target each region (data collection ongoing; current: N=19; N=23 by the time of FUN26), enabling causal perturbation of their function. Following a structural scan session for acoustic and thermal simulations (Fig. 1B), in subsequent sessions, we applied bilateral TUS (PRF=5Hz, PD=20ms, pulse train duration=80s, free field ISPPA=70-80W/cm2) to the BLA, NAc, or sham followed by task fMRI (for ~1hour post TUS). Participants successfully learned reward and punishment probabilities and used them to inform their choices. In line with behaviour, whole brain fMRI showed reliable engagement of the BLA and the NAc for mediating punishmentbased decisions and outcome learning, respectively (Fig. 1C). Preliminary analyses of TUS effects on behaviour suggest a differential role of the BLA and NAc in valence-specific learning. More specifically, BLA stimulation alters stay/switch behaviour making participants less prone to switch to the alternative after receiving a punishment in comparison to sham stimulation in blocks when punishments are displayed and not learned (Fig. 1D). Moreover, in conflict trials where a riskier higher reward-higher punishment option and a lower reward-lower punishment one were offered, NAc stimulation increased choice of the high reward option when reward probabilities had to be learned, but decreased its choice when probabilities were explicitly displayed (Fig. 1E). This suggests that the NAc has a central role in learning and integrating reward information, particularly under uncertainty. This study highlights the potential for TUS to causally dissociate the functional contribution of small nuclei of the human limbic system in decision-making.



Offline Transcranial Ultrasound Stimulation of the Subthalamic Nucleus Reorganises Resting-State Sensorimotor Network Synchronisation and Shapes Task-Related Cortical Oscillatory Dynamics in Healthy Humans

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The subthalamic nucleus (STN) acts as a critical hub in the fronto-striato-subthalamic network, integrating corticofugal input via the hyperdirect pathway and striatal signals via the indirect pathway to gate motor output. Deep brain stimulation of the STN and animal models demonstrate that altering STN activity reshapes cortical oscillatory signatures, including beta and alpha-band dynamics associated with motor control and action inhibition. Despite this, there are limited information about the causal role of the STN in establishing and maintaining the functional architecture of the cortico-basal network in healthy individuals in non-invasive scenarios. Here we addressed this gap by applying offline transcranial ultrasound stimulation (TUS) to the right STN of healthy participants (N=30) in a double-blind, sham-controlled crossover design. TUS was delivered between test blocks of electroencephalography (EEG) recordings using a continuous burst protocol (80 s; 1600 pulses; pulse duration = 5ms; PRF = 20Hz; Isspa free field = 60W/cm^2). To index network-level consequences of STN perturbation, we focused on resting-state cortico-cortical synchronisation - assessed via two complementary phase-based connectivity measures, the weighted Phase Lag Index (wPLI) and the Phase Slope Index (PSI), which describe the strength of coupling and directionality of information flow between cortical regions, respectively. We additionally characterised whether changes in resting-state network organisation were mirrored by modulations of task-related cortical oscillatory dynamics in a stop-signal task. Active TUS over the right STN produced significant and selective reorganisation of resting-state frontocentral synchronisation, with no equivalent changes following sham stimulation. Specifically, offline STN-TUS modulated both wPLI and PSI in the high-mu and low-beta band, suggesting a directional reorganisation of sensorimotor network synchronisation rather than a non-specific change in oscillatory coupling. This tonic perturbation of baseline sensorimotor network architecture was paralleled by corresponding state-dependent modulations of task-related oscillatory dynamics that may reflect downstream consequences of the resting-state reorganisation: TUS affected oscillation across theta, mu (frontal alpha), and low-beta bands during inhibitory control, and selectively modulated mu and low-beta during motor execution. The alignment of resting-state connectivity changes with task-related oscillatory modulations across the same frontocentral sensorimotor network provides convergent evidence that STN excitability shapes the baseline functional architecture of the cortico-motor circuit, with measurable consequences for the oscillatory dynamics recruited during action control. These results provide novel causal demonstration in healthy humans that offline STN-TUS is a tonic organiser of sensorimotor network synchronisation at rest, as evidenced by convergent phase-based beta-band modulations and that this reorganised baseline physiological state may constrain the oscillatory dynamics deployed during both movement execution and inhibitory control. By linking offline TUS-induced changes in resting-state network connectivity to task-evoked neurophysiological responses across the same frontocentral circuit, this work offers a principled framework for understanding how STN dysfunction in basal ganglia disorders disrupts the motor system at the level of its fundamental network architecture.

Task-fMRI following offline amygdala TUS reveals local and network-level changes during emotional face and feedback processing

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Humans flexibly adapt their behaviour in response to social-emotional cues, deciding when to update their actions based on changing emotional information. The amygdala is well positioned to support these processes: it contributes to facial emotion processing, approach-avoidance behaviour1, and learning from rewards2. While correlational studies implicate interactions between cortical and subcortical regions, particularly frontal cortex and amygdala, the causal role of these interactions remains unclear. Here, we used offline low-intensity transcranial ultrasound stimulation (TUS) to transiently modulate the human basolateral amygdala (BLA) and subsequently assessed task-evoked activity using ultrahigh-field 7T BOLD-fMRI. Healthy participants (n=29) completed three counterbalanced TUS-fMRI sessions targeting bilateral BLA, mid-insula as an active control site, or sham stimulation. Approximately 30 minutes after stimulation, participants performed an emotional approachavoidance learning task in which they learned, through probabilistic feedback, whether to approach or avoid happy, angry, or neutral faces. Published analyses focusing on behaviour, MR spectroscopy, and resting-state connectivity showed successful target engagement and revealed that BLA-TUS selectively increased approach toward emotionally ambiguous neutral faces, suggesting a causal role for the BLA in resolving affective ambiguity3. Here, we present unpublished task-fMRI results testing whether offline BLA-TUS induces local amygdala or remote network-level changes in task-related BOLD signals during emotional face processing and reward-based learning. First, we examined whether BLA-TUS changed the processing of emotional facial expressions. We found that BLA-TUS relative to sham was associated with increased BOLD responses in bilateral BLA, consistent with enhanced local task-evoked BLA activity during emotional face processing. Second, we examined feedback-related BOLD responses. This analysis suggested that BLA-TUS altered activity in regions involved in reward processing and feedback learning. Specifically, positive relative to negative feedback was associated with reduced signal in the ventral tegmental area and increased signal in ventromedial prefrontal and orbitofrontal cortex after BLA-TUS compared with sham. In conclusion, our findings provide insight into how the human BLA shapes activity in connected circuits during flexible emotional behaviour. They show that offline BLA-TUS influences both local activity within the targeted amygdala and distributed responses across interconnected brain networks. These results highlight the potential of combined TUS and task-fMRI to study causal interactions in deep brain circuits and investigate how focal perturbations propagate through functional networks in the human brain.

Testing the Causal Role of the Right Anterior Insula in Fatigue Using Transcranial Ultrasound Stimulation

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Cognitive fatigue reduces willingness to engage in cognitively demanding activities. The right anterior insula (rAI) has been proposed to play a central role in the subjective perception and interoceptive awareness of fatigue, but converging evidence also identifies it as a key node of the salience network involved in coordinating cognitive control and decision-making processes. Consequently, a major theoretical question remains unresolved: does the rAI contribute directly to the subjective experience of fatigue, or does it primarily regulate how fatigue-related signals are translated into motivated behaviour? Resolving this question has been challenging because most existing evidence is correlational, limiting causal inference regarding rAI function. Transcranial ultrasound stimulation (TUS) offers a unique opportunity to causally investigate this question through focal modulation of deep brain structures. Preliminary evidence from our transcranial temporal interference stimulation (tTIS) pilot study supports the feasibility of targeting this region. In 36 healthy participants, fatigue induction increased subjective fatigue ratings, while stimulation selectively modulated effort sensitivity following fatigue induction without affecting fatigue ratings or working-memory performance. These findings suggest that rAI perturbation may influence effort-based decision-making under fatigue. Building on these findings, we propose a randomized, sham-controlled, within-subject TUS study targeting the rAI. Participants will complete a cognitive fatigue paradigm involving repeated workingmemory blocks, with subjective fatigue ratings, behavioural performance, effort-based choices, and pupillometry collected throughout the task. This design will provide a causal test of whether rAI stimulation alters fatigue itself or primarily alters the influence of fatigue on motivated behaviour and effort-based decision-making. Beyond its theoretical significance, this work has important clinical and methodological implications. Fatigue is a disabling symptom across numerous neurological and psychiatric disorders. By identifying the causal contribution of the rAI to fatigue-related behaviour, this study may advance mechanistic understanding of clinical fatigue while demonstrating the potential of TUS for targeting deep brain circuits that remain difficult to access using conventional non-invasive neuromodulation approaches.

Keywords: Mental Fatigue, Anterior Insula; Transcranial Ultrasound Stimulation; Effort-Based Decision Making; Neuromodulation

Nucleus Accumbens ultrasound stimulation modulates feedback-related negativity associated with valence and reward sensitivity: Evidence from a multiregional study

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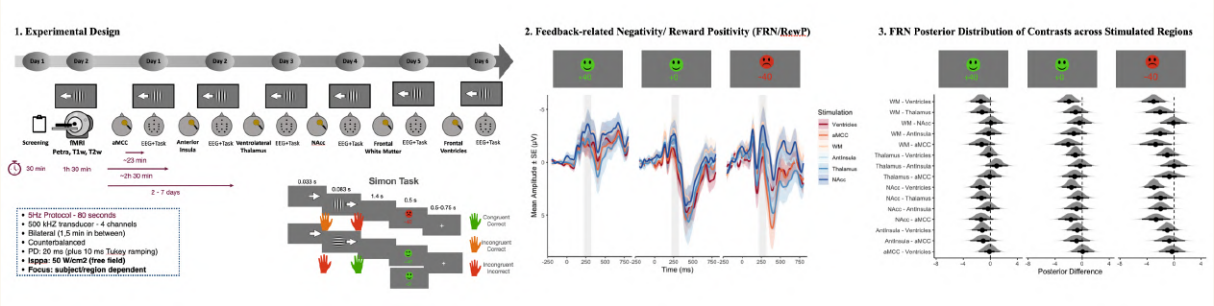
Goal-directed behaviour relies on monitoring conflict, performance, and rewards to optimise actions and achieve desired outcomes. Electrophysiological studies have identified event-related potentials (ERP) associated with these processes, including the frontocentral error-related negativity (ERN), which is thought to originate in the anterior midcingulate cortex (aMCC) [1–2], a central hub of performance monitoring. The aMCC interacts with several regions involved in cognitive control and reinforcement learning, including the ventrolateral thalamus [3], anterior insula [4], and nucleus accumbens (NAcc) [5]. Despite extensive evidence linking these regions to cognitive control, the causal relationships among neural activity, ERP markers such as the ERN and feedback-related negativity (FRN)/reward positivity (RewP), and behaviour remain poorly understood. In this study, we investigated the effects of transcranial ultrasound stimulation (TUS) applied to six different regions: the aMCC, anterior insula, ventrolateral thalamus, NAcc, frontal white matter (WM), and the frontal horns of the lateral ventricles (control). Eighteen participants (mean age = 24.4 ± 5.3 years; 8 women) completed one fMRI session and six TUS sessions (Fig. 1.1). During each TUS session, participants received an offline 5-Hz stimulation protocol followed by a Simon task incorporating feedback (positive or negative) and reward outcomes (-40, 0, or +40 points, associated with how fast they responded), while EEG was recorded. MRI data were used to perform acoustic and thermal simulations, which indicated that the selected TUS parameters were within established safety limits (overall I_{pa} = 5.76 W/cm^2 ($\pm$ 2.18) and I_{sppa} = 8.55 W/cm^2 ($\pm$ 2.51); MI = 0.68 ($\pm$ 0.11)). Bayesian mixed-effects models showed that accuracy was higher for congruent than incongruent tc trials (β=0.52, 95% CI [0.33, 0.71]), as expected. Most importantly, accuracy decreased following NAcc-TUS compared with ventricle-TUS (β=-0.16, 95% CI [-0.28, -0.02]). We also observed a positive interaction between NAcc stimulation and task progression (β=0.04, 95% CI [0.00, 0.07]), indicating a gradual change of performance over time relative to the ventricle condition. NAcc-TUS also modulated reaction times, with participants responding faster than after ventricle-TUS (β=-0.04, 95% CI [-0.10, 0.00]). A similar effect was observed following thalamus-TUS (β=-0.06, 95% CI [-0.11, 0.00]). Furthermore, NAcc-TUS increased the influence of feedback and reward on subsequent performance relative to ventricle-TUS (β=-0.02, 95% CI [-0.03, -0.01]). Specifically, participants responded faster on the following trial after receiving negative feedback and losing points, as an attempt to maximise their gains. A comparable effect was observed after thalamus-TUS (β=-0.03, 95% CI [-0.05, -0.02]). EEG analyses (Fig.1.2) revealed that FRN/RewP amplitudes were overall credibly smaller for positive feedback + large reward magnitude following NAcc-TUS compared to Ventricle-TUS (β=-1.5, 95% CI[-2.91, -0.09]), suggesting a modulation of reward prediction error after stimulation of NAcc. Pairwise analysis (Fig.1.3) indicated smaller FRN/RewP amplitudes for positive feedback + with no reward after NAcc-TUS (β=1.56, 95% CI [0.09, 2.98]) relative to ventricle-TUS, as well as for negative feedback + reward loss after (ventricle>NAcc: β=2.95, 95% CI [1.47, 4.4). For further comparisons, see figure 1.3. Together, these preliminary results suggest that TUS may have had a strong impact in the dopaminergic circuitry engaged with NAcc, modulating this region's and the entire network's sensitivity to different feedback valences and reward magnitudes.



Anterior Insula Cortex Causally Encodes Context-dependent Inequity in Social Valuation

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Inequity affects social valuation and well-being, and its effects are often context dependent. However, few studies have examined neural mechanisms by which context alters responses to social inequity and leads to different social valuations. In our fMRI task, each trial, after playing a competitive game against an opponent, participants rated the likability (1–4) of a bonus distribution between themselves and the opponent. The bonus distribution was randomly assigned and was independent of the outcome of the competitive game. Participants' social valuation depended critically on the interaction between inequity and context, particularly the game outcome, and that this context-dependent inequity was encoded in the dorsal anterior insular cortex. In order to further confirm the causal role that anterior insula play in social valuation, we applied transcranial focused ultrasound(tFUS) on dorsal anterior insula, and we found participants' reaction time under win_disadvantage and lose_advantage significantly increased. Together, our findings demonstrate that the dorsal anterior insular cortex plays a causal role in encoding how context modulates inequity and social valuation. Fig tFUS stimulation changed participants reaction time (N = 34), in win_dis situation, reaction time change ratio significantly higher than 0 (p = 0.010), and under lose_ad situation, there is also a same change (p = 0.039), which is consist with our fMRI finding

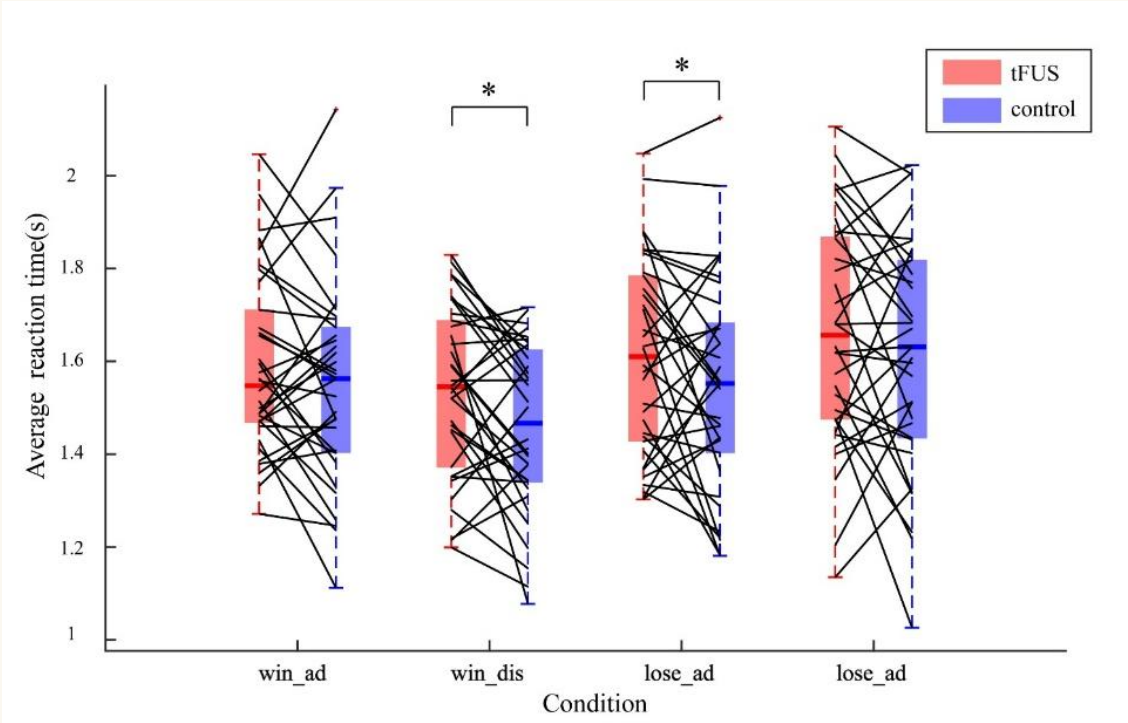

Figure 1: tFUS stimulation changed participants reaction time (N = 34), in win_dis situation, reaction time change ratio significantly higher than 0 (p = 0.010), and under lose_ad situation, there is also a same change (p = 0.039), which is consist with our fMRI finding

Examining the functional role of the subthalamic nucleus in inhibitory control in healthy individuals

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In our daily experiences alternative courses of actions and thoughts need to be inhibited allowing the occurrence of goal-directed actions. Action control is exerted through the action selection brain circuit, known as the cortico-basal ganglia network, that allow the suppression of inappropriate responses and the selection of one action rather than another. Uniquely among this network, the subthalamic nucleus (STN) plays a critical role in rapidly suppressing planned actions, a process known as 'response inhibition'. Converging evidence from clinical, animal, and correlational studies in healthy humans supports the involvement of the STN in response inhibition, highlighting its functional involvement in orchestrating the oscillatory dynamics within the cortico-basal ganglia network. However, findings are sometimes inconsistent due to limitations in patient studies, including medication eJects and comorbidities, and the inability of correlational approaches to establish causality. A critical major limitation to investigate the causal involvement of the STN in response inhibition in healthy individuals arises from the inability of conventional non-invasive tools to target deep brain areas. In this study we investigated how the STN regulates response inhibition and its associated oscillatory signatures in the healthy, intact brain. To achieve this aim, we combined transcranial ultrasound stimulation (TUS) with surface electroencephalography (EEG), for perturbing STN activity and then measuring changes in oscillatory responses during a well-established motor control task: the Stop Signal task. We adopted a cross-over design whereby participants (N=30) were randomly allocated to two groups: A and B, and they were tested in two separate experimental sessions. In each session, participants performed the Stop Signal task while their EEG motor-related activity and their speed and accuracy in Go and Stop trials was recorded. The task was performed in two blocks. Between the two blocks, Group A underwent a continuous TUS protocol (80 secs; 1600 pulses; 5ms pulse length; 50ms interpulse interval (20Hz), free field isspa = 60 W/cm2) aimed at enhancing STN excitability. Group B underwent the sham protocol (sound mimicking the verum TUS). During the second session, Group B underwent the continuous TUS protocol, whereas Group A underwent the sham protocol. Preliminary results show selective changes after perturbing STN activity with TUS in both the oscillatory and behavioural responses. The expression of these changes was state-dependent. This is, the perturbation of STN with TUS led to an increase of oscillatory amplitude responses across theta, alpha and low beta oscillatory responses in the Stop trials. These changes in oscillatory responses when stopping were presented in tandem with a decrease in the stopsignal reaction times, a cover index of the latency of the stop process. These changes were not present in the sham condition. These results represent novel evidence of the causal functional role of the STN in response inhibition directly relating EEG cortical oscillations with STN activity in healthy humans. These results advance our understanding of the neural mechanisms supporting inhibitory control and representing a stepping stone towards the development of translational interventions for motor control disorders.

The effects of transcutaneous auricular Vagus nerve stimulation on emotion regulation and memory: A comparative study of electrical and ultrasound stimulation

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Transcutaneous auricular Vagus Nerve Stimulation (taVNS) is a non-invasive neuromodulation technique that has shown potential to enhance human cognitive functions. This study synthesized findings from a single-blind, shamcontrolled, within subject experiment investigating the acute effects of either electrical (E-taVNS) or ultrasound (UtaVNS) neuromodulation on emotion regulation and memory: working memory, associative memory, semantic memory, and emotional bias. We hypothesized that active taVNS would enhance performance relative to sham across these domains and that both modalities would engage similar neuromodulatory mechanisms. Fifty-nine healthy participants were randomly allocated to each stimulation modality, received 30 minutes taVNS (EtaVNS: N = 30, U-taVNS: N = 29) and performed cognitive tasks before and after stimulation. Cognitive performance was assessed using a 3-back task for working memory [1], a cross-modal video-word task for associative memory [2], a semantic association task [3], and a facial emotion categorization task for emotion regulation [4]. Primary performance outcomes included accuracy, sensitivity index (d′), reaction time, and bias scores. Statistical analysis compared pre- and post-stimulation performance, as well as active against sham across modalities. Results revealed that both modalities showed enhanced performance after active stimulation across all cognitive tasks. Both E-taVNS and U-taVNS effectively modulated complex processing, suggesting potentially a shared mechanistic pathway for cognitive enhancement. In terms of tolerability, a higher proportion of participants receiving E-taVNS reported skin irritation compared to those receiving U-taVNS, showcasing the higher comfortability of ultrasound based stimulation against traditional electrical stimulation. These findings show that taVNS can acutely enhance complex cognitive performance, while U-taVNS may offer a better tolerated alternative. Our findings highlight the potential of taVNS to modulate cognitive function, while showing the importance of further research to clarify modality-specific effects and optimize stimulation parameters.

Figure 1: Schematic overview of the experimental procedure. Each participant completed two sessions (active and sham), separated by at least five days. At the start of each session, participants performed the cognitive tasks (pre-stimulation). Participants then received 30 minutes of taVNS using either E-taVNS or U-taVNS, depending on group assignment. Immediately following stimulation, the cognitive tasks were repeated (post-stimulation).

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Event-based FUS Neuromodulation of the Mediodorsal and Anterior Thalamus Affects Working Memory and Attentional Set Shifting

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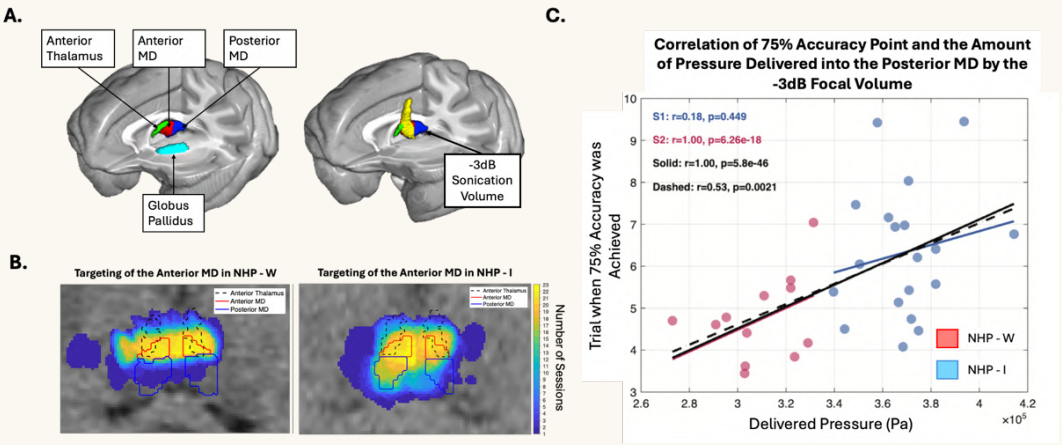
Introduction: The mediodorsal (MD) and anterior thalamic (AT) are two adjacent nuclei of the thalamus. Together, they support the cognitive processes regulated by the prefrontal cortex (PFC). Recent literature has shown MD and AT activity precedes PFC activity [1], suggesting if the MD and AT are impaired there would be downstream effects on PFC-regulated cognitive functions. In diseases like schizophrenia, where there is known MD degradation, a better understanding of the functions the MD and AT impact could improve clinical outcomes. However, MD activity is difficult to study because the MD is considered a deep brain target, and so methods like electrophysiology are considered highly invasive. Here, we noninvasively modulate the MD and AT with transcranial focused ultrasound (tFUS) in two awake and behaving non-human primates (NHP's) during cognitive task performance.

Methods: Two NHP's were sonicated across 23 behavioral sessions. tFUS was transiently delivered for 0.4 s while subjects fixated chosen visual objects in a probabilistic set shifting and a working memory task in three conditions: bilaterally (1) to AT and anterior MD, and (2) to posterior MD, or unilaterally (3) to the globus pallidus (sham) (Fig. A). We performed acoustic simulations for each session and calculated the pressure delivered into each brain region and the amount of volume overlap between each brain region and the -3dB pressure amplitude volume. We then correlated these metrics with behavioral performance.

Results and Discussion: Across both subjects, the AT and MD were consistently targeted (Fig. B) and sonicated with pressures between 0.26 - 0.51 MPa. Pressure delivered to the AT did not affect working memory, but enhanced overall performance in the set shifting task, with higher pressures improving consistency. In contrast, sonication-overlap with the posterior MD improved working memory updating, which tended to be more pronounced with higher pressures (Fig. C), but slowed set shifting. These findings document a functional dissociation of FUS effects in AT versus MD. We successfully modulated cognitive performance with a real-time and event-based tFUS targeting distinct thalamic nuclei. Our novel analysis framework correlates cognitive performance with therapeutic tFUS parameters, thus improving the neuroanatomical specificity for clinical and cognitive neuromodulation. **References:** [1]J. M. Phillips et al., "Primate thalamic nuclei select abstract rules and shape prefrontal dynamics,"



Neuron, vol. 113(12):2014-2027.e12, 2025.

A multimodal framework for ultrasound neuromodulation of persistence and switching in goal-directed behaviour

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Background: Deciding whether to persist with a goal or switch to an alternative is central to adaptive behaviour. For example, how long should you stay in a slow-moving queue, keep investing effort in a difficult project, or persevere in a strained relationship? Although persistence and switching are fundamental to everyday behaviour, the causal neural and affective mechanisms supporting goal commitment and adaptive flexibility remain incompletely understood.

Methods: We combine transcranial ultrasound stimulation (TUS), computational behavioural modelling, and continuous physiological recording to investigate how targeted brain circuits shape goal-directed behaviour. In a double-blind, sham-controlled, within-subject study, healthy adults complete a gamified goal-attainment task requiring sequential choices to either continue pursuing a current goal or abandon accumulated progress for an alternative. Across separate sessions, participants will receive bilateral nucleus accumbens TUS, multifocal bilateral anterior insula TUS, and sham stimulation, targeting circuits with complementary roles in value-based persistence and affective signalling.

Preliminary results: To establish affective markers of goal pursuit, we first analysed an online version of the same task (N = 279). Facial-expression classifiers tracked task-relevant affective states: classifier outputs varied with goal progress and option value, predicted self-reported emotions, and were associated with subsequent decisions to persist or switch. These findings support the task's sensitivity to affective states that unfold during goal-directed choice. Data collection for the current in-lab phase is ongoing, with behavioural and physiological feasibility data collected from the first N = 5 participants ahead of the TUS phase. This phase assesses whether facial-expression markers are recoverable under controlled laboratory conditions while extending measurement to pupil dilation, gaze behaviour, heart rate, and electrodermal activity. TUS sessions (NAcc, anterior insula, sham) will follow.

Discussion: This work aims to establish a multimodal framework for testing how ultrasound neuromodulation alters the behavioural, affective, and physiological processes that bias choice toward current goals or competing alternatives. By combining TUS with computational modelling and timeresolved physiology, the study lays the groundwork for future investigations of impaired motivation and behavioural flexibility. Study design and TUS targeting. Participants complete NAcc TUS, anterior insula TUS, and sham sessions while behavioural, facial, ocular, electrodermal, and cardiac signals are recorded during the goal pursuit task. Example targeting is shown with task-related fMRI z-maps from a previous study using the same task.

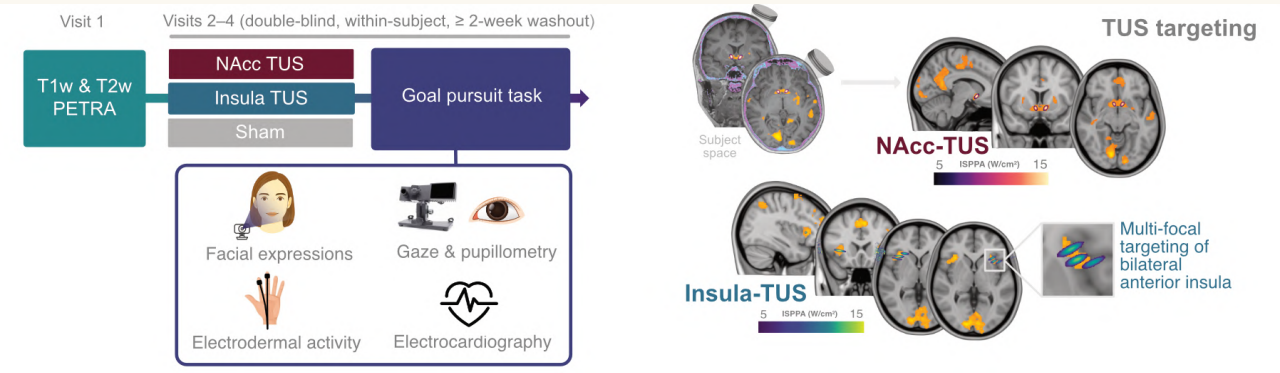

Figure 1: **Study design and TUS targeting.** Participants complete NAcc TUS, anterior insula TUS, and sham sessions while behavioural, facial, ocular, electrodermal, and cardiac signals are recorded during the goal pursuit task. Example targeting is shown with task-related fMRI z-maps from a previous study using the same task.

Investigating human pgACC-NAc interactions in cost-benefit decision making and probabilistic reward learning using transcranial ultrasound stimulation (TUS) network stimulation

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Balancing costs and benefits while tracking changing reward environments are fundamental components of adaptive decision-making. The pregenual anterior cingulate cortex (pgACC) and the nucleus accumbens (NAc) are heavily implicated in these processes, integrating cost-benefit arbitration and reward processing (Amemori & Graybiel, 2012; Friedman et al., 2015, Yaakub et al., 2025). However, causal evidence regarding how these distinct but connected regions independently and interactively drive human cost-benefit arbitration and probabilistic reward learning remains limited. While behavioural effects of transcranial ultrasound stimulation (TUS) have been shown when targeting a single node of this circuit (e.g., NAc: Yaakub et al., 2025), here we asked whether TUS can be used to probe the function of a connected network of two nodes (pgACC and NAc), and whether this has distinctive effects on behaviour compared to stimulation of NAc or pgACC alone. Interactions between NAc and pgACC and their individual causal contributions were examined in two tasks, investigating cost-benefit trade-offs and probabilistic reward reversal learning. In a within-subjects design, participants took part in four separate TUS sessions, in addition to an initial MRI session for planning, to dissect regional and network-level contributions: bilateral NAc stimulation, unilateral network stimulation (NAc and pgACC in the same hemisphere), bilateral network stimulation (NAc in one hemisphere and pgACC in the opposite hemisphere), and an unrelated white-matter (WM) active control site. We used a 100Hz PRF offline TUS protocol delivering a 120-second train with a 10% duty cycle (1ms pulse duration every 10ms) which has previously been shown to induce inhibitory changes in M1 (Zadeh et al., 2024). Following stimulation, participants completed two distinct behavioural paradigms. The first, a reward-effort decision-making task where reward/loss magnitude and physical effort (exerted via handheld dynamometer) were varied trial-wise to examine cost-benefit integration. The second, a three-stimulus probabilistic reward learning task with periodic but unpredictable reversals. On each trial, participants choose between a subset of two stimuli (with different reward probabilities), receiving feedback (reward/ no reward) for the chosen stimulus. This requires tracking and integrating relative option values of the chosen, the unchosen counterfactual, and the unchosen counterfactual. Two blocks of each task were interleaved ABAB in 15-minute blocks, counterbalanced between participants to maximise the likelihood that the TUS effects will be captured across both tasks. Data collection is ongoing (current: n=4 completed datasets; predicted at FUN26: n=8). Preliminary computational modelling of reward-guided choice behaviour will be presented alongside anticipated differences in the cost-benefit acceptance threshold between TUS sites. We hypothesize that this 100Hz protocol will exert an inhibitory effect on targeted nodes, based on growing research of its inferred inhibitory effects on M1 (e.g., Zadeh et al., 2024). Specifically, we predict that inhibiting the NAc and the NAc-pgACC network will alter cost-benefit trade-offs, shift decision boundaries and modulate the willingness to exert effort for reward. Furthermore, we hypothesize that NAc inhibition will impair flexible value updating during the probabilistic reward learning task, leading to slower adaptation or altered learning rates following reward reversals. We anticipate that the neuromodulatory effects will differ in magnitude as we inhibit the network in progressively more ways, from bilateral single node to unilateral network, and finally, bilateral network stimulation, where we anticipate that temporary inhibitory effects induced by TUS will effectively "disconnect" the two nodes of the network, not allowing intact communication between pgACC and NAc in either hemisphere. By doing this, our study aims to provide direct causal evidence for the individual and coordinated roles of the pgACC and NAc in human motivation and reward guided-choice.

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Transcranial Ultrasonic Stimulation of the Nucleus Accumbens to Modulate Prediction Error Signaling During Fear Extinction

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Anxiety disorders are highly prevalent, and exposure therapy is a first-line treatment. Its therapeutic effects are commonly modeled using extinction learning, where a previously threat-predictive stimulus (CS+) is repeatedly presented without the aversive outcome, leading to reduced conditioned fear. However, return of fear remains a major challenge and is associated with relapse risk. Using a large extinction-learning dataset, we previously identified distinct learner subgroups based on skin conductance responses, reflecting fast versus slow fear reduction (Andres et al., 2026). In addition, we found a prediction error-related signal in the ventral striatum/nucleus accumbens (NAcc) during omission of the expected aversive outcome at CS+ presentation (Andres et al., 2024; Thiele et al., 2021). This signal, resembling appetitive prediction error-like responses, emerged early in fast learners and later in slow learners (Andres et al., 2026). Building on these findings, the present ongoing study investigates whether extinction learning in humans can be modulated by non-invasive transcranial ultrasonic stimulation (TUS) of the left NAcc. TUS is delivered using a 500 kHz annular array transducer (Sonic Concepts Inc., USA; BranBox Ltd., UK). We use PlanTUS (Lueckel et al., 2025) as well as PETRA-based pseudo-CTs (Miscouridou et al., 2025) and acoustic simulations (from k-Plan; BrainBox Ltd., UK) for individual prospective planning of transducer placements to achieve optimal target exposure. Robotized frameless stereotactic neuronavigation is used to ensure precise and stable transducer positioning over longer sonication periods. Participants are assigned to one of three conditions: (i) offline 80 s 5-Hz rTUS to the left NAcc before and online sham stimulation of the left ventricle during fear extinction, (ii) offline sham stimulation of the left ventricle before and online TUS to the left NAcc during fear extinction, or sham ventricle stimulation both before and during fear extinction. Offline TUS follows an established 5 Hz protocol (PD=20 ms, PRI=200 ms) applied for a single pulse train of 80s (Zeng et al., 2022; Yaakub et al., 2025), while online TUS uses a 2.5 Hz protocol (PD=80 ms, PRI=400 ms), where each pulse train is 5.2 s long (Murphy et al., 2024) and delivered during the 8 s CS presentation to have the neuromodulatory effect build up and coincide with the expected US offset, that is, the moment of US omission. This design enables dissociation of offline and online TUS effects on prediction error processing and extinction dynamics. Preliminary data from the ongoing data collection will be presented. The study aims to advance mechanistic understanding of extinction learning and inform future nonpharmacological interventions for anxiety disorders.

Neuromodulation of Control Beliefs

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Motivated action is driven not only by reward anticipation (expected value) but also by beliefs about environmental controllability[1–3], as illustrated by learned helplessness[4]. The pregenual anterior cingulate cortex (pgACC) is thought to encode controllability[2,3,5,6] and to guide action selection via its connections with the striatum[7]. However, previous studies often confound controllability inference with reward anticipation. To disentangle these processes and test the causal contributions of pgACC and striatum, we combine transcranial focused ultrasound (TUS), task-fMRI, computational modelling, and a motivational Go/NoGo learning task. In a single-blind, sham-controlled, counterbalanced crossover design, participants will receive offline pgACC- or striatum-targeted TUS or sham stimulation across separate sessions. Stimulation targets are functionally informed3 and structurally constrained, with sequential bilateral sonication (3 x 60 s per hemisphere; 5 Hz PRF; 40 ms pulse duration; 10 ms on/off Tukey ramp; 80 W $I_{sppa\text{-}fw}$). Sham stimulation replicates acoustic conditions without ultrasound delivery. Following TUS, participants will perform a motivational learning task during fMRI. They will learn to make stimulus-specific Go/NoGo responses to win rewards or avoid losses, in separate high- and low-control blocks. The task dissociates controllability from reward anticipation by manipulating the degree to which stimulus-specific actions reduce outcome uncertainty, while enforcing higher received reward rates in low- than high-control blocks. Computational modelling is used to estimate model-free reward anticipation and model-based controllability inference. We hypothesize that striatal TUS selectively modulates reward anticipation through model-free reinforcement learning, whereas pgACC TUS selectively affects model-based controllability inference. Preliminary behavior data have demonstrated test-retest reliability of the task (N = 34), with simulations in PRESTUS8 showing feasibility and safety of individualized targeting (N = 10). This study aims to provide causal evidence for dissociable neural mechanisms underlying reward processing and controllability inference. Elucidating these circuits may advance understanding of disorders involving distorted controllability beliefs, such as depression and addiction, and inform targeted neuromodulatory interventions.

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Assessing Motor Cortical Excitability Using Concurrent Transcranial Ultrasonic and Magnetic Stimulation

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Previous studies combining concurrent transcranial ultrasonic- (TUS) and magnetic stimulation (TMS) in the human primary motor cortex (M1) have reported suppression of motor-evoked potentials (MEPs) during sonication. These studies suffered from auditory confounds, limited (TMS-based) target precision, and modest acoustic intensities at the target. Despite the high potential of TMS-MEPs serving as a framework for the development and evaluation of online TUS protocols in humans, the acute and transient effects of TUS on corticospinal excitability remain elusive. Here, we aim to re-establish this framework with improved targeting and control conditions. Participants complete two pseudorandomized conditions, targeting left M1 (experimental) and a deep white matter site (control). To concurrently deliver TUS and single-pulse TMS to left M1, we combine a powerful figure-of-eight TMS coil (MC-B70 MagVenture Inc., USA) with a 250 kHz two-element annular transducer (CTX-250 Sonic Concepts, Bothell, WA) and MR-informed neuronavigation (Localite, Germany) to evaluate the immediate effects of a new promising TUS protocol. TUS is driven with a pulse repetition frequency (PRF) of 2.5 kHz with a duty cycle (DC) of 20%, a pulse duration (PD) of 90 ms (incl. 10 ms ramps at the start and end of each pulse), a pulse repetition interval (PRI) of 400 ms, a pulse train duration (PTD) of 5.2 s, and a pulse train repetition interval (PTRI) of 45 s. This protocol is the ramped version of one previously shown to produce the strongest acute and transient neuromodulatory effects in mice (Murphy et al., Neuron 2024). Obtaining electromyographic (EMG) recordings from the contralateral first dorsal interosseous (FDI), abductor pollicis brevis (APB), and abductor digiti minimi (ADM) hand muscles, we quantify changes in TMS evoked MEP amplitudes to evaluate corticospinal excitability. We record 30 TUS-free MEPs before (pre sonication) and after (post sonication) the TUS application, respectively, as well as three runs of 14 concurrent TUS-TMS trials, with 5 TUS-free MEPs recorded in-between pulse trains. Targeting involves a two-step process. First, we use the neuronavigation software to create a grid of potential TMS coil positions by selecting a series of target coordinates along the hand knob area of the precentral gyrus. We then identify multiple TMS coil positions that consistently evoke robust MEPs in the presence of the transducer but without TUS. Next, we integrate the outcome of an fMRI-localizer of finger muscle representations in M1 with the recorded coil positions and run multiple acoustic simulations to converge on an optimized TUS target and maximize overlap between simulated focus and target. Since ramping alone does not eliminate PRF-related sensory confounds, we match the TUS power output across conditions which ensures equal energy delivery through the skull. This multimodal approach provides a controlled framework to investigate TUS-induced directional changes in cortical excitability.

Effects of low-intensity focused transcranial ultrasound stimulation of the deep cerebellar nuclei on movement and cognition

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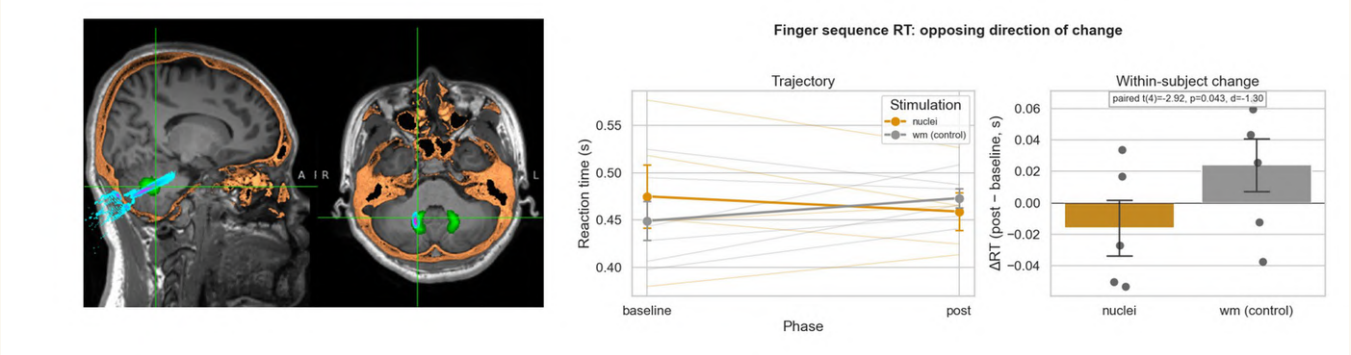
The cerebellum, once considered a purely motor structure, is now recognised as a central node in cognition and social behaviour. Dysfunction of this system is implicated not only in neurodegenerative conditions such as spinocerebellar ataxias, but also in neurodevelopmental and psychiatric disorders including ADHD and autism. Despite this, causal evidence for cerebellar contributions to human cognition remains limited, and non-invasive approaches to modulate cerebellar function are still in their infancy. Here, we use low-intensity transcranial ultrasound stimulation (TUS) to non-invasively target the human cerebellum with high spatial precision. We assessed the behavioural effects of offline stimulation using a task battery probing social, cognitive, and motor function. In a within-subject, counterbalanced design, healthy participants received bilateral TUS targeting the deep cerebellar nuclei, the principal output structures of the cerebellum, or an unrelated white matter site (control). Targeting was guided by individual anatomical MRI scans obtained prior to TUS sessions, using MRI-based neuronavigation and participant-specific TUS simulations based on pseudoCTs, to ensure precise focussing on the targeted regions. Stimulation consisted of 5Hz-patterned ultrasound (60 W/cm2 free-field I_{SPPA}, 5 Hz PRF; 30 ms pulses every 200 ms, DC=15%) delivered for 80 s at a 500 kHz carrier frequency. In each session, participants completed a baseline assessment, followed by sequential stimulation of both hemispheres and a post-stimulation task battery. To isolate stimulation-specific effects, a separate cohort completed the same behavioural task battery without TUS. While data collection is ongoing, preliminary within-subject analyses of the first six participants, cerebellar nuclei TUS produced a selective effect on a motor sequencing task: reaction times decreased following nuclei stimulation but increased following control-site stimulation, despite matched baselines (paired t-test, $t(4) = -2.92$, $p = .043$). We additionally observed a descriptive pattern in which social-cognition accuracy on a mentalizing task and an emotion recognition task was improved following nuclei stimulation but not after control site stimulation, though this contrast was not statistically reliable at the current sample size. Comparison with an independent no-stimulation cohort (n = 17) completing the same behavioural task battery confirmed that control-site baseline-to-post changes in finger-sequencing RT did not differ from no-stimulation changes ($d = +0.46$, $p = .42$), supporting the interpretation that the differential nuclei effect reflects cerebellar-specific modulation rather than nonspecific effects of ultrasound exposure. Together, these initial findings provide preliminary causal evidence for cerebellar contributions to human motor performance and motivate continued investigation of putative cerebellar modulation of social cognition. More broadly, this work demonstrates the potential of TUS as a precise, non-invasive tool for modulating cerebellar function, which may open a path toward targeted interventions in disorders characterised by cerebellar dysfunction, including cerebellar degeneration, ADHD, and autism.



Neuromodulation of Deep Cerebellar Nuclei: principles for Focused Ultrasound stimulation and EEG monitoring

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Non-invasive focused ultrasound neuromodulation of deep cerebellar nuclei offers a promising approach for basic neurophysiological research and therapeutic applications in movement disorders and beyond. In the present work, we evaluate the feasibility of a structured framework covering individualized targeting, stimulation delivery, experimental design and concurrent EEG monitoring for cerebellar human neuromodulation. We also demonstrate proof of target engagement and online stimulation effects of dentate nucleus with low (5%) and high (50%) duty cycle in a state-dependent manner. Together, this work provides a practical foundation for ultrasound-based neuromodulation of deep cerebellar structures in humans, positioning, for the first time, cerebellar tFUS as a feasible non-invasive methodological alternative to invasive techniques.

Ultrasound neuromodulation reveals a double dissociation between the roles of rmPFC and precuneus/PCC in private and social decision-making

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Correlational approaches such as functional magnetic resonance imaging (fMRI) have revealed the huge number of brain areas associated with processing the diverse variables we are basing our decisions on; however, their causal contributions to decision processes remain to be determined. To guide our choices, we estimate many parameters such as how rewarding and risky an option might be, while also evaluating the social context, or how much we might regret not choosing an alternative option. Here, we tested how the rostromedial prefrontal cortex (rmPFC) and the precuneus/posterior cingulate cortex (PCC) contribute to our private and social decisions by combining transcranial ultrasound stimulation (TUS) with fMRI. TUS to the rmPFC increased the influence of expected value and anticipated regret on choices and made participants less risk averse. In contrast, TUS to the precuneus/PCC selectively reduced regret anticipation. Our findings link core decision mechanisms with the roots of maladaptive behaviours and highlight the potential of ultrasound neuromodulation for targeted neurorehabilitation.

Exploring Potential Moderators of TUS from a Psychological Perspective: An Analysis of a Large-Scale Dataset from a Preregistered Study on the Effects of TUS on Electroencephalographic Conflict-Related Midfrontal Theta

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In a preregistered double-blind within-subjects study, our group used TUS on the right prefrontal cortex, which previously enhanced self-reported global positive mood, decreased negative self-reports of mental conflict (anxiety/worrying), and modulated associated midfrontal activity as reflected in functional magnetic resonance imaging. This study's large-scale dataset allowed us to publish recently on further TUS effects on physiology and behavior (N = 152), measured during a well-established virtual T-maze task for the investigation of motivational conflicts regarding whether participants execute approach versus withdrawal while allowing to record related electroencephalographic data such as midfrontal theta (MFT). In brief, we showed that TUS significantly decreased conflict-related MFT, which significantly explained increases in approach and decreases in withdrawal. Now, we were interested whether these global effects might differ based on individual moderating variables. Our large-scale dataset offers various data for such exploratory analyses (e.g., on demographics and personality). We did not find significantly relevant moderators but detected patterns by trend that can possibly be of relevance for future work. Eventually, this might provide more personalized neuromodulation for research and applications such as regarding emotional and motivational mental health.

Amygdala-Targeted TUS Modulates Reward-Punishment Learning During the Iowa Gambling Task

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Background: The amygdala is a key node in neural circuits involved in emotional salience, social evaluation, threat processing, and attentional prioritization of behaviorally relevant stimuli. These processes are clinically relevant to conditions in which emotion and attention influence symptom expression, including functional movement disorders and tic disorders. Social inclusion and exclusion paradigms such as Cyberball provide a controlled way to probe behavioral responses to socially salient events. Transcranial ultrasound stimulation (TUS) has emerged as a promising neuromodulation tool because it can target deep brain regions, including the amygdala, with high spatial precision. However, whether amygdala-targeted TUS can alter attentional responses during Cyberball-based social inclusion and exclusion remains unclear.

Objective: To assess whether bilateral 100 Hz amygdala-targeted TUS modulates reaction-time responses during Cyberball-based social inclusion and exclusion in healthy participants.

Methods: Six healthy participants completed a multi-visit, within-subjects study. Visit 1 included an anatomical MRI scan for individualized BabelBrain acoustic modelling and precision amygdala targeting. During Visits 2-3, participants received 100 Hz amygdala-targeted TUS or sham stimulation in randomized order. Active TUS was delivered bilaterally using a 4-channel NeuroFUS LT system, with each amygdala stimulated sequentially for 120 s. At each stimulation visit, participants completed the Cyberball task before and after stimulation, including social inclusion and exclusion conditions. Reaction time to ball reception was used as the primary behavioral outcome and served as an objective measure of attentional engagement during socially salient task events. Sham stimulation was delivered by flipping the transducer away from the scalp while maintaining similar auditory and tactile cues.

Results: Following 100 Hz amygdala-targeted TUS, mean reaction time decreased from 830 ± 112 ms pre-stimulation to 690 ±105 ms post-stimulation, corresponding to an average reduction of approximately 17%. The reduction was observed across both inclusion and exclusion conditions. No comparable pre- to post-stimulation change was observed following sham stimulation. A paired-samples comparison showed a significant reduction in reaction time after active TUS [$t(5) = 15.9$, $p < 0.001$].

Conclusion: Bilateral 100 Hz amygdala-targeted TUS reduced reaction times during Cyberball-based social inclusion and exclusion. No comparable change was observed after sham stimulation. Reaction time to ball reception reflects how quick participants attend to and respond to socially salient events. The observed reduction may therefore suggest altered attentional engagement or response efficiency after amygdala stimulation. These preliminary findings support further study of amygdala-TUS for modulating emotion-attention mechanisms in clinically relevant social contexts.

Frequency-Specific Modulation of Effort-Based Motivation Using Transcranial Ultrasound Stimulation of the Nucleus Accumbens

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Background: Transcranial focused ultrasound stimulation (TUS) has emerged as a promising neuromodulation tool because it can target deep brain regions with high spatial precision. One such region is the nucleus accumbens (NAc), a central node of the reward circuitry that contributes to motivation, reward valuation, and effort-based decision-making. These functions can be objectively probed using effort-based reward tasks, in which individuals choose between loweffort/low-reward and high-effort/high-reward options. Disruption of these processes is implicated in several neuropsychiatric disorders, making the NAc a clinically relevant target for non-invasive neuromodulation. However, the behavioral effects of NAc-TUS, and the stimulation parameters required to modulate effort-based motivation have not been established.

Objective: To evaluate the feasibility of frequency-specific bilateral NAc-TUS in healthy adults and examine its effects on effort-based motivation.

Methods: Seven healthy adults completed four study visits, including an anatomical MRI session for individualized acoustic modeling and three stimulation sessions. Anatomical MRI were used in BabelBrain to guide bilateral NAc targeting. During the stimulation visits, participants received bilateral NAc-TUS under one of three conditions: 5 Hz, 100 Hz, or sham stimulation. In the sham condition, the transducer was flipped with ultrasound directed away from the scalp while preserving the auditory and tactile cues associated with active TUS. Effort-based motivation was assessed before and after each stimulation session using the Effort-Expenditure for Rewards Task (EEfRT), which quantifies preference for high-effort/high-reward choices relative to loweffort/low-reward alternatives.

Results: 5 Hz NAc-TUS increased high-effort/high-reward choices (mean pre-minus-post difference = −0.105; $t(6) = -4.14$, $p = 0.006$). This effect was significantly greater than 100 Hz stimulation ($t(11.94) = -2.22$), $p = 0.047$). 100 Hz NAc TUS did not significantly change task selection (mean pre-minus-post difference = −0.004; $t(7) = -0.12$, $p = 0.911$).

Conclusion: Bilateral NAc-TUS may modulate effort-based motivation in a frequency-dependent manner, with 5 Hz stimulation increased high-effort/high-reward choices while 100 Hz showed no significant effect. Overall, this work supports further development of NAc-TUS as a potential noninvasive approach for conditions involving impaired motivation and reward processing, including apathy, anhedonia, depression, and addiction.

Ultrasound Neuromodulation of the Human Basal Forebrain: A Multimodal Approach

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Introduction: The basal forebrain (BF) provides widespread cholinergic input to the cortex and hippocampus, supporting attention, cortical state regulation, and memory. Increased cholinergic tone promotes cortical desynchronization and efficient sensory processing, whereas its decline is linked to cognitive impairment. Transcranial focused ultrasound stimulation (TUS) is a noninvasive technique capable of targeting deep brain structures with high spatial precision, enabling causal investigation of BF function in humans. This study aimed to test whether TUS applied to the left BF modulates cortical cholinergic tone, assessed via electrophysiological and physiological proxies. We hypothesized that BF stimulation would induce alpha desynchronization, theta synchronization, and increased pupil dilation, with no comparable effects during stimulation of an active control site (insula).

Methods: A within-subject design was used in healthy adults, each completing two sessions targeting the BF and insula in pseudo-randomized order. Both targets were accessed via the temporal bone window, with minimal transducer repositioning; the insula was stimulated at a similar lateral position but with reduced focal depth, ensuring effective blinding across conditions. TUS was delivered using a 545 kHz annular array transducer, positioned with MRI-guided neuronavigation and robotically guided alignment to ensure precise and stable targeting. Subtle translational and rotational deviations were continuously monitored and corrected online by the robotic system. Each session included pre-, online-, and post-stimulation recordings of EEG, ECG, and pupillometry. Stimulation consisted of 40 trials (pulse duration 90 ms with 10 ms Tukey ramping applied at onset and offset to minimize auditory confounds, pulse repetition interval 400 ms, pulse-train duration 5.2 s, inter-trial interval 40 s). Safety parameters were maintained within recommended limits. Online EEG assessed transient effects during stimulation, while offline analyses compared resting-state activity before and after stimulation, focusing on alpha and theta band power across cortical regions.

Results and Conclusions: Interim analyses (n = 12) showed a significant reduction in resting-state alpha power following BF stimulation relative to baseline, with strongest effects over centro-parietal regions, consistent with BF projection patterns. No comparable EEG changes were observed during insula stimulation. Measures of autonomic activity, including heartbeat-evoked potentials, heart rate, and heart rate variability, showed no significant differences between conditions. These findings indicate that BF-targeted TUS induces selective, sustained modulation of cortical oscillatory activity without measurable peripheral autonomic effects, supporting a central cholinergic mechanism. The use of a depth-matched active control site strengthens the specificity of these effects by minimizing perceptual differences between conditions. Offline EEG measures appeared more sensitive than online analyses, likely due to reduced variability and fewer stimulation-related artifacts. Completion of the full sample will enable more comprehensive multimodal analyses integrating EEG, ECG, pupillometry, and individualized acoustic factors. Overall, these results demonstrate that BF stimulation can reliably modulate cortical state and provide a robust framework for probing deep neuromodulatory systems with translational relevance.

Transcranial ultrasound stimulation of pgACC for modulating social basis functions

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How does the brain efficiently navigate complex social environments? Our recent studies suggest that beyond recognizing individual identities, prefrontal cortex employs a combinatorial code by tracking the relationships that exist in a social group - what we call social basis functions. Basis functions provide an efficient, compressed, and stepwise representational format. In particular, pregenual anterior cingulate cortex (pgACC) appears crucial for such combinatorial representations. However, casual testing on basis function encoding has been limited, as the underlying brain regions have not been accessible to conventional non-invasive brain stimulation methods in humans. Here, we used transcranial ultrasound brain stimulation (TUS) to causally modulate pgACC activity and test its role in representing social basis functions. TUS offers millimetre-precision altering neural activity in deep brain regions non-invasively in humans, which is uniquely suited to test our hypotheses. PgACC was targeted with four sonications of a 5Hz protocol, each lasting 80 seconds (20-ms ultrasound bursts every 200 ms). Inter-sonication intervals were at least 120 seconds to minimise thermal effects. Thirty-nine participants completed a four-player group decision-making task following TUS applied either to the pgACC or to the unconnected white matter control site (within-subjects offline TUS design). Participants teamed with a partner against two opponents, making performance comparisons between the two teams. Our previous work has shown that social basis functions enable stepwise decisions, using group structure as a mental scaffold to first identify teams and then specify relevant players. This model makes detailed predictions about the time course of how decision variables influence choice. We hypothesized that pgACC stimulation would diminish the influence of the social structure on decisionmaking, providing causal evidence that pgACC is important for relational embedding of social information. Preliminary results support our hypothesis. Compared to control stimulation, pgACC stimulation significantly reduced the early reliance on the social group structure on choice. Participants appeared to represent the involved players more independently, and less as part of their teams, particularly when participants responded quickly, as hypothesized. The net effect of this disrupted mechanism was that decisions were made in a more agent-centric manner, less influenced by social team relationships. Our study provides causal evidence that pgACC modulates social representation through social basis functions. This finding not only sheds light on the neural mechanisms underlying social cognition but also establishes ultrasound neuromodulation as an efficient and powerful tool for probing how deep brain regions contribute to human information processing.

Low intensity focused ultrasound to the bilateral hippocampi significantly improves associative memory on a face-name recall task

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Background: Low intensity focused ultrasound (LIFU) is a noninvasive brain stimulation approach that can stimulate deep human brain targets. In this study we investigated the effects of LIFU to the bilateral hippocampi on episodic memory in a double-blind, sham-controlled design.

Methods: We enrolled 14 healthy adult participants (28.5 ± 5.9 years old; 7M/7F) in this study. Participants underwent a face-name associative memory task that asked them to remember pairings of faces and names across different age (younger, middle aged, older) and sex (male, female) categories. Following baseline viewing of face-name pairings, participants received 10 minutes of LIFU (PETRA and T1 MRI-guided; 20% duty cycle, 25 Hz PRF for 30 s on/30 s off blocks) or diffuse unfocused sham before being tested for recall on the names paired to each face. In a second stimulation visit, participants received an additional LIFU session with the same condition as in Visit 1 (i.e., either active-active or sham-sham) with new face-name pairings, LIFU, and recall testing.

Results: We found a significant main effect of condition such that active LIFU led to higher recall accuracy in face-name pairings. More specifically, in Visit 1, active LIFU led to significantly higher recall rates (22.0% ± 4.2%) than sham LIFU (12.2% ± 3.0%). Similarly, in Visit 2, active LIFU recall accuracy (29.2% ± 4.7%) significantly outpaced sham LIFU (15.1% ± 3.3%). The active LIFU condition improvement from Visit 1 to Visit 2 had a trending significance level ($p = 0.055$).

Discussion: LIFU to the bilateral hippocampi led to significant improvements in associative memory. We are currently analyzing task evoked electroencephalography (EEG) data that we acquired in this study and will present these at the FUN meeting. Moreover, we will discuss key stimulation parameters in ultrasound and the importance of considering duty cycle, PRF, I_{SPPA} intensity, and brain target region when considering optimal parameter development.

Dissociating amygdala and dACC contributions to affective learning in volatile environments

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Successful social interactions require us to adapt our behaviour appropriately to emotional cues, such as the facial expressions of others. But how do we decide whether to approach or avoid emotional cues in environments where the appropriate response continuously changes? Previous fMRI work has suggested that the amygdala and dorsal anterior cingulate cortex (dACC) play a key role. The amygdala biases action selection based on the affective content of cues, and the dACC tracks environmental changes and adjusts the speed of learning. Here, we seek causal evidence by directly targeting these regions using non-invasive neuromodulation, while participants perform a reversal learning task in a social-emotional approach-avoidance context (AA-RL). In this newly developed AA-RL task, participants learn to make approach or avoidance responses to angry and happy face cues based on probabilistic monetary feedback. This feedback indicates whether affect-congruent (approach happy and avoid angry) or affectincongruent responses (approach angry and avoid happy) are currently optimal. We manipulate volatility by varying the number of trials between reversals of the optimal mapping: few trials between reversals in volatile blocks, many in stable blocks. This paradigm allows us to isolate affective biases on action selection from volatility-driven adjustments of the learning rate. To establish causal contributions, we apply offline bilateral Transcranial Ultrasonic Stimulation (TUS) to the amygdala or dACC for 120 seconds using 10-element annular array transducers at a 5 Hz Pulse Repetition Frequency and compare their elicited effects against a defocussed sham condition. Each participant completes three sessions on separate days; in each session, one of the three stimulation conditions (Amygdala-TUS, dACC-TUS, sham) is applied bilaterally outside the scanner, after which participants are transferred to the MRI scanner to perform the AA-RL task. We will quantify behavioural changes using accuracy, alongside reinforcement-learning models that aim to dissociate affective biases on action selection from the trial-by-trial adjustment of learning rate to volatility and link these behavioural and computational changes to task-evoked BOLD activity in the stimulated regions. Data collection is currently ongoing; behavioural, computational, and fMRI results from the sample collected by the time of the conference will be presented. In these results, we will test the following hypotheses:

1. Amygdala-TUS will lead to an increase in emotional bias. Behaviourally, this will be reflected in decreased accuracy in affect-incongruent trials. Neurally, this will be reflected in increased amygdala activity in affect-incongruent trials.
2. dACC-TUS will induce improved updating. Behaviourally, this will be reflected in increased learning rates in volatile conditions. Neurally, this will be reflected in increased activity in the dACC in volatile conditions.

Neuromodulation of Reinforcement Learning via Transcranial Ultrasound Stimulation of the Nucleus Accumbens: A Randomized Sham-Controlled fMRI Study

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Background: The nucleus accumbens (NAcc) is critically involved in reinforcement learning and motivational processes. While substantial evidence implicates the NAcc in reward-based learning, the extent to which it differentially contributes to learning from positive versus negative outcomes remains debated. Transcranial ultrasound stimulation (TUS) offers a novel, non-invasive approach to modulate deep brain structures with high spatial precision, providing new opportunities to causally probe the functional role of subcortical regions. Establishing the neuromodulatory effects of TUS on specific learning processes could inform therapeutic applications for disorders characterized by learning and motivational deficits, such as obesity, OCD and substance use disorders.

Objectives: This study investigates whether TUS targeting the NAcc modulates reinforcement learning processes, specifically positive reinforcement learning (learning from rewards) versus negative reinforcement learning (learning from punishment avoidance). We aim to establish the causal role of the NAcc in these learning processes and characterize TUS-induced changes in brain activity using task-based fMRI.

Methods: We employ a within-subjects, randomized, sham-controlled crossover design with N=50 healthy adults (18-40 years). Participants complete three experimental sessions separated by $\geq$1 week, receiving either: (1) active TUS targeting NAcc, (2) active control stimulation (anterior insula), or (3) sham stimulation. Following offline TUS, participants perform a probabilistic reversal learning task during fMRI, consisting of separate Reward (maximize gains) and Avoidance (minimize losses) blocks (280 trials total). Primary behavioral outcomes include positive-stay behavior, negative-switch behavior, learning rate, and accuracy. Computational modeling using hierarchical Bayesian Q-learning models will identify underlying learning mechanisms. fMRI analysis will assess TUS-induced BOLD response changes in NAcc and functionally connected networks.

Expected contributions: This study will provide causal evidence for the NAcc's role in reinforcement learning and establish whether TUS can selectively modulate learning from positive versus negative outcomes. Findings will inform the therapeutic potential of TUS for populations with learning and motivational deficits and contribute to our mechanistic understanding of subcortical contributions to adaptive decision-making.

Modulating Human Reward Function Using Transcranial Ultrasound Stimulation of the Nucleus Accumbens

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Treatment-resistant depression (TRD) remains a major clinical challenge, with anhedonia as a core symptom linked to dysfunction within the brain's reward circuitry. The nucleus accumbens (NAcc) is a central hub in this system, yet its precise role in human reward processing remains poorly understood due to limitations of existing neuromodulation techniques. Low-intensity transcranial ultrasound stimulation (TUS) offers a novel opportunity to study NAcc function in humans. As data collection is ongoing, this poster will focus on the study protocol, targeting approach, and current status. This project investigates the causal role of the NAcc in various aspects of reward processing by applying TUS to the NAcc in healthy participants with two control conditions: active control stimulation of the lateral ventricles (LV) and sham control stimulation. In a randomized, double-blind, repeated-measures design, 29 participants undergo three stimulation sessions one week apart. TUS sonications are delivered using a NeuroFUS DPX 500 system (500 kHz; PRF = 5 Hz; pulse duration = 20 ms; Tukey ramp = 10 ms; 10% duty cycle; a single 120-s pulsed sonication; free-field I_{SPPA} = 80). Primary outcomes include reward responsiveness measured with a probabilistic reward task and reward-related neural responses indexed by the Reward Positivity (RewP) event-related potential (ERP) recorded during a monetary gambling task (Doors task). Secondary outcomes include pupil dilation in response to rewarding stimuli, the ERP component stimuluspreceding negativity (SPN) and various indices from resting-state EEG pre- and poststimulation. Furthermore, several exploratory outcomes are assessed at baseline in an attempt to identify predictors of response, such as MRS over bilateral ventral striatum, DTI, rs-fMRI and two self-rating scales relating to reward function: Snaith-Hamilton Pleasure Scale (SHAPS) and Positive Valence Systems Scale (PVSS-21). In an attempt to selectively modulate the NAcc, this study aims to advance mechanistic understanding of human reward processing. The findings are expected to provide insights into the neurobiology of anhedonia and inform the development of precision neuromodulation approaches for TRD and related psychiatric disorders.

Real-time EEG-triggered transcranial ultrasonic stimulation (TUS) of the human thalamus during NREM to modulate sleep spindles

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Sleep supports memory consolidation through the coordinated reactivation and redistribution of newly encoded representations across hippocampo-neocortical networks. During non-rapid eye movement (NREM) sleep, this process is thought to depend on the hierarchical coupling of neocortical slow oscillations, thalamocortical sleep spindles and hippocampal ripples. Sleep spindles, generated through interactions between the thalamic reticular nucleus and thalamocortical relay neurons and projecting into neocortex and hippocampus, are therefore a candidate mechanism through which thalamic activity may gate cortical plasticity and support systems-level memory consolidation. Yet, causal evidence linking sleep spindles to memory consolidation in humans remains limited, partly because selectively modulating spindle activity through thalamic generators is technically challenging.

Here, we combine real-time state-dependent low-intensity focused transcranial ultrasonic stimulation (TUS) with individualized thalamic targeting to test whether modulation of thalamic spindle generation can alter sleep spindle activity in humans. This single-blind multi-session study includes stimulation of combined thalamic targets overlapping with anterior/reticular and mediodorsal/reticular regions, with the lateral ventricle as an active anatomical control. Within sessions, ultrasonic bursts are delivered in spindle-free periods at two free-field Isppa levels: active stimulation at 60 W/cm² and low-level sham at 1 W/cm². Stimulation targeting was optimized using a personalized pipeline based on individual structural MRI and atlas-based thalamic segmentation, with acoustic simulations performed prospectively and repeated post hoc; stimulation parameters followed ITRUSST biophysical safety guidelines.

Preliminary results from ongoing data collection will be presented, including stimulation-locked EEG responses during NREM sleep across thalamic and control stimulation sessions, analysed via time-frequency decomposition and cluster-based permutation statistics focused on spindle-band (12–15 Hz) and slow-oscillation (0.5–4 Hz) power. Initial pilot analyses suggested increased spindle-band power following active 60 W/cm² stimulation compared with 1 W/cm² sham within thalamic sessions, with a more pronounced response for thalamic than ventricle stimulation, although effects are currently variable across sessions and have not yet reached statistical significance.

Together, these preliminary findings support the feasibility of real-time EEG-triggered thalamic TUS during NREM sleep and suggest that this approach can engage sleep-relevant oscillatory activity in humans. Ongoing data collection will reveal whether thalamic TUS reliably modulates spindle activity across participants and whether stimulation-induced changes in sleep oscillations are associated with subsequent motor and declarative memory consolidation.

Other Ultrasound Applications

SECTION 04 / 06 · 1 ORAL PRESENTATIONS · 6 POSTERS

High-Frequency Focused Ultrasound targeting the Midbrain in the Guinea Pig Induces Activation and Plasticity of the Efferent System, and Protection Against Noise-Induced Hearing loss

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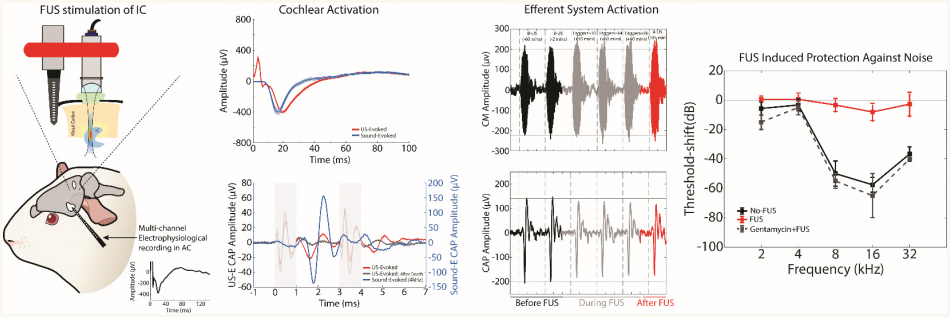
Introduction: Focused ultrasound (FUS) is an emerging noninvasive neuromodulation technique with greater spatial precision and tissue penetration compared with conventional brain stimulation approaches. Although previous studies have shown that FUS can modulate neuronal activity in central nervous system structures, recent work in guinea pigs demonstrated that low-frequency ultrasound stimulation of the auditory cortex indirectly activates the cochlea through mechanical or fluid vibrations rather than directly stimulating auditory neurons. Thus, whether FUS can directly excite neurons within the central auditory system in vivo remains unresolved. Here, we applied high-frequency FUS to the inferior colliculus (IC) of anesthetized guinea pigs and demonstrate that FUS stimulation activates the efferent system, thereby protecting the cochlea against subsequent acoustic trauma. Given that noise-induced hearing loss (NIHL) is a major cause of auditory disability and that effective preventive or restorative clinical strategies remain limited, these findings identify FUS as a potential noninvasive approach for hearing protection.

Methods: Craniotomies were performed over the IC and A1 to allow insertion of microelectrode arrays. Electrode recordings in the IC were first used to localize the central nucleus of the inferior colliculus (CNIC), after which a FUS transducer of center frequency 20 MHz was then positioned such that, its acoustic focus targeted the CNIC (approximately 4–5 mm below the visual cortical surface). FUS stimulation consisted of 3-ms pulses delivered at 90-s inter-stimulus intervals over a 2-hour period, with a peak acoustic pressure of 6.8 MPa. Microelectrode arrays were subsequently inserted into A1 to assess if FUS stimulation could activate afferent neurons in the IC. We also assessed the cochlear responses before, during and after FUS stimulation using compound action potential (CAP) and cochlear microphonics (CMs). The effects of FUS stimulation on NIHL (acoustic trauma was induced by a continuous 8kHz-tone, 115 dB, 1h after the FUS stimulation sequence) were also studied using auditory brainstem responses (ABRs).

Results & Discussion: We found that FUS elicited cortical responses, not through direct activation of the afferent pathway at the level of the IC, but through the activation of the cochlea. Ultrasound-evoked CAPs were predominantly detected in the ipsilateral cochlea compared to the contralateral side, supporting a cochlea-mediated origin of the cortical responses. Interestingly, we found that FUS could activate the efferent system, likely through the excitation of the medial olivocochlear (MOC) neurons. Indeed, FUS stimulation was associated with a reduction in CAP amplitude to 8-kHz tone pips and an increase in CM amplitude, an electrophysiological signature consistent with MOC-mediated modulation of cochlear function. Moreover, we observed that these effects on CAP and CMs were cumulative and long-lasting (up to 2h after FUS stimulation), suggesting that FUS stimulation is capable of triggering some kind of long-term plasticity of the efferent system. Furthermore, FUS stimulation applied before noise trauma almost completely prevented noise-induced hearing loss. FUS-treated animals showed an ABR threshold elevation following trauma of less than 10 dB for frequencies higher than 8 kHz whereas thresholds dramatically increased by 60 dB in control (no-FUS) animals. This level of protection against NIHL is far greater than that provided by other protective methods, including those designed to stimulate the activity of the MOC system. Finally, administration of gentamicin (aminoglycoside antibiotic known to block the MOC) before FUS stimulation eliminated the effects of FUS stimulation on CAP and CMs and abolished its protective action from noise trauma.

In summary, our results are the first to show that the central auditory system (efferent neurons) can be activated by ultrasound in vivo. They further indicate that the activation of the efferent system, possibly combined with cochlear excitation, could promote some form of plasticity at the cochlear level, thereby enhancing efferent-mediated protection against noise-trauma. The protection of approximatively 50 dB reported in this study is unprecedented. These findings open promising new perspectives for non-invasive neurostimulation of the central auditory system and the prevention of NIHL using FUS.



Functional Ultrasound Imaging for Decoding Forelimb Motor Intent in a Mouse Two-Alternative Forced-Choice Joystick Task

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Background: Motor brain-computer interfaces (BCIs) seek to translate movement-related neural activity into external control signals, offering a potential route toward restoring communication and assistive-device control in individuals with severe motor impairment. Intracortical electrophysiology provides millisecond temporal resolution and local neural specificity, but requires penetration of the dura and brain tissue and samples a relatively limited spatial extent. Functional ultrasound imaging (fUSI) measures cerebral blood volume dynamics with high spatial resolution across cortical and subcortical structures while operating through a chronic acoustic window with the dura preserved. This study aimed to establish a mouse fUSI platform for characterizing forelimb motor representations and supporting subsequent motor-intent analysis and decoding.

Methods: Head-fixed mice were trained on a two-alternative forced-choice auditory-motor joystick task in which two auditory cues instructed one of two mutually exclusive forelimb responses: 1) pushing or 2) pulling a joystick. A chronic polymethylpentene-sealed acoustic window implanted in the skull permits repeated high-frame-rate fUSI acquisition from a single sagittal plane encompassing motor-related cortical regions and dorsal striatum. Adapted from established chronic rodent fUS protocols, imaging used a 15-MHz linear-array probe with ultrafast plane-wave acquisition at 500 Hz. Auditory cues, joystick displacement, trial outcomes, and fUSI acquisition were synchronized, and pipelines for motion correction, atlas registration, regional and pixel-wise feature extraction, and trial-level supervised decoding were established.

Results: Behavioral training procedures, chronic-window preparation, probe positioning, synchronized fUSI-behavior acquisition, and analysis workflows were integrated into an operational experimental platform. The system supports repeated recording sessions during push and pull joystick behavior and aligns functional ultrasound signals with cue identity, joystick kinematics, and trial outcomes. This platform will be used to quantify task-locked hemodynamic responses across cue, delay, and movement epochs, evaluate trial-level push-versus-pull decoding performance, and compare the relative contributions of motor cortical and dorsal striatal signals to motor-intent readout.

Conclusion: This work establishes an integrated fUSI-joystick platform for studying forelimb action in mice. By combining a clearly defined two-choice push-pull behavior with chronic mesoscale imaging of cortical and subcortical regions, the platform provides a methodological basis for future motor-intent analyses and for the development of real-time ultrasound-based motor decoding, closed-loop BCIs, and state-dependent neuromodulation systems.

Repeated focal serotonin delivery with ultrasound is safe and increases serotonergic signal in the pgACC

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Low-intensity transcranial ultrasound stimulation (TUS), combined with microbubbles (MB), can transiently and focally open the blood–brain barrier (BBB). We recently demonstrated that this approach enables targeted delivery of serotonin to the pregenual anterior cingulate cortex (pgACC), resulting in measurable effects on brain function and behaviour. However, a key challenge for BBB-opening approaches is determining whether repeated interventions induce cumulative tissue damage or sterile inflammatory responses that could limit translational potential. Here, we aimed to: (1) assess the safety of repeated BBB opening over several months using histology; and (2) investigate evidence for local serotonin delivery at the target site. To assess safety, we performed histological analyses to evaluate tissue integrity following repeated BBB opening procedures. No evidence of overt tissue damage, cellular loss, or lesion formation was observed in either cresyl violet (CV) or haematoxylin and eosin (H&E) staining in animals that underwent repeated BBB opening sessions. To investigate local serotonin delivery, we performed serotonin immunostaining in the pgACC (area 24a) following focal serotonin delivery and compared this with a control region. Quantification revealed increased serotonergic axonal labelling density in the pgACC of animals receiving focal serotonin delivery relative to animals undergoing BBB opening alone. The elevated serotonergic signal is consistent with enhanced local serotonin availability at the target site. Together, these findings demonstrate that repeated BBB opening procedures are safe, effective, and well tolerated in non-human primates over periods of several months. These results position TUS-mediated neuromodulator delivery as a promising tool for probing brain circuits at the mesoscale.

Transcranial 4D Functional Ultrasound Imaging Guides and Monitors Focused Ultrasound Neuromodulation

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Background: Non-invasive tools that can modulate and monitor brain circuits are critical for understanding circuit function and enabling brain-machine interfaces. Existing neuromodulatory tools can stimulate or inhibit circuits, but targeting deep structures requires invasive approaches with separate targeting and monitoring modalities. Ultrasound uniquely supports both imaging and neuromodulation at shallow and deep brain locations. Here, 4D functional ultrasound imaging (fUSI) is combined with transcranial focused ultrasound (tFUS) neuromodulation into a single non-invasive platform for circuit modulation and monitoring, providing a pathway toward non-invasive brain-machine interfaces.

Methods: Four anesthetized rats and four awake, head-fixed mice underwent simultaneous fUSI and tFUS neuromodulation. fUSI used a 32×32 Vermon 8 MHz matrix array controlled by a 1024-channel Vantage System, and tFUS used a 1 MHz therapeutic imaging probe system (TIPS) co-registered to the fUSI transducer. For rats, a vibrotactile stimulus was applied to the left hind paw and the S1HL region was found (A) using an offline processing step was performed over one stimulation cycle (70 s), taking about fifteen minutes. Then, tFUS was applied to this region. Mice performed a reach-to-grasp task (1 reach/15 s) with tFUS targeted to contralateral M1, with onset aligned to pellet delivery and activation was calculated using GLM through time. Each session began with fUSI alone, followed by fUSI + tFUS at increasing pressures (MI: 0.22-0.34) until reaching ceased. Microbubble infusion enabled fUSI and ULM metrics including connectivity, cerebral blood flow, velocity, and vessel diameter to be calculated and compared before and after modulation, which can be related back to behavioral changes like reach attempt and velocity.

Results/Discussion: Super-resolution blood flow increased by 130% in a targeted vessel following neuromodulation, with three of four rats showing a significant increase (B). The target region showed 194% ± 179% higher β activation values than the global brain and 296% ± 197% higher β values than the off-target control region. In mice, reach attempts and velocity decreased by 34% and 27% at the highest pressure, with partial recovery at 63 min and full recovery by 14 days (C). Here, a system for combined ultrasound imaging and neuromodulation has been developed, paving the way for closed-loop, non-invasive, targeted neuromodulation.

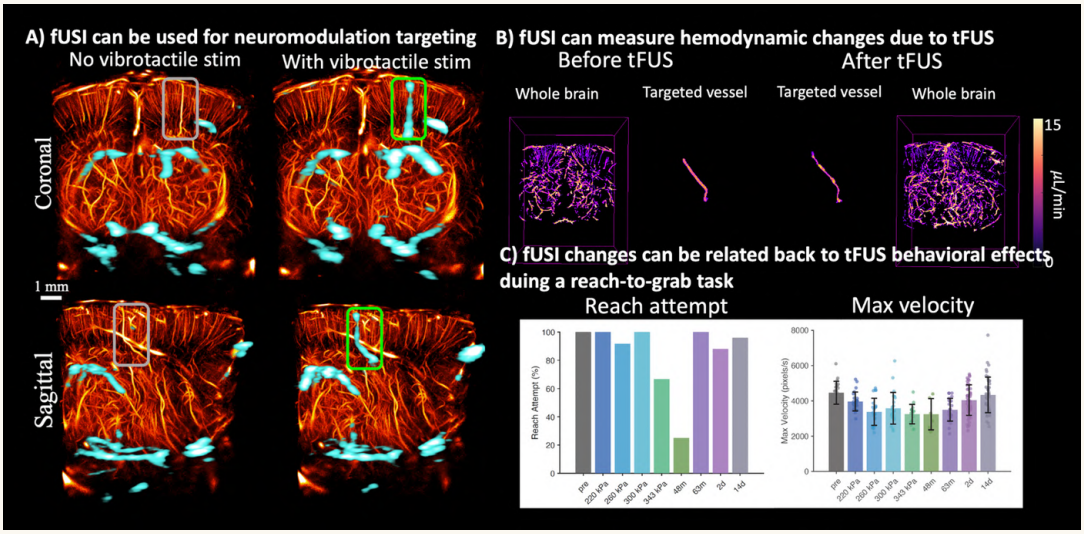


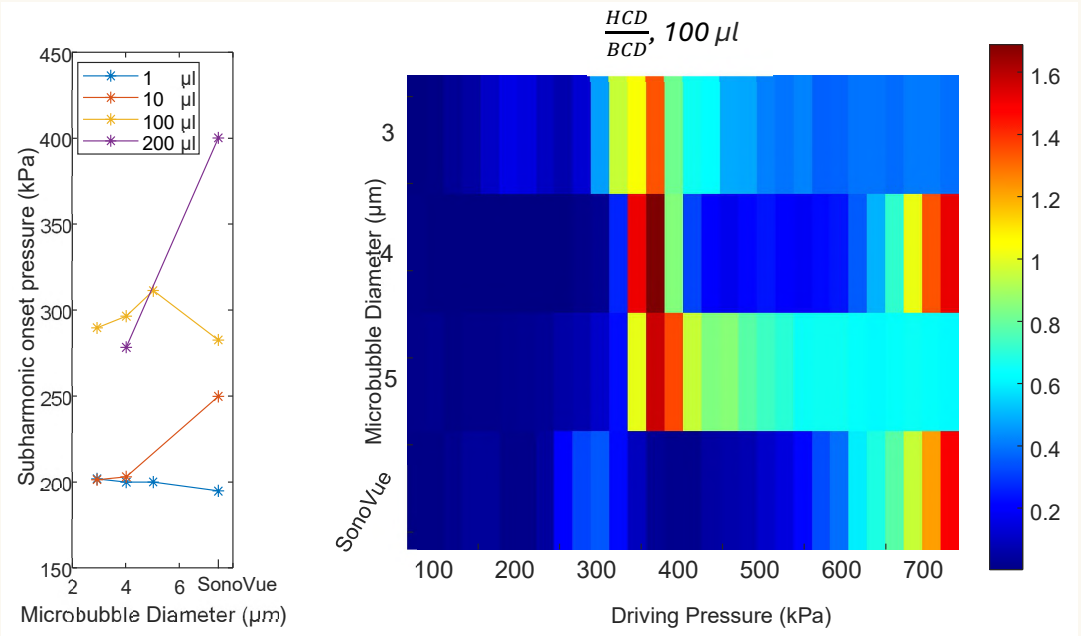
Figure 1: (A) fUSI based localization of S1HL in anesthetized rats via vibrotactile stimulation of the left hind paw, with tFUS subsequently applied to this region. (B) Super-resolution ULM blood flow increased in the targeted vessel pre and post neuromodulation. (C) In awake head-fixed mice, reach attempts and velocity decreased 34% and 27% at the highest pressure (MI: 0.22–0.34), with partial recovery at 63 min and full recovery by 14 days.

Optimization of Stable Cavitation for Blood–Brain Barrier Opening Using Monodisperse Microbubbles

Giulia Tuccio, Wim Van Hoeve

Solstice Pharmaceuticals

The blood-brain-barrier (BBB) acts as a protective barrier for the brain, preventing toxins from entering it, but also limiting the delivery of intravascular therapeutic molecules. Microbubble (MB) cavitation under focused ultrasound can increase BBB permeability, thereby facilitating drug transport. The extent and stability of BBB opening depend on both acoustic parameters and microbubble parameters. Monodisperse microbubbles, characterized by a narrow size distribution, have a more predictable and homogeneous acoustic response compared to polydisperse populations. This offers an opportunity to better control cavitation behaviour and optimize BBB-opening. To this end, the acoustic response of three monodisperse MB populations (mean diameter of 3, 4, 5 µm), produced using a proprietary microfluidic chip, is compared with that of SonoVue (diameter 1–10 µm). Different MB concentrations (1, 10, 100 and 200 µl) are excited by a 1.5 MHz focused ultrasound transducer using pulse lengths of 10 ms at a pulse repetition frequency of 10 Hz. A pressure range of 25-750 kPa with 25 kPa step is used. Sub- and ultra- harmonic emissions are associated with stable cavitation, which is the key mechanism for a reversible BBB-opening. As such, we evaluate subharmonic onset pressure and harmonic (HCD) and broadband (BCD) cavitation doses. Monodisperse populations exhibited lower subharmonic onset pressures, particularly at higher concentrations, compared to SonoVue. Furthermore, analysis of the normalized HCD-toBCD ratio as a function of pressure and MB size reveals distinct regions corresponding to high stable cavitation activity with minimal broadband emissions (values > 0.5 of the heatmap). These regions indicate optimal combinations of microbubble size and driving pressure for controlled BBB opening. Results show that monodisperse microbubbles enable a more distinct separation between stable and inertial cavitation regimes at clinically relevant driving pressures, providing improved control over cavitation dynamics. This enhanced control may facilitate safer and more efficient ultrasound-mediated BBB opening for drug delivery applications.



Transcranial Cavitation Monitoring at 300 kHz: From Free-Field Optimization to True Head Phantom Validation

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Introduction: Low-intensity focused ultrasound (LIFU) paired with intravenous microbubbles enables non-invasive, temporary blood-brain barrier opening (BBBO). However, tracking cavitation at a submegahertz driving frequency of 300 kHz is highly challenging; the average SonoVue microbubble resonates at ~2.6 MHz (f_0/fr = 0.12), demanding elevated acoustic pressures to trigger period-doubling oscillations like subharmonics and ultraharmonics. Along with this, the human skull's cortical and trabecular bones severely attenuate, scatter, and phase-aberrate both incident beams and returning emissions. To address these limitations, this study evaluates cavitation signatures across an experimental pipeline: first in a free-field setting, then through an ex vivo skull, and finally both inside and outside an MRI environment utilising a specialised True phantom head model (Adult Head Phantom, True Phantom Solutions).

textbfMethods: Experimental procedure involves four stages 1) free-field insonation of 0.2 mL SonoVue/1.3 mL saline in an 11-mm TPX tube via 300-kHz DPX-300 transducer (0.45–0.85 MPa, 20-ms pulse, 1000-ms PRI); 2) measuring cavitation in presence of 6-mm ex vivo calvaria at P_sptp, water (0.78 MPa–0.87 MPa) via 1.65 k-Plan factor; 3) CT/T2*-MRI of a three-layer skull phantom and Localite-navigated targeting of a 3-mm superior sagittal sinus via a 4-cm gel standoff (63-mm path, 78.3-µs TOF); 4) Using MRI sequences SWI or Multi-echo GRE (T2*), dynamic EPI ep2d_perf (Siemens) with 10 ml of 0.9% NaCl and 1 ml of Sonovue for capturing cavitation signatures in the targeted vessel of the true phantom.

Results: At 300 kHz, free-field testing showed a clear shift from stable cavitation at 0.45 MPa to inertial cavitation at 0.65 MPa. In the presence of ex vivo skull results, a severe detection mismatch was initially observed. At 0.78–0.85 MPa, the hydrophone captured intense stable cavitation (SCI 6.6–7.1), but the co-housed PCD registered only floor noise. While the skull caused a 4.8 dB loss, the real bottleneck was instrumental: the oscilloscope's 8-bit ADC at 50 mV/div quantised at 1.56 mV/step, completely missing the 0.3–0.8 mV subharmonic reflections. Optimising the acquisition outside the MRI (20 mV/div, baseline subtraction, 128× averaging) successfully restored through-skull PCD tracking. This setup resolved stable cavitation at 0.96 MPa (Itextsubscriptsppa = 31 W/cm²) and its transition to inertial cavitation at 1.30 MPa (I_{sppa} = 60 W/cm²).

Discussion: Free-field analysis shows stable cavitation at 0.45 MPa, while cavitation is limited by off-resonance bubble physics and ADC quantisation bottlenecks in the ex vivo study. Optimising receiver scales (20 mV/div) lowered this floor to 0.028 mV. Validated via a three-layer True Phantom, we resolved stable (0.96 MPa) and inertial (1.30 MPa) cavitation, proving that the transcranial monitoring barrier is an instrumentation bottleneck that can be overcome, rather than a lack of an acoustic signal.

Engineering Astrocyte-Expressed Acousto-Electric Reporter Proteins for Ultrasound-Based Monitoring of Neural Activity

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Background: Current methods for monitoring neural activity rely on optical imaging, electrophysiology, or hemodynamic signals, each of which presents limitations for scalable, minimally invasive brain interrogation. Molecular reporters capable of coupling neural activity to ultrasound-detectable contrast could enable a new class of ultrasound-based functional neuroimaging approaches. Here we describe the development of astrocyte-expressed acousto-electric reporter proteins (AERPs), engineered membrane proteins designed to translate cellular electrical state changes into measurable alterations in ultrasound backscatter. Unlike gas-vesicle-based acoustic reporter systems, AERPs are designed to operate through reversible modulation of membrane electromechanical properties rather than intracellular gas compartments. We hypothesize that engineered membrane proteins can couple physiologically relevant changes in astrocytic membrane state to measurable alterations in ultrasound backscatter, enabling indirect monitoring of local neuronal activity.

Methods: A dual-track engineering strategy was implemented. First, voltage-sensitive membrane proteins derived from electromechanically active protein families, including Prestin/SLC26A5, were evaluated as reference constructs. Second, de novo engineered acoustic-modulation domains were designed using computational protein engineering approaches to modulate membrane-associated acoustic scattering properties through changes in local membrane mechanics, hydration state, and protein-lipid interactions. Candidate constructs were expressed in astrocytic systems and characterized by RF backscatter measurements acquired under 5–20 MHz high-frequency focused-ultrasound readout conditions. Astrocytes were selected as an initial target cell population due to their extensive interactions with local neuronal networks, electrical responsiveness to neurotransmitter-driven activity, and suitability as distributed biological transducers. Acoustic signatures were evaluated during controlled electrical, pharmacological, or neuronal activation paradigms.

Results: We have established construct generation, expression/localization validation, high-frequency focused-ultrasound interrogation, synchronized RF acquisition, and acoustic feature-analysis workflows for astrocyte-expressed AERPs. The platform is being used to test whether neuron-driven activity, through astrocytic membrane-state changes, produces expression-dependent RF backscatter features across candidate, reference, and control constructs. RF amplitude, phase, spectral, and envelope features are quantified against neuronal stimulation timing or independent neural-activity references to identify reversible acoustic signatures consistent with local neuronal activity.

Conclusion: To our knowledge, this represents one of the first efforts to engineer genetically encoded ultrasound reporters that directly couple cellular electrophysiological state to acoustic contrast generation. Acousto-electric reporter proteins represent a potential molecular interface between cellular electrophysiology and ultrasound imaging. Successful development of AERPs could establish a molecular framework for ultrasound-based functional imaging, sonogenetic sensing, and future closed-loop ultrasound brain-computer interface systems.

Preclinical

SECTION 05 / 06 · 3 ORAL PRESENTATIONS · 4 POSTERS

Transcranial Focused Ultrasound Neuromodulation in Cerebellar Circuits: Dissecting Central and Peripheral Contributions

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Background: Transcranial focused ultrasound stimulation (TUS) has emerged as a promising neuromodulation technique capable of generating an acoustic field in the brain to directly modulate neuronal activity. However, the underlying mechanisms remain incompletely understood. Previous work has shown that, in addition to direct central effects, TUS can indirectly modulate neural activity by stimulating the cochlea and activating auditory pathways. Ultrasound has also been shown to stimulate peripheral nerves. Here, we recorded neural responses to TUS in the rat cerebellum and sought to disentangle neural effects driven by the intracranial acoustic field (central) from those arising from ultrasonic peripheral nerve stimulation.

Methods: Fourteen adult anesthetized Sprague-Dawley rats received TUS (500 kHz, 200 µs pulse duration, 50 Hz pulse repetition frequency, 1.32 MPa peak pressure). TUS was applied either over the cerebellum or to paraspinal muscles at the spinal level, providing a control condition in which peripheral pathways were stimulated while minimizing the acoustic field in the cerebellum. Neural activity was recorded from the superficial Purkinje cell layer (SUPER) and deep cerebellar nuclei (DEEP) using 32-channel silicon probes in pre-, during-, and post-stimulation periods (each 3 minutes). Single units were isolated using Kilosort 4.0. Changes in spontaneous spiking activity were quantified as changes in spike rate across stimulation periods (ΔSR). Evoked activity was assessed using two complementary approaches: (1) post-stimulus time histograms computed from TUS pulse–aligned spikes (TUS-PSTHs), from which a modulation index (MI) was calculated; and (2) evoked potentials obtained by averaging local field potentials time-locked to TUS pulses (TUS-EPs). Current source density (CSD) analysis was performed on TUS-EPs to characterize the spatiotemporal distribution of synaptic activity. To probe underlying mechanisms, the mechanosensitive ion channel blocker GsMTx4 was locally injected into the DEEP layer.

Results: When TUS was applied over the cerebellum: (1) spontaneous spiking activity in both SUPER (n = 112 units) and DEEP (n = 124 units) layers showed significant ΔSR changes; (2) evoked activity was absent in the SUPER layer; (3) in contrast, strong evoked responses were observed in the DEEP layer, with TUS-PSTHs showing significant MI changes, large short-latency (~1–2 ms) TUS-EPs, and CSD revealing a clear sink–source pattern; and (4) blockade of mechanosensitive ion channels significantly reduced changes in spontaneous spiking activity, but did not affect any evoked responses. When TUS was applied to paraspinal muscles (reduced acoustic field in the cerebellum): (1) changes in spontaneous spiking activity in both SUPER and DEEP layers were significantly smaller than during cerebellar TUS; (2) however, evoked responses in the DEEP layer (TUS-PSTHs, TUSEPs, and CSD patterns) were similar to those observed during cerebellar TUS; and (3) these evoked responses persisted during mechanosensitive ion channel blockade.

Conclusion: These results indicate that cerebellar TUS effects arise from at least two distinct pathways: a central pathway, in which the intracranial acoustic field directly modulates spontaneous neural activity, and a peripheral pathway, through which TUS drives evoked responses independently of direct brain stimulation. Further work is needed to fully elucidate the mechanisms underlying both pathways. Together with prior evidence for cochlear involvement, our findings indicate that progress toward reliable and translational TUS neuromodulation should explicitly consider the possibility that observed effects reflect a mixture of direct central modulation and indirect peripheral activation.

Focused ultrasound neuromodulation of the hypothalamic preoptic area promotes NREM sleep and reduces brown adipose tissue temperature in mice

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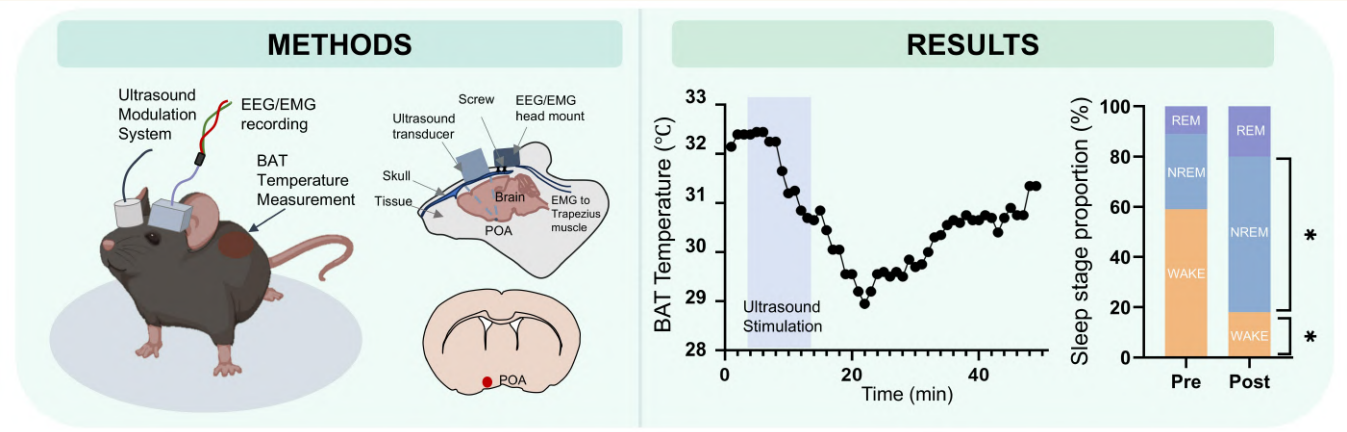
Background: The hypothalamic preoptic area (POA) is a key regulator of sleep and thermoregulation, controlling brown adipose tissue(BAT)thermogenesis via autonomic pathways. Non-invasive modulation of deep hypothalamic circuits remains technically challenging. Focused ultrasound provides a promising approach for precise and non-invasive neuromodulation of deep brain structures.

Methods: Low-intensity focused ultrasound was applied to the POA of freely behaving mice using a piezoelectric ceramic transducer. Ultrasound parameters included a center frequency of 1 MHz, acoustic pressure of 0.5 MPa, pulse repetition frequency of 10 Hz, and duty cycle of 50%. Sleep–wake states were monitored using electroencephalograph y (EEG) and electro myo graph y (EMG), and the proportion of time spent in each behavioral state was quantified. Brown adipose tissue (BAT) temperature was measured with infrared thermometry.Sham stimulation served as a control.

Results: Focused ultrasound neuromodulation of the POA significantly increased time spent in non-rapid eye movement (NREM) sleep and significantly decreased wakefulness compared to pre-stimulation baseline ($p < 0.05$). In addition, focused ultrasound neuromodulation resulted in an average decrease of approximately 3 °C in BAT surface temperature after stimulation. No abnormal behavior was observed under the applied stimulation parameters.

Conclusion: These findings demonstrate that focused ultrasound targeting the hypothalamic POA can modulate sleep state and peripheral thermoregulation. Focused ultrasound neuromodulation provides a non-invasive tool for investigating hypothalamic circuits regulating sleep and energy balance.



Parameter-dependent focused ultrasound modulates neuroinflammation and delays early Alzheimer's pathology

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Motivation: Neurodegenerative diseases affect millions of people worldwide and currently lack effective treatments. Increasing evidence suggests that these disorders are driven, in part, by neuroinflammation, which contributes to neuronal damage and the progression of early pathology. Focused ultrasound (FUS) is a promising noninvasive neuromodulation technology; however, the effects of different ultrasound parameters on inflammatory responses remain poorly understood. Improving this understanding is essential for the development of safe, targeted ultrasound protocols designed to reduce neuroinflammation in diseases like Alzheimer's. Here, we investigate how variations in pulse repetition frequency (PRF) and pulse duration influence neuroinflammation and the progression of Alzheimer's pathology.

Methodology: Female C57BL/6 mice received an intraperitoneal injection of lipopolysaccharide (LPS; 0.75 mg/kg, 7 days) to induce neuroinflammation, followed by a single whole-brain FUS (0.5 MHz, 0.35 MPa) treatment using 0.01, 0.1, or 10 ms pulse durations delivered at 1 or 100 Hz PRF. Tissue was collected 24 h later for cytokine quantification using enzyme-linked immunosorbent assay, microglial morphology, and RNA-sequencing. In the second study, female APP-NL-G-F mice that mimic early-stage amyloid pathology received whole-brain FUS twice a week for 5 weeks using the 100 Hz, 10 ms parameter selected from the LPS study (0.5 MHz, 0.35 MPa). Brain tissue was collected 24 h after the final treatment for Aβ42 protein quantification, microglial morphology analysis, and RNA-sequencing.

Results: LPS induces a sustained inflammatory state in the brain, characterised by increased levels of proinflammatory cytokines such as TNF-α, IL-1β and IL-6, and a transcriptional shift towards a high metabolic demand environment. We found that the effects of FUS were parameter dependent: 1 Hz at 0.01 ms, reduced hippocampal TNF-α and IL-1β protein levels. This parameter set was associated with a partial restoration of mTOR signalling, which results in reduced immune activation and recovery of cellular maintenance pathways. In contrast, 100 Hz at 10 ms increased the levels of anti-inflammatory proteins, IL-4 and IL-10. This parameter also reversed the LPS-associated hypermetabolic inflammatory state while increasing phagocytic clearance and inflammatory resolution by upregulating IL-6/JAK/STAT3 and TGF-β signalling. Overall, 1 Hz partially suppressed the inflammatory signalling, whereas 100 Hz produced a broader shift in the inflamed brain towards a clearance and repair-associated state. The 100 Hz at 10 ms parameter set was then applied in an early-stage Alzheimer's disease mouse model to test whether repeated FUS treatments with this parameter set could delay disease pathology. In the early stages, APP-NL-G-F mice start to develop amyloid precipitates in the frontal cortex. We found that following repeated FUS treatments, cortical Aβ42 protein levels were significantly reduced compared with sham controls, despite no changes in hippocampal amyloid levels. Interestingly, RNAsequencing found that this effect was also associated with suppression of metabolic stress pathways, along with remodelling of synaptic, vascular, and immune signalling. Notably, this suggests that FUS is modulating the disease mechanisms during a critical window of pathology development.

Impact: The study highlights how FUS pulse parameters can induce distinct changes in molecular pathways, including immune activation, clearance, and metabolic stress, across inflammation and Alzheimer's models. This suggests that parameter mapping is important for disease-specific therapies.

Hippocampal neurogenesis and transcriptional responses to repeated multifocal transcranial ultrasound stimulation in young and aged mice

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Transcranial ultrasound stimulation (TUS) is an emerging non-invasive neuromodulation approach with potential applications for age-related cognitive decline. While TUS has been shown to alter neural activity and plasticity-related signaling, its effects on structural markers of hippocampal plasticity in aged animals remain incompletely understood. Here, we assessed whether repeated multifocal TUS alters neurogenesis, perineuronal nets, glial reactivity, and transcriptional profiles in young and aged mice. Methods: Young (8-10 weeks old) and aged (80-90 weeks old) C57BL/6J mice received six bilateral TUS or sham sessions over three weeks. Ultrasound was delivered using a 550 kHz focused transducer with sequential multifocal targeting intended to cover the bilateral hippocampus, nucleus reuniens, and prefrontal cortex. Sonications were delivered using 5 Hz pulse repetition frequency, 10 ms pulse duration, 1 MPa peak negative pressure, 12 s pulse trains, and 5% duty cycle, repeated six times per session across seven targets. Twenty-four hours after the final sonication, brain tissue was collected for immunofluorescent quantification of hippocampal neurogenesis markers, perineuronal nets, GFAP immunoreactivity, as well as qPCR and RNA-seq. Results: Across age groups, TUS significantly increased BrdU+ and BrdU+/NeuN+ cell densities, consistent with enhanced survival or maturation of newly generated neurons. In aged mice, TUS significantly increased BrdU+/DCX+ cell density relative to aged sham controls (4.6-fold increase, $p < 0.05$), suggesting enhanced immature neuron generation or persistence. In the hippocampus, repeated TUS resulted in a 43% reduction in Bax/Bcl2 expression ratio relative to sham ($p < 0.05$). This shift toward pro-survival signaling may support survival or maturation of adult-born neurons. RNA-seq revealed negative enrichment of oxidative phosphorylation pathways in the hippocampus and prefrontal cortex of aged mice relative to sham. Repeated TUS did not significantly alter WFA+ perineuronal net density or WFA+/PV+ perineuronal net density across the dentate gyrus, CA1, or CA3. No evidence of astrogliosis or transcriptional indications of inflammation were observed. Conclusion: Together, these findings suggest that repeated multifocal TUS can enhance select hippocampal neurogenesis-associated outcomes in aged and young mice, potentially driven by a shift towards pro-survival signaling.

Investigating the Effect of Non-Invasive Low-Intensity Focused Ultrasound Stimulation of the Greater Occipital Nerve on Emergence in an Anesthesia-Induced Mouse Model of Disorders of Consciousness: A Preliminary Study

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Background: Severe brain injury often leads to Disorders of Consciousness (DoC), characterized by a profound dissociation between wakefulness and awareness. Current therapeutic options are extremely limited, and traditional non-invasive methods often lack the spatial penetration depth needed to effectively modulate deep subcortical arousal networks. The Greater Occipital Nerve (GON) projects to the upper cervical spinal cord and is functionally coupled with the locus coeruleus (LC, the primary source of norepinephrine) and the ventral tegmental area (VTA, dopamine). We hypothesize that targeted focused ultrasound (FUS) applied to the GON can act as a "bottom-up" somatosensory input to trigger the LC and VTA. This triggers the release of norepinephrine and dopamine into the thalamocortical network, thereby remodeling functional connectivity and accelerating emergence from DoC.

Objective: This pilot study aims to evaluate the feasibility and preliminary efficacy of noninvasive FUS of the GON (FUS-GON) in accelerating emergence in a propofol-induced DoC mouse model.

Methods: A stable and controllable surrogate DoC model was established in C57BL/6 mice using propofol. A custom miniaturized FUS transducer was coupled to the shaved back of the mice's necks using degassed ultrasound gel. The experimental group received FUS stimulation with a carrier frequency of 450 kHz, a pulse repetition frequency (PRF) of 1 kHz, and an intensity of 300 mVpp for 10 minutes. The primary endpoint was the time to Return of Righting Reflex (RORR). Secondary outcome measures included heart rate, breathing rate and blood oxygen.

Preliminary Results: An initial trial was conducted on a small cohort (n=5). The FUS-GON protocol was successfully implemented. In Vitro thermometry confirmed that the temperature during the 20-minute stimulation remained between 35.9°C and 36.3°C, remaining strictly within the safety limit. No macroscopic mechanical damage was observed at the target site. Mice receiving FUS-GON achieved RORR at 40 minutes, compared to 53 minutes for the sham group. Furthermore, effects of FUS on heart rate, breathing and blood oxygen will be analyzed.

Conclusion: Initial data suggest that FUS-GON is a feasible, non-invasive intervention that can modulate brainstem arousal networks and potentially shorten RORR time in a DoC model. Ongoing studies will expand the sample size, compare FUS with electrical GON stimulation, and incorporate in vivo electrophysiological recordings to dissect the underlying thalamocortical dynamic mechanisms.

Transcranial Focused Ultrasound Stimulation of Deep Brain Structures: Impact on the Primate Cortical EEG during General Anesthesia

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Disorders of consciousness (DoC) remain a major clinical challenge, with limited therapeutic options available. It has previously been demonstrated that electrical deep brain stimulation of the central thalamus could restore consciousness and long range brain communication following anesthesia in non-human primate (NHP) model of DoCs (Tasserie et al., Science Advances, 2022). However, clinical translation requires the development of non-invasive neuro modulation approaches without neurosurgery. Here, proposed is focused ultrasound technology to modulate thecentral thalamic activity recordedbyEEG. In this set of four preclinical pilot experiments, we investigated the effects of transcranial low-intensity focused ultrasound stimulation (LIFU) targeting the centromedian (CM) thalamus -an area associated with arousal and conscious state regulation- in two anesthetized rhesus macaques as a NHP model of consciousness loss. Werecorded scalp EEG activity before, during and following LIFU. The primary stimulation conditions consisted of low (5%) and high (70%) duty cycle protocols, varying pulse repetition frequencyand pulse intensity, all with fundamental frequency of 500 kHz, for a duration of 10, 12 or 20 minutes, with sequential stimulation paradigms (bilateral stimulation) explored across sessions. Resting-state scalp EEG was recorded in a custom setup compatible with the large LIFU transducer. We performed spectral power analysis across canonical frequency bands up to 40 Hz, comparingprevs post LIFUepochswith paired statistical tests. Ultrasound stimulation was associated with measurable changes in the structure of the EEG activity, including modulation of low-frequency dynamics and signal complexity measures associated with consciousness recovery. Responses varied across stimulation parameters and conditions, suggesting that electro physiological effects may depend on factors such as duty cycle, pulse intensity, and sequential application. These preliminary findings support further investigation of non-invasive focused CM thalamus ultrasound neuro modulation and highlight the importance of optimizing stimulation parameters for potential future translational applications of LIFU for consciousness restoration in DoC patients.

Developmental transcranial ultrasound stimulation rescues social and cognitive deficits in Rett syndrome mice

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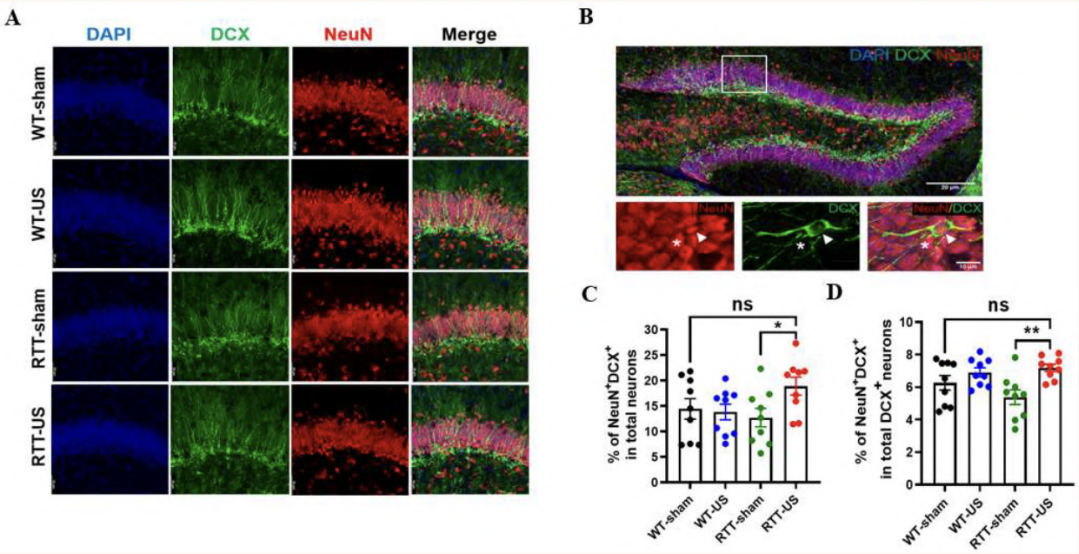
Introduction: Rett syndrome (RTT): Caused by mutations in the X-linked Mecp2 gene
A severe neurodevelopmental disorder in young females
Symptoms include neurological and motor defects such as abnormal hand movements, cognitive and autism
No effective treatment available; Deep brain stimulation (DBS) treatment
Increases neurogenesis and hippocampal memory
Invasive; Not suitable for clinical application

Methods: The mice were then subjected to 900 Hz ultrasound (US) stimulation (500 kHz center frequency, 900 Hz repetition frequency, 5-second duration, 20% duty cycle), which was targeted at the right hemisphere of the brain centered on its hippocampus for 1 hour per day for 14 consecutive days.

Results: 1. LI-TUS stimulation in juvenile RTT mice restores memory performance in adulthood
2. LI-TUS stimulation in juvenile RTT mice rescues social novelty in adulthood
3. LI-TUS on Juvenile RTT mice promotes neuronal maturation

Conclusions: 1. 900 Hz ultrasound stimulation rescues RTT mciecognitive function and social skills. 2. ultrasound stimulation opening the door for future noninvasive therapies. **Acknowledgments:** This work was financially supported by Guang High Level Innovation Research Institute.No.2021B0909050004, NSFC.No.32371151. Hong Kong Research Grants Council Collaborative Research Fund (C5053-22GF)General Research Fund (15224323 and 15104520). Hong Kong Innovation Technology Fund (MHP/014/19).



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Technical/Engineering

SECTION 06 / 06 · 4 ORAL PRESENTATIONS · 29 POSTERS

Fast Geometric Re-planning Compensates for Small Transducer Placement Offsets in Transcranial Ultrasound Stimulation

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Background / Objective: Transcranial ultrasound stimulation (TUS) enables noninvasive neuromodulation of deep brain structures, but efficient and safe application requires sufficient focal intensity through the skull while respecting mechanical and thermal safety limits. Individualized simulation frameworks such as k-Plan (Brainbox Ltd., Cardiff, UK) or BabelBrain[1] can estimate acoustic and thermal effects from imaging data and optimize phased-array element phases to compensate for skullinduced aberrations. However, translating a simulated setup to the actual TUS session remains challenging: exact transducer positioning, fixation, and acoustic coupling are time-consuming and difficult, even with neuronavigation. Small deviations from the planned pose may substantially affect engagement of small deep targets. We present a method to perform a real-time update of the pre-planned element phases via geometric beam steering ("replanning"). The method is fully integrated into a neuronavigated TUS system applied inside the MRI scanner in combination with a specialized MR head coil[2]. Here, we evaluate its performance and safety using numerical simulations.

Methods: In an intake session, a realistic transducer position for a 256-element phased-array transducer (Fraunhofer IBMT, Sankt Ingbert, Germany) at the left temporal window was documented using neuronavigation (TUS Navigator, Localite GmbH, Bonn, Germany) for ten subjects. Cranial T1w and PETRA MRI data were processed with petra2density[3] to generate density maps. Baseline k-Plan simulations targeted the atlas-derived left subgenual anterior cingulate cortex (sgACC) and were performed with an online and an offline protocol, with target intensities of 5 W/cm² and 4 W/cm², respectively. Five subjects were selected for further analysis whose baseline acoustic and thermal simulations complied with ITRUSST safety recommendations[4] for MItc and thermal dose; maximum tissue temperature was considered as a secondary safety metric. For these subjects, simulations with deviated transducer poses were performed under three conditions: "k-Plan," with full recalculation and aberration correction; "orig," applying the original baseline planned phases to the deviated poses; and "rp," updating baseline planned phases using the proposed re-planning approach. Deviations included ±2 mm tangential translations, 2 mm outward orthogonal translation, and ±2° rotations around all transducer axes, yielding 1230 simulated sonications. Larger deviations of 6 mm and 4° were additionally explored in one exemplary subject. Conditions were compared for targeting accuracy, focal size, target pressure, focus–ROI overlap, MItc, thermal dose, and maximum temperature. The primary hypothesis was that "rp" would outperform "orig"; the secondary hypothesis was that "rp" would approximate "k-Plan" performance. Per-subject mean deviations from "k-Plan" were compared between conditions using paired t-tests with Benjamini–Hochberg (BH) FDR control within each contrast. The secondary analysis quantified per-subject recovery as the percentage of original deviation compared to "k-Plan" removed by "rp", tested against zero by one-sample t-test applying BH FDR control.

Results: The Euclidean distance of the peak pressure position relative to the planned target position within a 60 mm3 cubed bounding box around the target was 1.0 ± 4.0 mm (mean ± SD) for "k-Plan", 9.1 ± 12.5 mm for "orig" and 3.9 ± 9.3 mm for "rp", respectively, which means a significant ($p < 0.05$) improvement in targeting accuracy of "rp" compared to "orig" relative to the "kPlan" reference. It should be noted that the large spread of distances to target is mainly explained by one subject for which the target ROI was located close to the skull base resulting in reflections classified as focal regions for some transducer poses. Excluding this subject from the analysis resulted in distances between peak pressure and target position of 0.4 ± 0.06 mm (mean ± SD) for "k-Plan", 4.7 ± 6.3 mm for "orig" and 1.0 ± 2.7 mm for "rp", respectively. The strongest effect of "rp" compared to "orig" was observed for the acoustic pressure at the intended target. On average, "rp" achieved a target pressure of 357.3 ± 20.2 kPa for the online protocol and 319.6 ± 18.1 kPa for the offline protocol – compared to 321.1 ± 38.7 kPa for the online and 287.2 ± 34.6 kPa for the offline protocol for "orig". This translates to a recovery of 55.1% [95% CI: 43.6, 66.6] towards the target pressure of 387.3 and 346.4 kPa achieved via full k-Plan aberration correction for the online and offline protocols, respectively. Analogous trends could be observed for the exemplary simulations with larger deviations for which "rp" achieved pressures of 279.1 ± 53.13 kPa for the online and 249.6 ± 47.5 kPa for the offline protocol, compared to 150.5 ± 93.8 kPa and 134.6 ± 83.9 kPa, respectively, with "orig". In terms of biophysical safety parameters, MItc and TD remained within the established limits across all sonications, subjects, and conditions. Notably, peak temperatures above 39 °C (up to 40.8 °C for a simulation applying k-Plan aberration correction) were observed for the offline protocol for all three conditions across some sonications. For the 6 mm and 4° deviation simulations, MItc and TD also remained within limits and maximum temperature stayed below 39 °C (max. 38.7 °C).

Conclusion / Significance: These simulation results provide initial evidence that the proposed re-planning method can compensate for small offsets, 2 mm and 2°, between planned and realized TUS transducer placements. The exploratory analysis with larger deviations, 6 mm and 4°, suggests potential for broader applicability, although the small sample size and limited variation in subjects, initial transducer poses, transducer layout, and driving frequency restrict generalizability. Nevertheless, the findings support the practical potential of real-time re-planning for TUS applications within defined limits.

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Acknowledgements: This work is supported by the EIC (Pathfinder project CITRUS, Grant Agreement No. 101071008).

Conflict of interest: J.K. is a paid employee of Localite GmbH, Bonn, Germany. A.S. is a co-founder and general manager of Localite GmbH, Bonn, Germany.

Ray-Tracing based automated workflow for fast skull aberration correction, in-situ pressure level estimation and 3D pressure field display

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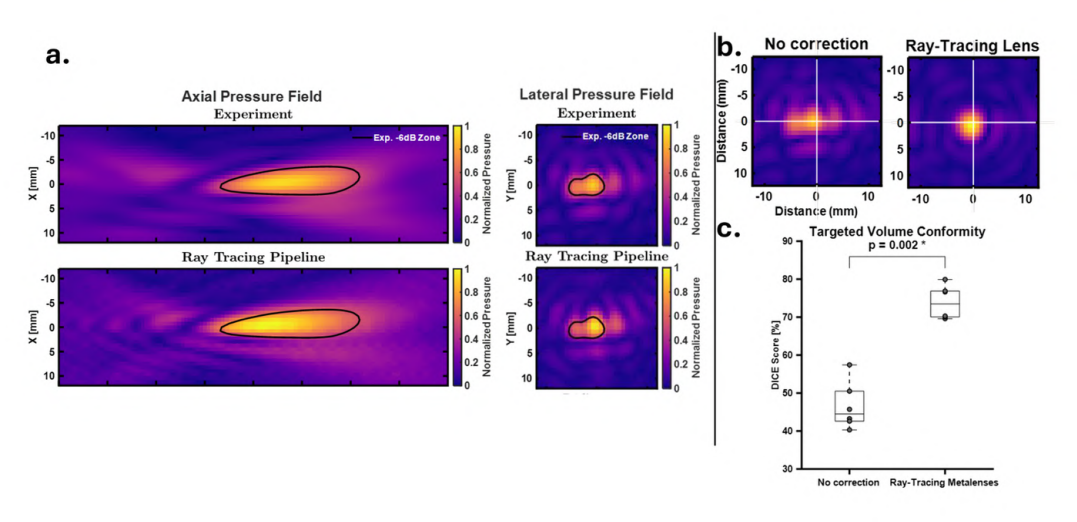
Background / Objective: Transcranial ultrasound neuromodulation requires accurate skull aberration correction for patient safety and treatment efficacy. While patient-specific acoustic lenses have proven effective, clinical treatment planning is limited by computational bottlenecks. To address this, we present a fast, Ray-Tracing - based automated workflow integrated into 3D Slicer to design these lenses and simulate the in-situ pressure field.

Statement of contribution / Methods: Based on a CT image of the skull, this automated workflow includes: (i) evaluation of the in-situ pressure field by combining Ray-Tracing and Angular Spectrum; (ii) estimation of the transcranial pressure transmission; (iii) computation of the skull-induced phase shifts to design acoustic metalenses for aberration correction. We validated this approach experimentally on 3 human calvarias (n=6 experiments) with a custom singleelement transducer (R_c = 100mm, Aperture = 100mm, Central Frequency = 500kHz). For evaluation of the aberration correction, target volume conformity was quantified by calculating the DICE score between the -6dB pressure volume through the skull and the reference -6dB volume in water.

Results / Discussion: (i) The simulated in-situ pressure-fields (Fig a) were in good agreement with the experimental ones (RMSE = (11 ± 3) % within the -6dB region). (ii) The transcranial pressure transmission was accurately estimated, with an absolute error of (5 ± 4) %. (iii) The acoustic metalenses manufactured with the above-mentioned workflow were tested experimentally (Fig b-c) and achieved a significant aberration correction, with an increase of the target conformity compared to the uncorrected case: $DICE_{6dB,\ Lens}$ = (74 ± 4) % / $DICE_{6dB,\ no\ Lens}$ = (47 ± 6) %.

These results pave the way for a fully adaptive automated and fast workflow, allowing for treatment planning and real-time simulation of the in-situ pressure field.



Measurement of ultrasound-induced thermal effects in skull bone using 3D thermometry with X-ray Computed Tomography: Preliminary Results

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Background: Experimental reports of the thermal effects in skull bone caused by transcranial ultrasound have been elusive, severely hindering the development of adequate predictive models for safety purposes. In this report, we present a method and preliminary results based on X-ray computed tomography (CT) to produce 3D thermal maps of the skull bone when ultrasound is transmitted through it. CT-based thermometry relies on the principle that for most materials, electron density reduces with increasing temperature, slightly reducing X-ray attenuation and, consequently, CT Hounsfield units (HU) measurements (Fani et al., DOI:10.3109/02656736.2014.922221).

Methods: Calibration was conducted with a degassed skull sample immersed in degassed water. A human skull cap was imaged with a CT scanner (GE Lightspeed) using 15-s-duration cinescan (CS, temporal resolution=0.25 s, FOV=150x150x20mm, pixel size=0.3mm, slice thickness = 6.25 mm, kVp = 120 Kev, bone kernel) acquisitions at temperatures (T) ranging from 20 to 45 °C in 2 °C increments. The change in HU was also measured in the water volume and in a 10-mm-thick piece of ultrasound absorber (AptFlex48, Precision Acoustics). Linear fitting coefficients for HU(T) were calculated for each material. Transcranial ultrasound experiments were conducted using a transducer (focus = 50 mm, diameter = 32 mm) operating at 750 kHz and an acoustic power of 20 W with the absorber placed behind the skull (Fig. 1A). Exposure lasted 10s and started 2s after CS initiation. Measurements were repeated in the absence of the skull. CS data were convolved with a spatiotemporal kernel of radius 5 mm, height 1.3 mm, and 5 temporal steps. Linear fitting of HU changes between 2 and 12s was used to smooth the total HU changes during ultrasound delivery, and the total HU change was converted to a relative temperature change using the material calibration.

Results: Figure 1B shows the calibration of HU changes as a function of the temperature of water, skull at two regions, and the absorber. It can be observed that the CS is sensitive enough to detect temperature changes over a span of 25°C. Figure 1C shows the maximal temperature change in the presence of the skull, while Figure 1D shows the maximal temperature change in the absence of the skull. The slope for the skull was averaged from two measured regions for calibration. Conclusions. To the best of our knowledge, this is the very first demonstration of volumetric thermometry measurement of skull bone under the effects of ultrasound. The basis of the method presented here will significantly impact efforts to better determine the safety of transcranial ultrasound interventions.

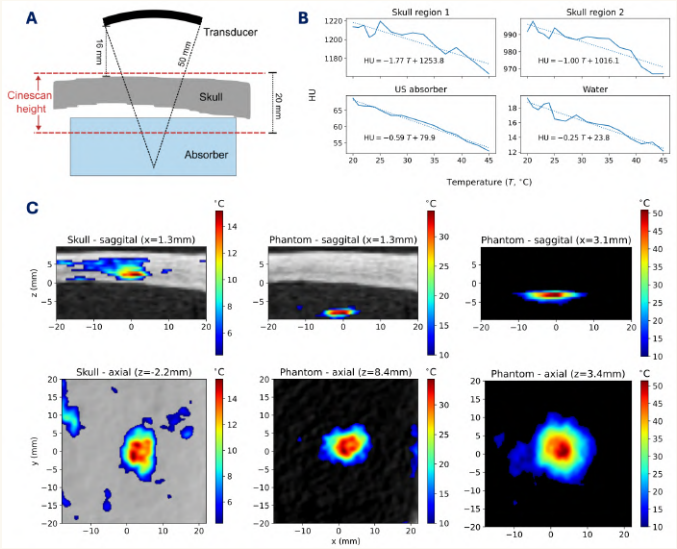

Figure 1: A) Setup for CS acquisition for transcranial ultrasound heating measurement. B) Calibration of change of HU vs. temperature for two regions in the skull bone (top row), ultrasound absorber (bottom left) and water (bottom right). C) Sagittal and axial planes of thermal maps of skull and phantom regions. Thermal maps are overlay over CT images. Left and central columns show the results of the experiment with the skull present, where each other region is removed for better visualization. Right column shows the thermal maps for the experiment where the skull was removed. In the latter, the field of view was slightly moved to better cover the phantom.

Real-Time Intracranial Pressure Field Prediction in tFUS Using a Physics-Informed Fourier Neural Operator

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Background: Transcranial focused ultrasound (tFUS) treatment planning requires accurate prediction of the intracranial pressure field from patient-specific CT. However, conventional numerical solvers require high computational cost. This limits their use in real-time human experimentation setups. We propose a physics-informed Fourier Neural Operator (PINN-FNO) trained on CT and free-field data to predict the intracranial pressure field in real time.

Methods: Simulations were performed across 94 patient-specific CT datasets and split into 75 subjects for training and 19 for testing using a subject-wise split to evaluate generalization to unseen subjects. Fifty-five electro-encephalography (EEG) locations were selected as targets for tFUS simulations using BabelBrain (DOI:10.1109/TUFFC.2023.3274046). A transducer with a focal length of 50 mm and f#=1.0 operating at 500 kHz was used. For each EEG location, a target was placed 30 mm deep from the scalp. Patient-specific acoustic tissue properties —density, speed of sound, and attenuation — were derived from CT data. The 3D pressure field volumes were cropped around each target and stored as paired CT and free-field inputs, while the corresponding BabelBrain-simulated pressure field was used as ground truth. A 3D physics-informed Fourier Neural Operator (PINN-FNO) was trained to predict the complex intracranial pressure field. The model takes two inputs: the CT volume and the free-field reference pressure. The network uses four spectral convolution layers with modes=32 and width=32, augmented with 3D positional grids. The training loss combines a relative L2 loss, a Sobolev H1 gradient loss (λ=0.1), and a heterogeneous Helmholtz PDE residual loss with dynamic warm-up weighting over 50 epochs. Training used the AdamW optimizer with cosine annealing over 150 epochs. Data augmentation with random 90° XY-plane rotations was applied to improve generalization. Model performance was evaluated across the whole head using a structural similarity index measure (SSIM) and peak signal-to-noise ratio (PSNR). Intracranial peak pressure distance (PPD) and peak pressure error (PPE) were evaluated in the whole head and in the brain region only.

Results: The PINN-FNO model predicted the intracranial pressure field with high accuracy. The average (± std.) SSIM and PSNR were 0.9501 (± 0.0275) and 37.76 (± 1.94) dB, respectively. The whole-head absolute PPE and PPD were, respectively, 5.30 (± 5.65) % and 5.99 (± 10.40) mm. In the brain region, the PPE and PPD were, respectively, 2.70 (± 4.99) % and 0.93 (± 1.53) mm. The model inference time was 40 ms on GPU (NVIDIA RTX PRO 6000). Figure 1 shows examples of the ground truth, predicted pressure field, signed relative error map.

Conclusions; The proposed PINN-FNO accurately predicts patient-specific intracranial pressure fields in real time, with subsecond inference time compared to several minutes required by conventional solvers. This demonstrates that physics informed neural operators can replace computationally expensive numerical methods and enable practical integration of tFUS treatment planning into clinical workflows.

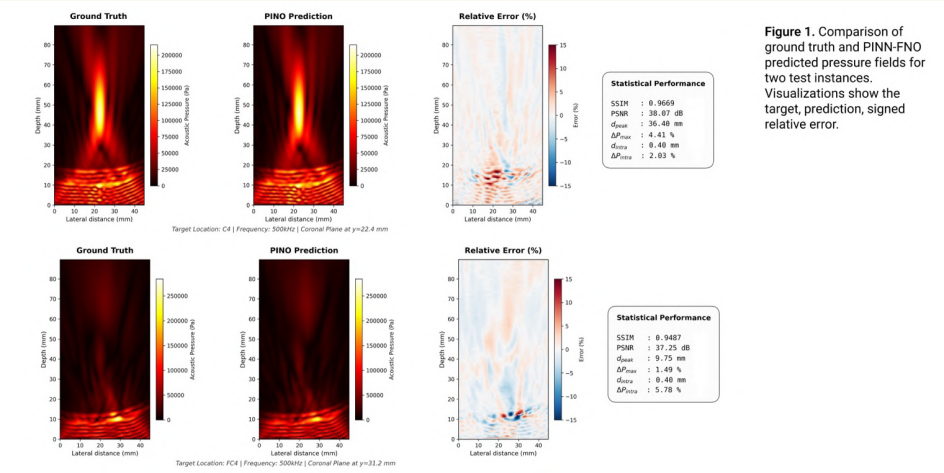

Figure 1. Comparison of ground truth and PINN-FNO predicted pressure fields for two test instances. Visualizations show the target, prediction, signed relative error.

Multiscale Model of Mechanotransduction for Single-Cell Ultrasound Neuromodulation

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Ultrasonic neuromodulation enables non-invasive modulation of neuronal activity, yet the underlying mechanisms remain incompletely understood at the single-cell level. Here, we present a multiscale mechanotransduction framework linking acoustic stimulation to neuronal electrophysiology through a physics-informed extension of a Hodgkin–Huxley (HH) regular-spiking cortical pyramidal neuron model. The framework describes the cascade from acoustic radiation force (ARF) to membrane deformation, mechanosensitive (MS) ion channel activation, intracellular calcium dynamics, and membrane electrical response. In the low-frequency (<1 MHz), low-intensity regime, the model integrates three coupled levels: (i) a viscoelastic membrane deformation model driven by quasi-static ARF, producing physiologically relevant membrane tension variations ; (ii) tension-dependent gating of mechanosensitive ion channels, including direct mechanosensitive channels (Piezo1/2, K2P), indirect calcium-permeable channels (TRPC1, TRPP1/2), and calcium-dependent amplifiers (TRPM4, T-type Ca^{2+}), and (iii) incorporation into a conductance-based neuronal framework adapted from Pospischil et al. 2008. Validation was performed at both functional and mechanistic levels. First, simulated intracellular Ca^{2+} dynamics were transformed into fluorescence signals using a Hill-type mapping and compared directly with experimental GCaMP6f recordings from Yoo et al. 2022. The model reproduces the experimentally observed temporal rise and decay, peak amplitude, and nonlinear dependence on ultrasound intensity and pulse duration. Increasing acoustic intensity produced stronger early Piezo-mediated activation followed by enhanced recruitment of TRPC1/TRPP1/2 pathways and calcium-dependent amplification, leading to larger and more sustained Ca^{2+} transients. Second, channel-specific perturbation analysis was performed by selectively disabling individual channel populations, demonstrating the minor amplitude reduction from initiators, major amplitude reduction from second messenger and reduction of the calcium decay from amplifiers. These trends are consistent with published pharmacological and genetic studies [Yoo et al. 2022]. Additional validation against voltage fluorescence imaging data from the same study further supports the electrophysiological realism of the framework. Finally, a comparative study was performed for different ultrasound pulsing schemes, reproducing trends previously reported experimentally by Murphy et al 2024. Increasing pulse repetition frequency (PRF) or reducing duty cycle (DC) led to a significant weakening of the calcium response, consistent with experimentally observed PRF-dependent neuromodulation behavior. Overall, the proposed model provides a predictive and physiologically grounded description of ultrasonic neuromodulation at the single-cell level, enabling systematic investigation of stimulation parameters and future extension toward heterogeneous neuronal populations.

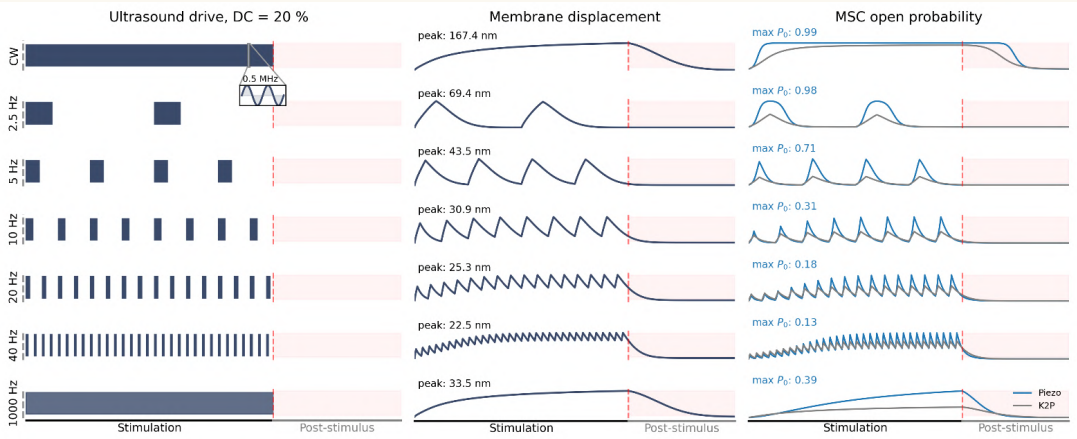

Figure 1: Effect of PRF on membrane deformation and MS channel activation at fixed duty cycle (DC = 20%). Lower PRFs produce larger membrane displacements and higher MSC open probabilities, while increasing PRF progressively weakens the response and approaches a quasi-continuous regime.

Improving Rigor in tFUS Experimentation

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BrainSonix; UCLA Semel Institute; Soterix Medical

Introduction: Several methodological gaps exist in the current state of tFUS experimentation, including limitations in the current parameter space, the rigor of blinded experiments, and the verification of output by tFUS transducers.

Materials and Methods: Several projects were designed to address these gaps:
• A clinical trial in 10 healthy volunteers studied the safety and efficacy of 4 different tFUS parameter sets
• Visually and mechanically indistinguishable acoustic coupling pads were engineered

Parameter Set	ISPTA.3 (W/cm2)	ISPPA.3 (W/cm2)	Pr.3 (MPa)	Mechanical Index	Duty Cycle (%)	Pulse Repetition Frequency (Hz)	Pulse Duration (ms)
A	0.72	1.03	0.177	0.220	70	1000	0.7
B	5.76	8.23	0.477	0.592	70	1000	0.7
C	10.08	14.4	0.635	0.788	70	1000	0.7
D	10.08	201.6	2.26	2.803	4.97	71	0.7

using Dragon Skin NV silicone to enable true double-blind stimulation while controlling acoustic transmission
• A tableside quality assurance tester (QAT) device was developed to provide real-time verification of transducer output, coupling integrity, and system performance.

Results: All stimulation paradigms were well tolerated, with no adverse events or MRI-detectable structural changes, supporting the safety of intensities substantially exceeding current FDA diagnostic limits. The coupling pad system achieved <5% acoustic loss for transmitting pads and >40 dB attenuation for sham pads, while remaining indistinguishable to both operators and participants, enabling effective double-blinding. The QAT device provided rapid, on-demand validation of waveform fidelity, impedance, and output consistency, identifying subtle deviations in system performance that would otherwise go undetected.

Discussion and Conclusion: FDA diagnostic limits may underestimate the effective neuromodulatory parameter space, particularly given skull attenuation, and our results further support the safety of higher-intensity stimulation. The development of acoustically distinct yet indistinguishable coupling pads enables true double-blind designs by isolating ultrasound-specific effects from sensory confounds, while the QAT device provides a practical solution for on-demand verification of system performance. Together, these advances establish a more rigorous and reproducible framework for tFUS experimentation, supporting its continued development toward clinical translation.

Approaches for Functional Ultrasound Imaging of the Deep Brain in Awake, Behaving Non-Human Primates

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Background: Functional ultrasound imaging (fUSI) is a novel neuroimaging modality that allows for quantification of neurovascular changes with high spatial and temporal resolution [1]. fUSI has most often been implemented in rodents, with removed or thinned skulls to decrease ultrasound attenuation [2]. More recently, fUSI through a recording chamber has been performed in non-human primates [3], and in humans, has been done through an acrylic cranial window [4]. These previous studies have been limited to recording in the cortex. Here, we present two methods to conduct functional ultrasound imaging in awake, behaving, non-human primates beyond the cortex into the deep brain.

Methods and Results: In one non-human primate, we designed a custom titanium recording chamber, similar to what has been done previously [3], and implanted it for imaging through the visual cortex and into the thalamus. The fUSI transducer was fastened to a custom 3D printed head frame that was mounted on previously installed skull pins, for repeatable imaging in the same position across experiments. Transducer position was then registered to an MRI of the animal to target the lateral geniculate nucleus (LGN). In a second non-human primate, an ultrasound-translucent polymethyl methacrylate (PMMA) cranial window was implanted in an identical location. With both implants, experiments were conducted with lights flashed in the animal's eyes for 10 seconds on and 10 seconds off, repeated 15 times. fUSI was collected from the LGN in both animals. There was a statistically significant difference in blood flow in the LGN between lights on and lights off conditions with both the chamber ($p = 0.035$) and cranial window ($p = 0.005$) methods.

Discussion: fUSI can be done in awake, behaving non-human primates to quantify neurovascular coupling in the deep brain, via both a recording chamber and a PMMA cranial window. This method could be used to directly quantify neurovascular effects of focused ultrasound neuromodulation in various regions of the deep brain of awake, behaving, non-human primates, providing a powerful alternative to technically challenging and rarely used fMRI.

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Pseudo-CT Synthesis from Bone MRI for MR-Guided Transcranial Focused Ultrasound: A Multi-Sequence Comparison

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Introduction: Transcranial focused ultrasound for blood–brain barrier opening and neuromodulation requires skull-density maps typically obtained from pre-operative CT scans. Replacing CT with pseudo-CT derived from bone-selective MRI would eliminate ionising radiation and simplify the clinical workflow. Conventional T1-weighted imaging cannot capture cortical bone because its echo times (several milliseconds) exceed the sub-millisecond T2* of bone, leaving the skull invisible. We therefore evaluated four ultrashort-echo-time (UTE) sequences designed to acquire signal before bone signal decays, to determine which best approximates CT bone contrast.

Methods: Head CT and four bone MRI sequences, PETRA, UTE inversion recovery (UTE_IR), UTE single-echo (UTE_SE), and a novel UTE pseudo-CT sequence (UTE_pCT) were collected from five subjects as a part of an ongoing study. Each sequence was registered to CT space via rigid alignment followed by SyN nonlinear registration with mutual information (ANTs 2.6.5). Per-sequence linear calibration converted MRI intensity to HU within a brain-dilated skull mask (150–2000 HU). Multi-sequence fusion of the three MR-bone sequences employed ridge regression with 5-fold cross-validation. Accuracy was assessed by voxel-wise R^2 and bone MAE (mean absolute error in HU) against the reference CT, evaluated within the skull bone mask (150–2000 HU).

Results: Of the four sequences tested, UTE_IR delivered the strongest agreement with CT (Subject 1: R^2 = 0.75, MAE = 108 HU $\approx$ 73 kg/m^3 ; Subject 3: R^2 = 0.78, MAE = 154 HU $\approx$ 104 kg/m^3). while PETRA (R^2 = 0.73, MAE = 159 HU $\approx$ 108 kg/m^3) and UTE_pCT (R^2 = 0.74 and MAE = 164 HU $\approx$ 113 kg/m^3) offer variable alignment with clinical CT. Ridge regression combining all three sequences consistently exceeded the best individual sequence (mean ΔR^2 = +0.033), yielding bone MAE values of 104 - 140 HU ($\approx$ 70 - 98 kg/m^3) across all the subjects. SyN nonlinear registration improved R^2 over rigid alignment across every sequence and subject (mean ΔR^2 = +0.078, range +0.019 to +0.161).

Discussion: Ultrashort TE provides better bone contrast in comparison with conventional T1w imaging, but TE alone (UTE_SE) is not enough without additional contrast mechanisms. UTE_IR provides the strongest single-sequence bone contrast, likely because T1-based soft-tissue suppression sharpens the skull boundary. Combining PETRA, UTE_pCT, and UTE_IR via ridge regression adds a small gain, reducing bone density error to 70–101 kg/m^3 across subjects. As a pilot study limited to five subjects, these findings need further validation in a larger subject pool (target n > 30). We will also investigate pseudo-CT generation through CycleGAN and Pix2Pix image translation methods on paired multi-sequence MRI-bone imaging and CT as part of this study for higher pseudo-CT accuracy.

Simulating transcranial focused ultrasound from a dense matrix array through an ex vivo human skull modeled with micro-CT and high-resolution PETRA-MRI

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Transcranial ultrasound stimulation (TUS) is an emerging neuromodulation technique whose reproducibility depends on well-characterized acoustic exposure parameters and reliable imaging data for planning. TUS devices often consist of single-element transducers with a fixed geometric focus or of few-element annular arrays that can shift the focus axially but cannot steer laterally; 2D matrix arrays instead allow steering without physically moving the transducer. However, commonly used TUS planning platforms (e.g. BabelBrain, k-Plan) are currently still limited in their representation of phased-array devices, electronic beam-steering and array-specific phase-aberration correction (PAC), motivating a validated, open simulation model of the steerable array for accurate beam planning and dosimetry. Yet applying such a model through the skull depends on acoustic property maps conventionally derived from clinical CT, whose resolution cannot capture the trabecular microstructure that governs the speed of sound and attenuation in skull bone, leaving the mapping from image intensity to acoustic properties ill-determined [1]. Here we implement and validate a k-Wave-based model of a previously reported 256-element 2D matrix array [2], characterizing its free-field steering and focusing performance against measured pressure fields to establish a benchmarked, transducer-specific model for human TUS application. Simulated pressure distributions were used to quantify focal position, focal dimensions and grating-lobe levels, compared against corresponding hydrophone measurements. To demonstrate the model's applicability, we further simulate focused pressure fields through transcranial models of an ex vivo human skull derived from micro-CT, clinical CT and 0.4 mm isotropic PETRA MRI-based pseudo-CT. The k-Wave model reproduced the measured focal positions and beam profiles across the tested steering configurations [2], with a median focal-position deviation of 1.5 mm axially and axial focus size within at least 86% of the hydrophone measurements (Fig. 1a,b). Initial transcranial simulations based on multimodal imaging are plausible (Fig. 1d-f), but the high-resolution PETRA protocol and the derivation of acoustic properties from it require further optimization and validation for accurate, reliable planning. We present a validated, free-field k-Wave model of a steerable 256-element TUS array, establishing the simulation infrastructure required for subject-specific acoustic dosimetry, reproducible parameter selection and safety-oriented treatment planning. We are extending the model to transcranial planning in an ex vivo skull, using (micro-)CT for skull-specific PAC and assessing high-resolution pseudo-CT as a radiation-free alternative that may be better suited to assess the skull microstructure underlying acoustic aberration [1].

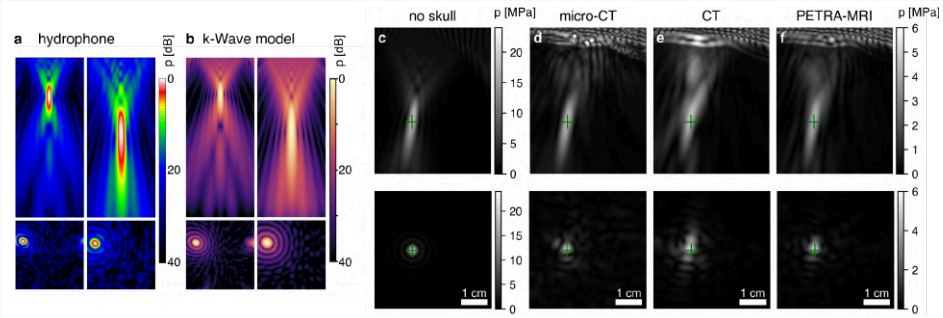

Figure 1: (a) Examples from hydrophone measurements [1] compared to (b) simulation results of the same delay settings using our k-Wave-based model. (c) Reference and (d-f) transcranial simulations of a TUS focus of our phased array. Targeted focus position indicated by green cross. Acoustic properties are set to (c) those of water, and derived from either (d) micro-CT, (e) CT, or (f) PETRA-MRI. (first row) Slices for x = 0, (second row) Slices for z = focus position.

References: 1. Clinard S et al., The speed of sound in skull-mimicking digital phantoms depends on the microstructure. Phys Med Biol (2025).
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Equivalent source modelling of multielement array transducers for ultrasound neuromodulation

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Accurate source modelling of multielement arrays is critical for effective aberration correction and steering in ultrasound neuromodulation. In many cases, the behaviour of ultrasound sources differs from ideal models based on nominal parameters. It is therefore critical to include real transducer performance using measurement-based source definitions to ensure reliable field prediction. In this study, source definitions were derived from measurements of the acoustic fields generated by three multielement arrays operating at 286 kHz and 465 kHz, intended for human neuromodulation studies. All arrays were based on a grid pattern of 2.6 mm square elements over a flat circular aperture: two were fully populated 256-element arrays, and the third was a 128-element array with elements distributed in a sparse random arrangement over the same aperture. Hydrophone measurements were acquired for each array both with single elements operating individually, and with all elements focusing to axial distances from 40 mm to 120 mm on the beam axis, and to several off-axis positions. Pressure amplitude profiles were extracted along axial and lateral directions from each set of measurements. The effective circular element diameter was determined by constrained optimisation, minimising the difference between measured fields and free-field steady-state simulations performed using the k-Wave acousticFieldPropagator function. Optimisation using the single-element planar field measurements first provided an initial estimate of element diameter, which served as the starting point for a whole-array optimisation. The error function was the sum of differences between measured and simulated spatial peak pressure at focal positions from 40 mm to 120 mm, normalised to the focal pressure at 40 mm (the position of highest focal gain). Average errors in relative spatial peak pressure, focal position, and focal dimensions were then calculated across all on-axis and off-axis positions. Optimised element diameters of 5.1 mm, 4.5 mm, and 4.4 mm were obtained for the full-aperture 286 kHz array, full-aperture 465 kHz array, and sparse-aperture 465 kHz array, respectively. Simulated fields showed close agreement with measurements, accurately reproducing the dependence of focal pressure on position for both on- and off-axis foci, with errors increasing as the focus was moved further from the beam axis. Mean absolute error in relative spatial peak pressure was below 2% at 286 kHz and 3.5% at 465 kHz, with excellent agreement in focal size and position, particularly at the higher frequency (Fig 1.), where average absolute error in focal position was 1 mm. Measurement-based transducer definitions using effective element size provide a simple and viable approach for characterising the real behaviour of multielement array transducers in which inter-element interaction or crosstalk is present. The resulting models were implemented as transducer definition files in k-Plan for use in subsequent studies.

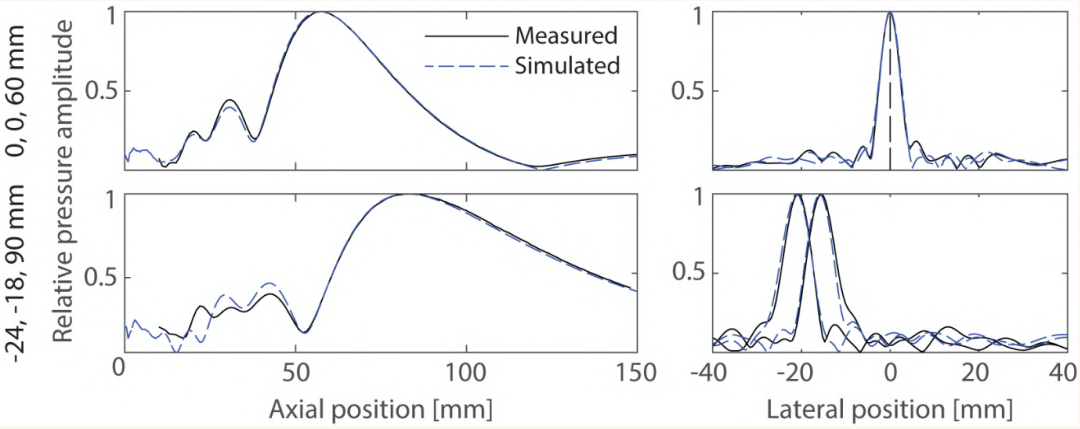

Figure 1: Measured and simulated pressure profiles generated by the 465 kHz sparse array for focal set positions of 0, 0, 60 mm and -24, -18, 90 mm, normalised to the peak pressure for 0, 0, 40 mm set focus.

Calculating Tissue Heating from Simultaneous TUS and MRI

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3 New York University | 4 Vanderbilt University
5 University of Calgary | 6 Stanford University

Transcranial ultrasound stimulation (TUS) is an emerging neuromodulation modality. MR-acoustic radiation force imaging (ARFI) and functional MRI (fMRI) are techniques used to target treatment and monitor the effects of TUS. Both TUS and MRI result in tissue heating. The goal of this work is to provide researchers with an understanding and guidance for the safe application of TUS under MRI. SAR maps were calculated for MRI and TUS using the Duke body model. A CTX-500 transducer was positioned 1 cm away from the surface of the skull. Acoustic intensity maps were calculated in k-wave[1], and TUS SAR was calculated following: SAR = $2\alpha_a$ I_{SPTA} / ρ, where α_a is acoustic absorption, a fraction of total attenuation, I_{SPTA} is spatial peak temporal average intensity, and ρ is density. The following values were used in the acoustic simulation, c_{skull} = 2000 m/s, c_{tissue} = 1500 m/s, ρtextsubscriptskull = 1800 kg/m^3, ρ = 1000 kg/m3, αtextsubscriptskull = 8.26 dB/cm/MHz, α_{tissue} = 0.49 dB/cm/MHz, $\alpha_{a,skull}$ = 0.3α_a , $\alpha_{a,skull}$ = 0.85α_{tissue} . Using XFDTD[2] and the same transducer and body model, EM simulations were performed to calculate MRI SAR at 3T using a birdcage coil. MRI and TUS SAR maps were input to a thermal solver[3] to determine thermal rise for representative MRI and TUS sequences. A single TUS for a stimulation sequence with a free-field I_{SPTA} of 8.25 W/cm^2 was simulated. The maximum allowed head-average MRI SAR of 3.2 W/kg was used in the simulation. To validate our implementation of the thermal model, a transducer was placed in the scanner coupled to a phantom, and a thermometry sequence was performed while inducing a focal thermal rise with the transducer. This setup was replicated in simulation. Simulated and experimental focal thermal rise agreed within 4%. Further, B1+ mapping was performed as a proxy to validate the EM model. B1+ maps were acquired in a ball phantom, and the setup was replicated in simulation. Preliminary results show that although the maximum local SAR due to combined TUS is 59.08 W/kg, the maximum temperature rise in the skull was 0.689°C, and 0.36°C at the focus for a head-average MRI SAR of 3.2 W/kg. Although thermal rise was highest in the skull, the highest simulated temperature occurred at the focus at 37.54°C. Simulated thermal rise was below the 2°C limit recommended by ITRUSST. Based on these simulations, the skull is most at risk of thermal rise due to combined TUS and MRI, whereas the focus is most at risk of the highest absolute temperature.

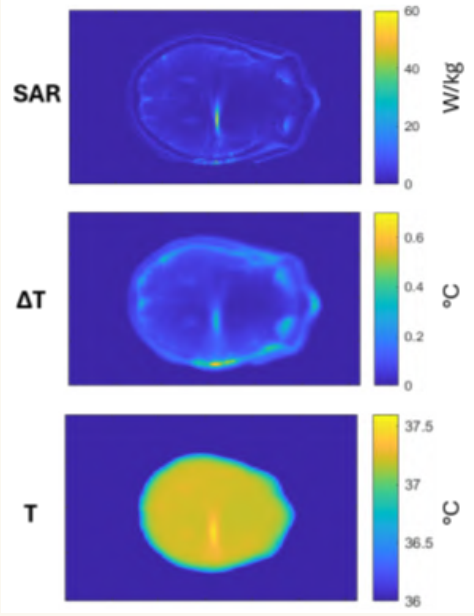

Figure 1: Combined MRI and TUS SAR map (top). Thermal rise is highest at the skull (middle). Absolute temperature is highest at the focus (bottom).

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petra2density – an MRI processing pipeline to create a density map of the head

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Transcranial ultrasonic stimulation (TUS) is an emerging non-invasive neuromodulation technique that uses low-intensity, focused ultrasound to modulate neuronal activity. TUS depends on precise acoustic simulations to predict the shape of the pressure field and to ensure participant safety during the stimulation. Accurate tissue density maps are essential for modeling ultrasound propagation through the skull and brain. CT images can be directly converted to density values using a specialized density phantom. However, deriving these maps from MR images remains challenging as the signal that MR scanners measure is not directly related to material density. Petra2density [1] is an open-source tool that converts a T1-weighted MRI and a PETRA MRI of the head into a density map (kg/m^3) for TUS simulation. We created a mapping from PETRA values to density using paired MRI and low-dose CT data from 20 healthy participants to capture a large variety of skull density distributions. The linear fit between the normalized PETRA values and the pseudo-CT values was developed by segmenting the skull in each participant and performing robust orthogonal distance regression (ODR) on the standardized values of PETRA and CT. A linear mapping is provided for both a 1 degree and a 2 degree flip angle (FA) PETRA image. The mapping from CT (HU) to density (kg/m^3) was created using a density phantom that was imaged in the CT scanner after most participants using the same scanning protocol. To do the conversion, petra2density relies on CHARM [2] for segmentation and bias-field correction, followed by mapping of normalized PETRA values to density and HU. In addition to the primary density map (p2d_density.nii.gz), the pipeline generates a pseudo-CT (p2d_pct.nii.gz), bias-fieldcorrected MRI, bone mask, and soft-tissue/bone segmentation. The density map is compatible with kPlan and BabelBrain acoustic simulation software. When using the density map with k-Plan, it is recommended to use the density calibration file that is included in the petra2density repository (density-calibration.kct). Petra2density builds on the previous work of the petra-to-ct [3] pipeline by improving the preprocessing steps, fitting on more participants, and converting to well-defined density values rather than HU. Additionally, we provide mappings for 2 degree FA PETRA which may improve the signal-tonoise ratio and appears to have a relationship to density that is as linear as the 1 degree FA PETRA. **References:** 1. https://github.com/simnibs/petra2density 2. Puonti, Oula et al. “Accurate and robust whole-head segmentation from magnetic resonance images for individualized head modeling” 3. https://github.com/ucl-bug/petra-to-ct

TUS Calculator: a browser-based tool for rapid parameter conversion and exploration for transcranial ultrasound stimulation

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In the rapidly growing field of transcranial ultrasound stimulation (TUS), the large number of parameters impedes both comparison across partially reported studies and fast exploration of new study designs. Existing tools such as k-Plan, BabelBrain, and PRESTUS are well-suited for accurate, imaging-informed planning, but less practical for metric conversion in study review or for rapid parameter exploration in the early design phase. Here we present the TUS Calculator, a free, open-source, browser-based tool designed for exactly this purpose: instant parameter conversion and exploration alongside ITRUSST biophysical safety guidelines (Aubry et al. 2025). Beyond the main interface, dedicated tabs provide estimates of temperature rise and thermal dose in brain tissue, with skull heating estimated using the Thermal Index for Cranial bone (TIC); heat deposition estimates for MRI-TUS combination protocols are also included. Acoustic assumptions are adjustable via a dedicated tab. Outputs align with ITRUSST reporting recommendations (Martin et al. 2024), supporting standardised and reproducible protocol reporting. The tool provides estimates with inherent uncertainty and complements, rather than replaces, individual acoustic simulation. The TUS Calculator lowers the barrier to protocol design by enabling instant parameter conversion, providing insight into parameter relationships and proximity to ITRUSST safety guidelines, and allowing rapid iteration before full simulation. The tool is openly available and actively maintained. We invite the TUS community to use, share, and contribute.

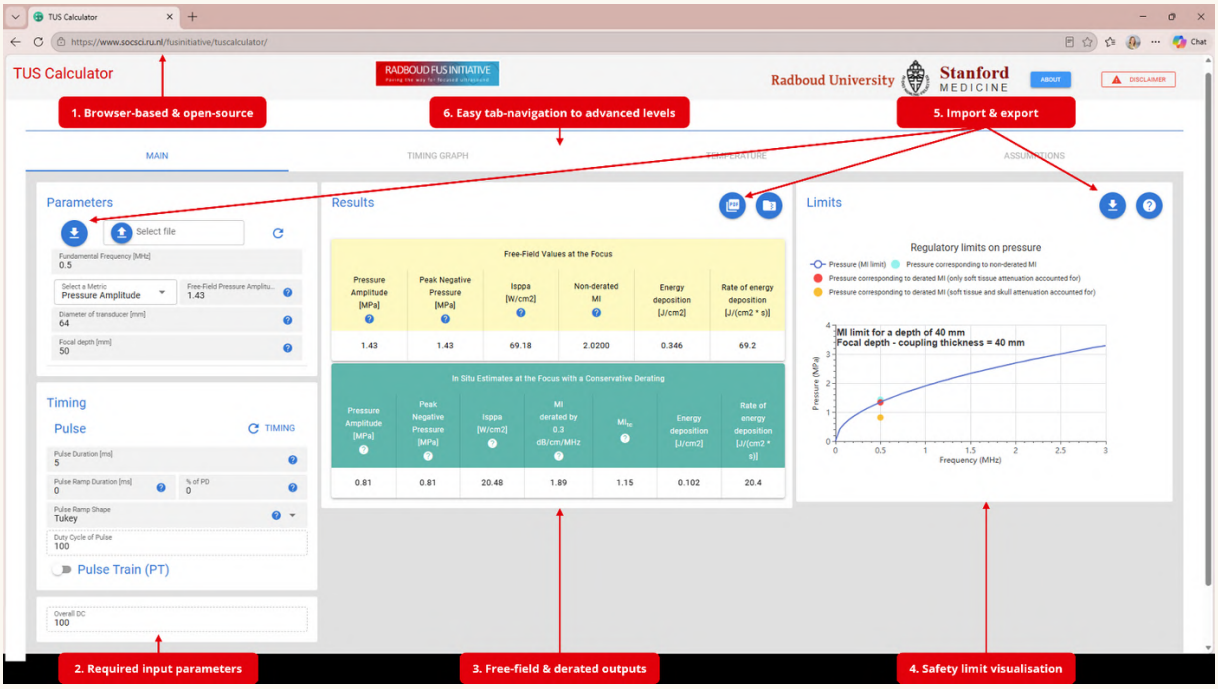

Figure 1: Interface of the TUS Calculator (v1.4.0; https://www.itrusst.com/tus-calculator). 1. Browser-based and open-source, requiring no installation. 2. Required input parameters: fundamental frequency, selectable pressure metric (pressure amplitude, Isppa, non-derated MI or MI), transducer diameter, focal depth, and pulse timing up to three levels including ramping. 3. Results panel: free-field values at the focus and in situ estimates with conservative derating (pressure amplitude, peak negative pressure, Isppa, non-derated MI, MI, MItc, energy deposition). 4. Regulatory limits panel: pressure–frequency plot with the ITRUSST MI $\leq$ 1.9 safety guideline and current protocol operating point overlaid. 5. Import and export of protocols (YML/JSON) for reuse and sharing with additional export of timing diagrams (SVG) and full protocol reports (PDF/CSV). 6. Tab navigation to advanced views: a visual representation of the protocol (Timing Graph), temperature estimates, and adjustable assumptions.

References: 1. Aubry et al. (2025). DOI: 10.1016/j.brs.2025.10.007. 2. Martin et al. (2024). DOI: 10.1016/j.brs.2024.04.013 3. Cornelissen et al. (2026). TUS Calculator (v1.4.0). DOI: 10.17605/OSF.IO/48F2S

3D Element Localization of a 128 Element Transcranial Ultrasound Transducer Array Using a Pseudoinverse Triangulation Algorithm

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Therapeutic focused ultrasound has emerged as a promising modality for neuromodulation and ablation. To concentrate ultrasonic energy for therapeutic ultrasound, an array of piezoelectric elements are positioned so that they generate a high pressure focus via superposition of the acoustic field from individual elements. Rapid prototyping via 3D printing of a manifold to position the elements offers advantages in development speed and geometric flexibility compared to traditional fabrication methods but introduces susceptibility to millimeter-scale placement errors that can cause deviations in the focused beam behavior. If the locations of the mispositioned elements are known, they can be electronically corrected through the application of phase shifts to the input signal. Here, we assessed the impact of mispositioned elements on beam formation using simulations and implemented an element localization algorithm using pseudoinverse triangulation to improve focal gain and steering capabilities of a 128-element transducer array.

Using the MATLAB toolbox k-Wave, simulations a 128-element transducer were completed with artificial error in element placement ranging from 0mm, ±0.3mm, ±0.5mm, ±0.75mm, ±1mm, and ±2mm. Pressure measurements at the focus were collected from the simulations to evaluate the effects of element misplacement on focal gain and focal shape. To implement the element localization, element-wise signal data from the physical 128-element human transducer array was collected in a water tank using a fiber optic hydrophone positioned at distinct locations. For each element, differences in signal arrival at the measured locations were calculated using the cross correlation of each signal, then converted to differences in path lengths. The estimated path differences are used for element localization by applying the pseudoinverse of a matrix relating the hydrophone positions and path differences to determine the x, y, and z positions of the elements. Beam maps of the acoustic field were collected to characterize changes in maximum focal pressure and focal shape when driving the transducer with the original vs. the triangulated element positions.

Simulations of the artificially misaligned arrays showed a consistent decrease in maximum focal pressure as the range of error in element placement increased, underscoring the importance of accurate element localization. The pseudoinverse triangulation methodology localized the elements of the physical array and identified a root mean square distance of 2.0mm from the planned element locations. Using the triangulated element locations to drive the array improved the maximum peak negative pressure from 0.54 MPa to 0.78 MPa. Additionally, the triangulation improved focal shape, reducing maximum sidelobe pressure by approximately 3dB.

We successfully implemented a pseudoinverse-based element localization algorithm which identified the threedimensional position of each element in a 128-element transducer array designed to transmit through the human skull. The updated element positions improved the maximum focal pressure by approximately 40% and decreased off target pressure. These results demonstrate that the geometric uncertainties introduced by rapid prototyping can be effectively compensated through post hoc element localization, enabling flexible array fabrication without sacrificing beam quality.

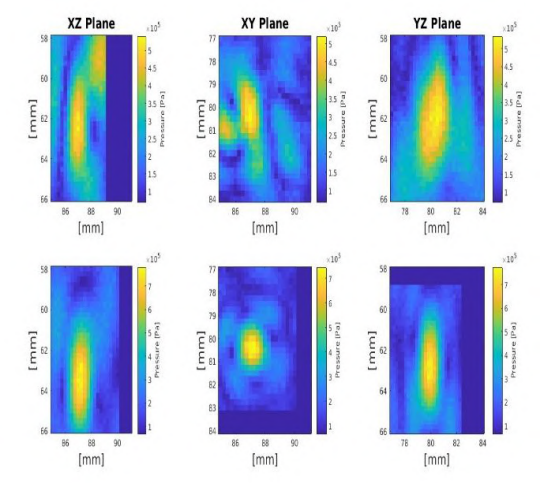

Figure 1: Improved Beam Shape and Peak Pressure with Triangulated Element Positions. Comparison of maximum pressure maps at the focus across three at the orthogonal planes (axial, sagittal, and coronal) for arrays driven by original element positions (top row) and triangulated element positions (bottom row). Arrays driven using triangulated positions exhibit a ~40% increase in peak negative pressure at the geometric focus, along with a significant improvement in beam shape.

Ultra2: a hybrid hardware technology for concurrent multi-focal LIFU neuromodulation and whole-brain MRI at 7T

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Introduction: Simultaneous ultra-high-field MRI could enable precise targeting and sensitive functional and metabolic characterization [1,2] of LIFU neuromodulatory effects; however, existing MR-guided ultrasound systems are not compatible with 7T MRI. Here, we present Ultra2, a novel strategy for multi-focal LIFU neuromodulation and whole-brain MRI at 7T exploiting the dual functionality of acoustic couplers as dielectric resonator (DR) elements.

Methods: Each Ultra2 module was designed as a flexible structure conforming human head, acting as an acoustic coupling medium and a DR for MRI signal transmission/reception. Ultrasound transducers (500 kHz, diameter = 60 mm, ROC = 60 mm) were positioned above the modules (Fig. 1A), while a dual RF feed composed of a coupling loop and dipole antenna was integrated laterally [3]. Eight Ultra2 modules were combined into a 16-channel DRA array integrated with ten ultrasound transducers for wholebrain 7T MRI and multi-focal LIFU neuromodulation. The MRI antenna array was also extended into 32-channels to evaluate potential SNR gains. Electromagnetic and acoustic simulations were conducted in Sim4Life using FDTD and LAPWE solvers, respectively.

Results: Electromagnetic simulations showed a central transmit efficiency of 0.67 $\mu T/\sqrt{W}$ in CP mode for the 16-channel array with integrated ultrasound transducers (Fig. 1B). The 32-channel array showed superior whole-brain SNR performance vs. 16-ch (Fig. 1C).

Discussion and conclusions: These results demonstrate the feasibility of a hybrid multi-channel platform enabling simultaneous multi-focal LIFU neuromodulation and whole-brain 7T MRI. The proposed dual-function acoustic coupler/DR architecture provides efficient ultrasound transmission while preserving high RF performance, establishing a foundation for integrated ultra-high-field MR-guided neuromodulation systems.

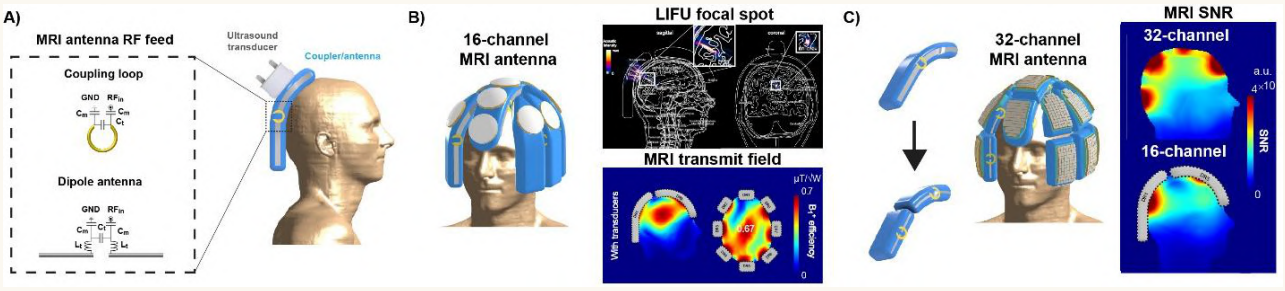

Figure 1: A) Ultra2 concept: flexible acoustic coupler operating as a loop–dipole-fed dielectric resonator. B) Integrated 16-channel RF / 12transducer LIFU system with simulated focal spot and MRI transmit field distribution in a human head model. C) Extended 32-channel MRI configuration and corresponding whole-brain SNR distribution.

References: 1. Ai et al. BMC Neuroscience (2018), 2.Yaakub et al. Nat Communications (2023), 3. Wenz and Dardano, MAGMA (2023).

A short-readout 7T PETRA sequence for acoustic simulations comparable to established 3T PETRA

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Background: The information about bone and tissue density provided by computed tomography (CT) scans is the current gold standard for estimating the acoustic properties needed for transcranial ultrasound stimulation (TUS) simulations. However, the use of CT scans exposes subjects to ionizing radiation, motivating the development of alternative approaches using magnetic resonance imaging (MRI). Previous work has optimized a Pointwise Encoding Time Reduction with Radial Acquisition (PETRA) sequence using 3-Tesla MRI for skull imaging, which was validated against CT scans. Ultra-high field 7 Tesla MRI is an advanced imaging modality that provides enhanced image resolution and has become increasingly popular in neuroimaging research. The current 3-Tesla PETRA protocol cannot be directly applied to the 7-Tesla MRI due to high magnetic field inhomogeneities and shorter T2* relaxation time. Therefore, we have developed a modified version of the 7-Telsa PETRA scan to address the B0 and B1 inhomogeneities and reduced skull signal decay of the vendor-supplied 7-Tesla PETRA and generate an equivalent pipeline to the established 3T PETRA. Here we compare simulations between the established 3-Tesla PETRA, vendor-supplied 7-Telsa PETRA, and our improved 7-Tesla PETRA images.

Methods: 3-Tesla and 7-Tesla vendor-supplied sequences were acquired on Siemens scanners. A modified 0.8 mm isotropic 7-Telsa PETRA sequence was implemented in Pulseq with a shortened readout duration by increasing the radiofrequency and readout bandwidth. The SimNIBS version 4.6.0 charm segmentation tool with settings optimized for skull segmentation was executed using the T1 structural scan from the 7-Tesla MRI. A new SimNIBS project was created using Brainsight version 2.5.10 to plan a TUS trajectory with the nucleus accumbens as the target region. This project was replicated three times, once for each PETRA scan, to ensure that target location and TUS trajectory remained consistent across all PETRA comparisons. Acoustic simulations comparing the three PETRA scans: the established 3-Tesla PETRA, the vendor-supplied 7-Telsa PETRA, and our modified 7-Tesla PETRA, were performed using BabelBrain version 0.8.0.

Results: Acoustic simulations showed that the free-field ISPPA, ISPPA at target, mechanical index, and increase in CEM values for our modified 7-Tesla PETRA scans remained consistent with the values derived from the established 3-Tesla PETRA scan. The values from the vendor-supplied 7-Telsa PETRA showed greater variability relative to the established 3-Tesla PETRA scans.

Conclusion: These findings suggest that our modified 7-Telsa PETRA sequence is comparable to the established 3Tesla sequence, supporting its potential utility for pseudo-CT generation at 7T.

Effect of Image Modality and Resolution on Skull Microstructure Mapping for Transcranial Ultrasound

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Accurate prediction of intracranial pressure fields in transcranial focused ultrasound (tFUS) depends critically on the acoustic properties assigned to the skull. These properties are derived from clinical images, most commonly CT or more recently pseudo-CT synthesised from MRI. Several attenuation models map acoustic properties directly from image-derived porosity, making its accurate estimation essential. However, whilst it is well established that clinical imaging cannot fully resolve skull microstructure, the magnitude and spatial distribution of the resulting uncertainties in image-derived structural properties remain largely underinvestigated. Here we present the first spatially resolved, quantitative comparison of skull structure across micro-CT (µCT), clinical CT, and pseudo-CT (pCT), quantifying the resolution- and modalitydependent differences in skull thickness and porosity. Five ex-vivo human calvaria were imaged using micro-CT, clinical CT, and MR PETRA, from which pCTs were generated. µCT images provided a high-resolution reference image. A mesh-based framework was developed to obtain image intensity profiles along surface-normal vectors, for each registered image volume. This enabled a spatially matched, point-wise comparison of internal structure at every skull location. Segmentation pipelines were developed for each modality: a k-means clustering approach for CT and pCT and a novel intensity gradient-based boundary detection method for µCT to eliminate operator bias. Skull thickness, trabecular thickness, and porosity were extracted for each mesh element across all image modalities and compared. Skull thickness was well-estimated by CT and pCT relative to µCT, with average mean absolute errors of 0.61 mm (CT) and 0.34 mm (pCT), across all skulls. Porosity showed substantially larger and more variable discrepancies, with mean absolute errors ranging from 4.8% to 9.3% across skulls and modalities. The errors in porosity scaled linearly with average skull porosity ($R^2 = 0.853$, $p < 0.001$), indicating that uncertainties in mapping of acoustic properties of highly porous skulls, which are often also the most attenuating, are likely to be greater. pCT showed the largest deviations from µCT within the trabecular region specifically, reflecting fundamental differences in tissue contrast between MRI and CT acquisitions that prevent identical reconstruction of trabecular features. These findings suggest that further investigation is needed to quantify uncertainties and determine acoustic properties in the case of highly porous skulls. Additionally, the discrepancies observed in pCT may also affect sound speed and density maps derived from them, warranting careful evaluation as pCT becomes more widely adopted for tFUS planning. Future work involves propagating these structure-informed maps and segmentation techniques into acoustic simulations and validating against experiments, with the aim of reducing uncertainty in participant-specific treatment planning for tFUS.

Development of a 32-channel Focused Ultrasound Helmet Interface for Somatosensory Neuro modulation and Safety Validation in Non-human Primates

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Focused ultrasound (FUS) can non-invasively engage primate somatosensory circuits, but future bidirectional brain-computer interfaces require a repeatable interface capable of targeting the somatosensory homunculus while controlling skull-through exposure and safety. Prior macaque studies have demonstrated FUS-evoked somatosensory network activation, but translation toward sensory neuroprosthetic feedback requires a device platform that integrates array steering, helmet-based positioning, subject-specific anatomical compensation, and pre-in vivo safety validation. We developed a helmet-mounted 32-channel FUS array interface for somatosensory neuromodulation in nonhuman primates. The system targets macaque S1 using MRI/atlas-guided alignment and a helmet module designed to accommodate inter-individual cranial variability. The array module uses a concave 750-kHz architecture with 32 active elements and 4 dummy elements, lateral beam steering, a 36.1° field of view, an approximately 1.1-mm element pitch, an 8.5-mm elevation aperture, a 17.5-mm elevation focal depth, and a 46 × 13 mm footprint. The helmet concept incorporates inward radial module adjustment, elevation tilt near the acoustic contact surface, facial and occipital fixation, and optional low-force ear-bar referencing. A three-channel wired prototype sample was fabricated and characterized electrically and acoustically. Impedance measurements of the cable-plus-ceramic samples at approximately 751.5 kHz showed residual capacitive loading, with impedance magnitudes of approximately 1.77–1.92 kΩ and phase angles of −42.7° to −50.0°, indicating the need for impedance matching before pulser drive. Estimated low-frequency capacitance was approximately 128–131 pF across the measured traces. After matching, pulser-driven operation produced radiated acoustic output that increased monotonically over the tested drive range, with radiation-force-derived output increasing from approximately 1.1 W to 2.2 W. A one-channel lateral pressure scan acquired 17 mm from the transducer demonstrated formation of a focused main lobe, with the largest observed secondary lobe at −8.77 dB. These preliminary measurements support the feasibility of the electrical drive, the scalability of acoustic output, and the early beam-formation capability of the prototype architecture. The pre-in vivo workflow combines free-field and macaque-skull-through hydrophone mapping, pressure transmission estimation, focal shift, and −6-dB field characterization, BSA-based thermal-visualization phantom testing, and MRI safety surveillance. Candidate stimulation parameters include 750 kHz, 300-µs tone bursts, 1kHz PRF, 300-ms sonications, 3–5 s inter-stimulus intervals, and stepwise free-field pressure escalation from 0.60 to 0.95 MPa, corresponding to an estimated in-situ PNP range of approximately 0.35–0.55 MPa. MRI safety assessment will include baseline, immediate post-sonication, and 24-h follow-up scans using DWI/ADC, SWI/T2*, T2, and FLAIR to screen for diffusion restriction, hemorrhage, edema, and lesion formation. This engineering platform integrates a 32-channel helmet-mounted FUS array, adjustable cranial-coupling mechanics, preliminary electrical and acoustic characterization, skull-through acoustic validation, thermal phantom testing, and MRI safety monitoring. The system provides a preclinical foundation for repeatable, noninvasive S1 homunculus stimulation and future somatosensory feedback studies in non-human primate BCI research.

Acknowledgments: This work was supported by the Challengeable Future Defense Technology Research and Development Program through the Agency for Defense Development (ADD), funded by the Defense Acquisition Program Administration (DAPA) in 2025 (No. 915122101), and the Glocal 30 University Project.

Advancing a translational pipeline for transcranial ultrasound neuromodulation in 3MP-FUS: MR-ARFI-based target verification and concurrent fMRI–TUS toward pain modulation

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Background: Transcranial ultrasound stimulation (TUS) enables spatially precise modulation of cortical and deep brain targets, but its translational potential depends on robust in-brain targeting and on integrating the modality with multimodal MR readouts. Within the 3MP-FUS consortium, we are advancing a fully MRI-guided TUS platform that couples a 256-element matrix-array transducer with high-gradient 3T MRI and image-guided neuronavigation. Here we describe the platform, present current MR-ARFI phantom results and outline a planned clinical application targeting central pain processing at both cortical and subcortical levels.

Methods: The 3MP-FUS platform integrates an MR-compatible 256-element phased-array TUS device with 3D electronic beam steering and phase aberration correction into a workflow built around coupled control of the transducer and a Cima.X 3T MRI scanner via the Localite TUS Navigator. Participant-specific trajectory planning and post-hoc simulations are performed in BabelBrain. For target engagement verification, we are establishing magnetic resonance acoustic radiation force imaging (MR-ARFI), which encodes tissue displacement at the TUS focus into the MR signal; the high gradient strengths of the Cima.X system (up to 190 mT/m) improve displacement sensitivity at safe ultrasound pressures.

Results: Phantom MR-ARFI measurements successfully visualized the predicted focal spot of the matrix-array transducer, with the displacement maximum spatially co-localized with simulated targeting. The setup tolerates the low I_{SPPA} values consistent with safe human exposure, and ongoing work is now translating MR-ARFI into in-vivo measurements. In parallel, coupled neuronavigation–MRI control is operational across sonication and structural/functional MR sequences within a single session, establishing the technical readiness required for concurrent online TUS–fMRI studies in humans. Clinical Significance and Next Steps: Building on this technical foundation, we are designing a clinical study to test whether TUS modulates central pain processing in an online, event-related paradigm with concurrent fMRI. The study will compare two targets along the ascending nociceptive pathway (the thalamic ventral posterolateral nucleus (VPL) and a cortical target in primary somatosensory cortex or posterior insula) and two TUS protocols selected to engage mechanistically distinguishable biophysical regimes. Experimentally induced pain will serve as the behavioral readout, with concurrent BOLD fMRI capturing both local target engagement and downstream effects along the pain network; where feasible, MR-ARFI will provide additional in-scanner verification of the acoustic focus. Together, the 3MP-FUS pipeline couples online TUS-fMRI with neuronavigation-guided, simulation-validated targeting and, increasingly, with MR-ARFI-based focus localization to accelerate clinically scalable, hypothesis-driven ultrasound neuromodulation, with central pain as a first translational application.

CoperniFUS: An open-source software for precise stereotaxic targeting in focused ultrasound neuromodulation studies

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Introduction: The development of new focused ultrasound (FUS) neuromodulation applications[1,2,3,4] relies heavily on preclinical investigations in small-animal models. However, whole-brain studies in rodents present several technical challenges, including accurate target definition, stereotaxic navigation, acoustic simulation, and reproducible positioning of the ultrasound focus. To address these challenges, we developed CoperniFUS[5], an open-source software platform dedicated to stereotaxic planning and navigation for preclinical FUS experiments. The software was evaluated in two independent studies targeting the rat striatum, a brain region involved in motor control and metabolic regulation. Neuromodulatory effects were assessed using two monitoring approaches: microdialysis coupled with high-performance liquid chromatography (HPLC) for neurochemical measurements, and ^{18}F-FDG microPET/CT imaging for metabolic assessment.

Method: CoperniFUS integrates anatomical calibration, stereotaxic navigation, image registration, and acoustic simulation tools within a unified workflow. Spatial coordinates for FUS targeting were computed from the Waxholm Space Atlas of the Sprague-Dawley rat and registered to individual anatomical landmarks (bregma and lambda). Co-registration of brain and skull anatomical structures enabled subject-specific acoustic simulations using k-Wave to estimate pressure fields and thermal deposition at the target site. The software was deployed in two experimental paradigms. In the first study, CoperniFUS guided the stereotaxic placement of both the FUS focus and a microdialysis probe within the striatum. Extracellular neurochemical changes were quantified before, during, and after sonication using HPLC-based analysis of collected dialysates. In the second study, CoperniFUS was used within a three-step workflow combining CT-based planning, image-guided repositioning, and FUS stimulation. A low-dose CT scan acquired before each session was automatically registered to the planning scan, allowing accurate repositioning of the acoustic focus. Neuromodulatory effects were subsequently evaluated using ^{18}F-FDG microPET imaging in a sham-versus-stimulation design.

Results: CoperniFUS successfully enabled stereotaxic targeting of the rat striatum across both experimental paradigms (Fig. 1). Acoustic and thermal simulations predicted safe operating conditions, remaining within commonly accepted neuromodulation safety limits ($\Delta T < 2°C$, MI < 1)[6]. In the microdialysis study (Fig. 1c), FUS stimulation was associated with changes in extracellular concentrations of several amino acids involved in neural signaling, including glutamate, GABA, leucine, and tyrosine. Inter-individual variability was observed, highlighting the importance of precise targeting and anatomical guidance. In the microPET study (Fig. 1d),, the software enabled reproducible repositioning of the acoustic focus. No scalp lesions or adverse effects were observed. Under the tested stimulation conditions, no significant differences in glucose metabolism were detected between sham and stimulated animals.

Discussion: CoperniFUS provides a robust and versatile framework for image-guided FUS neuromodulation studies in small-animal models. By integrating stereotaxic navigation, multimodal image registration, and acoustic simulations within a single open-source platform, it facilitates reproducible and safe targeting of deep brain structures. The successful deployment of CoperniFUS in both microdialysis and microPET experiments demonstrates its adaptability to a wide range of neuromonitoring techniques and preclinical neuromodulation applications.

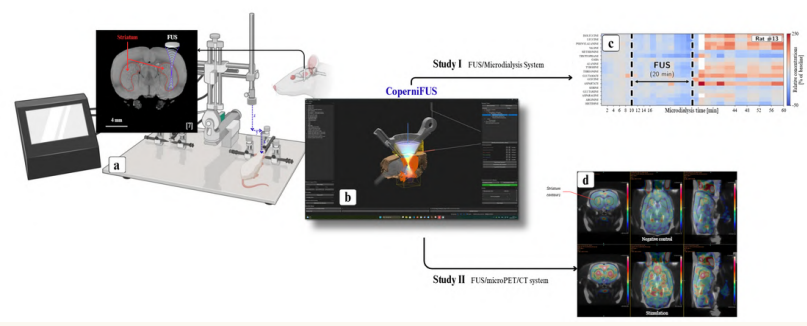

Figure 1: (a) Experimental setup and targeted zone. (b) Capture of CoperniFUS software. (c) Concentrations of 18 amino acids in collected microdialysates throughout experiment. (d) Example of 18F-FDG PET imaging results obtained from rat 4.

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Acknowledgments: This work was supported by the following projects and organizations: ANR-16-TERC0017, ANR-21-CE19-0007 and ANR-21-CE19-0030, the Focused Ultrasound Foundation, the Centers of Excellence program, and the Inserm PCSI program.

Numerical characterization and experimental validation of a 32-element phased-array Focused Ultrasound transducer at 1 MHz for selective sonication in non-human primate models.

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Low-intensity transcranial focused ultrasound (tFUS) stimulation is gaining increasing attention as a non-invasive, highly selective, and precise neuromodulation technique capable of targeting both cortical and deep brain regions. A growing body of research conducted on non-human primates (NHP) is highlighting its potential for the treatment of neurological and neuropsychiatric disorders, as well as for the modulation of brain functional connectivity. In this context, different studies have demonstrated that tFUS can alter behaviour in NHP [1-3] using custom single-element transducers operating at low frequencies, typically in the range of 250–500 kHz. These low frequencies enable improved ultrasound transmission through the skull and reduce skull-induced aberrations, but at the cost of an axial focal length typically exceeding 10 mm, thereby limiting spatial selectivity. Here, we present a low-cost, 32 element phased-array tFUS transducer operating at 1 MHz, geometrically optimized for applications in NHPs, specifically rhesus macaques. The device was designed and characterized through acoustic numerical simulations performed with k-Wave software and further validated both in free-water and transcranial environments through water tank acoustic measurements. The emitted pressure field was recorded using a needle hydrophone (Precision Acoustics), while transducer and skull positioning was ensured using Brainsight optical neuronavigation system. Results show strong spatial agreement between simulations and measurements, thus validating both the free-water and transcranial numerical models. The focal spot size at the geometrical focus of the transducer exhibits a full width at half maximum of approximately 8x2 mm. The axial steering range reaches tens of mm both inward and outward along the propagation axis, while the maximum lateral steering range is 5 mm. This work demonstrates that accurate and selective transcranial sonication through NHP skull models can be achieved with a phased-array transducer comprising only 32 elements. The reduced focal size, below 10 mm, enables the targeting of small brain nuclei, while lateral beam-steering capabilities allow for the sonication of larger targets. The accessibility and performance of this transducer may facilitate future tFUS applications in NHP, investigating brain connectivity and behaviour with significantly improved spatial selectivity. **References:** 1. Deffieux T. et al., “Low-Intensity Focused Ultrasound Modulates Monkey Visuomotor Behavior”, Curr Biol, 23(23), pp. 2430-2433, 2013.

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Development of Bioadhesive and Wearable Focused Ultrasound System for Long-Term Neuromodulation

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Transcranial focused ultrasound has emerged as a promising non-invasive approach for neuromodulation, particularly in the treatment of neurodegenerative diseases and psychiatric disorders. However, its translation into wearable neuromodulation systems has been limited by the large size of existing devices, which require external supporting hardware for operation. In addition, the reliance on ultrasound gel for acoustic coupling between the device and the skin undermines long-term usability due to dehydration and poor adhesion, preventing the formation of a stable interface. In this talk, I will first introduce a wearable, miniaturized ultrasound device comparable in size to standard EEG/ECG electrodes and integrated with a bioadhesive hydrogel to enable efficient acoustic transmission and long-term, wearable primary somatosensory cortical stimulation.(1) Leveraging our wearable ultrasound transducer, we were able to suppress somatosensory evoked potentials elicited by median nerve stimulation via functional electrical stimulation over 28 days.(1) Secondly, I will demonstrate the integration of an adhesive-hydrogel–coupled transducer with a miniaturized electronic circuit and a lithium-ion battery embedded in a fabric armband, which we applied for peripheral nerve stimulation in pain management. Our results showed a significant increase in pain thresholds, with an average improvement of approximately 15%.(2) Finally, I will introduce the development of our focus-adjustable, wearable focused ultrasound patch system for deep brain stimulation at Subthalamic Nucleus (STN), integrated with real-time electroencephalography (EEG), electrooculography (EOG), electromyography (EMG) recording capability for sleep staging. Stimulation of the left STN was delivered throughout the night and was associated with a 25% increase in REM (Rapid Eye Movement) sleep duration and a 43-minute reduction in REM sleep latency compared to a sham night in a study of 26 subjects(3).

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Real-Time Acoustic Field Prediction for tFUS Simulation-Guided Navigation Using Deep Learning Models

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Background: Transcranial focused ultrasound (tFUS) is an emerging noninvasive neuromodulation technique that enables precise targeting of deep brain regions. Accurate prediction of acoustic fields is essential to ensure effective and safe stimulation. However, conventional numerical simulation methods are computationally expensive, limiting their applicability in real-time guidance. Building upon previous study [Park et al., NeuroImage, 2023] on real-time acoustic simulation-guided navigation systems, this study investigates the integration of two deep learning architectures into the SGN system and analyzes their prediction characteristics under real-time constraints. The system uses a single-element transducer for deep-target stimulation.

Methods: A transformer-based model (Swin-UNETR) and a GAN-based model were developed and integrated into the simulation-guided navigation system (SGN). Both models were trained on CT based k-Wave acoustic simulations from 36 subjects with multiple randomized source-target configurations, resulting in approximately 1024 training samples. Quantitative evaluation was performed using Dice similarity coefficient (DSC) at 50% and 90% maximum pressure thresholds (FW50%M and FW90%M), peak pressure ratio, and focal distance error. Inference time was also measured in the SGN system to assess real-time feasibility.

Results: The system inference times were 0.12 s for Swin-UNETR and 0.08 s for the GAN-based model, confirming real-time feasibility. Regarding FW50%M, Swin-UNETR showed slightly better and more stable DSC performance compared to the GAN model (0.8073 ± 0.0917 vs. 0.8061 ± 0.1188). For the high-intensity core, the GAN model achieved a higher DSC at FW90%M than SwinUNETR (0.7728 ± 0.1302 vs. 0.6519 ± 0.1532). Although the GAN model exhibited a tendency toward a flat peak profile spanning multiple voxels this characteristic did not present a critical issue given the high FW90%M accuracy. The focal localization error was lower for the GAN model (1.02 ± 0.91 mm) than for Swin-UNETR (2.22 ± 1.39 mm), while peak pressure ratios remained comparable (0.06 ± 0.11 for GAN vs. 0.11 ± 0.08 for Swin-UNETR).

Conclusion: This study demonstrates the integration of transformer-based and GAN-based acoustic field prediction models into a real-time tFUS simulation-guided navigation framework. While both approaches achieved comparable broad field reconstruction performance, they exhibited distinct characteristics in high-intensity focal representation and computational efficiency. These findings suggest that different deep learning architectures provide complementary trade-offs in real-time acoustic simulation-guided navigation systems.

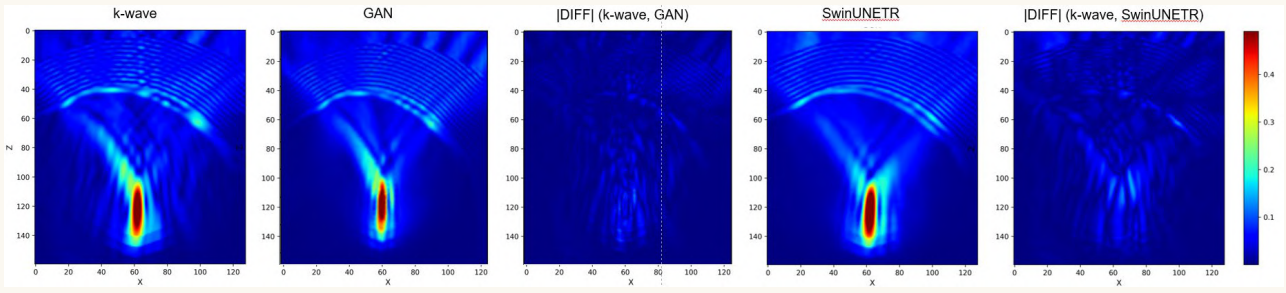

Figure 1: Comparison between numerical simulation, GAN prediction, and Swin-UNETR prediction of acoustic pressure fields within the real-time guidance system.

Local contrast influence in MRI-based synthetic computed tomography scans for planning of transcranial ultrasound stimulation

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Objective: To evaluate how local MRI contrast and scanner platform influence MRI-based synthetic computed tomography (CT) generation for transcranial ultrasound stimulation (TUS) planning, and to compare scanner-specific PETRA-to-Hounsfield Unit conversion equations. Background. Accurate skull characterization is essential for TUS modelling because skull density, thickness, and local bone structure influence acoustic transmission, phase aberration, and focal pressure estimates. CT is the gold standard for estimating skull acoustic properties; however, it involves exposure to ionizing radiation and may not be feasible in all research workflows. MRI-based synthetic CT (sCT), using bone-sensitive sequences such as Pointwise Encoding Time Reduction with Radial Acquisition (PETRA), provides an alternative for MRI-only planning. However, conversion from MRI intensity to CT-derived Hounsfield Units (HU) may depend on local image contrast, scanner platform, acquisition quality, and image noise. This raises an important question for tools such as BabelBrain, where implementing a single "one-size-fits-all" PETRA-to-HU conversion factor may not fully account for scanner-specific differences. Understanding these effects is important to improve individualized acoustic modelling and to determine whether universal or scannerspecific conversion equations are more appropriate.

Methods: Paired CT and PETRA MRI scans were analyzed in eight subjects acquired on two scanner platforms. Five subjects were patients with essential tremor undergoing clinical focused ultrasound surgery assessment and were scanned on a clinical Siemens 3T Magnetom VIDA scanner. Three healthy subjects were scanned on a Siemens 3T PRISMA scanner. CT scans were obtained using the same protocol in a Toshiba Aquilion helical CT scanner. For all subjects, PETRA intensity values were paired with corresponding CT-derived HU values by normalizing the PETRA signal based on soft-tissue segmentation and applying a PCA-based linear fitting approach between PETRA and CT in the skull bone region (DOI:10.48550/arXiv.2508.01050). Scanner-specific pooled fits for the PRISMA and Magnetom datasets were produced, as well as an overall pooled fit across both scanners. The resulting conversion equations were compared with an existing PETRA-to-HU formula (DOI: 10.48550/arXiv. 2508.01050) and a recently refitted formula
(https://github.com/simnibs/petra2density/tree/develop) to assess whether the scanner-specific and pooled fits aligned with existing approaches or suggested the need for scanner-specific calibration.

Results: The pooled all-subject PCA analysis produced the conversion fitting of [−1950.63 × + 2126.71]. The PRISMA subset produced a conversion fitting of [−1778.07 × + 1935.83], while the Magnetom VIDA subset produced a conversion factor of [−1973.50 × + 2220.42]. Visual comparison showed that the PCA-derived fits followed the main distribution of the data and aligned more closely with the recently published equation (petra2density repository) compared to the existing PETRA-to-HU formula. The Magnetom VIDA data appeared substantially noisier than the PRISMA, with a broader distribution of intensity-HU values, making the VIDA-specific fit more uncertain.

Conclusions These findings suggest that local contrast, scanner platform, and image noise likely influence MRI-based sCT calibration for TUS planning. Scanner-specific calibration may improve synthetic CT generation, particularly for high-quality PRISMA-acquired data, while noisier acquisitions such as the Magnetom VIDA dataset may require additional preprocessing or larger validation samples.

A Roadmap for High-Performance k-Wave: Accelerated Acoustic, Elastic, and Thermal Solvers

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k-Wave is an open-source toolbox for time-domain acoustic and ultrasound simulations, widely used for modelling wave propagation in complex, tissue-realistic media. Its numerical core is based on the k-space pseudospectral method, which combines high numerical accuracy with computational efficiency and makes the toolbox suitable for biomedical acoustics, ultrasound, and photoacoustic applications. This abstract presents the roadmap for the forthcoming high-performance computing releases of k-Wave, focusing on accelerated acoustic, elastic, and thermal solvers for modern heterogeneous platforms.

The planned development extends the accelerated k-Wave ecosystem from single-node workflows towards a broader range of architectures, including shared-memory CPUs, NVIDIA and AMD GPUs, distributed-memory clusters, and multi-GPU workstations. This will allow users to select an implementation appropriate to the available hardware and simulation scale, from desktop studies to large three-dimensional simulations requiring thousands of CPU cores or terabytes of aggregate memory.

The roadmap spans four releases. HPC 1.4 (July 2026) delivers accelerated fluid solvers (Fluid-OMP, Fluid-CUDA, Fluid-MPI) with streamed sources and broader CPU/GPU/compiler support. HPC 1.5 (December 2026) adds AMD GPU support (Fluid-HIP) and the first accelerated elastic and thermal solvers for CPUs, NVIDIA and AMD GPUs. HPC 1.6 (July 2027) introduces a multi-GPU CUDA fluid solver for single-node systems with up to eight NVIDIA GPUs connected via PCI Express or NVLink. HPC 2.0 (December 2027) provides a native MEX interface, labelled materials, weighted and off-grid sources/sensors, and performance monitoring.

Impact of Acoustic Property Uncertainty on Transcranial Ultrasound Simulation

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Introduction: Personalized simulations are a prevalent approach to plan and report exposure during transcranial ultrasound interventions. However, the impact of acoustic property assumptions on simulation outcomes remains poorly characterized to date. While multiple simulation platforms enable personalized simulations of predicted intensity and heating, their accuracy depends on adequate estimates of acoustic tissue properties, such as sound speed and attenuation in the skull. Point estimates of such properties based on published measurements are variable, and a "ground truth" consensus has not yet emerged. Quantifying and minimizing this uncertainty are necessary for accurate and consistent estimation of intensity and heating across platforms.

Methods: A literature review identified plausible upper and lower limits of multiple acoustic properties (sound speed [c], density [ρ], attenuation [α], thermal conductivity [κ], specific heat capacity [c], perfusion [ω], absorption fraction [β]) for brain and skull tissue layers. Two multi-layer media were created to test the impact of varying parameter estimates: (1) water–soft tissue and (2) water–skull–soft tissue (Fig. 1; 120×70 mm, 0.5 mm resolution). A single-element focused transducer (500 kHz, 64 mm aperture/focal length) was driven to a target free-water ISPPA of 60 W/cm². Two independent simulation platforms tested reproducibility of outcomes: PRESTUS (Kosciessa et al., 2026) used an axisymmetric grid solver (kspaceFirstOrderAS) for compressional wave propagation and kWaveDiffusion for thermal modeling via the Pennes bioheat equation as implemented in k-Wave. BabelBrain (Pichardo, 2023) used compressional wave propagation with a viscoelastic skull model (BabelViscoFDTD). Each tissue property was varied independently between literature informed upper and lower bounds with others held constant at mid-range values. Joint parameter default constellations of three major platforms (PRESTUS, k-Plan, BabelBrain) were modeled within PRESTUS.

Results: Variation in skull attenuation and absorption fraction yielded the largest outcome uncertainty: higher skull attenuation red uced brain ISPPA, while variable absorption fraction had the most pronounced impact on thermal rise in the skull. For example, the sonication protocol yielded peak pulse-averaged intensity in the brain between 4 and 16 between tested bone attenuation values, or a 300% difference. Brain tissue parameters had a more limited impact on target intensity in the presence of a skull. The impact direction of individual parameters was reproducible across platforms and generalized across a more transmissive skull thickness (3 mm) and reduced input intensity (30 W/cm2). Different property defaults between toolboxes predict variable estimates of target intensity and thermal rise that fall between parameter constellations that maximize or minimize transmission. Conclusions. Acoustic properties of skull and brain tissue impact intensity and heating estimates. To more comprehensively inform safety, efficacy, and reproducibility, simulation setups should indicate exposure uncertainty. Setups that explicitly incorporate acoustic property ranges can quantify uncertainty in practical setups beyond the benchmarks performed here. Refined measurements of skull acoustic properties, particularly attenuation and absorption fraction, are needed to reduce uncertainty about property estimates and simulated exposure.

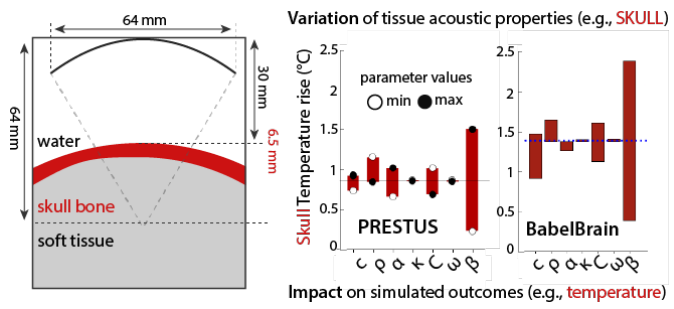

Figure 1: Methodology. Acoustic properties of skull and soft tissue in axisymmetric phantoms (left) were varied between literature-informed minimum and maximum values to assess uncertainty regarding risk- and efficacy-relevant simulation outcomes (e.g., thermal rise in skull; right).

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The effect of hair on the transmission of ultrasound

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Many TUS studies involve placing a transducer onto the head, coupled through a coupling pad or liquid and the participants hair. However, the effect of the hair on the transmission of ultrasound in this context is not well understood and could introduce additional variability in exposure. One solution, common with helmet arrays, is to require head shaving to eliminate any effect of the hair or possibility of trapped bubbles; however, this deters some patients and trial volunteers. Hair is a complex material with a rough hydrophobic surface which encourages bubble adhesion and in which hysteresis with respect to water sorption is well documented. In combination these characteristics present significant challenges for predicting acoustic behaviour over time. This study considers the effect of hair on the propagation of ultrasound under different methods of hair sample preparation, by monitoring transmission loss over time. Five human hair samples from two different sources and of different thicknesses were placed in a deionized water tank (at room temperature) between a 500 kHz plane piston transducer and a 4 mm needle hydrophone. The hydrophone signal was acquired every 300 seconds for periods up to 22 hours. The voltage squared integral and peak voltage of the signals were compared to a reference signal acquired with no hair sample present. When each dry hair sample was placed in a tub of deionized water, briefly brushed to remove visible bubbles and then transferred to the tank with no other preparation, waveform distortion and significant transmission loss were initially observed, with the voltage squared integral requiring hours to approach an equilibrium, as shown in Fig. 1(a). Initial transmission loss varied widely from negligible loss to almost 100%, with the thicker samples causing more than 80% initial loss. The ultimate loss after stabilisation and the time to reach equilibrium also varied between samples, and at the stabilised level, the transmission loss showed moderate agreement with previous studies that reported power transmission loss of up to 20% (1). Waveform shape matched the reference signal at equilibrium, without distortion. Degassing the samples in a vacuum chamber for a short time (up to 8 min) significantly decreased time to achieve equilibrium, to minutes rather than hours, but this is not a practical solution. However, a similar result was obtained by pre-washing the hair samples for approximately 60 seconds in water at shower temperature (37-40 °C) before transferring to the room-temperature tank as shown in Fig. 1(b). The threshold temperature for this improvement was also investigated. Our findings demonstrate that hair preparation is important in minimising and stabilising the effect of hair on ultrasound propagation in TUS. Prewashing in warm water is a simple and practical approach that reduces the transmission loss of hair in a short time and produces predictable, temporally stable results. Further study is needed to determine the effect in practice.

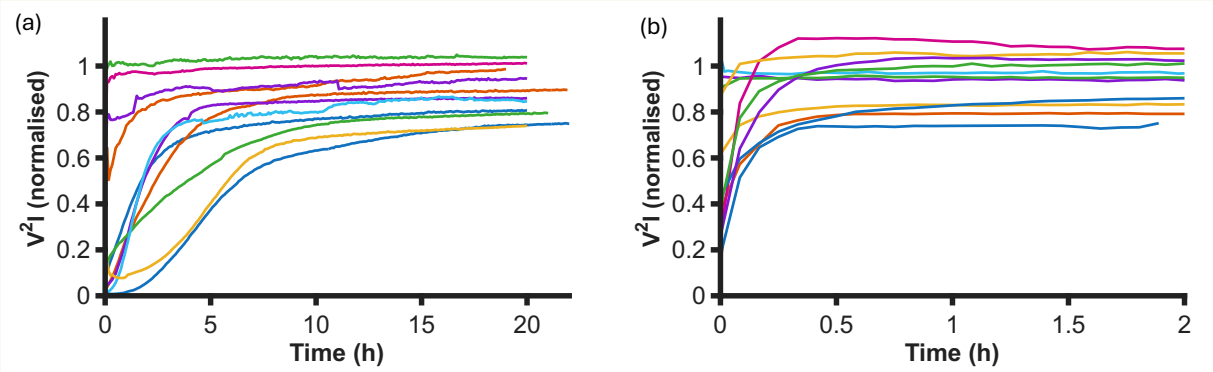

Figure 1: Voltage Squared Integral, normalised by the reference signal, for (a) samples with no preparation, and (b) samples pre-washed in warm water

References: (1) Raymond, S.B. and Hynynen, K. (2005) 'Acoustic transmission losses and field alterations due to human scalp hair', IEEE Trans. Ultrason., Ferroelectr, Freq Contr, 52(8), pp. 1415–1419.

Rapid transducer localization using semi-active MR tracking coils for accurate neuromodulation

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Introduction: A small focal size in transcranial focused ultrasound neuromodulation is useful for engaging specific brain regions while limiting effects in off-target regions. A key challenge with a small focus is ensuring accurate targeting. Previous work has shown that active tracking coils can be used to localize the transducer and acoustic focus, but these require connections to the scanner transmit/receive hardware. Image-space markers have also been used, but these typically require volumetric imaging, which can be time consuming. Here, we present a method using wireless LC-tuned semi-active tracking coils to localize the transducer and register the transducer coordinate system to MR space. This enables rapid prediction of the beam location for subsequent sonications.

Methods: We used custom-built semi-active tracking coils consisting of an inductor-capacitor circuit tuned to the scanner resonance frequency and coupled to a sample of $MnCl_2$-doped water. An image-based sequence was used to localize the coil positions along each scanner dimension. Five coils were placed on a custom 128-element FUS array with a radius of curvature of 150 mm, diameter of 255 mm, and center frequency of 650 kHz. Experiments were performed in a gelatin-milk phantom with a 3D-printed replica skull. MR-ARFI was used to measure the acoustic focus location using a motion-encoding gradient duration of 7 ms, motion-encoding gradient strength of 31 mT/m, trigger delay of 1 ms, and FUS duration of 8 ms. Two sets of experiments were performed. First, a self- calibration was performed to determine the tracking coil locations in FUS space by sonicating seven known steering locations and registering the measured ARFI focus locations to these coordinates. This produced an MR-to-FUS transform, from which the tracking coil locations could be transformed into FUS space. Second, focus prediction accuracy was tested by estimating where the geometric and electronically steered foci would appear in MR space. The transducer was repositioned and tracking coil localization and MR-ARFI measurements were acquired for four FUS coordinates. The tracking coil locations were then used to generate a FUS-to-MR transform and predict the focus location.

Results: The semi-active coils were reliably detected using the localization sequence and did not visibly interfere with other imaging. The detection sequence ran in under 2 seconds, enabling rapid localization of the transducer. Registration between the known steering coordinates and measured ARFI locations produced a fiducial registration error of 0.78 mm, indicating good steering and localization accuracy. Across validation measurements, the predicted focus location differed from the measured focus location by 0.97 ± 0.56 mm.

Conclusions: We present a method for rapid localization of a FUS transducer coordinate system in MR space using wireless LC-tuned semi-active tracking coils with millimeter scale accuracy. The method does not require additional transmit/receive hardware, allowing compatibility with standard MR coil setups. Gradient nonlinearity-related distortions were observed, and future work will focus on correcting these errors to further improve the accuracy and robustness of the system.

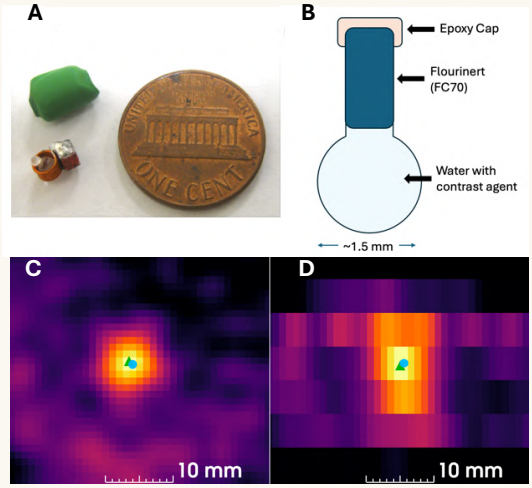

Figure 1: A: A picture showing two tracking coils, one wrapped in heat shrink, next to a penny for scale. B: The sample which is placed inside of the tracking coils. C and D: Axial and coronal views of the MR-ARFI displacement map in the phantom. The predicted focus is marked with a blue circle, and the measured focus is marked with a green triangle. The focus was electronically steering 10 mm in this image and the error between the points was 0.84 mm.

Short-readout 7T PETRA improves skull structure details

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Background: Translation of Pointwise Encoding Time Reduction with Radial Acquisition (PETRA) acquisitions from 3-Tesla (3T) to 7-Tesla (7T) Magnetic Resonance Imaging (MRI) remains challenging, because ultra-high-field imaging increases susceptibility effects and accelerates T2* decay in bone. Skull visualization is limited in conventional MRI sequences because bone has extremely short T2* relaxation, causing substantial signal decay prior to echo formation. The 3T PETRA addresses this limitation through ultra-short echo-time (TE) center-out radial acquisition with single-point imaging (SPI) recovery of central k-space data missing during radiofrequency (RF) dead time. However, outer k-space samples with high frequency information are acquired later during radial traversal. At 7T, accelerated T2* decay causes greater attenuation of these later-acquired signals, which suppresses high-spatial-frequency information responsible for skull edge and fine details. Therefore, 7T vendor-supplied PETRA exhibits increased edge blurring and reduced skull structure details, leading to inaccurate pseudo-CT skull depiction.

Methods: A modified short-readout PETRA acquisition was implemented in Pulseq on a 7T Siemens scanner to reduce the T2*-dependent signal decay during radial k-space traversal. By increasing the RF and readout bandwidth and shortening the excitation RF pulse, the temporal interval between central and outer k-space sampling locations is reduced, thus mitigating the attenuation of high-spatial-frequency data acquired later. 3T PETRA was acquired on a Siemens Prisma scanner using vendor-supplied sequence with TE = 70 µs, TR = 3.61 ms, flip angle = 1°, and 0.75 mm isotropic resolution. Both vendorsupplied and modified 7T PETRA were acquired using a 3D radial trajectory with TE = 70 µs and 0.8 mm isotropic resolution. For all 7T PETRA acquisitions, corrections were applied for B0 field inhomogeneities as well as B1 transmit and receive field inhomogeneities. Pseudocomputed tomography (pseudo-CT) generated from 3T PETRA, vendor-supplied 7T PETRA, and modified 7T PETRA were compared for skull boundary information and calibrated Hounsfield unit (HU) distribution characteristics.

Results: We used 3T PETRA as the reference standard for comparison. Our modified 7T PETRA demonstrated a higher skull boundary gradient magnitude than both 3T PETRA and vendorsupplied 7T PETRA. Skull signal intensity in the modified 7T PETRA was more closely aligned with 3T PETRA than with vendor-supplied 7T PETRA. Pseudo-CT images generated from the three PETRA acquisitions demonstrated distinct calibrated HU distributions. Across multiple distribution metrics, including mean HU, skewness, kurtosis, probability density distributions, and empirical cumulative distribution functions (ECDFs), the modified 7T PETRA pseudo-CT more closely resembled the 3T-derived pseudo-CT than the vendor-supplied 7T PETRA pseudo-CT.

Conclusion: These findings suggest that shorter radial readout duration improves skull detail and pseudoCT bone depiction at 7T.

From Pascal to Blackwell: Benchmarking Multi-GPU k-Wave with a Global FFT Solver

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The k-Wave toolbox is widely used for accurate time-domain ultrasound simulations, including focused ultrasound applications in which acoustic waves propagate through heterogeneous bone and soft tissue. Realistic three-dimensional transcranial simulations often require both large computational domains and short turnaround times, particularly when multiple source positions or simulation settings must be evaluated. These demands can exceed the memory capacity and performance limits of a single GPU, motivating multi-GPU implementations that preserve the accuracy of the original pseudospectral formulation.

We present a benchmark study of a multi-GPU k-Wave solver based on the Global FFT formulation. The solver retains the full-domain pseudospectral update used in the original single-GPU implementation, while distributing the computational domain across multiple GPUs. Consequently, each time step involves distributed three-dimensional FFTs and repeated global data redistribution s. This preserves the numerical character of the original method, but makes performance strongly dependent on memory bandwidth, available GPU memory, peer-to-peer communication speed, and interconnect topology. The benchmark covers NVIDIA systems from Pascal and Turing PCIe platforms to Ampere NVLink/NVSwitch servers and recent Blackwell PCIe 5.0 hardware. For every system, all feasible GPU counts are tested, from one device to the full node population. Simulations use FFT-friendly cubic domains from 32^3 to the largest size fitting into available GPU memory, and runtime is reported as the average time per simulation step over 400 time steps. FFT-friendly sizes are used because similarly sized FFT-unfriendly domains can be substantially slower and would make hardware comparisons less reliable.

Figure 1 summarizes four-GPU runtime over increasing domain size. The fastest full-node performance is obtained on A100 systems with high-bandwidth interconnects, while the Blackwell RTX PRO 5000 platform is the strongest PCIe-only alternative. Older PCIe-only systems still benefit from multiple GPUs for large domains, but their scaling is increasingly constrained by repeated global redistribution s. The results show that measured P2P bandwidth explains much of the multi-GPU behaviour, although memory bandwidth, GPU generation, topology, memory capacity, and FFT efficiency also contribute. The strong-scaling results in Fig. 2 highlight the main practical message for focused ultrasound workloads: multi-GPU execution is most useful for sufficiently large domains. Small simulations are dominated by communication, synchronization, and launch overheads, so adding GPUs may provide little or no benefit. Larger domains amortize the cost of distributed FFTs and redistribution s over more computation, leading to better scaling and shorter runtimes.

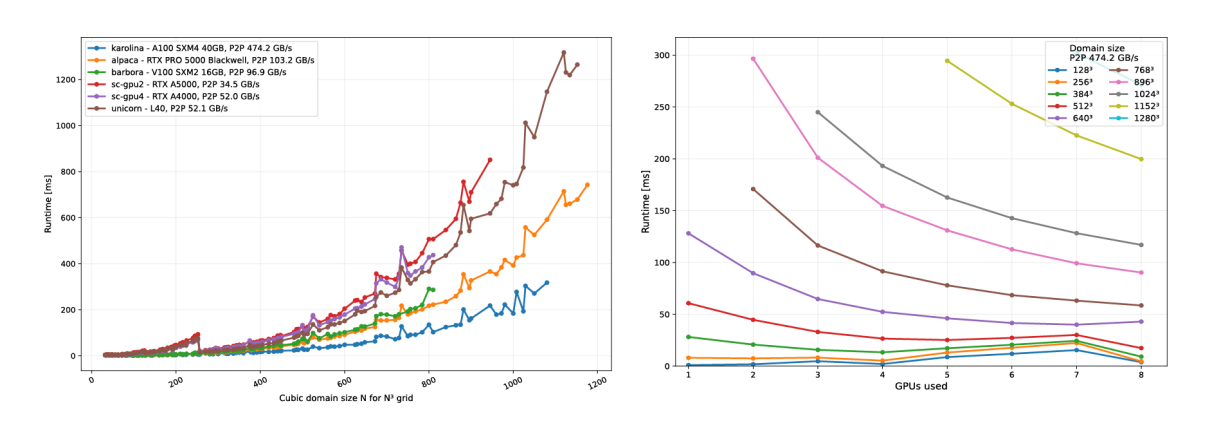

Figure 1: Left: Four-GPU runtime across FFT-friendly cubic domains. Right: Strong scaling on the Karolina A100 SXM/NVSwitch node.

Acoustic Radiation Force and Displacement Simulations for Ultrasound Neuromodulation

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Introduction: Simulation of the field distribution for treatment and study planning in transcranial focused ultrasound is often limited to the harmonic pressure. While this is an important quantity, this does not give the full picture. Other quantities, such as the acoustic radiation force (ARF) and tissue displacement, have been linked to neuromodulation. Various formulations of the ARF have been proposed. However, it is not yet known how these formulations compare in terms of numerical convergence for transcranial ultrasound neuromodulation treatment planning. This study starts with investigating the influence of grid parameters on the numerical accuracy of the resulting ARF and displacement. Subsequently, the intersubject variability of pressure, ARF, and displacement in 50 subjects is investigated.

Methods: The influence of parameters such as grid points per wavelength (ppw), Courant-Friedrichs-Lewy (CFL) number, and perfectly matched layer (PML) properties on the numerical accuracy of the resulting pressure, ARF and displacement are investigated for three different formulations of the ARF: attenuation force (AF), momentum flux density tensor (MFDT), and Reynold's stress (RS). Using this information, an intersubject variability study was performed to investigate the variability in pressure, ARF, and displacement in ultrasonic neuromodulation. For this study, the CT scans from the cq500 database are used. A transducer with an aperture of 29 mm and a radius of curvature of 38 mm is used. Simulations are performed in k-Wave. Spearman correlation is tested for all combinations of metrics describing the field distributions and the skull. Lastly, the distributions of the field metrics are examined.

Results and discussion: A CFL <= 0.05 is required for numerical stability in a heterogeneous medium for the pressure field and displacement simulation. For a homogeneous skull model, a PML of at least 2 mm and a grid resolution of 17 ppw is needed to get accurate results across all ARF formulations (relative error <= 5% than case of 25 ppw). However, for CT-based heterogeneous skull models, numerical convergence of the MFDT formulation was not observed for all tested grids (there is still a difference of 660% compared with the AF at 20 ppw). The MFDT formulation, although mathematically the most complete form, is prone to oscillations due to the Gibbs phenomenon. To study intersubject variability, a pressure of 1 MPa is used at the transducer surface. This resulted in a mean maximal pressure of 0.6 MPa (+- 0.19 MPa), a mean maximal ARF of 106 N/m^3 (+-67 N/m^3), and a mean maximal displacement of 180 nm (+- 19.3 nm) across all subjects. The focal distance of the pressure distribution and the location of maximal ARF are largely the same: 25.3 mm (+- 6.6 mm) for the pressure, 25.5 mm (+- 6.4 mm) for the ARF . The location of peak displacement is larger (31.2 mm +- 8.9 mm). Conclusion Based on our results, we recommend the AF formulation over the MFDT formulation for ARF simulations that include a realistic heterogeneous skull model. The AF is a good approximation of the mathematically more complete MFDT in the low attenuation limit, and is robust to oscillations present in the pressure field. In general, the location of peak displacement does not coincide with the pressure field focal spot. Furthermore, from the field distributions, it can be concluded that large intersubject variation exists with no clear one-on-one trends between field and skull metrics.

An interactive planning tool for in vivo mouse transcranial focused ultrasound experiments

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Transcranial focused ultrasound (tFUS) has emerged as a promising non-invasive technique for precision neuromodulation, and in vivo rodent experiments remain fundamental to understanding its effects. Planning these experiments conventionally involves transducer calibration, beam profile characterisation, manual placement of sonication points across the target, and verification with acoustic simulation to confirm correct targeting and exposure levels. This process is tedious, requires prior expertise in computational wave propagation, and is not standardised across research groups, particularly in how the transducer is positioned to cover the whole brain or specific regions of interest. As a result, planning methods vary substantially between studies, which limits reproducibility and creates a barrier for groups new to the technique.

We set out to build an accessible tool that allows researchers to plan in vivo mouse tFUS experiments. Our aim is to bring both planning and exposure estimation into a single workflow, by first computing optimal transducer positions for a chosen target and outputting hardware-ready coordinates, and second by estimating the exposure metrics increasingly expected in reporting standards.

We developed a code-free, Python-based interface that, given a chosen brain target, determines the transducer positions needed to cover it efficiently. The optimisation algorithm represents each sonication as a hexagonal mask in the transverse plane and considers the full 3D extent of the target when selecting positions, ensuring coverage of deep or asymmetric regions that would be missed by optimising on a single slice alone. Users can adjust inclusion parameters such as the minimum percentage of volume covered. The user then specifies a stereotaxic reference landmark, and the app outputs a PDF planning summary together with a CSV of coordinates that integrates directly with positioning hardware. To estimate exposure metrics (e.g. peak temperature rise, ISPTA, ISPPA), we are integrating an established k-Wave-based acoustic simulation solver into the same interface.

We demonstrate the planner on an open-source mouse dataset registered to the Allen Reference Atlas, generating targeting plans for both region-specific sonication and whole-brain coverage, where the optimal arrangement takes the form of a honeycomb grid.

This tool is intended as a step toward standardised and reproducible pre-clinical tFUS protocols that are accessible to labs without specialist simulation or programming expertise.

Investigating Effects of Shear Waves on Shallow Focusing of Transcranial Focused Ultrasound using the Spectral-Element Method

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Among all the advancements in transcranial focused ultrasound, shallow focusing remains a significant technical challenge as our knowledge of how ultrasound passes through the curved, multilayered, and porous structure of the human skull is still incomplete. Targeting cortical regions offers multiple opportunities to treat and understand the human brain. However, this approach presents challenges because shear waves in shallow regions influence and distort the focal spot. Oblique incidence causes shear wave mode conversion, while high acoustic impedance and the diplo¨e's highly attenuative properties introduce significant wavefront aberration to the transmitted ultrasound. Accurate numerical modelling of transcranial ultrasound propagation is essential for optimizing therapeutic and neuromodulatory transcranial focused ultrasound. This study uses the spectral-element method (SEM) to develop a computational framework for characterizing shallow-field transcranial wave propagation. The simulation replicates an ex-vivo experimental configuration using a bowl transducer source (20 mm radius of curvature) oriented at a 40° oblique angle with respect to skull to facilitate the observation of shear wave mode conversion in the wavefield. The SEM solves the coupled acoustic-viscoelastic wave equation in 3D by using conforming hexahedral meshes to discretize geometrically complex domains, such as the human skull. This approach mitigates staircasing effects, and also allows for wave simulations in environments with coupled acousticviscoelastic properties. Since the numerical solution of the acoustic wave equation requires significantly fewer computational resources than its viscoelastic counterpart, the SEM framework restricts the viscoelastic solver strictly to the elements discretizing the skull. Because the bone occupies a relatively small volume of the total domain, this targeted approach fully accounts for shear wave effects without a substantial increase in the total computational cost. We use the simulated wavefield to investigate the influence of shear waves on shallow focusing to refine models of transcranial ultrasound propagation, ultimately enhancing the safety and effectiveness of ultrasound therapy in cortical brain regions. We investigate methods of stimulating parts of the brain that might be otherwise hard or yet unexplored to target for neuromodulation.

Keywords: transcranial focused ultrasound, spectral-element method, viscoacoustic-viscoelastic medium, shear waves 1