Neural correlates of alcohol use disorder and treatment-related recovery

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Introduction

Chronic stress precipitates the development of **alcohol use disorder (AUD)** and is associated with **high rates of relapse** and **treatment failure** in alcohol treatment (Sinha, 2001; Koob & Schulkin, 2018; Milivojevic & Sinha, 2018).

Recent research suggests that **AUD-related disruptions in the stress pathophysiology jeopardizes alcohol recovery**:

- Disrupted stress and reward brain neurocircuitry (Koob, 2003; Sinha, 2011)
- Altered neural responses to stress and alcohol cues (e.g., Seo, 2013)
- Disrupted prefrontal-striatal and HPA axis function (Blaine et al., 2020)

Yet, the extent to which these alterations are **restored and stabilized with treatment** and whether **stress intervention helps recover these functions** remains unclear.

<u>The Current Study</u>

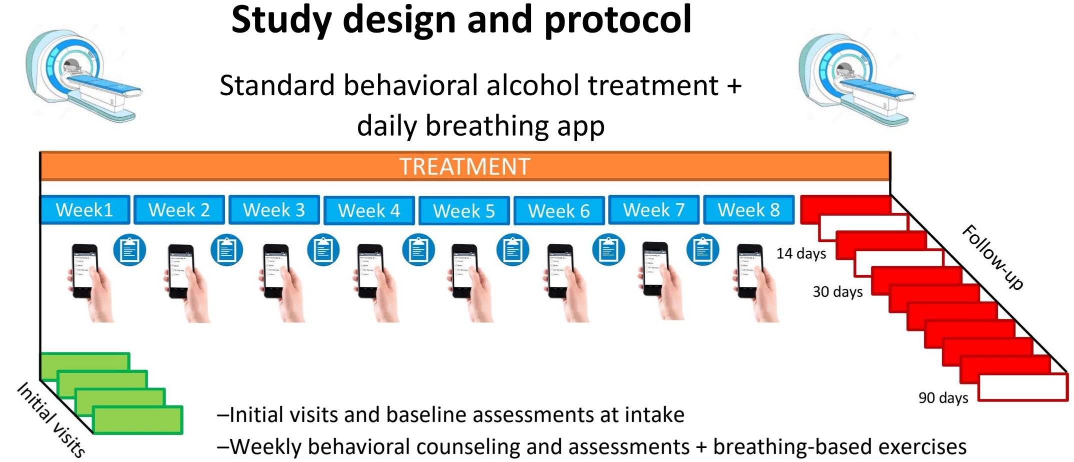
Using functional magnetic resonance imaging (fMRI), the current study investigated **altered neural patterns and correlates of recovery** in **individuals with alcohol use disorder (AUD)** who participated in a **standard cognitive-behavioral alcohol treatment** combined with **breathing-based stress reduction techniques**.

Methods

Participants

- **30** demographically and clinically matched **AUD treatment-seeking community adults (AUD)** and **55 moderate drinkers (MD)** (M_{age}=32.3, 43 females).
    - **fMRI task** (stress, alcohol, and neutral-relaxing cues)
- **AUD patients** underwent an **8-week outpatient treatment** and were daily assessed using a **smartphone app**.
- **17 AUD patients** also completed a **second fMRI after treatment** with the same task using a different set of pictures with similar emotional intensity.

Study design and protocol



–Initial visits and baseline assessments at intake
–Weekly behavioral counseling and assessments + breathing-based exercises
–Daily ecological momentary assessment using smartphone application (MetricWire, Inc.)

Sample information

Basic Demographic information

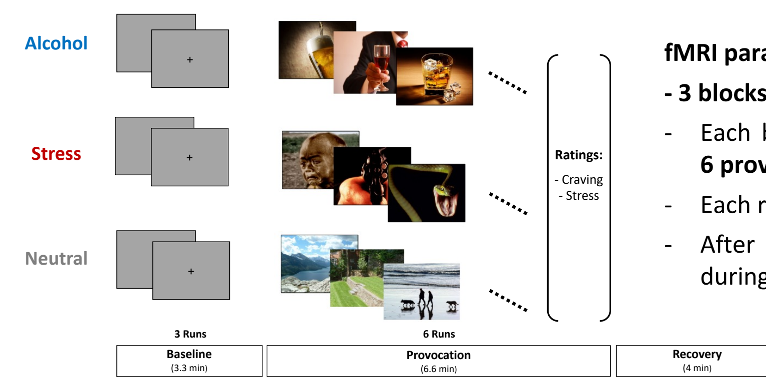
	AUD	MD
Sex (% Female)	53.33%	49.99%
Age (in years)	33.10(7.92)	31.80(7.28)
Education (in years)	16.00(2.34)	16.30(2.54)
Race (% White)	53.33%	47.27%

AUD = alcohol use disorder
MD = Moderate drinkers

No significant differences in basic demographics were observed (all *p*'s > 0.05).

fMRI paradigm

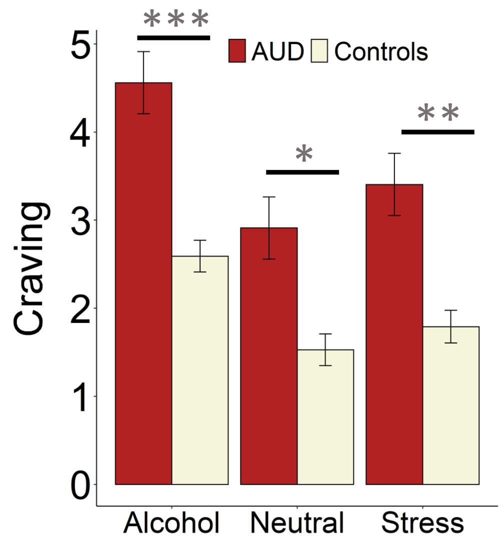
During an **fMRI session**, an **emotion provocation task** (e.g., Sinha et al., 2016) was administered, where participants viewed **stress**, **alcohol**, and **neutral cues** and rated their alcohol **craving** and **stress**.



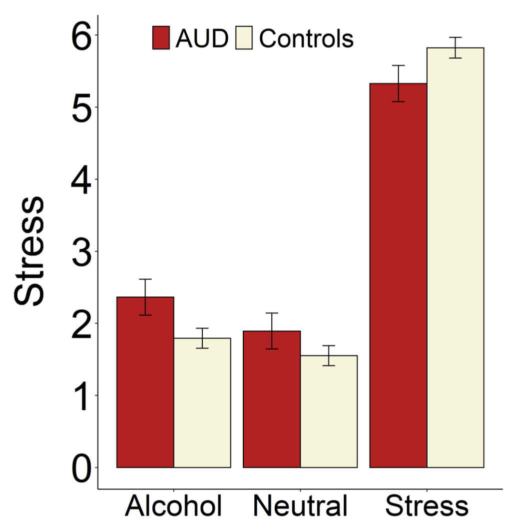
fMRI paradigm–Emotion Provocation task:

- 3 blocks: stress, alcohol, and neutral-relaxing
- Each block: **3 baseline runs** (grey blanks) + **6 provocation runs**
- Each run: 11 images + ratings
- After the provocation runs, rest for 4 min. during the recovery phase (no images)

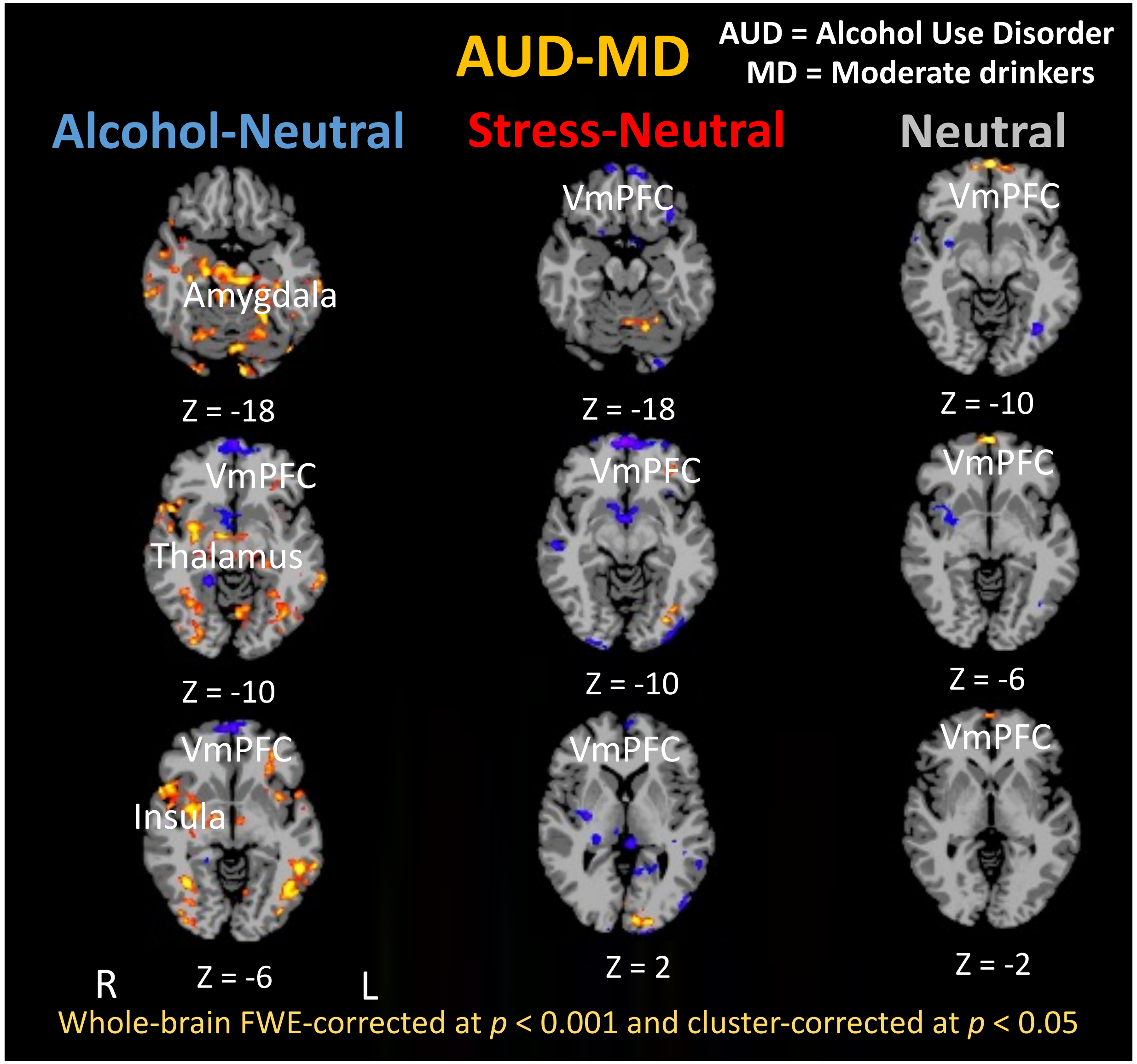
Altered Brain Responses to Stress and Alcohol Cues in AUD Patients



Group: $\chi^2(1) = 17.95$, $p < 0.001$

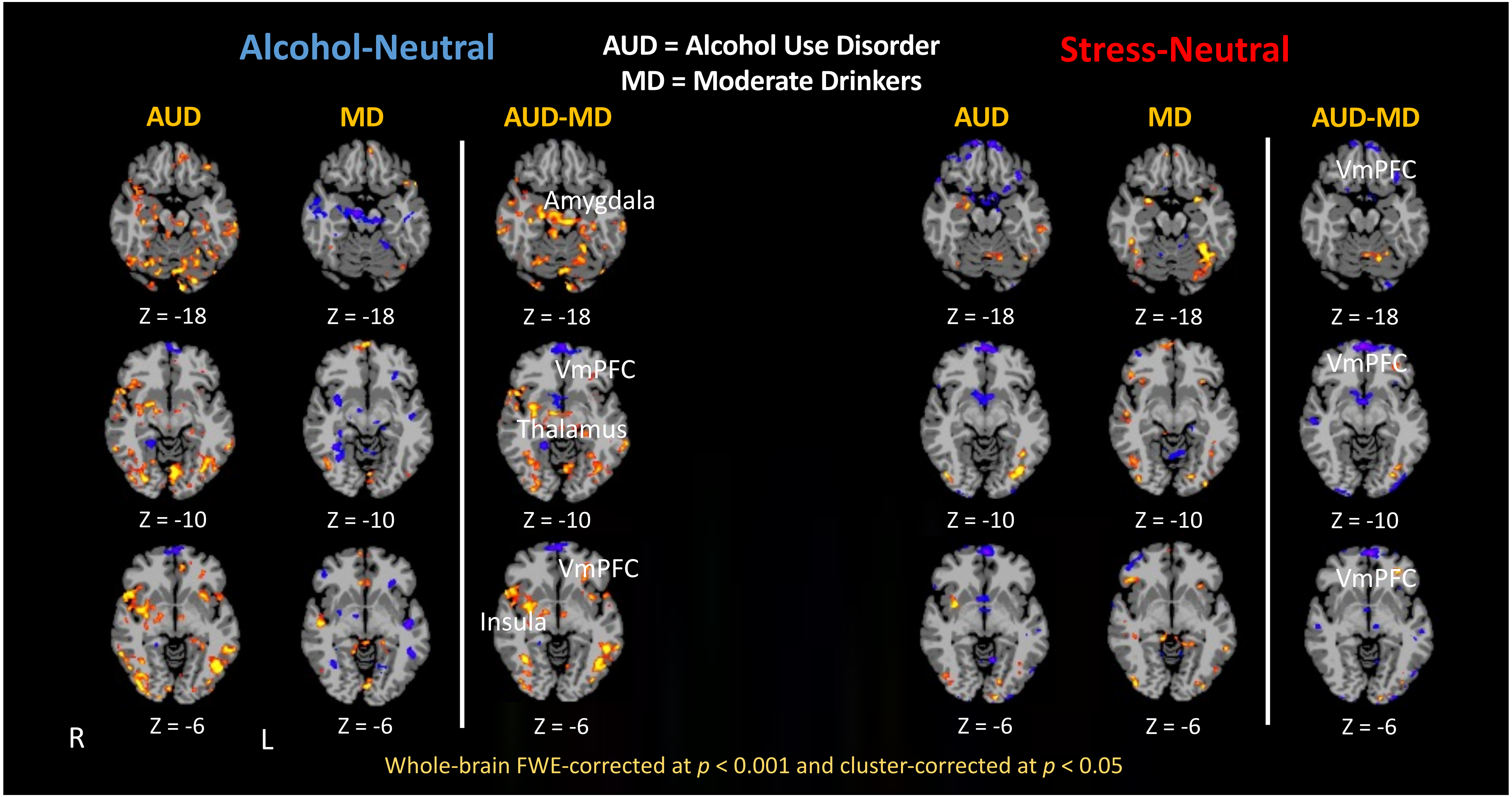


Group × Task: $\chi^2(2) = 9.87$, $p = 0.007$



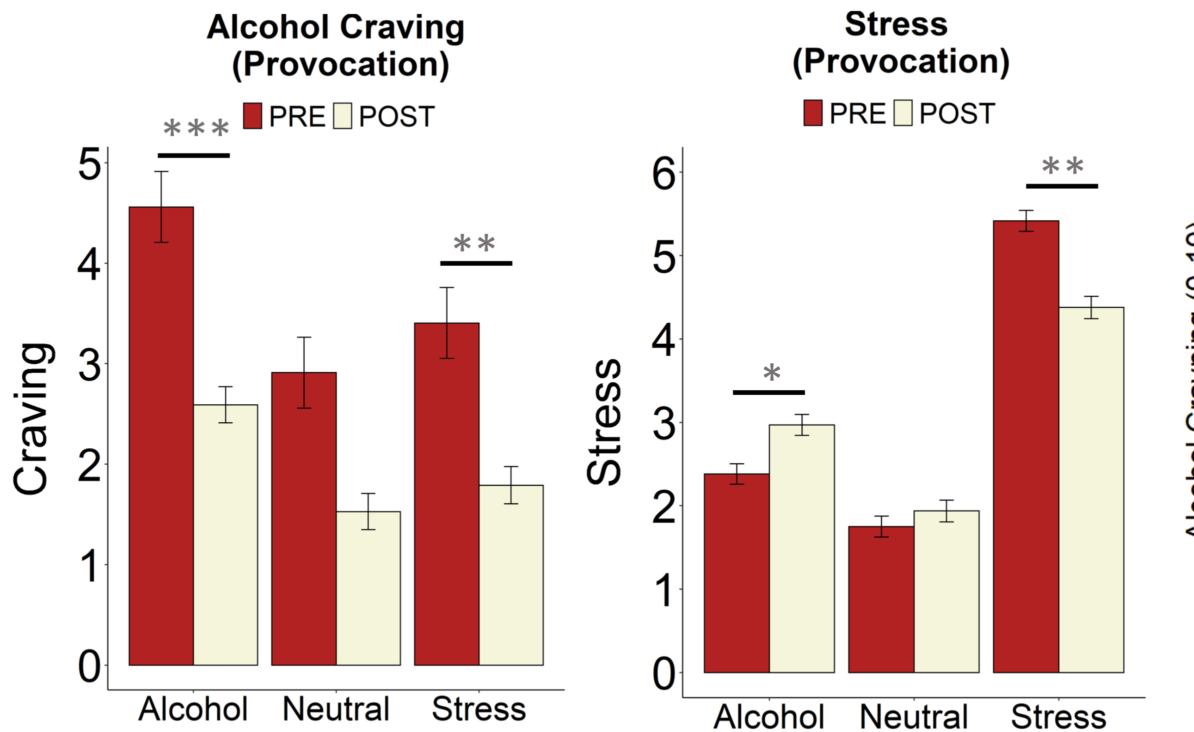
AUD vs. MD showed **greater craving** and **hypoactive VmPFC** but **hyperactive limbic responses** (amygdala, insula, hippocampus, and thalamus) to alcohol cues and showed **hypoactive VmPFC** to stress cues

Altered Brain Responses to Stress and Alcohol Cues in AUD Patients



AUD Treatment-Related Recovery: Pre- vs. Post-Treatment

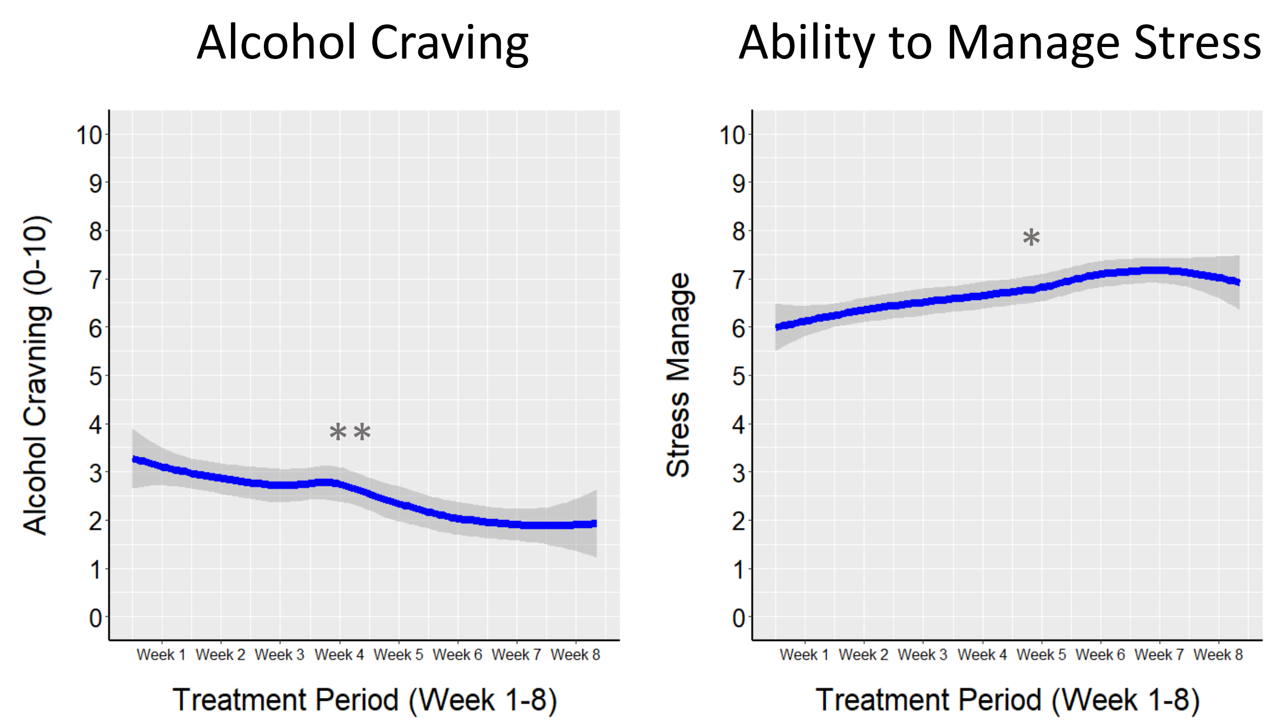
Initial vs. Post-Treatment Craving and Stress Ratings



Task × Session: $\chi^2(2) = 10.49$, $p = 0.005$

Task × Session: $\chi^2(2) = 24.40$, $p < 0.001$

Treatment-Related Changes over the Treatment Period (Weeks 1-8)

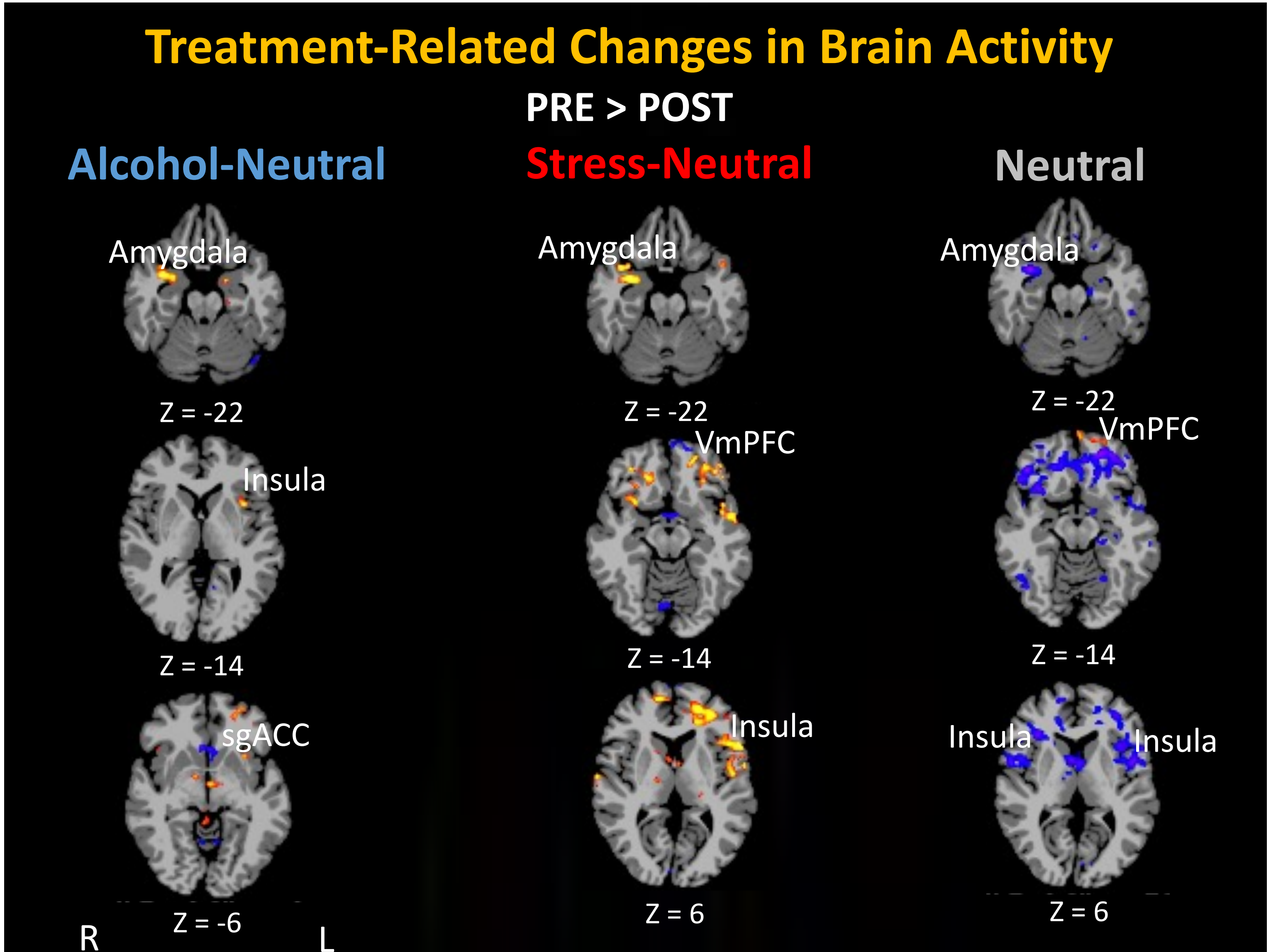


Time (day): $F(1,20.55) = 8.32$, $b = -0.033$, $p = 0.009$

Time (day): $F(1,23.33) = 5.43$, $b = 0.015$, $p = 0.029$

Craving ratings were **reduced** during **stress and alcohol cues**, along with **reduced stress ratings during stress** after treatment. **Alcohol craving decreased** and the **ability to manage stress improved** with treatment.

Neural Correlates of AUD Treatment-Related Recovery



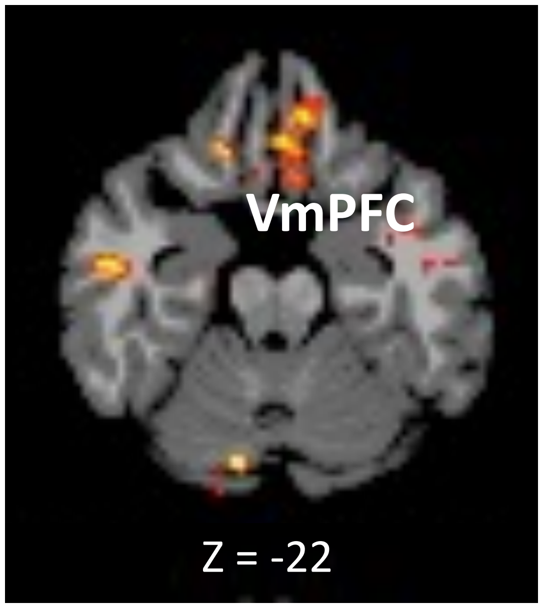
Whole-brain FWE-corrected at $p < 0.001$ and cluster-corrected at $p < 0.05$

When comparing initial vs. post-treatment fMRIs among AUD:

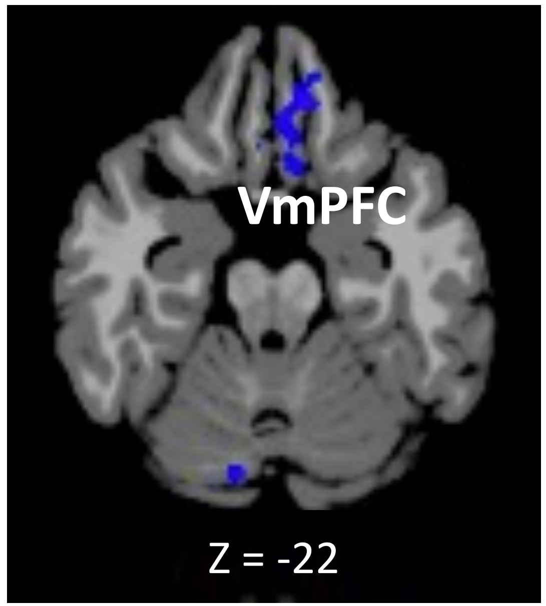
- **amygdala** and **insula** responses to **stress** and **alcohol cues** were **reduced**;
- **VmPFC** and **subgenual anterior cingulate cortex (sgACC)** activity was **increased** during **stress** and **alcohol cues**, respectively.

Ability to Manage Stress During Treatment and Changes in VmPFC activity during Stress (Pre- vs. Post-Treatment)

Stress Manage × Task (PRE-POST)

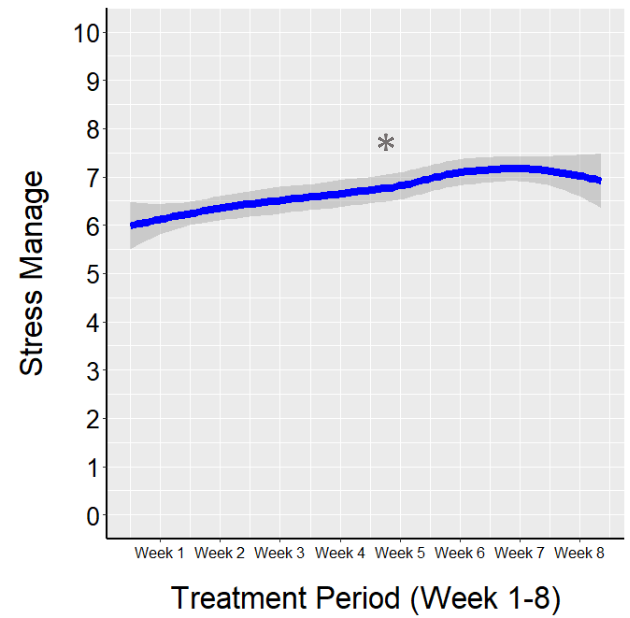


Stress Manage on Stress (PRE-POST)



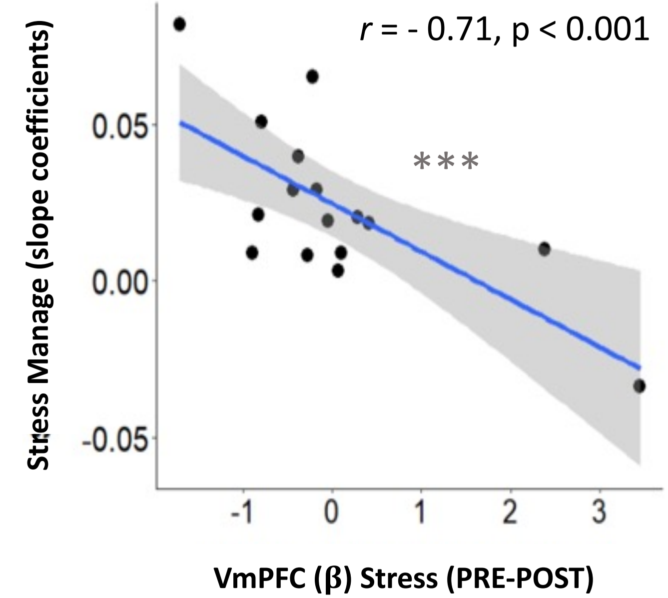
Whole-brain FWE-corrected at $p < 0.001$ and cluster-corrected at $p < 0.05$

Treatment-Related Changes in Stress Manage



Time (day): $F(1,23.33) = 5.43$
$b = 0.015$, $p = 0.029$

Stress Manage and VmPFC (Stress) Recovery



VmPFC recovery during stress was associated with **greater improvements in stress management ability** during treatment.

Conclusion

<u>**The current study identified**</u>**:**

(1) **disrupted neural responses** to **stress** and **alcohol cues** in **AUD patients** in **prefrontal and limbic regions**:

– **AUD patients** have **altered neural circuits** of **stress** and **emotion regulation**, marked by **decreased VmPFC**, and **sgACC** but **increased limbic responses** in the **amygdala**, **hippocampus**, and **thalamus**.

(2) **this neural pattern** that appears to **improve after treatment**:

– **reduction** of **amygdala** and **insula responses** to stress and alcohol cues

– **improvement/recovery** of **VmPFC** and **sgACC** activity during stress and alcohol cues

(3) **recovered VmPFC** responses were associated with **greater improvements in stress regulation**

<u>**Significance & Implications**</u>**:**

Our findings suggest that **targeting stress dysfunction with behavioral treatment** may help **stabilize and restore altered neural brain functions in AUD patients** and promote better treatment outcomes.

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Yale Stress Center

FCT Fundação para a Ciência e a Tecnologia

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NIH National Institute on Alcohol Abuse and Alcoholism