Imaging deep target engagement of transcranial ultrasonic stimulation

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON53361

Source
ToetsingOnline

Brief title
Deep brain transcranial ultrasonic stimulation

Condition

- Other condition

Synonym
normal brain function

Health condition

fundamental neuroscience in healthy adults

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universiteit Nijmegen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Amygdala, Thalamus, Transcranial ultrasonic stimulation

Outcome measures

Primary outcome

Intrinsic functional connectivity profiles and task sensitivity of the target

regions (amygdala, mediodorsal thalamus, pulvinar thalamus) are the primary

dependent measures that will be used to assess TUS target engagement.

Secondary outcome

We will test the activation of the mediodorsal thalamus and pulvinar thalamus

when a flexible processing task engages these regions.

Study description

Background summary

To understand mind and brain, and to intervene in their disorders, we need techniques to safely interact with specific brain circuits. A critical step in the development of non-invasive neuromodulation is the ability to verify target engagement. Such verification remains particularly challenging for deeper brain structures, despite their fundamental contributions to brain function and cognition. Here, we propose to leverage the high spatial resolution and whole-brain coverage of functional magnetic resonance imaging (fMRI). We will image circuit-specific neuromodulation following Transcranial Ultrasonic Stimulation (TUS) to three deep brain targets: (a) the amygdala, and two regions of the thalamus: the (b) mediodorsal nucleus and (c) the pulvinar nucleus. By probing the spatial, temporal, and state specificity of TUS effects using neuroimaging, the current study aims to validate TUS as a rigorous tool for non-invasive deep brain modulation. The study aims to bridge the gap between correlational neuroimaging and causal neuromodulation, and to pave the

way for targeted interventions.

Study objective

Our primary objective is to elucidate the neurophysiologic effects of short-term TUS on deep brain circuits in humans. We will map the effects of TUS targeting the amygdala vs. two subregions of the thalamus (mediodorsal & pulvinar nucleus) on spontaneous coupling profiles using resting-state fMRI. Our secondary objectives are to (1) assess the duration of TUS effects and to (2) examine the functional relevance of TUS target engagement during task recruitment of the target region.

Study design

The study will be a four-visit, single-blind, randomized, crossover trial. During the first session, structural and baseline fMRI scans will be obtained. The second, third, and fourth sessions are ultrasound intervention sessions. We will use a factorial design with stimulation (amygdala TUS, mediodorsal thalamus-TUS, pulvinar thalamus-TUS) as a within-subject factor.

Intervention

Participants receive TUS targeting the amygdala/mediodorsal thalamus/pulvinar thalamus.

Study burden and risks

Participants will receive no direct benefit from participating, though they often report enjoying their participation and the opportunity to experience MRI and TUS. Participants will receive a standard financial compensation where applicable (¤15/hour; ¤165 in total for all four sessions). Before participation, all subjects will be screened for contraindications with respect to non-invasive brain stimulation and MRI. The estimated risk for participating in MRI measurements and TUS-based interventions is minimal. The noise and the relative confined space of the MRI scanner may cause discomfort to some subjects. TUS for human neuromodulation has never resulted in serious adverse events (Blackmore, Shrivastava, Sallet, Butler, & Cleveland, 2019; Pasquinelli, Hanson, Siebner, Lee, & Thielscher, 2019; Sarica et al., 2022). Similar to applications of well-established biomedical ultrasound (ter Haar, 2010), safety of study participants is ensured by adherence to internationally recognized practices and guidelines (e.g., from the U.S. Food and Drug Administration (2017)). In all cases we will adhere to the recommendations of the International expert group on Transcranial Ultrasonic Stimulation Safety and Standards (ITRUSST, https://itrusst.com). Minor side effects of participating in a TUS experiment may include light transient headache and fatigue (Legon et al., 2020). To conclude, the risk and burden associated with participation is

considered minimal, and we do not expect any (serious) adverse events during the project.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Between 18-40 years of age;
- The ability and agreement to provide informed consent in sound body and mind, and the ability to fulfil the study*s requirements.

Exclusion criteria

• Under 18 years of age;

• Current pregnancy;
• Claustrophobia;
• A history or brain surgery or serious head trauma;
• A history of or any close relatives (parents, siblings, children) with epilepsy, convulsion, or seizure;
• Predisposition for fainting spells (syncope);
• A cardiac pacemaker or intra-cardiac lines;
• An implanted neurostimulator;
• Implanted medication infusion device;
• Implanted metal devices or large ferromagnetic fragments in the head or upper body (excluding dental wire), or jewellery/piercing that cannot be removed;
• Use of a medical plaster that cannot or may not be taken off (e.g., nicotine plaster);
• Cochlear implants;
• Metal in the brain, skull, or elsewhere in your body (fragments, clips, etc.);
• Diagnosed neurological or psychiatric disorders;
• Use of psychoactive (prescription) medication (excluding anti-conception);
• Skin disease at intended stimulation sites;
• The consumption of more than four alcoholic units within 24 hours before participation
• The consumption of recreational drugs within 48 hours before participation;
• Calcifications in the brain.
• All other criteria relevant to non-invasive brain stimulation as reported in the Donders Standard Operating Procedures for Non-Invasive Brain Stimulation.

Study design

Design

Study type: Interventional

Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-05-2023
Enrollment:	45
Type:	Actual

Medical products/devices used

Generic name:	NeuroFUS Pro - low intensity transcranial ultrasonic stimulation
Registration:	No

Ethics review

Approved WMO Date:	30-03-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-06-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-05-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL83639.091.23