Probing the Craving Neurocircuitry in Cannabis Use Disorder Using Real-Time fMRI Neurofeedback

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AIMS

- The aims were to (a) characterise and modulate brain activity, specifically anterior cingulate cortex (ACC), during real-time upregulation of cannabis craving and (b) examine its effects on subjective craving, focus and anxiety in cannabis use disorder (CUD).

BACKGROUND

- CUD is a common addiction characterised by greater brain function during cue-induced craving fMRI tasks (1).
- A key region involved in cannabis craving is ACC (2).
- Real-time fMRI neurofeedback (NFB) is a novel technique that allows participants to receive immediate feedback from their brain function and consciously regulate it (3). Preliminary work suggests that NFB during drug-induced craving can identify the craving neurocircuitry at the individual level in addiction to various substances (e.g., alcohol) and subjective craving (4). Yet, no study has tested NFB to change craving-related brain function in CUD.

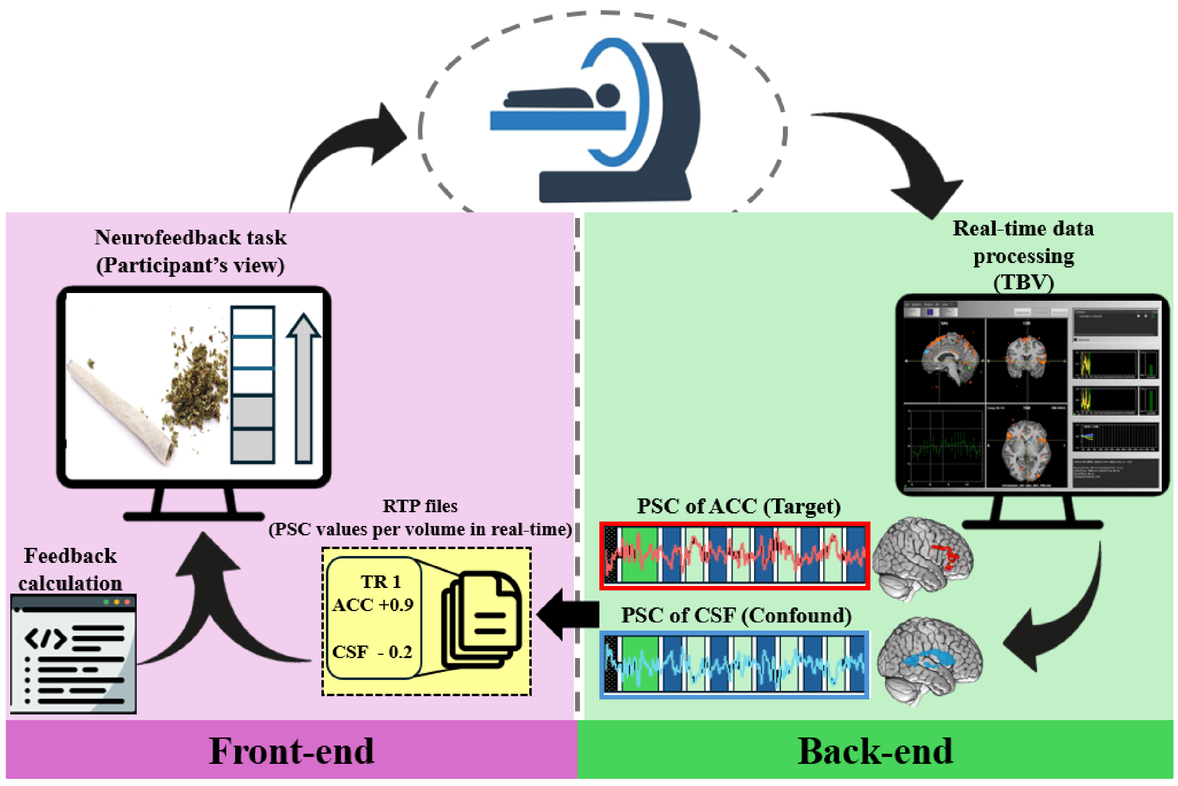

Figure 1: **The overview of the NFB system.**

METHODS

- Ten individuals with moderate-to-severe CUD were tested using a novel and validated NFB system and 7 Tesla scanner at the Melbourne Brain Centre Imaging Unit, with customised support from the radiographer team (5).
- Multi-band fMRI data (TE= 22ms, TR= 1000ms, Voxel size = 1.6 x 1.6 x 1.6mm) was acquired and streamed to the data analysis workstation for real-time analysis using Turbo-BrainVoyager software version 4.2 (i.e., back-end).
- The target voxels of interest (VOIs), which are the 33% most activated voxels located within the ACC; were personalised based on an fMRI cue-reactivity task (i.e., functional localiser) to map the craving neurocircuitry.
- A confound ROI (i.e., cerebrospinal fluid (CSF)), was used to measure and account for nuisance physiological effects.
- The NFB task script (i.e., front-end), was developed using Psychtoolbox 3.0.19 in MATLAB 2023a, which was running on a visual stimulation computer, linking to the scanner display.
- This front-end concurrently presented: (i) cannabis-related cues to induce craving, (ii) 1-to-10 visual analogue scale (VAS) to rate craving experienced in real-time before and after the functional localiser and NFB tasks, (iii) feedback calculation in real-time using GLM model with signal from the target & confound VOIs.
- Subsequently, these feedback values representing change in brain function, were converted to brain computer interface (Figure 2) and were presented to the participant as a thermometer and were updated every TR.

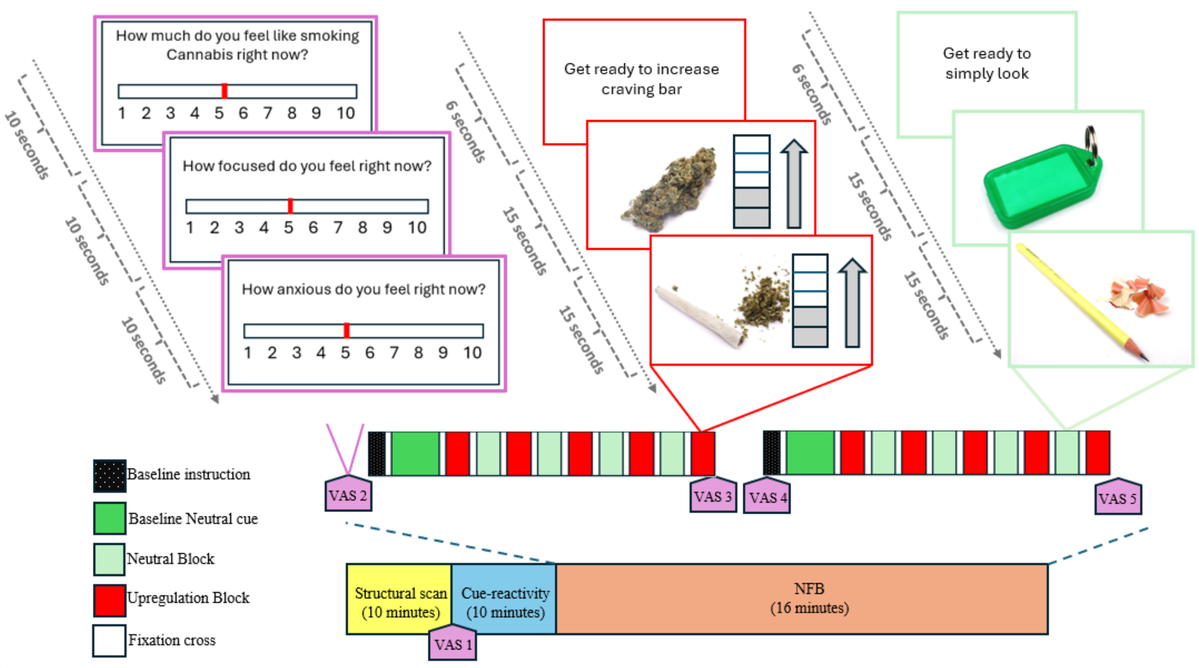

Figure 2: NFB task presentation. Participants were asked to focus on upregulating their craving-related brain activity during regulation blocks, while cannabis-related cues were presented alongside the feedback thermometer. After each NFB regulation block, a neutral block including neutral images matched in content with the cannabis images of the previous NFB regulation block was presented.

RESULTS

- The VOIs size varied across participants, with a mean of 830.5 voxels (SD = 716.7) (Figure 3).

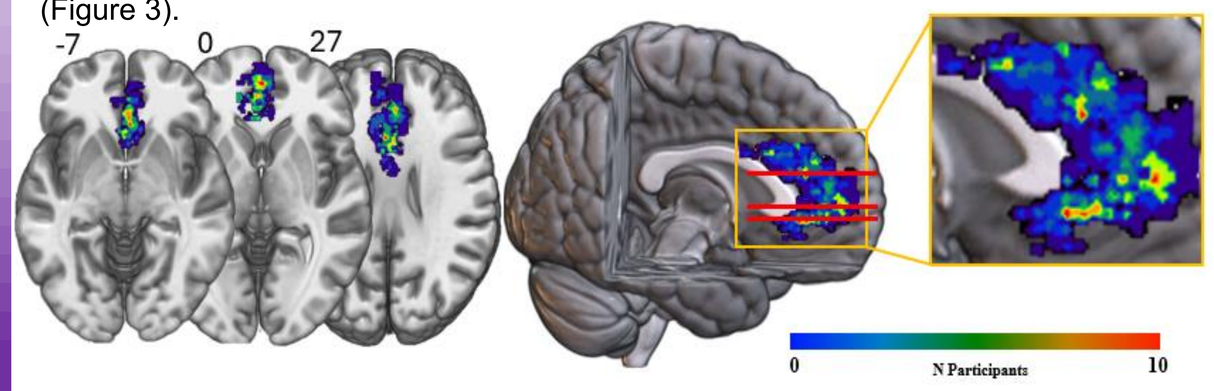

Figure 3: Voxel-wise overlap of VOIs, generated during the functional localiser task and cannabis > neutral contrast.

- Mean percent signal change (PSC) of VOIs fluctuated between runs without showing a consistent upregulation pattern across blocks (Figure 4, B).
- PSC of VOIs decreased during upregulation blocks but increased during neutral blocks, and this pattern was consistent across both runs (Figure 4, C).
- ROI analysis revealed no significant activation for upregulation > neutral, but a significant cluster within the ACC for upregulation < neutral (t = 6.57, p < .05, FDR-corrected)(Figure 4, D).
- There was an increasing trend in craving after the cue-reactivity task, while focus and anxiety showed a decreasing trend, although these results didn't reach significance.
- Craving remained stable after the NFB task, focus significantly increased in run 1 but decreased in run 2, and there was a decreasing trend in anxiety that didn't reach significance in both NFB runs (Figure 4, E).

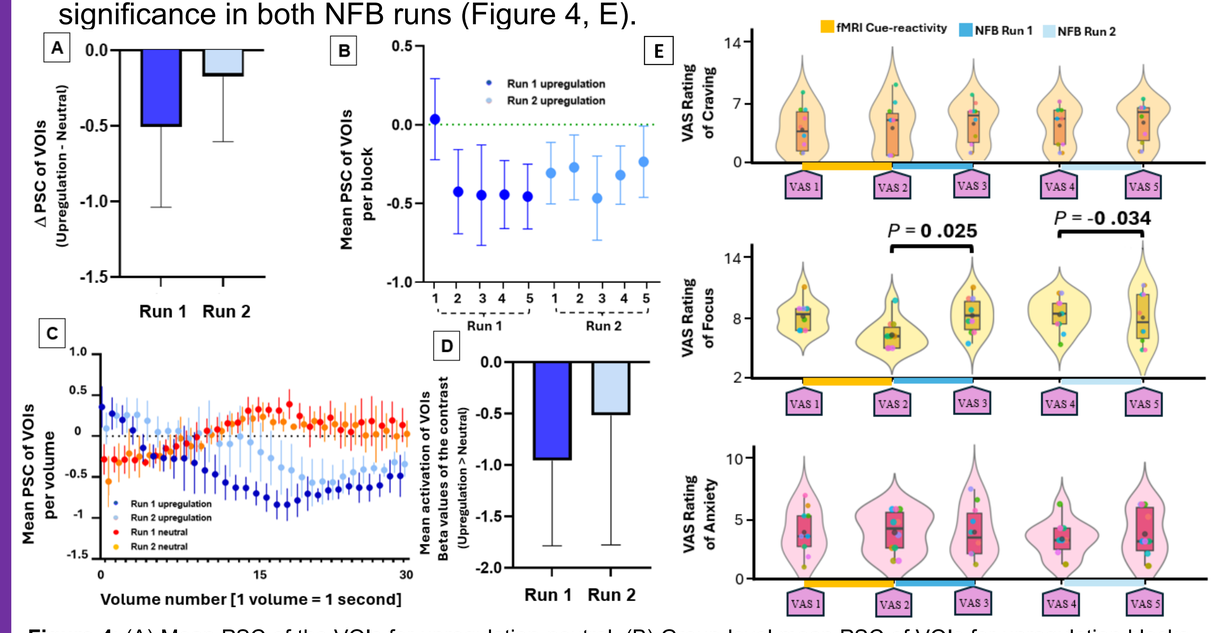

Figure 4: (A) Mean PSC of the VOIs for upregulation-neutral. (B) Group-level mean PSC of VOIs for upregulation blocks. (C) Time course of mean PSC of VOIs for every volume of upregulation and neutral blocks. (D) Mean activation of VOIs for the upregulation > neutral contrast. (E) Changes of subjective ratings during cue-reactivity (T1: pre, T2: post) and run 1(T2: pre, T3: post) and run 2 (T4: pre, T5: post) of the NFB task.

- Whole-brain analysis results (upregulation > neutral) showed significant deactivation in frontal, parietal, insular, and occipital regions (p < .05, FDR-corrected) (Figure 5).

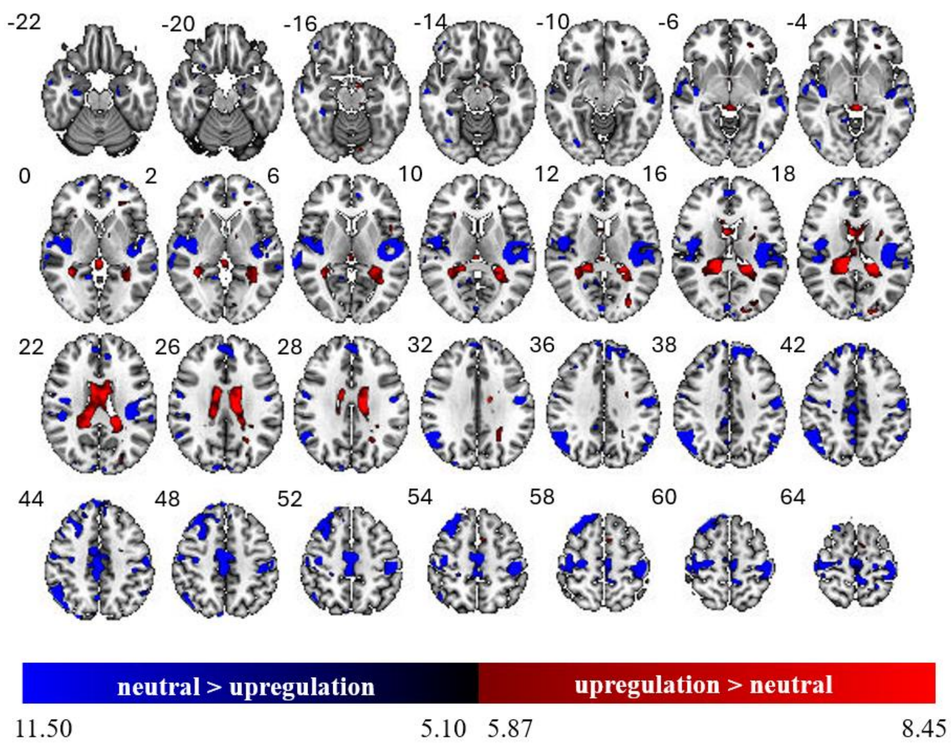

Figure 5: Whole-brain activation maps for upregulation > neutral and neutral > upregulation contrasts

CONCLUSIONS

- Preliminary results suggest that the direction and location of brain changes during cravings differ from prominent neuroscientific theories of addiction and need to be validated in larger samples.

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