Characterisation of the neural correlates of central sensitisation induced by the high frequency stimulation (HFS) model in healthy humans using functional magnetic resonance imaging (fMRI)

KEY POINTS

- AIM: To characterise how central sensitisation induced by HFS modulates brain activity as measured by fMRI
- MAIN FINDING: Compared to baseline, mechanical stimulation applied after HFS resulted in increased neural activity in cortical and sub-cortical pain processing areas and key brainstem nuclei such as the nucleus cuneiformis – an area shown to be implicated in both human and animal models of central sensitisation[1,2].

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INTRODUCTION

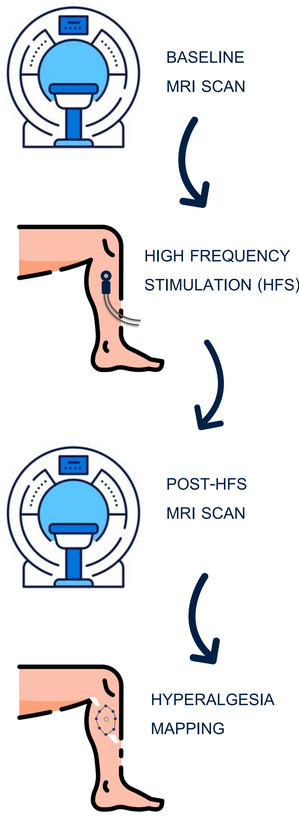
Central sensitisation (CS) is characterised by an increase in pain response to noxious stimuli (hyperalgesia). Experimental CS models can elicit hyperalgesia in healthy humans[3]. These experimental CS models have been shown in previous imaging studies to be associated with activity in the brainstem[2]. This study aimed to characterise how CS induced by HFS modulates brain activity as measured by fMRI. The HFS model to induce CS in humans has been shown to modulate electroencephalogram (EEG) recordings[3] and RIII reflex variables reflecting CS[5]. Data were collected during the screening visit of the IMI-PainCare-BioPain-RCT4 trial; a multicentre trial investigating biomarkers of analgesic efficacy. This preliminary dataset was collected from 18 subjects, at the Oxford site (REC Reference 20/SW/0017).

METHODS

After an initial baseline 3T MRI scan, HFS was applied to the left lower leg of 18 healthy subjects (mean age 26.4, range 22 to 38, 9 female). A second 3T MRI scan was conducted 20 minutes after HFS application.
HFS consisted of five 1s trains of 100 Hz electrical pulses separated by 9s intervals.

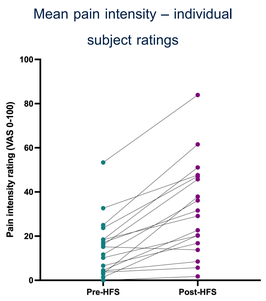
Scans measured blood oxygen level dependent (BOLD) signal changes to 18 punctate 512mN mechanical stimuli applied 1cm outside the HFS site (secondary hyperalgesia area). Participants rated pain intensity for each stimulus, and rated average pain unpleasantness following all 18 stimuli, both using a visual analogue scale from 0 (no pain at all/not unpleasant at all) to 100 (most intense pain imaginable/extremely unpleasant).

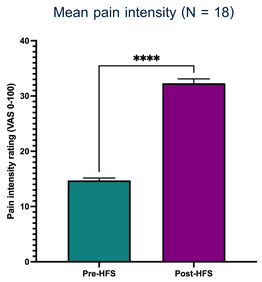
Analysis of pain ratings was completed with GraphPad PRISM. A whole brain, mixed effects analysis with cluster-based correction for multiple comparisons was performed using FSL software, to identify differences in stimulus evoked neural activity post-HFS vs. baseline.

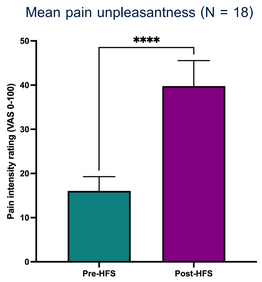


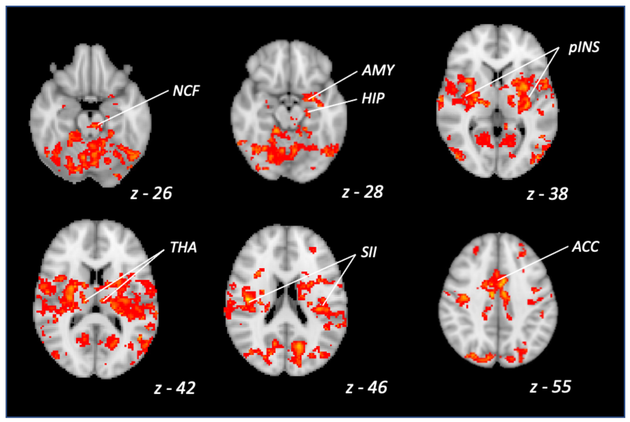
RESULTS

Following HFS, mean pain intensity increased from 14.73 to 32.31 ($p < 0.0001$, paired t-test) compared to baseline, and mean pain unpleasantness increased from 16.06 to 39.78 ($p < 0.0001$, paired t-test).

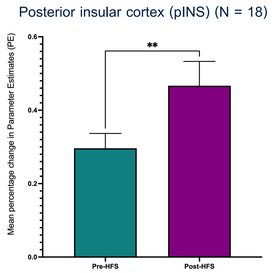


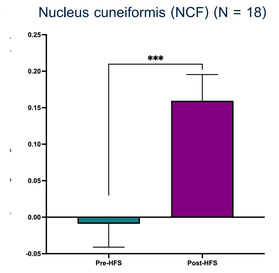






This was associated with significantly increased activation during the post-HFS scan vs. baseline (mixed effects analysis, $Z > 3.1$, $p < 0.05$) in areas involved in pain perception such as the posterior insula cortex (pINS), anterior cingulate cortex (ACC), amygdala (AMY), hippocampus (HIP), nucleus cuneiformis (NCF), thalamus (THA) and secondary somatosensory cortex (SII).





Subsequent region of interest (ROI) analysis showed that the mean BOLD response in the contralateral posterior insular cortex (pINS) and in the contralateral nucleus cuneiformis (NCF) was significantly increased following HFS compared to baseline ($p = 0.0019$ and $p = 0.0008$ respectively, paired t-test).
The increase in activation in the NCF region is a key result due to the previously shown specificity of NCF area activation for the state of CS rather than general pain perception[2].

CONCLUSIONS

Overall, we demonstrate that HFS induced CS results in modulation of brain activity that is consistent with other CS models that have been widely studied using fMRI, namely topical capsaicin. HFS offers a long and stable duration of CS. In conjunction with neuroimaging, it has good potential to be a valuable model for assessing analgesic target engagement in early analgesic drug development.

References: 1. Zambreanu et al. Pain. 2005. 2. Lee et al. 2008. 3. Quesada et al. European Journal of Pain. 2021. 3. van den Broeke et al. Clinical Neurophysiology. 2020. 4. Leone et al. Clinical Neurophysiology. 2021.

Links: www.imi.europa.eu; www.imi-paincare.eu