



Cannabinoid Modulation of Fear Extinction Learning and Underlying Brain Circuitry in Healthy Humans

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INTRODUCTION

- A major limitation of exposure-based therapies, which relies on extinction processes, is that it is a temporary phenomenon.
- Animal studies have shown that activation of the cannabinoid system within the ventromedial prefrontal cortex (vmPFC) and hippocampus (HPC), brain structures critical to fear extinction learning, enhances fear extinction and its retention.
- THC enhances vmPFC reactivity and attenuates amygdala reactivity, a structure known to be involved in fear responding, to repeated presentation of threat cues in humans.
- However, the role of cannabinoids on the retention of extinction memory and its effect on the underlying neural circuits in humans remains unknown.
- Will administration of an exogenous CB1 agonist during extinction learning subsequently enhance the retention and maintenance of fear extinction memory and are these effects mediated via increased recruitment of vmPFC and HPC?

MATERIALS & METHODS

Subjects: 37 healthy right-handed volunteers; no history of Axis I psychiatric disorders; marijuana use less than 10x in lifetime; no use of marijuana in the past 30 days prior to starting the study
 **23 participants (THC = 12; PBO = 11) were in the fMRI Study

N = 37	THC = 20; PBO = 17
Mean Age (SD)	25.51 (5.17)
Gender	Female = 19; Male = 18
Race	Caucasian = 27; African American = 5; Asian = 3; More than one race = 2

Study Medication: Participants ingest a capsule containing either 7.5 mg of dronabinol (THC = 20) or a placebo sugar pill (PBO = 17) 120 min prior to the start of the extinction session; double-blind; randomized; between-subjects

Behavioral Measures:

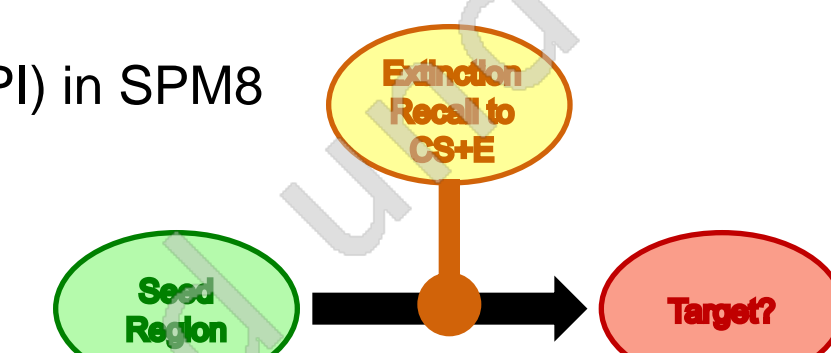
- Skin conductance response (SCR):** Maximum peak that occurs 0.5-4 sec after the presentation of the CS minus average SCR 2 seconds prior to CS presentation; All raw SCR difference scores are square root transformed and standardized to each subject's SCR to the unconditioned stimulus (US)
- US Expectancy Rating:** Occurred with each presentation of the CS during every session:
 - "Will you hear a loud noise?"
 - 1 = Definitely Not;
 - 3 = Unsure;
 - 5 = Definitely;
- Subjective Units of Distress Scale (SUDS):** Rating given prior to session, in the middle, and after session during extinction learning and each memory test:
 - "Using the following scale please indicate how you feel right now:"
 - 0 = No anxiety, calm, relaxed;
 - 25 = Mild Anxiety, alert, able to cope;
 - 50 = moderate anxiety, some trouble concentrating;
 - 75 = severe anxiety, thoughts of leaving;
 - 100 = very severe anxiety, worst ever experienced;

Imaging: 3T whole brain acquisition, T2*-weighted reverse spiral sequence, (TE = 30 ms, TR = 2000 ms, 64 x 64 matrix, flip angle = 90°, FOV = 22 cm, 43 contiguous 3 mm axial slices per volume, aligned with the AC-PC line. Functional data were processed and analyzed using Statistical Parametric Mapping software (SPM8; Wellcome Trust Centre for Neuroimaging, London; www.fil.ion.ucl.ac.uk/spm/).

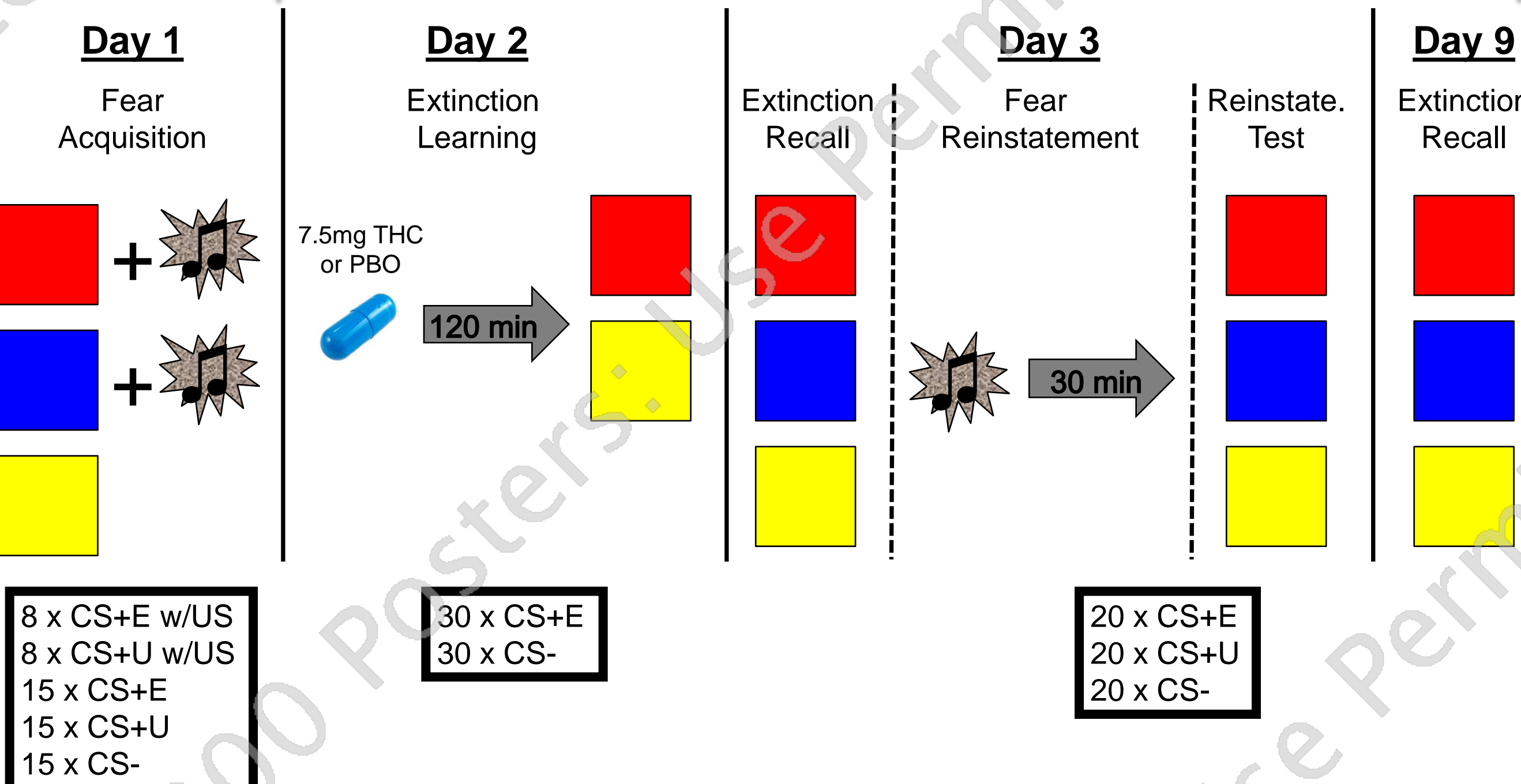
Functional Connectivity Analysis: Psycho-Physiological Interactions (PPI) in SPM8

- The contribution of one brain region to another changes significantly with the experimental or psychological context

$$x_i = x_k \beta_{ik} + G \cdot \beta_G + \epsilon_i$$



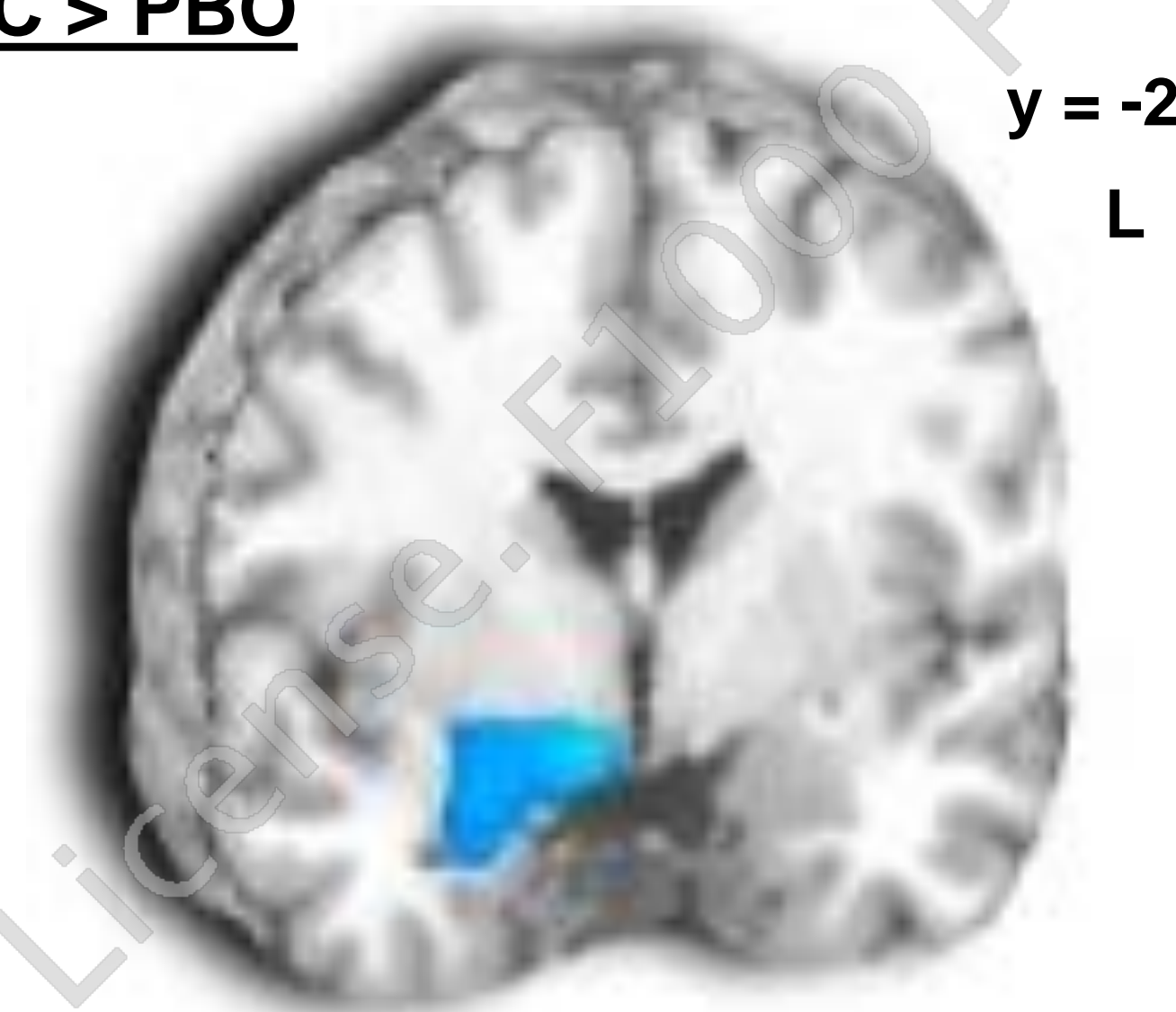
In the scanner



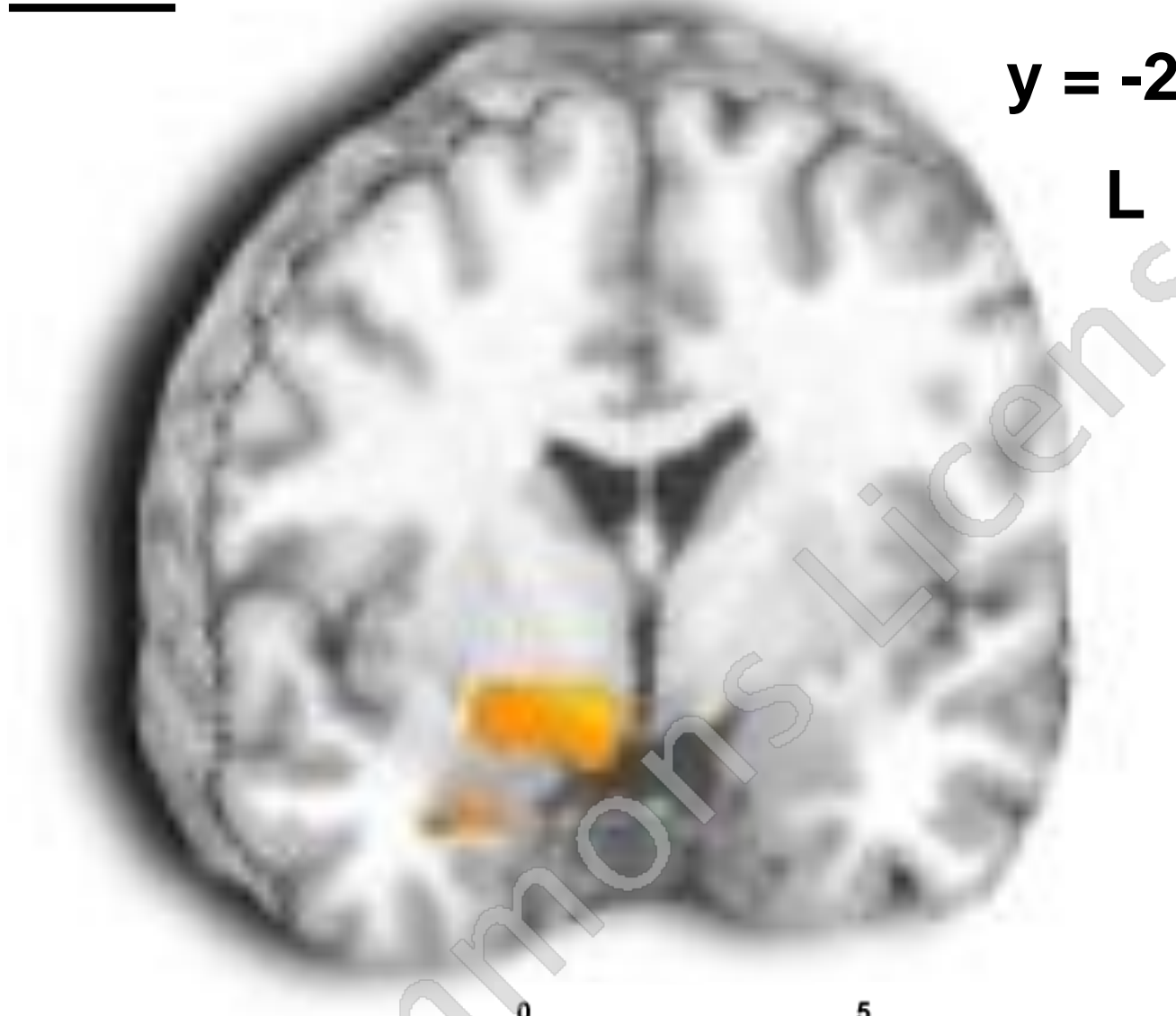
RESULTS

Early Extinction Learning: CS+E > CS-

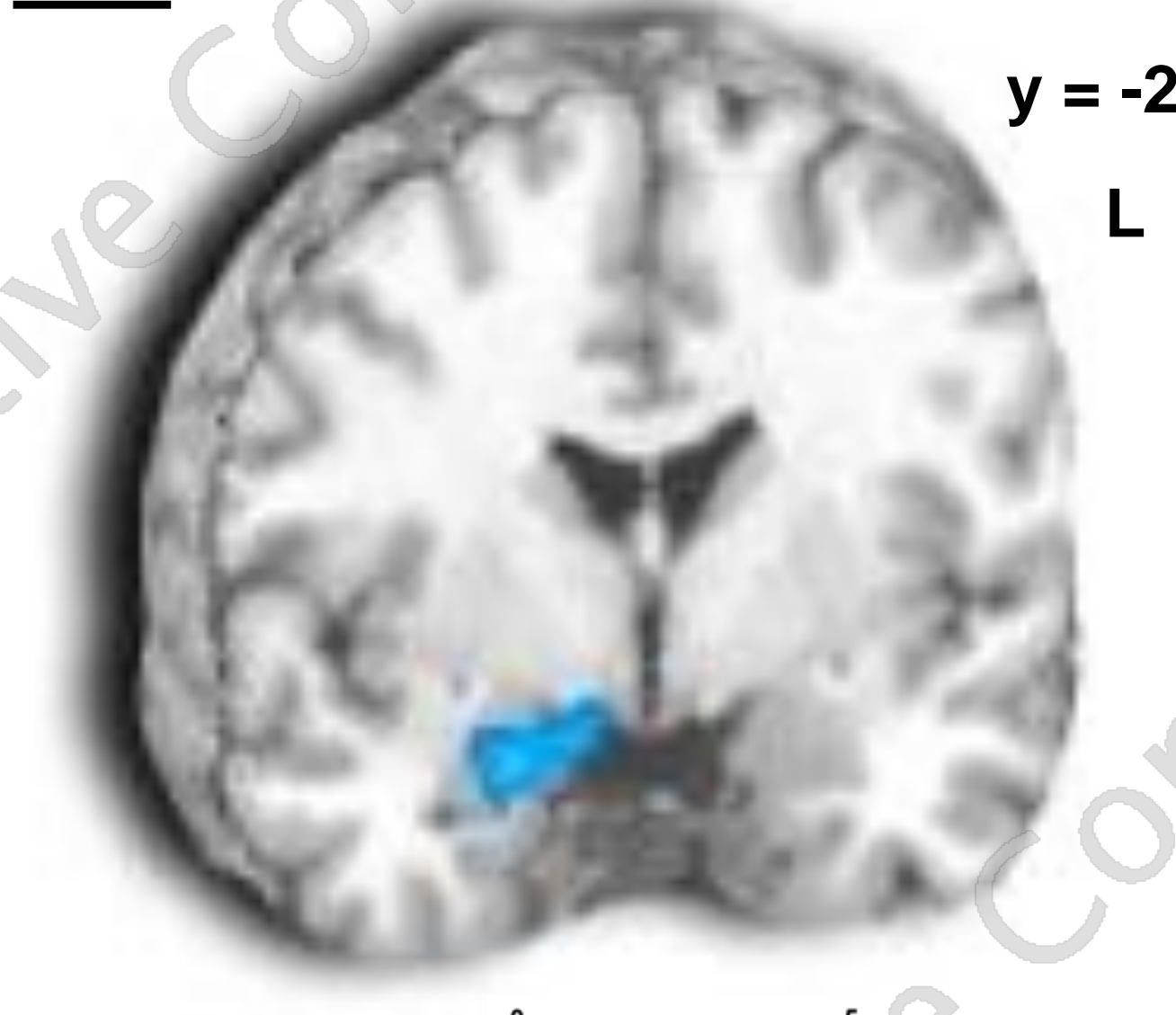
THC > PBO



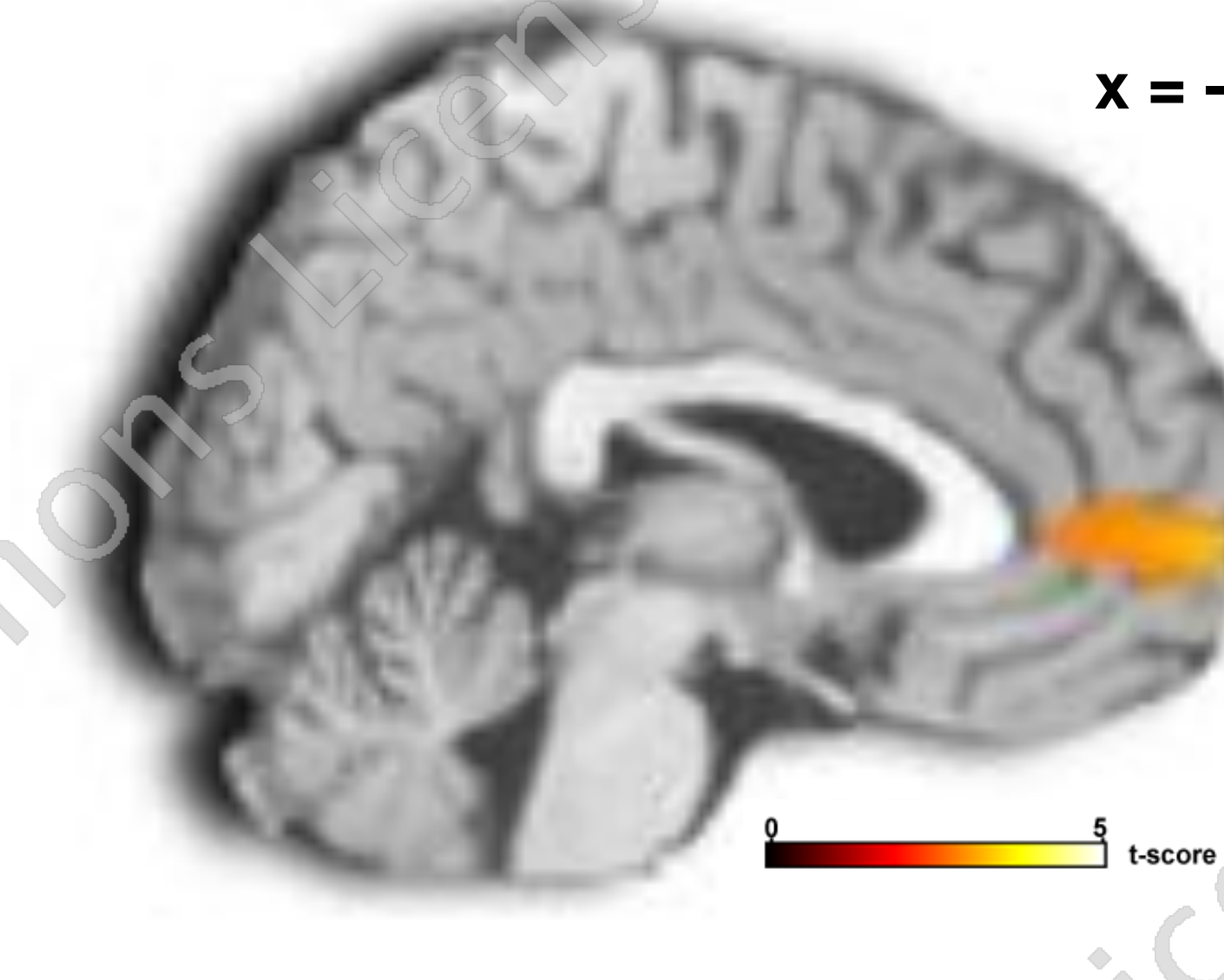
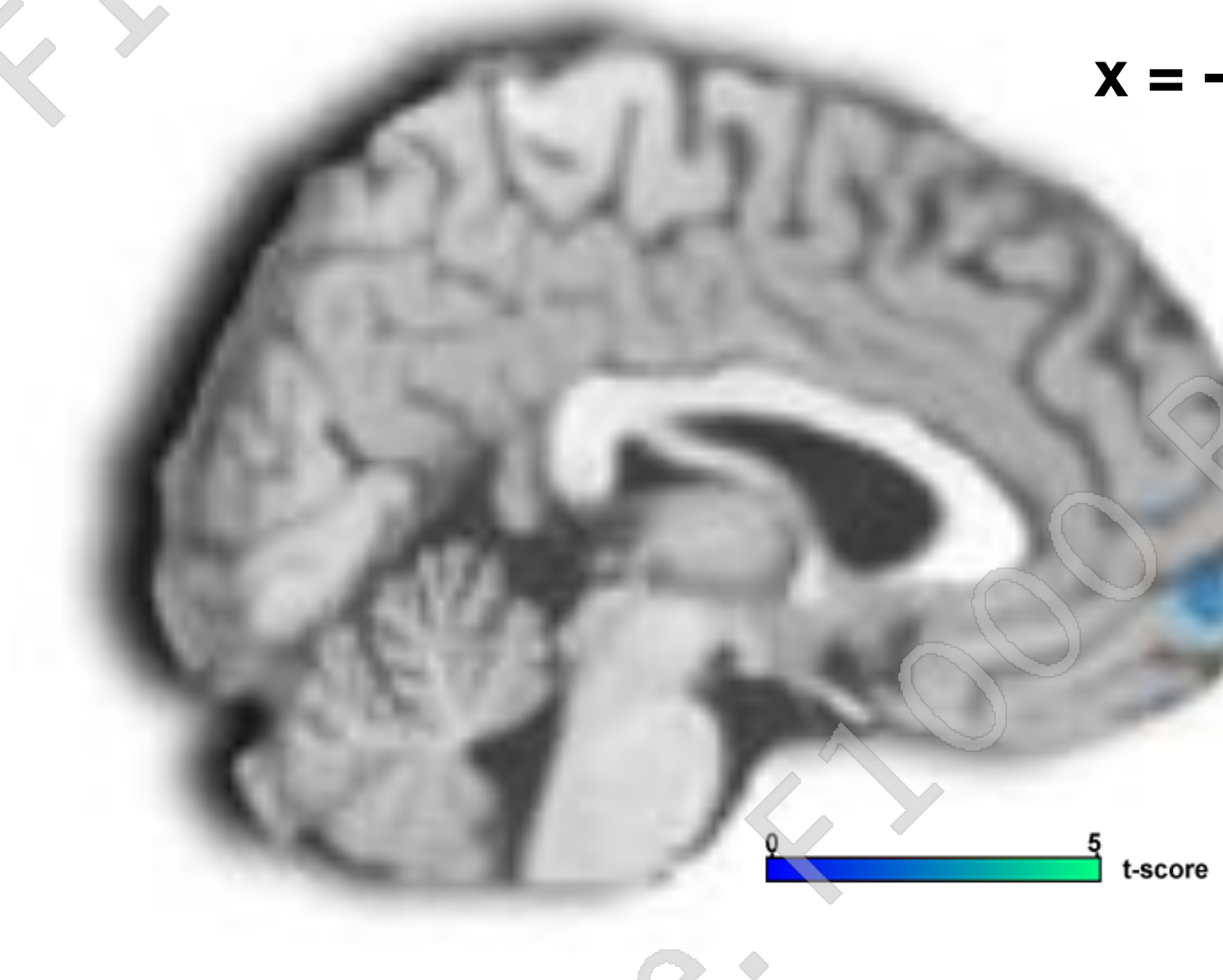
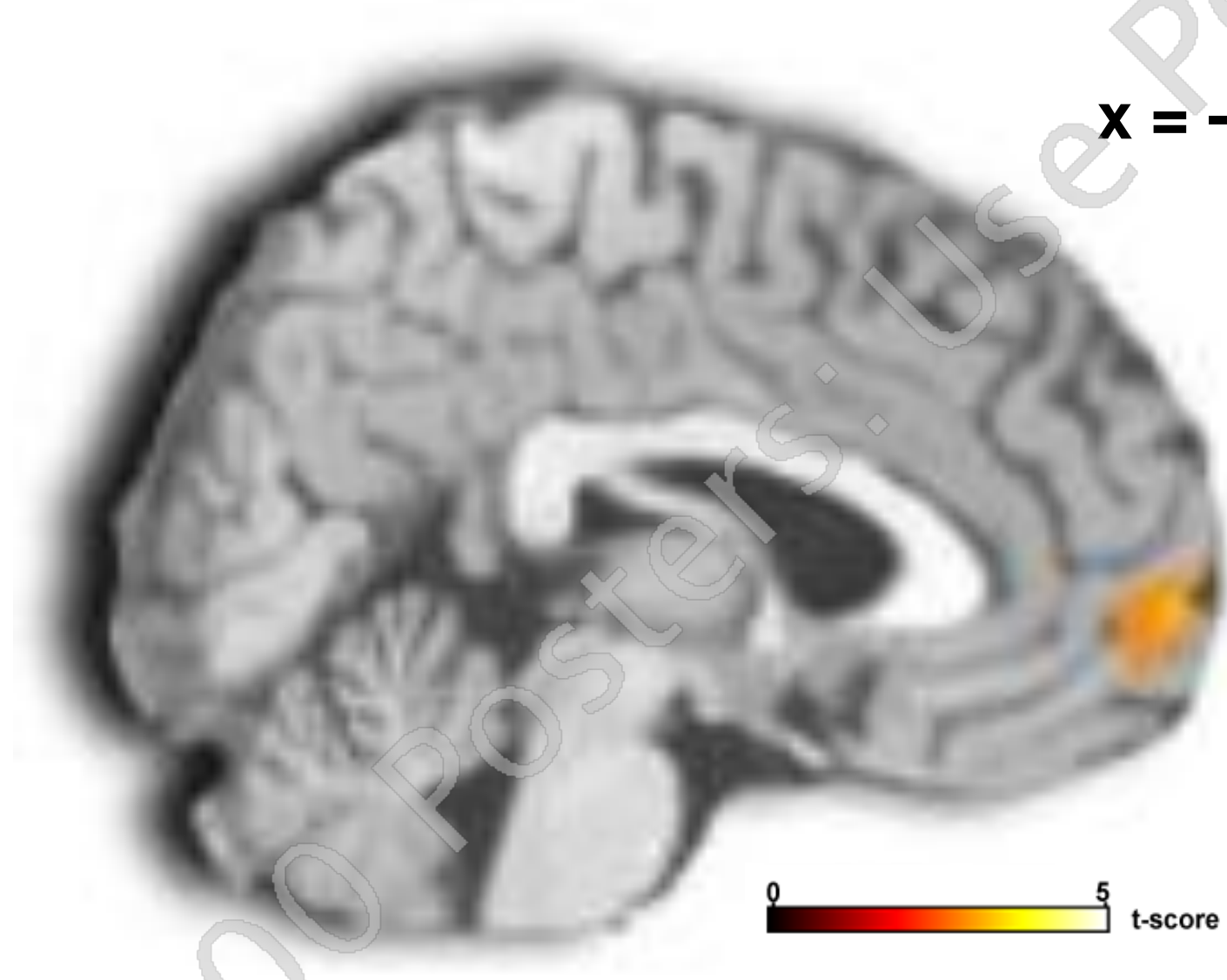
PBO



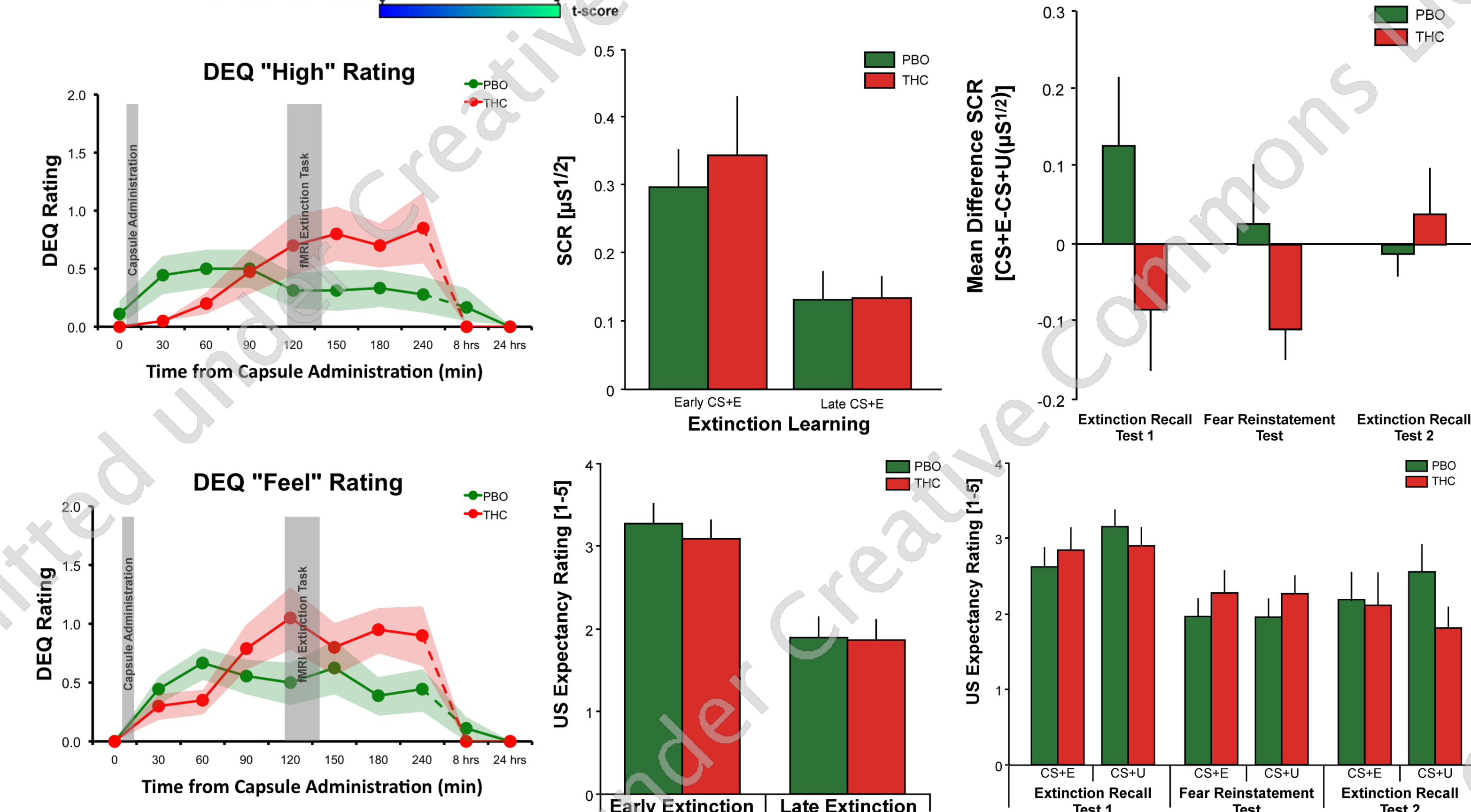
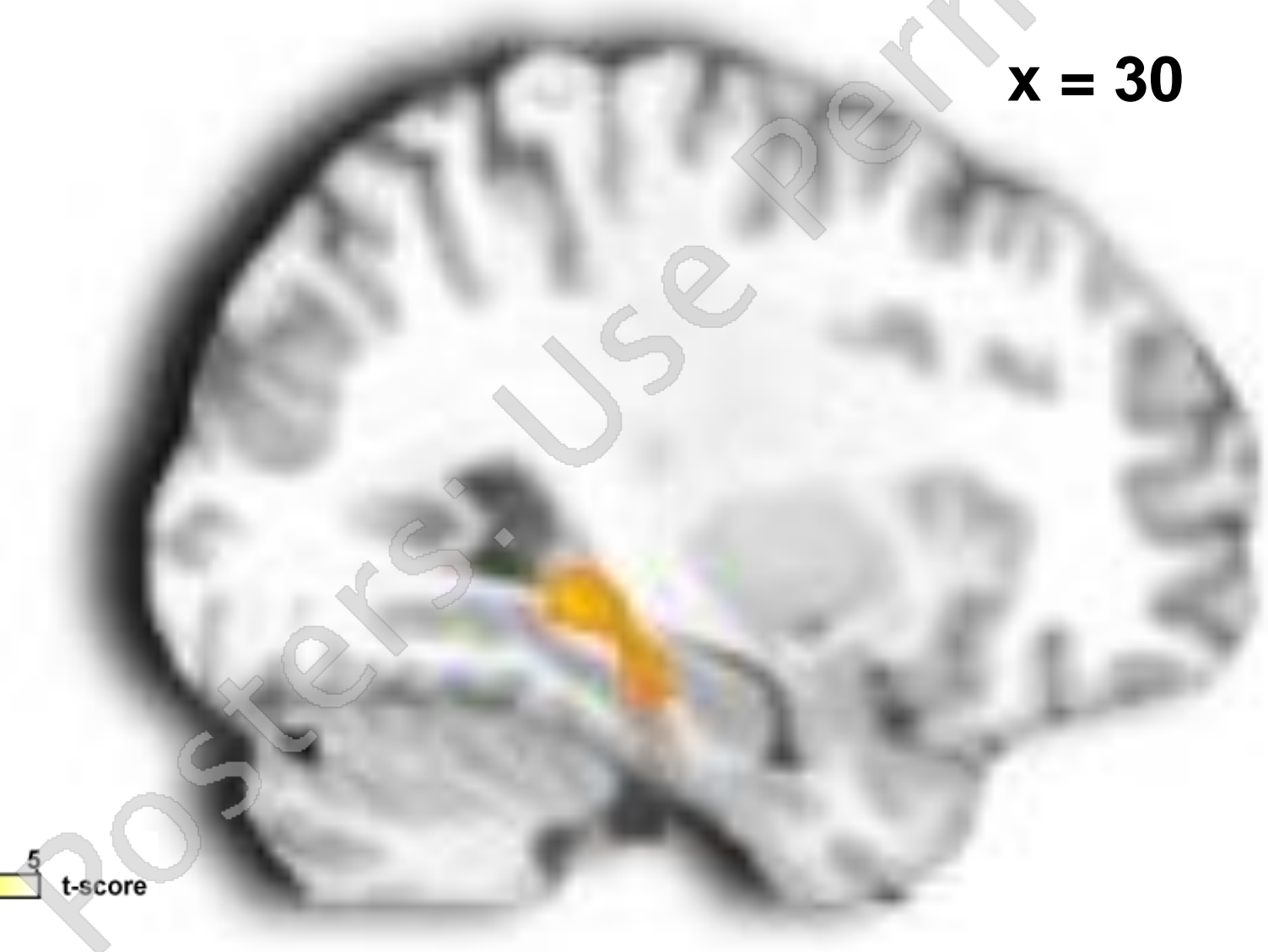
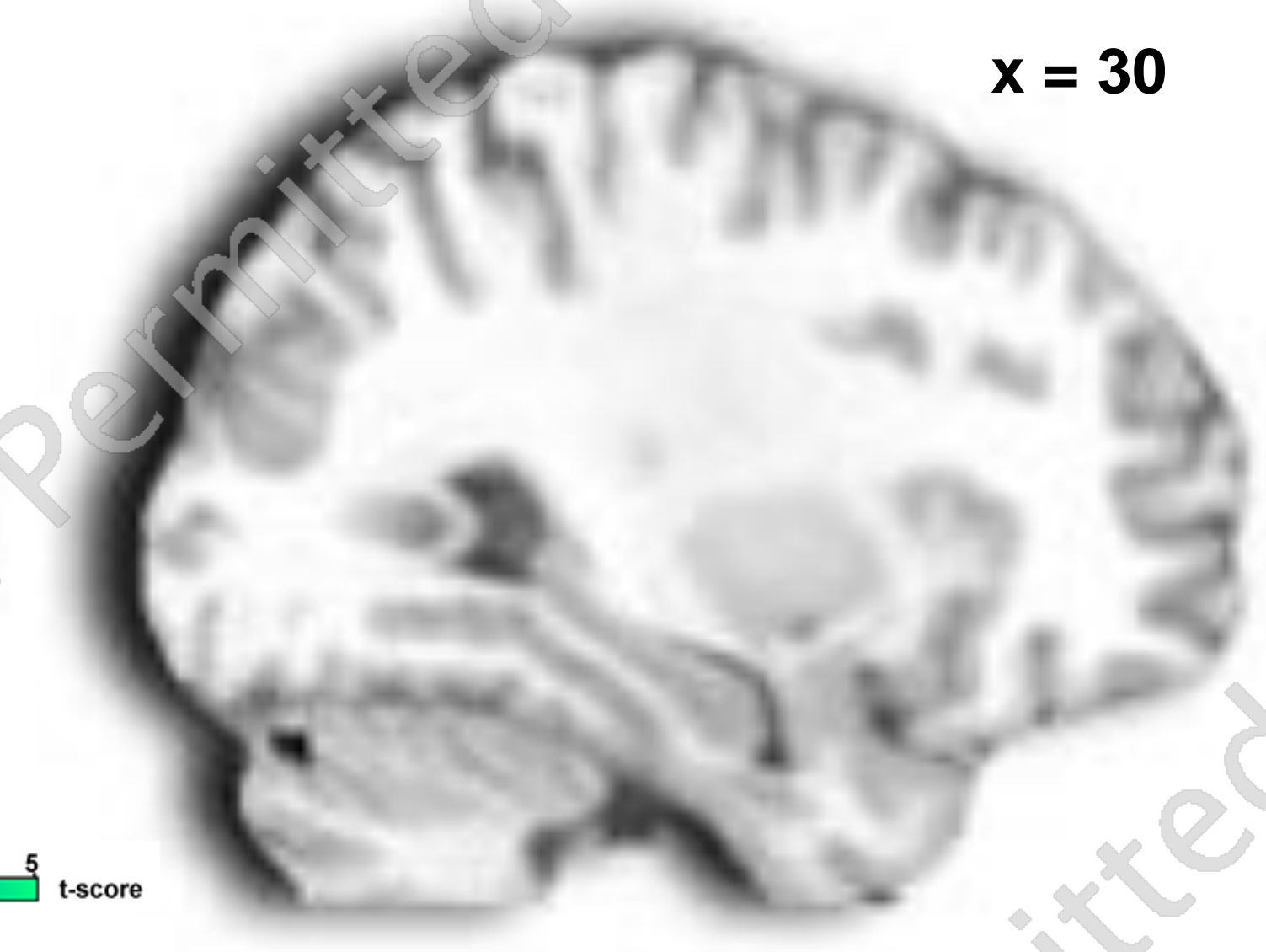
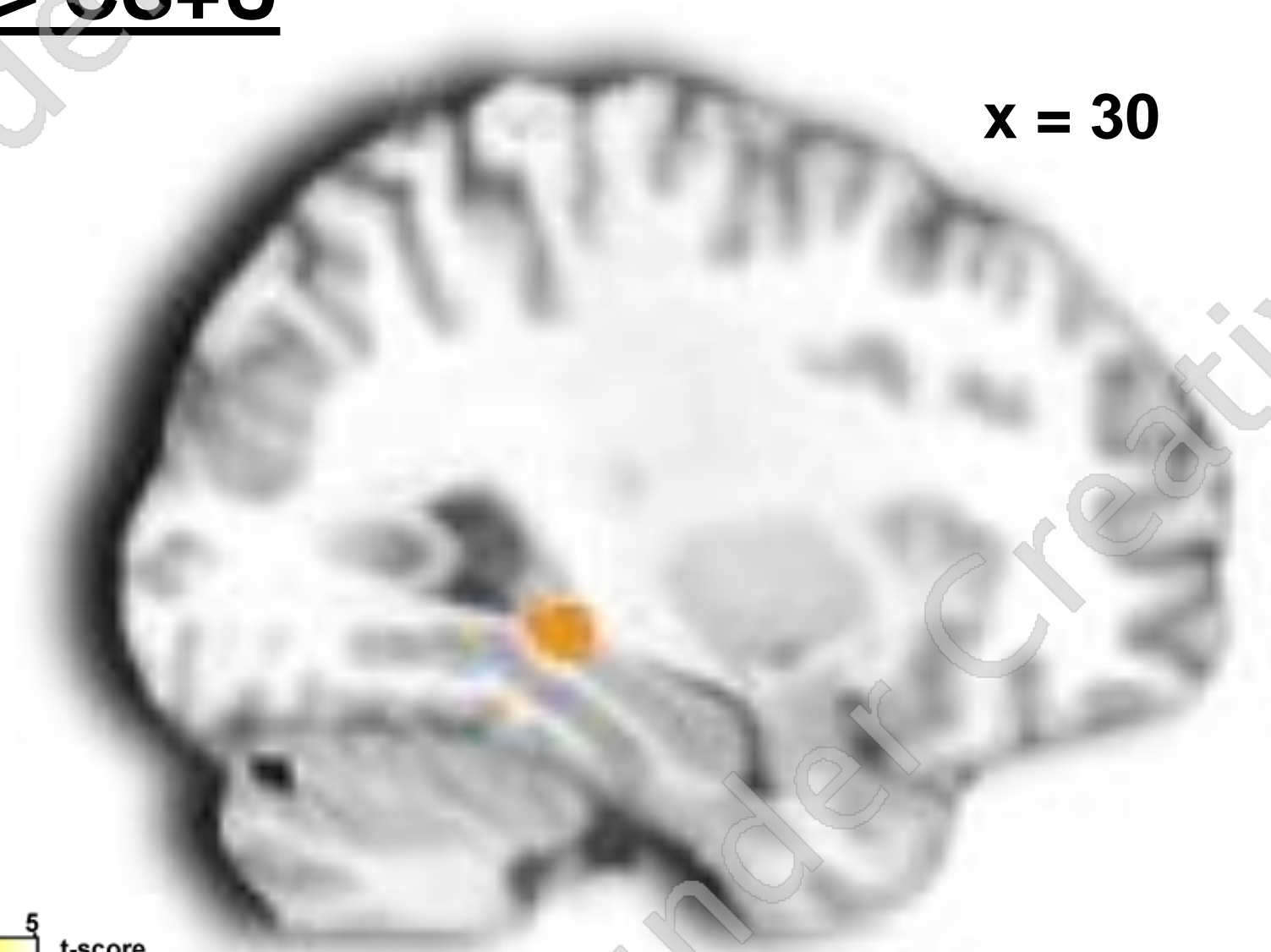
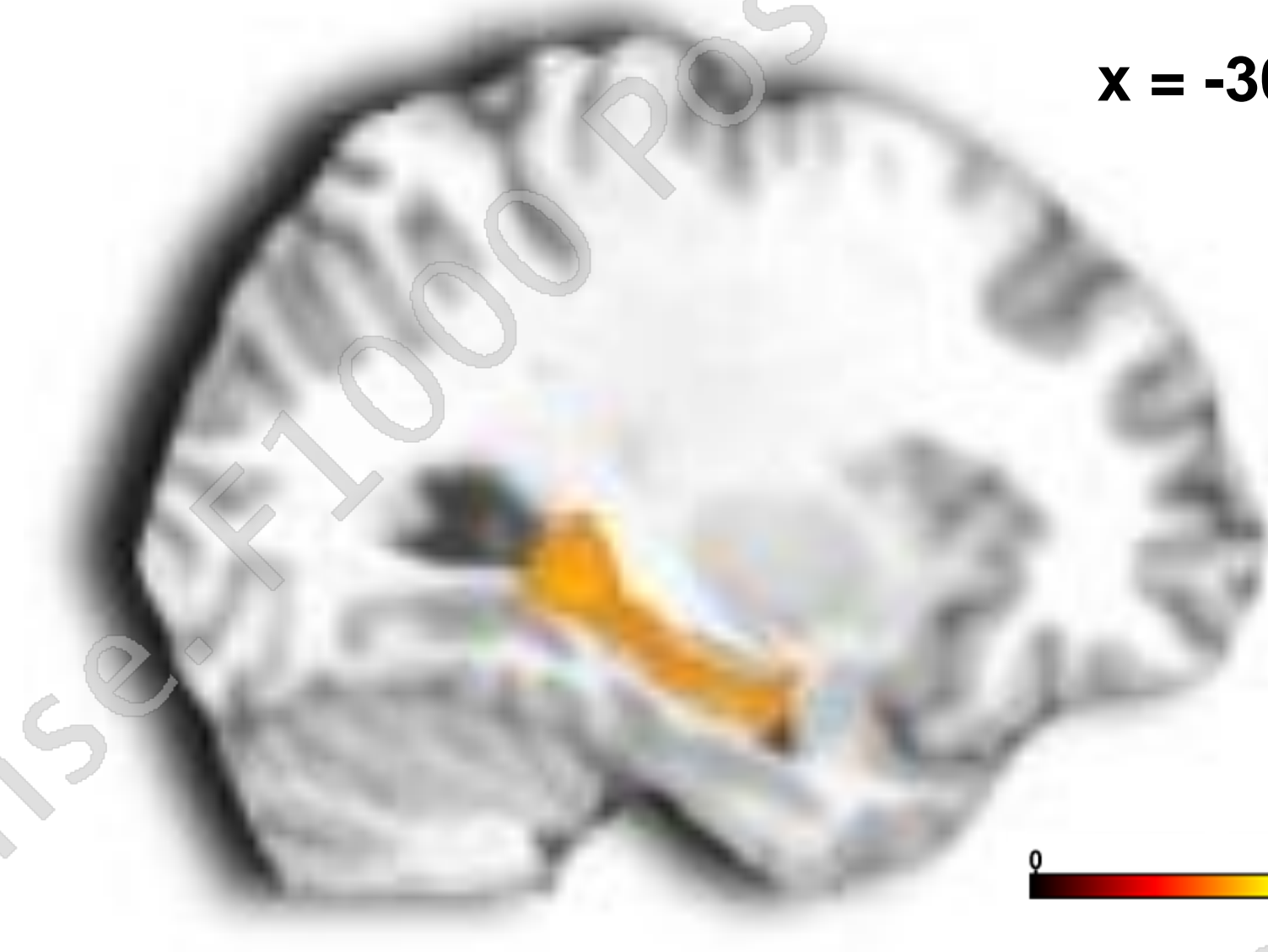
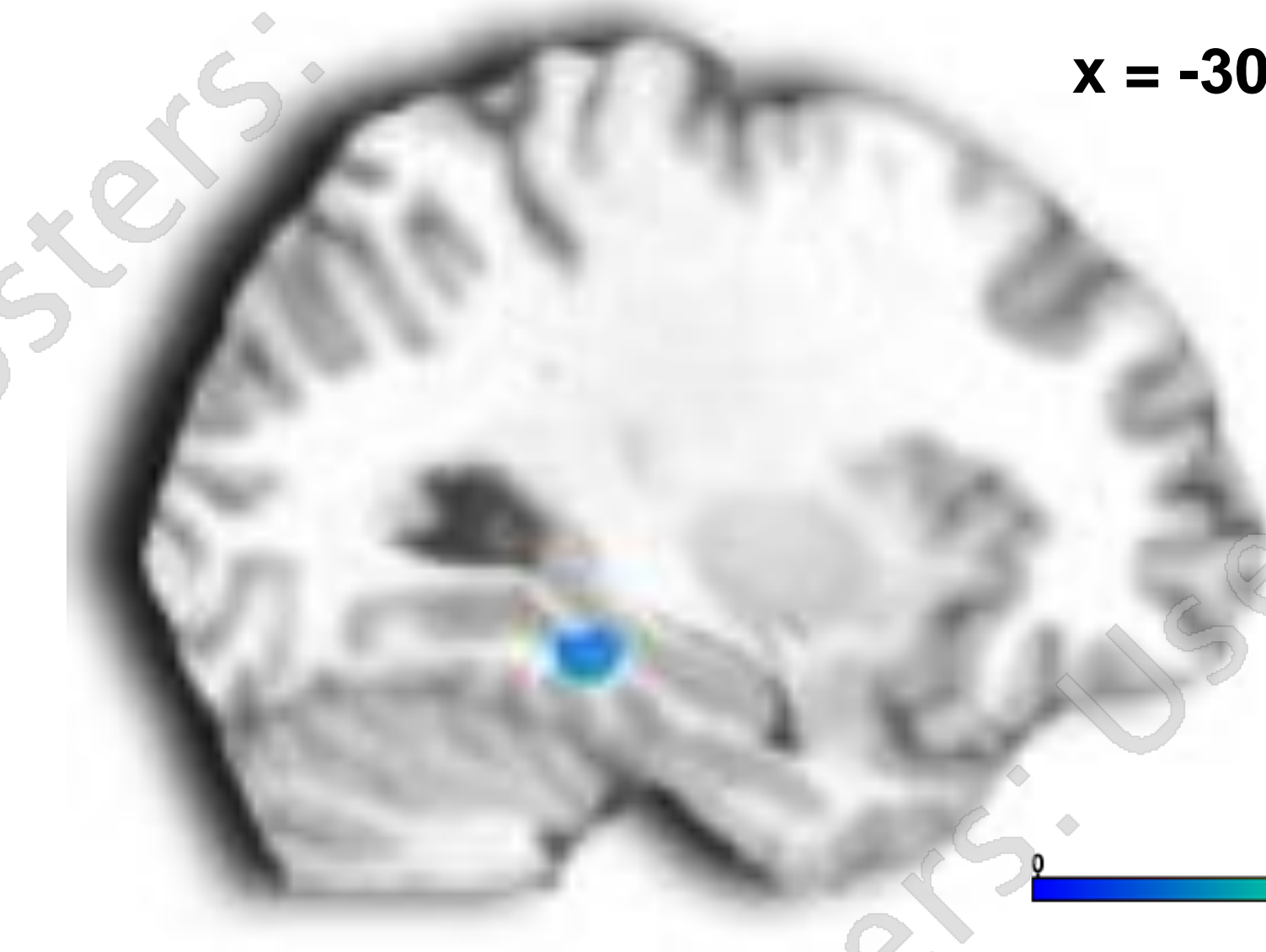
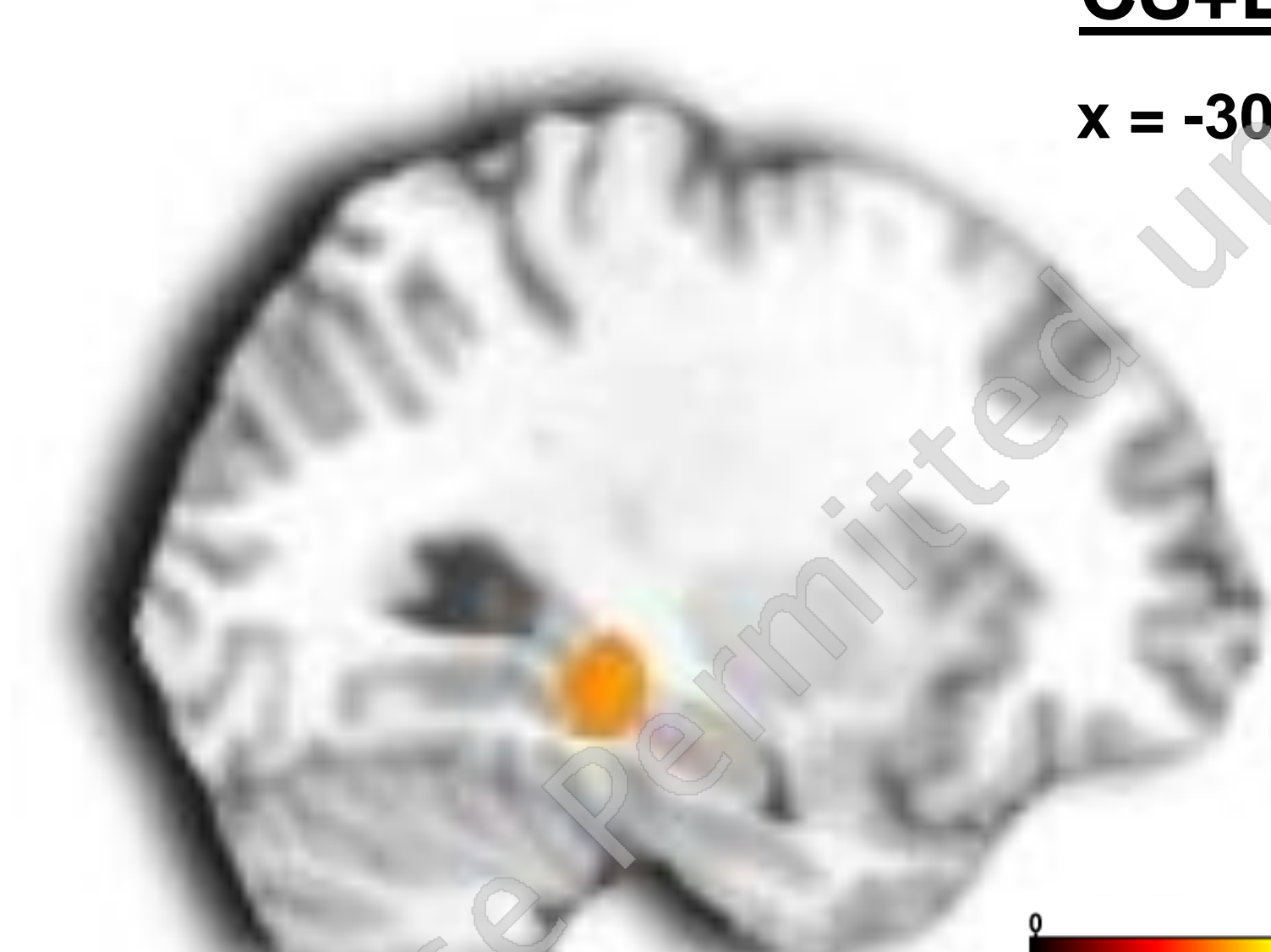
THC



Extinction Recall Test: CS+E > CS+U



Extinction Recall Test: vmPFC 'seed' PPI CS+E > CS+U



SUMMARY

- Increased amygdala activation to the CS+E during early extinction on PBO is suppressed by THC.
- THC administered during extinction learning subsequently increases vmPFC activation and functional coupling with the HPC to the CS+E during recall of extinction memory.
- Compared to subjects that received PBO, subjects that received THC showed low SCR to a previously extinguished CS when extinction memory recall was tested 24 hours after extinction learning, suggesting that THC prevented the recovery of fear.
- These findings are preliminary and the fMRI portion of the study is currently ongoing. Based on these preliminary results we hypothesize that THC facilitates retention of extinction memory via increased recruitment of the vmPFC and HPC.

ACKNOWLEDGMENTS

This work was supported by a grant from the National Center for Research Resources through the Michigan Institute for Clinical and Health Research (UL1RR024986) to CAR and KLP. The authors would like to thank Shoko Mori, Maryssa Lyons, Christy Harrison, and Daanish Chawla for their assistance in recruitment, screening, running participants, and data analyses.