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Modulating reward function in the human brain using focused ultrasound

Submission date 29/07/2026	**Recruitment status** Recruiting	[_] Prospectively registered [X] Protocol
Registration date 09/09/2026	**Overall study status** Ongoing	[X] Statistical analysis plan [_] Results
Last Edited 09/09/2026	**Condition category** Other	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
The brain's reward system is important for motivation, pleasure and learning from rewards. This system is often affected in conditions such as depression, where people may experience reduced pleasure and motivation.
The nucleus accumbens is a small brain region that plays an important role in reward processing. However, it has been difficult to study this region directly in healthy people because it is located deep inside the brain.
This study will use transcranial ultrasound stimulation, or TUS, to temporarily influence activity in the nucleus accumbens. TUS is a non-invasive method that uses focused ultrasound waves to reach specific areas deep in the brain.
The aim is to investigate whether stimulation of the nucleus accumbens changes how healthy people respond to and learn from rewards. The study may improve our understanding of the brain's reward system and could contribute to the development of future treatments for conditions such as depression.

Who can participate?
Healthy adults aged 18 to 60 years who understand Swedish and are able to provide written informed consent may participate.
People cannot participate if they have a current or previous serious psychiatric or neurological disorder, a history of alcohol or drug dependence, current psychiatric medication, pregnancy, or a contraindication to magnetic resonance imaging or TUS. This may include certain metal implants, metal fragments in the body, or severe claustrophobia.

What does the study involve?
Participants will attend five study visits.
At the first visit, participants will receive information about the study, provide informed consent, complete questionnaires and take part in a clinical interview.
At the second visit, participants will undergo a magnetic resonance imaging scan. The brain images will be used to plan the ultrasound stimulation individually and to study brain structure and connectivity.
Participants will then attend three stimulation sessions, approximately one week apart. During these sessions, they will receive the following conditions in a randomized order:

1. TUS directed at the nucleus accumbens
2. TUS directed at the lateral ventricles, which are fluid-filled spaces used as an active control condition
3. Sham TUS, where the transducer is placed on the head but no ultrasound is delivered
The participant will not know which condition is being given during a session.
Before and after stimulation, brain activity will be measured using electroencephalography (EEG) during rest. Participants will also complete two computer tasks that measure reward learning and responses to monetary feedback. Eye movements and pupil responses will be recorded during the tasks. Each stimulation session will take approximately 1.5 to 2 hours.

What are the possible benefits and risks of participating?
There are no direct medical benefits for participants. The study may improve scientific knowledge about the brain's reward system and may support the development of future treatments for conditions involving reduced motivation and pleasure.
TUS has generally been well tolerated in previous studies. Possible temporary side effects include headache, discomfort, pain, pressure sensations on the scalp or a temporary reduction in wellbeing. Participants must also sit relatively still for up to 2 hours, and gel will be applied to the hair.
MRI does not use ionising radiation, but the scanner is noisy and enclosed, and some people may find this uncomfortable. Participants will need to lie still during the scan. Unexpected findings on anatomical brain images will be reviewed by a neuroradiologist, and the participant will be informed if further medical assessment is recommended.

Where is the study run from?
The study is run from Uppsala University and Uppsala University Hospital, Uppsala, Sweden. The MR-scanning, TUS-stimulation and EEG sessions will all take place at Uppsala University Hospital.

When is the study starting and how long is it expected to run for?
February 2026 to February 2027

Who is funding the study?
Uppsala University Hospital (Sweden)

Who is the main contact?
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Contact information

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Study information

Scientific Title
Modulating reward function using focused ultrasound aimed at the nucleus accumbens in healthy adults: a neurophysiological and behavioural randomized crossover comparison over three conditions.

Study objectives
In this project we will use low-intensity transcranial ultrasound sonication (TUS) to investigate subcortical functions in the reward circuit. The aim is to investigate the role of the nucleus

accumbens (NAcc) in reward functions by brief modulation of the NAcc with TUS in healthy participants, using active LV sonication and inactive sham sonication as controls. We aim to do so by considering both behavioural and neurophysiological outcome measures, as well as investigating several potential predictors of NAcc functioning. In the long term we believe that using this technique to further our understanding of the healthy brain's reward system might pave the way for novel treatment methods for treatment-resistant depression (TRD) and other psychiatric disorders.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 05/11/2025, Ethics Review Authority (Etikprövningsmyndigheten, Uppsala, Box 2110, 75002, Sweden; +46 (0)10-475 08 00; registrator@etikprovning.se), ref: 2025-06859-01

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Blinded (masking used)

Control
Active

Assignment
Crossover

Purpose
Basic science

Study type(s)

Health condition(s) or problem(s) studied
Nucleus accumbens (NAcc) function in the healthy human brain's reward system

Interventions
This study utilizes a randomized experimental repeated-measures design. Participants are randomized in an approximately 1:1:1 ratio to one of three predefined Latin-square intervention sequences (A–B–C, B–C–A, or C–A–B). A computer-generated allocation list containing 29 assignments was created in advance and uploaded to the REDCap randomisation module. The list contains 10 assignments to A–B–C, 10 to B–C–A, and 9 to C–A–B, arranged in random order. No stratification is used. All participants receive all three interventions, and randomisation determines the order in which they are administered.

Participants will receive bilateral, sequential TUS-NAcc, TUS-LV (active control) or TUS-sham (inactive control) in a randomized counterbalanced order 1 week apart. TUS-sham is operationalized as placing the transducer on the participant's scalp without turning it on, mimicking the active conditions. It is primarily used for validation of the other control condition,

TUS-LV, as the lateral ventricles as a sonication target is a novel and relatively untested control stimulation site. All three conditions are treated equally in the subsequent data analysis. The procedures following the administration will remain identical between the three sessions, and the intervention will be single-blinded. To assess blinding, the participant is asked to rate which condition they believe they have received and how strongly they believe this.

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
TPO-203 coupled with a DPX-500-4CH transducer

Primary outcome(s)
1. Amplitude of the ERP component Reward Positivity (RewP) measured using a 32-channel EEG system in conjunction with a Doors task at post-sonication for every condition

2. Reward responsiveness (response bias) measured using a Probabilistic Reward Task (PRT) at post-sonication for every condition

Key secondary outcome(s)
1. EEG spectral analysis of theta power, individual alpha band frequency and aperiodic activity measured using a 32-channel EEG system during rest at pre and post interventions

2. Stimulus preceding negativity event-related potential (ERP) component measured using a 32-channel EEG system during anticipation phase of door task at post-sonication for every condition

3. Pupil dilation measured using the Tobii Pro Spectrum eye tracker during psychological paradigms at post-sonication for every condition

4. Experimental blinding, measured using guessing of the type of stimulation received as well as how strong this is belief is from 1 (guessing) to 10 (very sure), at post-sonication for every condition

5. Reward-dependent response repetition (win-stay behaviour) measured using a Probabilistic Reward Task (PRT) at post-sonication for every condition

Completion date
02/02/2027

Eligibility

Key inclusion criteria
1. Healthy individuals between 18 and 60 years of age
2. Signed informed consent sheet
3. Sufficient understanding of the Swedish language to be able to comprehend the information given about the project and take part in the interventions

Healthy volunteers allowed

Yes

Age group
Adult

Lower age limit
18 Years

Upper age limit
60 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Previous or current neurologic disorder or serious mental illness
2. Previous or current diagnosis of depression
3. Previous or current alcohol or drug addiction/dependency
4. Currently on psychopharmacological treatment for a psychiatric condition
5. Contraindications for MRI and TUS, including metal in the body, metal implants, metal fragments after working with metals or serious claustrophobia
6. Pregnancy - current or planned in the near future
7. Physically incapable of sitting still in a chair with neck support for up to 2 hours
8. Physically incapable of lying still on the back for up to 1 hour

Date of first enrolment
02/02/2026

Date of final enrolment
31/12/2026

Locations

Countries of recruitment
Sweden

Sponsor information

Organisation
Uppsala University Hospital

ROR
https://ror.org/01apvbh93

Organisation
Uppsala University

ROR
https://ror.org/048a87296

Funder(s)

Funder type

Funder Name
Akademiska Sjukhuset

Alternative Name(s)
Uppsala University Hospital

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
Sweden

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other files	Informed consent version 1	05/09/2025	10/08/2026	No	No
Participant information sheet			10/08/2026	No	Yes
Protocol file			10/08/2026	No	No
Statistical Analysis Plan			10/08/2026	No	No