# Modulation of deep cortical regions by means of low intensity transcranial focused ultrasound (tFUS) neuromodulation

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Measuring tFUS-dependent changes in behaviour (in our target tasks) when targeting deep brain regions [Behavioral Objective]

| | |
|---|---|
| **Ethical review** | Not approved |
| **Status** | Will not start |
| **Health condition type** | Other condition |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON49840

**Source**
ToetsingOnline

**Brief title**
Deep Ultrasound Neuromodulation (DUNe)

### Condition

- Other condition

**Synonym**
emotions, empathy

**Health condition**

The experiment is conducted on healthy participants. Using the proposed technique we aim at understanding the neural substrate of empathy

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Netherlands Institute for Neuroscience
**Source(s) of monetary or material Support:** NWO VIDI Grant

## Intervention

**Keyword:** affective empathy, cingulate, insula, neuromodulation

## Outcome measures

### Primary outcome

Primary outcome of the study will be participant performance in our task.

(Behavioural Outcome)

### Secondary outcome

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# Study description

### Background summary

The discovery of mirror neurons in the macaque premotor cortex (di Pellegrino et at., 1992), active while the monkey performs an action and vicariously while viewing similar actions performed by others, was a game changer. It suggested that we process what goes on in other people not only by abstract thoughts, but also by mapping their states onto our bodily states (Rizzolatti and Sinigaglia, 2010; Gallese and Sinigaglia, 2011). In humans, using fMRI, we showed that somatosensory cortices, normally active while we sense our bodies move or be touched, are also vicariously activated while witnessing others move (Gazzola et al., 2006; Gazzola and Keysers, 2009) or experience neutral (Keysers et al., 2004) or painful (Meffert et al., 2013) sensations on their skin. The anterior insula (AI), and the mid- to anterior cingulate cortex (abbreviated ACC), normally active while we experience emotions, are also vicariously activated while witnessing the emotions of others (Carr et al., 2003; Singer et al., 2004, 2006; Jackson et al., 2005; Lamm et al., 2007, 2011; Meffert et al., 2013; Morrison et al., 2013).

That people reporting more empathy show stronger vicarious activations in

primary somatosensory cortex (SI) (Gazzola et al., 2006) and AI (Singer and Lamm, 2009), led many to consider vicarious activations (VA) as the neural basis for empathy (Engen and Singer, 2013). Recently, this line of research has become the target of criticism: although no one now doubts humans have vicarious activations, the function of these activations (Hickok, 2013), and how they influence empathy is the topic of many speculations and few hard facts. All there is, is encouraging correlational evidence. We now must directly tackle the function of these systems, by going beyond correlation into causation. The biggest obstacle to this approach so far is that the key vicarious pain regions (AI and ACC), lie centimetres below the surface of the brain, beyond the reach of traditional non-invasive tools including transcranial Direct Current Stimulation (tDCS) or Transcranial Magnetic Stimulation (TMS). Transcranial focused ultrasound (tFUS) is a new and very promising non-surgical low-energy technique for modulation neural activity with high spatial resolution, adjustable focus and low tissue attenuation. tFUS has been used safely and effectively for neural stimulation in mouse, rabbit and monkey (Tufail et al., 2010; Yoo et al., 2011; Deffieux et al., 2013), and has recently been shown to also be a safe and effective method of transient cortical modulation in humans (Legon et al., 2014; Mueller et al., 2014; Sanguinetti et al., 2014; Lee et al., 2015).

We will therefore aim to selectively modulate activity within brain regions vicariously activated during observation of others* emotions. In order to achieve this goal, we will use transcranial focused ultrasound stimulation (tFUS).

The scientific benefit of US as neuromodulation tool is enormous: the scientific community will finally be able to test causality between deep brain activity and behaviour, opening a new era of knowledge. Transcranial focused ultrasound could additionally replace deep brain stimulation, offering a cheap and safe method for the treatment of brain disorders such as essential tremor or Parkinson's disease. There is currently no way to affect brain tissue deep to the cortex without surgery, genetic alteration or viral vectors (the latter two are not approved for human use). This technology is non-surgical and as invasive as any diagnostic ultrasound exam. With success, transcranial focused ultrasound could become useful world-wide as a cheap, portable and effective tool for human brain mapping efforts as well as for the diagnosis and potential treatment of a broad range of psychiatric and neurological disorders. The anticipated risk is minimal; the immediate benefit is zero, though the potential future benefits for the academic and medical community at large justify the low risk and limited immediate benefit.

**Study objective**

Measuring tFUS-dependent changes in behaviour (in our target tasks) when targeting deep brain regions [Behavioral Objective]

### Study design

A total of 40 healthy neurologically intact voluntary participants will be recruited.

During the recruitment phase participants will be informed of all the procedures they will undergo. Moreover, they will be screened for tFUS stimulation.

The experimental session will start by positioning, through neuronavigation, the tFUS transducer. The optimal location will be chosen in order to target either the anterior Insula or the cingulate cortex. The specific target will be selected based on a fMRI study performed before this project. In the preliminary fMRI study, participants will be shown a set of emotional facial expressions and their brain activity will be recorded, this will instruct us on the specific region to target with tFUS.

After positioning the transducer, participants will be asked to watch short video-clips depicting emotional facial expressions. After observation they will be asked to rate the emotional facial expressions.

The full set of video-clips will include: 25 painful, 25 disgusted and 25 happy facial expressions. Each clip used in the study has a duration of 2 seconds.

During observation, a short ultrasound burst (0.5 seconds) will be applied to the target region. In counterbalanced blocks we will also include sham trials, in which the transducer is turned upside down and NO ultrasound stimulation is applied. Sham trials will be included to control for possible unspecific placebo-like effects on brain activity (possibly caused by vibration on the skin produced by the transducer or the chirping noises at times present). Participants will thus undergo 75 active trials and 75 sham trials.

Using this design, we can investigate the effect of tFUS on participants* rating of the emotional facial expressions (behavioural objective). The session will also include an anatomical scan, which will facilitate post-processing.

### Study burden and risks

No burden is associated with our study. Risks are minimized by our screening procedure.

## Contacts

### Public

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

healthy participants, age 18-35

## Exclusion criteria

A potential subject who does not meet any of the following criteria will be excluded from participation in this study:

- Proficiency with the English language
- Potential participants will be asked to fill a standard questionnaire for neuromodulation studies (TMS/tDCS) to exclude any participant with contraindications to brain stimulation/neuromodulation.

* EXAMPLE OF SAFETY SCREENING
* Have you ever:

Had an adverse reaction to neuromodulation or ultrasound?
Had a seizure?
Had an EEG?
Had a stroke?
Had a head injury (include neurosurgery)?
* Do you have any metal in your head (outside of the mouth,) such as shrapnel, surgical clips, or fragments from welding or metalwork?
* Do you have any implanted devices such as cardiac pacemakers, medical pumps, or intracardiac lines, cochlear implants, implanted brain stimulators, implanted defibrillator?
* Do you suffer from frequent or severe headaches?
* Have you ever had any other brain-related condition?
* Have you ever had any illness that caused brain injury?
* Are you taking any medications? (e.g. Tricyclic anti-depressants, neuroleptic agents, and other drugs that lower the seizure threshold)
* If you are a woman of childbearing age, are you sexually active, and if so, are you using a reliable method of birth control?
* Does anyone in your family have epilepsy?
* Do you need further explanation of the technique and its associated risks?

# Study design

## Design

**Study type:** Observational invasive

| | |
|---|---|
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Other |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Will not start |
| Enrollment: | 40 |
| Type: | Anticipated |

## Medical products/devices used

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|---|---|
| Generic name: | H-104 4-element Annular Array (transducer) |
| Registration: | No |

# Ethics review

Not approved

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|---|---|
| Date: | 16-02-2021 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |

# 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 | NL74100.018.20 |