Mapping the brain circuit of pain modulation with transcranial ultrasound stimulation

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BACKGROUND AND INTRODUCTION

- In general, there is a need for improved pain treatments. Many of the pain network structures are found deep within the brain, inaccessible by TMS or tDCS. Therefore, TUS is very promising, as a non-invasive, deep neuromodulation approach to access pain associated brain structures [1].
- The dorsal anterior cingulate cortex (dACC) integrates sensory input from ascending pain pathways and modulates pain perception through descending pathways, influencing both the perception of pain intensity and the emotional response to pain. TUS to the dACC has been shown to modulate pain [2].

STUDY AIMS:

This study aims to investigate the effects of TUS of the dACC;

a) on functional connectivity between pain-related brain regions during a tonic cold pain stimulus using functional magnetic resonance imaging (fMRI), and
b) on conditioned pain modulation (CPM) and temporal summation of pain (TSP) paradigms.
c) Overall, it aims to further our understanding of the role of the dACC in pain modulation.

METHODS

Healthy participants attended 3 sessions; one to acquire T1-weighted, T2-weighted and PETRA images for acoustic simulations, followed by two main TUS-fMRI sessions with either TUS or sham (double-blind, randomised).

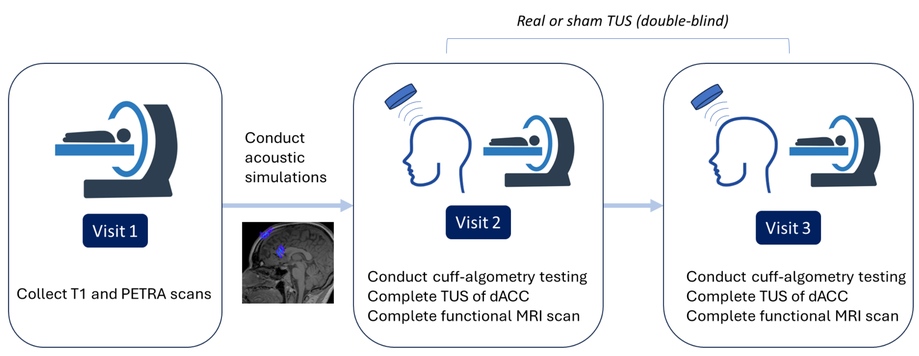


Fig 1. Study overview

At each main session, first pre-TUS CPM and TSP assessments are conducted using cuff-algometry, then TUS is applied to the dACC, followed by the MRI scan, and post-TUS CPM and TSP assessments. Tonic pain was induced using a modified cold pressor test with gelled water (temp range: 3.8+/-2.3oC).

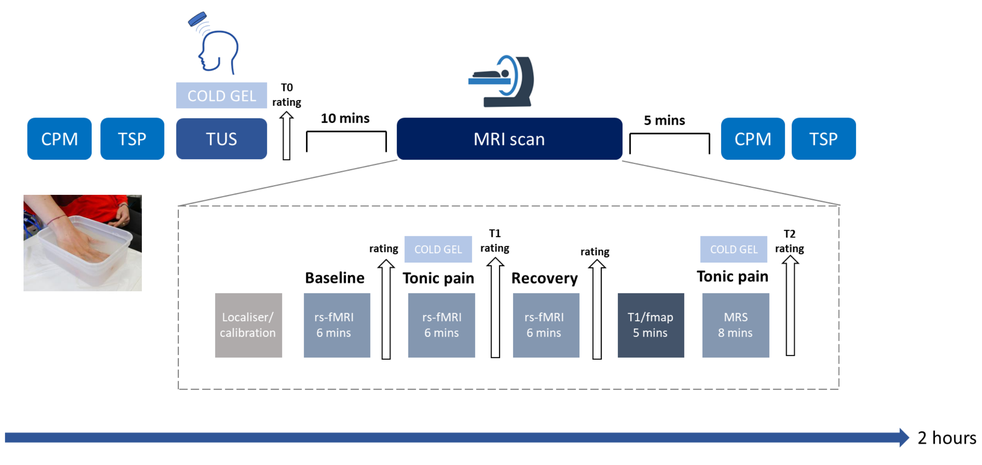
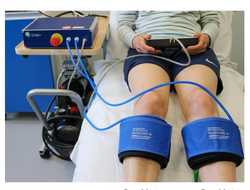


Fig 2. Experimental Design

CPM and TSP paradigms were conducted with cuff-algometry. For CPM, baseline pain detection threshold (PDT) and pain tolerance threshold (PTT) measured during pressure applied by inflating cuff 1. PDT and PTT re-measured during inflation of cuff 1, while cuff 2 delivers constant pressure stimulus to other leg. For TSP, ten pressure stimuli applied successively by rapidly inflating and deflating cuff 1, with participants asked to rate the pain intensity of each of the stimuli.



CPM and TSP paradigms assess different aspects of endogenous pain modulation [3]:

- **CPM → Descending inhibitory**
- **TSP → Ascending facilitatory**

Fig 3. CPM and TSP paradigms

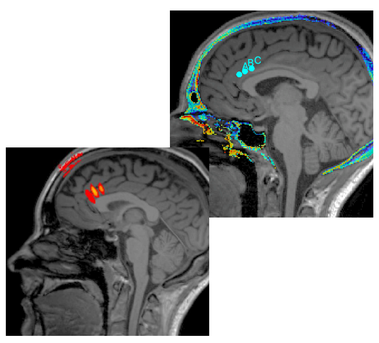


Fig 4. TUS targets

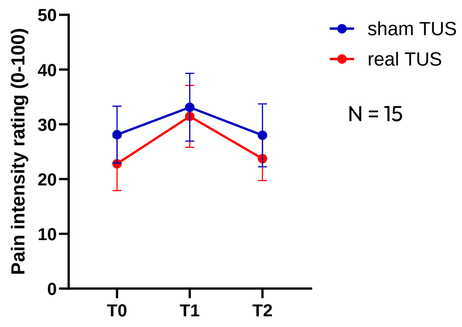
TUS was applied to three sites in the dACC consecutively with the following protocol; fundamental frequency (ff) = 500kHz, pulse repetition frequency (prf) = 10Hz, duty cycle (DC) = 10%, spatial peak pulse average intensity (ISPPA) in water = 54w/cm2, duration = 80s.

Sham condition consisted of matched auditory stimulus via bone conducting headphones worn by participants. Real or sham TUS sessions were double-blinded, with a separate researcher administering either real or sham stimulation hidden from participants and study researchers during each session

RESULTS

Interim analysis has been conducted (n = 15). Data collection and analysis is ongoing.

PAIN RATINGS



T0: During real or sham TUS to the dACC
T1: During resting state MRI block
T2: During MRS block

Fig 5. Pain ratings

- Pain ratings given after approximately 6 mins tonic cold stimulus at three timepoints
- General linear model (GLM), with condition (real/sham-TUS), timepoint (T0, T1, T2), gel temperature and subject as covariates, showed no significant main effect of condition, $F(1, 71) = 2.696$, $p=0.1050$, but did show significant effects of gel temperature and subject, $F(1, 71) = 7.563$, $p=0.0076$ and $F(14, 71) = 10.20$, $p<0.0001$, respectively.

SEED-BASED FUNCTIONAL CONNECTIVITY

- Seed-based functional connectivity analysis showed altered connectivity between the dACC (seed region) and pain related brain regions, increasing with the caudate nucleus, primary somatosensory cortex and temporal pole, and decreasing with the PAG and thalamus, following real-TUS compared to sham-TUS.

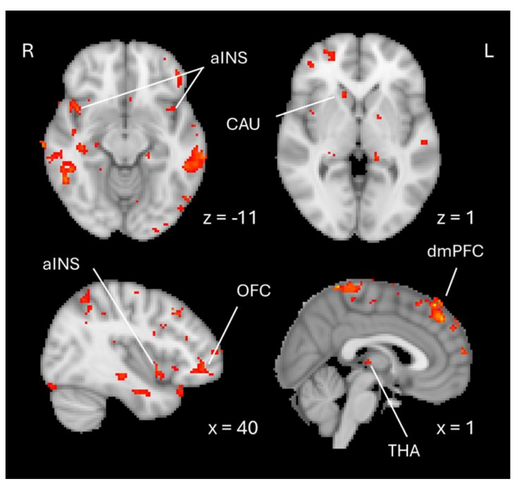


Fig 6. Whole-brain functional connectivity with dACC seed region

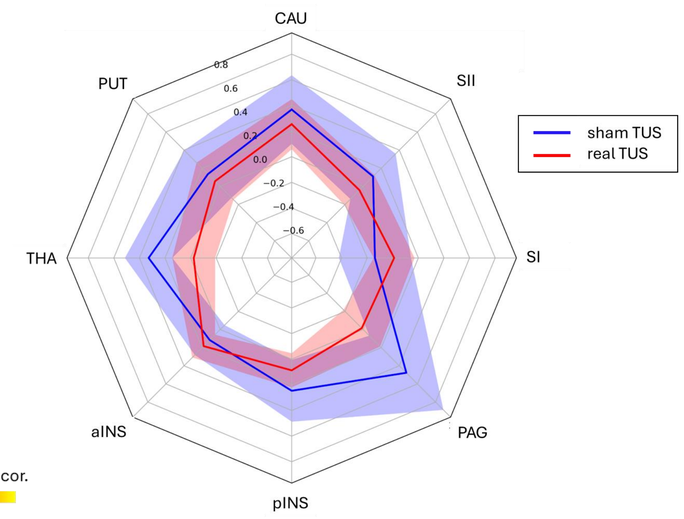


Fig 7. Functional connectivity with specific brain regions

CAU; caudate nucleus, aINS; anterior insular cortex, pINS; posterior insular cortex, PUT; putamen, OFC; orbito-frontal cortex, dmPFC; dorso-medial prefrontal cortex, THA; thalamus, PAG; periaqueductal grey, SI; primary somatosensory cortex, SII; secondary somatosensory cortex

MEASURES OF ENDOGENOUS PAIN MODULATION: CPM and TSP

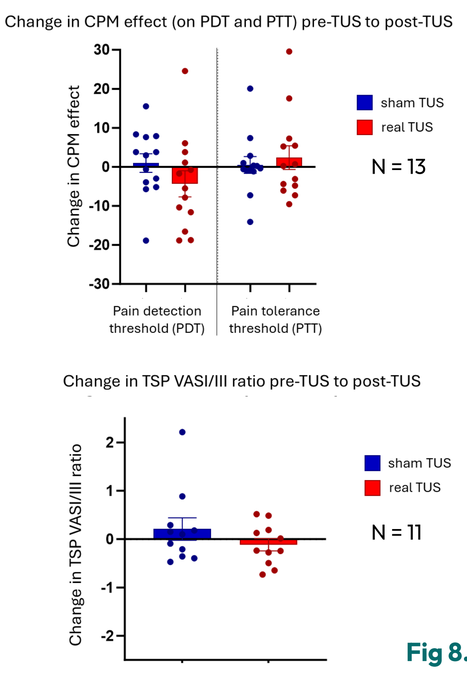


Fig 8. CPM and TSP changes following TUS

- Change in CPM effect (difference between baseline and CPM) between the pre-TUS (baseline) and post-TUS tests, compared between sham TUS and real TUS
- Closer to zero (no difference between pre-TUS and post-TUS) for the sham condition in both PDT and PTT
- For PDT there was a reduced CPM effect and for PTT there was an increased CPM effect for the real TUS condition

- TSP VASI/III ratio used as a measure of the TSP effect (increase in pain over repeated stimuli), defined as the ratio between the average of the ratings to the first 3 stimuli and the average of the ratings to the last 3 stimuli
- Change in VASI/III ratio between the pre-TUS (baseline) and post-TUS tests, compared between sham TUS and real TUS
- No difference between pre-TUS and post-TUS in either condition, two outliers removed

CONCLUSIONS AND NEXT STEPS

- Initial analysis of rs-fMRI data indicates that TUS may modulate functional connectivity between the dACC and brain regions involved in pain processing, including the anterior insular, thalamus and PAG
- CPM data indicates TUS of the dACC may alter descending inhibition since the CPM effect is different in the TUS compared to sham conditions

- **Next...**
- Complete data collection for this study and conduct further analyses on the full sample
- Explore magnetic resonance spectroscopy (MRS) data, which has not yet been analysed, to assess changes in GABA concentration in the dACC following TUS stimulation

REFERENCES

1. Badran and Peng. Neuropsychopharmacology (2024).
2. Strohman et al. The Journal of Neuroscience (2024).
3. Arendt-Nielsen and Yarnitsky. The Journal of Pain (2009).

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