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Joshua Zhao **March 28, 2024**

Neural Correlates of Response Inhibition Linked to Alcohol Use in Trauma-exposed Males and Females

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Abstract

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PTSD and other trauma-related disorders can lead towards excessive alcohol consumption. Impaired response inhibition could potentially be a mechanism in which both of these conditions develop. Using data from the AURORA clinical dataset, we performed a Go/NoGo task on n=329 recently trauma-exposed participants in order to measure neural activity during response inhibition in the ventromedial prefrontal cortex (vmPFC), right inferior frontal gyrus (rIFG), and the bilateral hippocampus. Participants were placed in three groups: an increasing alcohol change group, a decreasing alcohol change group, and a no change group based on their change in alcohol usage from pre-trauma to 8 weeks post trauma and 6 months post trauma. Due to sex differences in response inhibition, alcohol use, and vulnerability to PTSD, two-way ANOVA was used to examine the interaction between sex and alcohol change group on brain activation at 8 weeks and 6 months. Separate one-way ANOVA on each sex were run to better understand the within-sex differences between different alcohol change groups. At 8 weeks, females in the no change group had significantly greater rIFG activation compared to females in the decreasing group, while males in the no change group had significantly lower right hippocampus activation compared to males in the decreasing group. Females in the no change group had significantly higher right hippocampus activation compared to males in the no change group. At 6 months, females in the increasing group had higher right hippocampal activation than males in the increasing group. These findings suggest that the rIFG and right hippocampus are highly important regions in the progression of PTSD and could potentially be involved in inhibiting alcohol use. The sex differences that were observed in the right hippocampus reveals a potential target for sex-specific interventions.

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Abstract

Posttraumatic stress disorder (PTSD) and other trauma-related disorders can lead to excessive alcohol consumption. Impaired response inhibition could potentially be a mechanism in which both conditions develop. Using data from the AURORA clinical dataset, n=329 recently trauma-exposed participants (n=329) completed a Go/No-Go task to measure neural activity during response inhibition in the ventromedial prefrontal cortex (vmPFC), right inferior frontal gyrus (rIFG) and the bilateral hippocampus. Participants were placed in one of three groups: an increasing alcohol change group, a decreasing alcohol change group, and a no change group based on their change in alcohol usage from pre-trauma to 8 weeks post-trauma and 6 months post-trauma. Due to literature highlighting biological sex differences present in response inhibition, alcohol use, and vulnerability to PTSD development, a two-way ANOVA was used to examine the interaction between biological sex and alcohol change group on brain activation at 8 weeks and 6 months. Females in the no change group had significantly higher right hippocampus activation compared to males in the no change group. Separate one-way ANOVAs were conducted for each biological sex to better understand the within-sex differences in alcohol change groups. We observed greater rIFG activation in females in the no change group (at 8 weeks post-trauma) compared to females in the decreasing group. We also observed greater right hippocampus activation in females in the no change group (at 8 weeks post-trauma) compared to males in the no change group. Additionally, we observed greater right hippocampal activation in females in the increasing group (at 6 months post-trauma) compared to males in the increasing group. These findings suggest that the rIFG and right hippocampus are important regions in the progression of PTSD and could potentially be involved in inhibiting alcohol use. The biological sex differences observed in the right hippocampus reveal a potential target for sex-specific interventions.

Introduction

Alcohol use has become increasingly prevalent in the United States. According to the National Center for Drug Abuse Statistics, online liquor sales rose 262% year-over-year in the first 3 weeks of March 2020, coinciding with most state-wide lockdowns. Additionally, alcohol use disorder (AUD) in the US is seeing a disturbing rising trend. According to the DSM-5, AUD is defined as "a problematic pattern of alcohol use leading to clinically significant impairment or distress." SAMHSA's National Survey on Drug Use and Health (NSDUH) found that approximately 14.8 million people aged 12+ suffered from AUD in 2018, while in 2021 that number doubled to 29.5 million. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), there were 4.9 million alcohol-related emergency department (ED) visits and 140,557 alcohol-related deaths in 2021. The escalating prevalence of alcohol consumption in the United States is a disconcerting trend. Many factors can lead to alcohol use disorder, including both genetic and environmental factors, such as family history, mental health problems, and history of trauma (Mayo Clinic, 2022).

In recent years, the American populace has faced a wide array of stressors, with the COVID-19 pandemic, issues related to racial injustice, and political polarization dominating the headlines and social media platforms. The American Psychological Association's (APA) Stress in America Survey found that the impact of stress on daily functioning and productivity is rising. On a scale ranging from 1 to 10, where 1 signifies minimal or negligible stress, and 10 represents an overwhelming amount of stress, the average reported stress level over the past month among all adults has remained constant at 5.0 since 2020 whereas in 2017 and 2016 it was at a 4.8. Additionally, a concerning portion of adults stated that stress significantly impacts their daily functioning, with over a quarter (27%) expressing that they are so stressed on most days that it hampers their ability to function effectively (Bethune, 2022).

Stress is an important risk factor for alcohol use. According to the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions, the number of past-year stressors was positively associated with current drinking, binge drinking habits, and AUD. Other studies have shown that the number of general life stressors is associated with alcohol consumption and problem alcohol use (Cole et al. 1990; King et al. 2003). Traumatic experiences that elicit stress responses are also strong predictors of alcohol use (Keyes et al., 2012). Posttraumatic stress disorder (PTSD) can be a potential consequence of trauma, and is frequently comorbid with AUD (Straus et al., 2018).

The Centers for Disease Control and Prevention defines PTSD as an intense, uncontrollable emotional and physical reaction to a reminder of a traumatic event or distressing memories. The percentage of Americans who experience PTSD sometime in their lifetime remains relatively stable at around 5-7% (Griswold, 2023), (National Center for PTSD, 2014), (Wolmark, 2023). There are sex-based differences in how people respond to

trauma. Women have a two to three times higher risk of developing PTSD compared to men. The lifetime prevalence of PTSD is about 10–12% in women and 5–6% in men (Olff, 2017).

One possible mechanism of PTSD is an impairment or attenuation of response inhibition. Response inhibition refers to the suppression of actions that are inappropriate in a given context and that interfere with goal-driven behavior (Mostofsky & Simmonds, 2008) and it is a mechanism of interest because decreased inhibition-related hippocampal activation soon after trauma has been shown to predict future PTSD symptom severity (van Rooij et al., 2018). Another study found that individuals with PTSD and those that were trauma-exposed but did not have a formal PTSD diagnosis, made more inhibition-related errors than individuals without trauma exposure (Falconer et al., 2008). PTSD patients also display neural alterations in regions that underlie cognitive control. Studies have found that response inhibition is associated with brain activation in the ventromedial prefrontal cortex (vmPFC), right inferior frontal gyrus (rIFG), and hippocampus. During response inhibition, the rIFG plays a critical role due to its involvement in monitoring attention and detecting the stop signal (Duann et al., 2009; Hampshire et al., 2010). The key inhibition circuits affected in PTSD are the vmPFC and the hippocampus. Neuroimaging studies have consistently shown reduced activation in these areas using both fear inhibition and response inhibition tasks (Jovanovic et al., 2013; van Rooij et al., 2018). Previous studies have found that impaired inhibition of fear is a potential neurobiological mechanism increasing risk for PTSD (van Rooij and Jovanovic, 2020). The hippocampus is a crucial mediator of the fear inhibition response and lesser hippocampus activation during a response inhibition task has been linked with increased PTSD symptoms (van Rooij et al., 2016), showing that hippocampus activation and inhibitory control are positively associated. Impaired response inhibition has been identified as a mechanism for PTSD development, and Borst and colleagues found that males and females exhibit differences in how they respond to trauma. More specifically, they showed sex differences in the relationship between inhibition-related brain activation and PTSD symptom severity and progression (Borst et al., 2024). Research has consistently shown that female alcohol usage patterns tend to exhibit heightened sensitivity to negative affect and stress (Verplaetse et al., 2018) and women who are heavy drinkers have greater impaired inhibition compared to male heavy drinkers (Smith et al., 2016). Based on these findings, we found it prudent to examine the moderating effect of sex.

Our study will analyze the relationship between the neural correlates of response inhibition and alcohol usage patterns. It has been widely known that alcohol affects inhibitory control. Evidence of this has been shown in intoxicated participants with delayed stop-signal reaction times (SSRTs) compared to placebo (Gan et al., 2014). Performance on tasks of response inhibition has been demonstrated to be impaired in individuals with AUD compared with controls in most studies (Goudriaan et al., 2006; Maurage et al., 2011) . Lower levels of inhibitory control can be both the cause and the consequence of excessive alcohol consumption. Deficits in response inhibition may lead to vulnerability to addictive behaviors (Goldstein & Volkow, 2002). Another study found that failures during response inhibition task could predict binge drinking among social drinkers (Henges & Marczinski, 2012).

As described above, prior literature has identified separate links of trauma-inhibition and alcohol use-inhibition. Impaired inhibition may be a mechanism through which recently-traumatized individuals increase their alcohol usage and potentially lead to AUD. However, none of the current literature has linked trauma, impaired response inhibition, and alcohol use together. This study intends to illuminate the relationship between trauma and alcohol use through a neurobiological mechanism of impaired response inhibition. Our research question asks whether post-trauma neuroimaging correlates of response inhibition are associated with certain alcohol use patterns in a recently-traumatized population. By studying the neural mechanisms and risk factors that can precede AUD, we can develop more effective treatments, development of early interventions, and efficient identification of at-risk individuals. We hypothesize that among a recently-traumatized population, impaired response inhibition (lower inhibition-related activation in the vmPFC, rIFG, and hippocampus) would be observed among those with increasing alcohol usage at eight-weeks and six-months post trauma. Additionally, we hypothesize that the relationship between impaired response inhibition and alcohol usage will be stronger in females than in males. We investigated alterations in alcohol use following a traumatic event between the three-month and six-month marks. This timeframe has often been emphasized because it's a period when post-trauma symptoms tend to either subside or intensify (Blanchard et al., 1995; Perez Benitez et al., 2013; Schock et al., 2016; Warren et al., 2014).

Methods

Participants

Participants were enrolled as part of a multisite longitudinal study (AURORA; U01 MH110925) from 22 U.S. emergency departments (EDs). To be eligible for the study, participants needed to have experienced a traumatic event meeting the criteria outlined in the DSM-5 within the past 72 hours.

MRI scans were conducted at five locations in proximity to participating emergency departments. Exclusion criteria for MRI encompassed the presence of metal or ferromagnetic implants, reluctance to undergo MRI, a history of seizures, epilepsy, Parkinson's Disease, dementia (including Alzheimer's Disease), prior experience of moderate to severe traumatic brain injury, and ongoing pregnancy. Each participant granted written informed consent, which was approved by the Institutional Review Board of each study site.

Clinical Assessment

Upon enrollment in the study, participants were asked to complete questionnaires assessing demographics and trauma characteristics at various intervals. Demographic information, including race/ethnicity, sex assigned at birth, marital status, income, education level, and

employment status, was gathered. Participant demographic and clinical data are presented in Table 1.

Participants provided reports on alcohol use at several time points: pre-trauma (evaluated in the emergency department at enrollment), weeks 2 and 8 (denoted as 2w and 8w, respectively), months 3 and 6 (3m and 6m, respectively). Trauma severity was gauged through participants' subjective ratings of their perceived likelihood of dying. In light of previous research linking childhood trauma to reward-related neurocircuitry, childhood trauma was evaluated using the Childhood Trauma Questionnaire Short Form (CTQ-SF), a 28-item scale examining exposure to traumatic experiences during childhood (Bernstein et al., 2003).

To assess alcohol quantity and frequency, the PhenX Toolkit Alcohol – 30-Day Quantity and Frequency Measure, a two-item questionnaire, was employed. Participants were asked about the number of days they had consumed alcohol in the past 30 days (excluding small tastes or sips) and the average quantity of drinks per day on those occasions. The primary alcohol use outcome of interest was the product of frequency and quantity over the 30 days, with a focus on the difference between 8 weeks post-trauma and pre-trauma (ED enrollment). This outcome of interest was referred to as alcohol QuanFreq. The reference period for all assessments was the past 30 days, except for the 2w time point, where data was assessed over the past 14 days. For longitudinal analysis, this variable was multiplied by 2 to align more closely with other time points.

Functional MRI task

We conducted an assessment of response inhibition using an inhibition-related task, in our case, the Go/NoGo task administered at 2 weeks post-trauma. In addition, neuroimaging using fMRI was used to assess BOLD signals among brain regions typically associated with impaired response inhibition-- vmPFC, rIFG, and hippocampus.

During the Go/NoGo task, participants were presented with either an X or an O and instructed to rapidly press 1 for the X and 2 for the O (designated as Go trials). However, they were required to refrain from responding when the "NoGo" sign was displayed, indicated by a red square appearing behind the X or O. A blood oxygen level-dependent (BOLD) contrast specifically for correct NoGo trials compared to Go trials was generated to assess activation related to response inhibition.

fMRI Data Analysis

Blood oxygenated level-dependent (BOLD) activation data in response to the Go/NoGo was available for 327 participants. Participants underwent screening to assess MRI eligibility and to identify any other exclusion criteria. Functional MRI scans were conducted utilizing 3T scanners at five distinct locations: Emory University, McLean Hospital, Temple University, Wayne State University, and Washington State University in St. Louis. T1-weighted structural scans were acquired using a multi-echo magnetization prepared rapid acquisition gradient

echo (ME-MPRAGE) technique, maintaining consistent parameters to achieve a 1mm isotropic resolution across all sites. Functional scans were also obtained with the same parameters, although the scan duration varied slightly among the scanners at the five sites. The scanner site was incorporated as a covariate in all analyses using dummy variables.

Region of Interest (ROI) Analysis

We obtained BOLD contrast estimates for the bilateral hippocampus, right inferior frontal gyrus (rIFG), and ventromedial prefrontal cortex (vmPFC) reflecting correct NoGo>Go. This is a contrast of interest representative of brain activation exclusive to the inhibitory process (Simmonds et al., 2008) and has been used in other studies measuring response inhibition (Fryer et al., 2018). These predefined regions of interest were guided by prior research. The vmPFC was anatomically delineated according to established coordinates from a previous study, the bilateral hippocampus was defined based on the Hammers atlas, and the rIFG was anatomically defined using the Automated Anatomical Labeling Atlas.

Statistical Analysis

We divided the participants into three groups: an increasing, a decreasing, and a no change group based on their change in alcohol usage from pre-trauma to 8 weeks post trauma. In order to place each participant in their respective group we created change scores by subtracting the pre-trauma alcohol QuanFreq from the 8 week QuanFreq.

Additionally, we divided the participants into an increasing, a decreasing, and a no change group depending on their change in alcohol usage from pre-trauma to 6 months post trauma using the same method but using 6 month QuanFreq instead.

We performed two-way ANOVA to examine the effect of sex and alcohol change groups on brain activation. If a significant interaction between sex and alcohol change groups was observed, we ran follow-up one-way ANOVA controlling for site on females in order to determine the differences in brain activation among each alcohol change group within females, and did the same for males. Tukey post-hoc tests were used to reveal significant pairwise differences in brain activation between different alcohol change groups within a sex, as well as between sexes. Sensitivity analyses were conducted to test the strength of the findings, including the following covariates: age, trauma type, trauma severity, CTQ, and baseline alcohol usage.

Results

Neuroimaging data was available for 327 individuals (208 females). Demographic and clinical characteristics are presented in Table 1. Of the pre-trauma to 8w alcohol change groups, there were n=115 in the decreasing group, n=117 inthe increasing group, and n=95 in the no change group. Of the pre-trauma to 6m alcohol change groups there were 122

members of the decreasing group, 108 members of the increasing group, and 97 in the no change group.

A two-way ANOVA was conducted that examined the effect of sex and alcohol change groups (8w) on brain activation. All ANOVAs corrected for the site in which the neuroimaging scan took place. There was a statistically significant interaction between the effects of sex and alcohol change group on right hippocampal, $F(2,317)=3.98$, $p=0.02$, and rIFG activation $F(2,317)=4.43$, $p=0.01$. See Table 2.

Sensitivity analysis was conducted to correct for the potential confounding factors of age, trauma type, trauma severity, CTQ, and baseline alcohol usage. Upon running a sensitivity analysis, we found that the 8w interaction between sex and alcohol change group in the rIFG was still significant when adjusting for age, trauma type, and trauma severity, CTQ, and when all covariates were added ($p=0.03$). However, the interaction in the right hippocampus was nonsignificant when adjusting for CTQ ($p=0.10$), and marginally significant when all covariates were added together ($p=0.05$). Thus, our findings are robust even when controlling for all of these variables.

Given the significant interaction found, post-hoc one-way ANOVA was performed to better understand differences in brain activation between alcohol change groups (8w) within females. A significant difference of rIFG activation among female alcohol change groups $F(2,201)=3.21$, $p=0.04$ was found (see Table 3), whereby females in the no change group ($M=0.23$, $SD=0.47$) had significantly greater rIFG activation compared to females in the decreasing group ($M=0.026$, $SD=0.46$) ($p_{adj} = 0.03$) (see Figure 1). This difference in rIFG activation was not observed among males.

Post-hoc one-way ANOVA was performed to better understand differences in brain activation between alcohol change groups (8w) within males. A marginally significant difference of right hippocampus activation among male alcohol change groups $F(2,112)=2.70$, $p=0.07$ was found (see Table 4), whereby males in the no change group ($M=-0.009$, $SD=0.48$) had significantly lower right hippocampus activation compared to males in the decreasing group ($M=0.21$, $SD=0.46$) ($p_{adj} = 0.08$) (see Figure 2). This difference in right hippocampus activation was not observed among females.

Post hoc analysis using a Tukey test for the right hippocampus showed that females in the no change group ($M=0.41$, $SD=0.57$) had significantly higher right hippocampus activation compared to males in the no change group ($M=-0.009$, $SD=0.48$) ($p_{adj} = 0.0007$) (see Figure 2). Post-hoc analysis for the rIFG showed that all pairwise comparisons were nonsignificant ($p=0.11$). No other comparisons were significant.

A two-way ANOVA was conducted that examined the effect of sex and alcohol change groups (6m) on brain activation. There was a marginally significant interaction between the effects of sex and alcohol change group on right hippocampus activation $F(2,317)=2.902$, $p=0.056$. See Table 5.

We found that the 6m interaction between sex and alcohol change group in the right hippocampus was still marginally significant when adjusting for age, trauma type, trauma severity, CTQ, and when all covariates were added together (p=0.05).

A one-way ANOVA on females using alcohol change group (6m) corrected for site showed no significant comparisons. See Table 6. A one-way ANOVA on males using alcohol change group (6m) corrected for site also showed no significant comparisons. See Table 7.

Post hoc analysis using a Tukey test for the right hippocampus showed that, among those who had increasing alcohol use, females (M=0.37, SD=0.52) had higher right hippocampal activation than males (M=0.065, SD=0.40) (p_{adj} = 0.02) (see Figure 3). No other comparisons were significant.

Discussion

The primary aim of this study was to investigate the relationship between post-trauma neuroimaging correlates of response inhibition and subsequent alcohol use among a recently-traumatized sample. We hypothesized that among recently-traumatized individuals, impaired response inhibition (lower inhibition-related activation in the vmPFC, rIFG, and hippocampus) would be observed among those with increasing alcohol usage at eight-weeks and six-months post trauma. Additionally, we hypothesized that the relationship between impaired response inhibition and alcohol usage would be stronger in females than in males. Our results did not support our first hypothesis, but our findings did partially support our second hypothesis. We did not observe a difference in activation in any of the ROIs between the alcohol change groups and thus our hypothesis that impaired response inhibition would be observed in the increasing alcohol group was not supported. Contrary to our first hypothesis, we did not observe a relationship between the increasing alcohol group and brain activation in any of the ROIs across the group, and there was no main effect of alcohol change group on inhibition-related brain activation at either time point. However, we demonstrated an interaction with sex such that females in the decreasing alcohol group had lower rIFG activation compared to females in the no change group, and males in the no change group had lower right hippocampus activation compared to males in the decreasing alcohol group at 8 weeks. We did not observe any significant differences in vmPFC or left hippocampus activation among the different alcohol change groups in either males or females.

There were two within-sex findings, and both were observed at 8 weeks. First, females who had decreasing alcohol usage had lower rIFG activation compared to females who did not change their alcohol usage patterns. The increasing group did not significantly differ from the decreasing or no change group. This finding did not support our hypothesis of lower rIFG activation in those who had increasing alcohol usage. Other studies have focused on the rIFG in the context of comparing the rIFG activation of binge drinkers or heavy drinkers to

controls during an inhibition-related task. One study found that higher rIFG activation is necessary to inhibit responses to alcohol-related cues when craving is high and that higher rIFG activation predicts a better drinking outcome at 3 months (Grieder et al., 2022). However, another paper showed that during successful inhibition trials, binge drinkers showed greater rIFG activity relative to controls (Suárez-Suárez et al., 2020). Another study observed greater activation of the right inferior frontal cortex (rIFC) in binge drinkers than in controls during successful inhibition (López-Caneda et al., 2012). The authors attributed this to a compensatory mechanism, as the increased activity in the rIFG could be interpreted as a greater recruitment of neural resources to inhibit a response successfully. This compensatory mechanism is also consistent with our findings, seeing as those with higher rIFG activation are in the no change group rather than the decreasing group. Our study is one of the first to link rIFG activation to decreasing alcohol usage patterns among a recently traumatized population. It should be noted that our findings cannot be explained by pre-existing drinking patterns, as our findings remained significant after controlling for baseline alcohol use. Therefore, although response inhibition and alcohol use have a bidirectional relationship, our findings were independent of alcohol's effect on response inhibition. These findings offer support for the theory that lower rIFG activation could potentially lead to better alcohol outcomes among females who are recently traumatized.

Second, a marginally significant finding was found where males who did not change their alcohol usage patterns had lower right hippocampus activation compared to males who had decreasing alcohol usage. This finding should be interpreted with caution, as it was marginally significant to begin with, did not hold up under sensitivity analysis, and lacked previous literature to support the finding. The contrasting findings in different regions of interest for males and females, in the right hippocampus and rIFG respectively, may offer support for different neurobiological mechanisms in males versus females that lead to the same function, which will be expanded on later.

There were two between-sex differences observed. Given the main effect of sex that we observed in the bilateral hippocampus during both timeframes, females have higher activity in the bilateral hippocampus relative to males, not considering the alcohol use group. Additionally, based on the interaction between sex and alcohol change group at 8 weeks, females who did not change their alcohol usage had significantly higher right hippocampus activation compared to males who did not change their alcohol usage. Similarly, in the 6-month timeframe, females who had increasing alcohol usage had significantly higher right hippocampal activation than males who had increasing alcohol usage.

There is evidence that the hippocampus is affected differently by stress based on sex, and that stress exposure may drive sex-specific consequences in neural function. The hippocampus is rich in sex steroid receptors, which confers a unique susceptibility of the hippocampus to the consequences of stress, positioning this region as a locus for interaction between sex and stress hormones to drive stress-induced changes in cognition (Luine et al., 2017; McEwen, 1999). These studies suggest sex-specific effects in the recruitment of these brain regions during response inhibition. Previous studies have proposed that differences could be

attributed to sex-specific hormones. One study showed that the hippocampal neurons in the CA3 area in male mice atrophy with chronically elevated glucocorticoids, while female mice show minimal morphological changes with comparable glucocorticoid regimens (Liu et al., 2006). Repeated estradiol administration affects adult neurogenesis and cell death in the dentate gyrus of adult female, but not male, rats (Barker and Galea, 2008), demonstrating that estradiol differentially affects hippocampus structure in adult male and female rats. Our findings demonstrated greater right hippocampus activity in females compared to males in two types of alcohol change groups, which suggests that hormones could be playing a sex-specific role in development of excessive alcohol use through physiological changes in the right hippocampus.

Lesser hippocampus activation during a response inhibition task has been linked with increased PTSD symptoms (van Rooij et al., 2016). Here, we observe lesser hippocampus activation during a response inhibition task being present in males with increasing alcohol usage compared to females with increasing alcohol usage. This suggests that in males, impaired response inhibition could potentially be the same mechanism in which PTSD and excessive alcohol use progress. Hypoactivation of the right hippocampus during response inhibition may help identify males at risk of developing excessive alcohol consumption after experiencing a trauma.

Seeing as applications such as transcranial magnetic stimulation (TMS) require a high degree of accuracy in targeting a specific brain area to lead to therapeutic effects, our research may allow for future interventions to be more localized to the relevant regions of interest to maximize efficacy. However, because TMS can only affect cortical brain regions (Pascual-Leone et al., 1999), future applications of TMS would most logically apply to the rIFG. Due to the compensatory mechanism in the rIFG observed in females that was mentioned earlier, downregulation of the rIFG using TMS could lead to better alcohol outcomes, but further research is needed in this area. Additionally, interventions targeting the right hippocampus may be warranted depending on the individual's sex.

Strengths

This study is unique in several aspects. Firstly, it examines the interplay between trauma, impaired response inhibition, and subsequent alcohol use, offering valuable insights into the neurobiological pathways potentially contributing to AUD development following traumatic experiences. Secondly, the longitudinal design of the study allowed us to track changes in alcohol use over time, providing a comprehensive understanding of post-trauma alcohol consumption patterns. The strength of this investigation lies in its rigorous methodology and utilization of a large, diverse sample obtained from multiple emergency departments across the United States. By using three different alcohol change groups, we are able to analyze not only the neural correlates of worsening alcohol outcomes, but also stable outcomes and improving outcomes which may provide better insight into how to develop interventions. Moreover, by assessing the moderating effect of sex, our analysis provides a nuanced exploration of sex differences in the relationship between response inhibition, trauma, and alcohol use.

Limitations & Future Work

Despite its strengths, this study has several limitations that warrant consideration. Firstly, the reliance on self-reported measures of alcohol use may introduce bias and inaccuracies in the assessment of drinking behaviors. Future studies could incorporate objective measures, such as biomarkers of alcohol consumption, to enhance the reliability of alcohol use data. For future studies, a model that analyzes the functional connectivity between the three ROI could be utilized to gain a deeper understanding of the relationship between alcohol usage patterns and brain activation. Non-trauma-related stress within participants should also be accounted for by using a stress measure such as the Perceived Stress Scale (PSS) and corrected for if there is an association with brain activity. More research is needed on the sex-specific differences in mechanisms that can lead to vulnerability towards increased alcohol usage. Future research must provide more detailed mechanistic validation of our findings, potentially using preclinical studies to manipulate estradiol and glucocorticoid levels early-post stressor. Furthermore, TMS could be used to temporarily lesion areas of interest, allowing us to downregulate regions associated with response inhibition and observe corresponding changes in alcohol use and PTSD symptoms. Additionally, further studies on response inhibition should be performed on humans in order to identify sex-specific differences in the inhibitory network.

Conclusion

In conclusion, this study provides valuable insights into the neurobiological mechanisms linking trauma, impaired response inhibition, and alcohol use in a recently-traumatized population. By elucidating these relationships, we contribute to the growing body of literature on AUD etiology and pave the way for targeted interventions aimed at reducing alcohol-related harm in trauma-exposed individuals. By identifying impaired response inhibition as a potential risk factor for post-trauma alcohol use, clinicians can implement targeted interventions aimed at enhancing inhibitory control and reducing alcohol-related harm in trauma-exposed individuals. Our findings suggest that the rIFG and right hippocampus are highly important regions that could potentially be involved in inhibiting alcohol use. The sex differences that were observed in the right hippocampus reveals a potential target for sex-specific interventions.

Table 1. Demographics and Clinical Characteristics

Characteristic		Females (N=208)	Males (N=119)	Statistic	p value
Age, years		**33.46 ± 12.3**	**34.95 ± 13.9**	**t = 0.97**	**.33**
Race				**χ^2 = 3.15**	**.37**
	Black Americans	**101**	**46**		
	White Americans	**68**	**43**		
	Hispanic	**32**	**23**		
	Other	**7**	**6**		
Income				**χ^2 = 3.31**	**.65**
	$19,000	**52**	**23**		
	$19,001 - $35,000	**61**	**33**		
	$35,001 - $ 50,000	**29**	**14**		
	$50,001 - $75,000	**19**	**9**		
	$75,001 - $100,000	**12**	**7**		
	>$100,000	**16**	**15**		
Broad trauma type				**χ^2 = 10.21**	**.33**
	Motor vehicle collision	**154**	**79**		
	Non-motorized collision	**6**	**6**		
	Fall >= 10 feet	**3**	**3**		
	Fall < 10 feet	**14**	**8**		
	Physical assault	**18**	**14**		
	Sexual assault	**3**	**0**		
	Animal related	**5**	**4**		
	Other	**5**	**5**		

Clinical characteristics					
	PTSD Symptoms (PCL-5, scale 0-80) during Pre Study	**28.9 ±15.5**	**29.3 ± 14.1**	**t = 0.23**	**.81**
	PTSD Symptoms (PCL-5, scale 0-80) at 8-weeks	**28.1 ± 18.4**	**23.1 ± 16.6**	**t = 2.54**	**.01***
	PTSD Symptoms (PCL-5, scale 0-80) at 6-months	**23.5 ± 18.3**	**16.8 ± 15.1**	**t =3.53**	**.0005*****

***p<0.05 , ** p<0.01, ***p<0.001**

Table 2. ANOVA ROI analyses for Increasing, Decreasing, No Change Groups for Both Sexes for 8 week timeframe

	p-value				
Region of Interest	**Sex**	**Alcohol Change Group**	**Site**	**Sex x Alcohol Change Group**	**Sex x Alcohol Change Group with Covariates**
Model 1: vmPFC	0.57	0.52	0.67	0.24	0.12
Model 2: Left Hippocampus	0.019 *	0.97	0.45	0.72	0.57
Model 3: Right Hippocampus	0.0014 **	0.80	0.36	0.020 *	0.052 †
Model 4: rIFG	0.46	0.66	0.17	0.013*	0.035

† p<0.10, *p<0.05 , ** p<0.01, ***p<0.001

Table 3. ANOVA ROI analyses for Increasing, Decreasing, No Change Groups for Females for 8 week timeframe

	p-value	
Region of Interest	**Alcohol Change Group**	**Site**
Model 1: vmPFC	0.97	0.60

Model 2: Left Hippocampus	0.94	0.85
Model 3: Right Hippocampus	0.19	0.85
Model 4: rIFG	0.043 *	0.0049 **

***p<0.05 , ** p<0.01, ***p<0.001**

Table 4. ANOVA ROI analyses for Increasing, Decreasing, No Change Groups for Males for 8 week timeframe

	p-value	
Region of Interest	**Alcohol Change Group**	**Site**
Model 1: vmPFC	0.18	0.82
Model 2: Left Hippocampus	0.66	0.28
Model 3: Right Hippocampus	0.072 †	0.90
Model 4: rIFG	0.33	0.50

† p<0.10, *p<0.05 , ** p<0.01, ***p<0.001

Table 5. ANOVA ROI analyses for Increasing, Decreasing, No Change Groups for Both Sexes for 6 month timeframe

	p-value				
Region of Interest	**Sex**	**Alcohol Change Group**	**Site**	**Sex** x **Alcohol Change Group**	**Sex** x **Alcohol Change Group with Covariates**
Model 1: vmPFC	0.57	0.11	0.68	0.34	0.48

Model 2: Left Hippocampus	0.018 *	0.91	0.45	0.10	0.14
Model 3: Right Hippocampus	0.0014 **	0.94	0.40	0.056 †	0.052 †
Model 4: rIFG	0.47	0.60	0.18	0.50	0.55

† p<0.10, *p<0.05 , ** p<0.01, ***p<0.001

Table 6. ANOVA ROI analyses for Increasing, Decreasing, No Change Groups for Females for 6 month timeframe

	p-value	
Region of Interest	**Alcohol Change Group**	**Site**
Model 1: vmPFC	0.52	0.57
Model 2: Left Hippocampus	0.59	0.85
Model 3: Right Hippocampus	0.27	0.32
Model 4: rIFG	0.28	0.01*

***p<0.05 , ** p<0.01, ***p<0.001**

Table 7. ANOVA ROI analyses for Increasing, Decreasing, No Change Groups for Males for 6 month timeframe

	p-value	
Region of Interest	**Alcohol Change Group**	**Site**

Model 1: vmPFC	0.10	0.90
Model 2: Left Hippocampus	0.12	0.29
Model 3: Right Hippocampus	0.21	0.91
Model 4: rIFG	0.96	0.57

***p<0.05 , ** p<0.01, ***p<0.001**

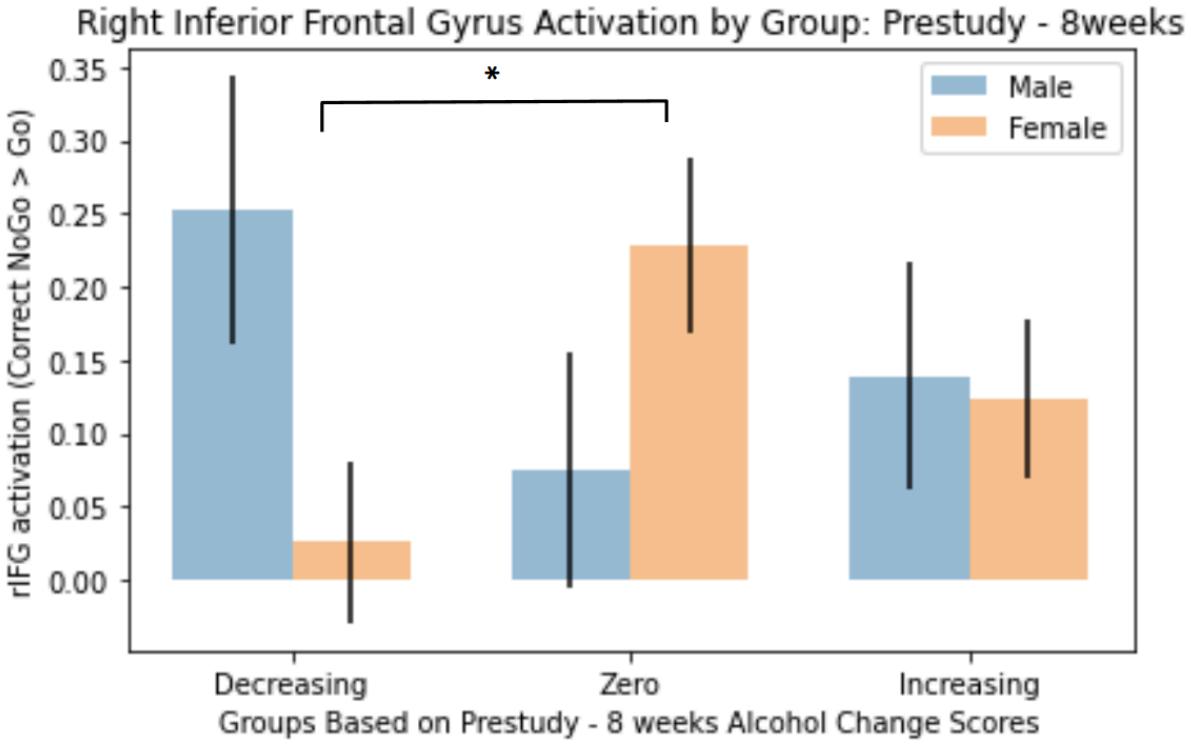

Figure 1. Mean rIFG activation separated by alcohol change group and sex for the 8 week timeframe. Error bars represent standard error of the mean; Zero = No Change Group. *p<0.05

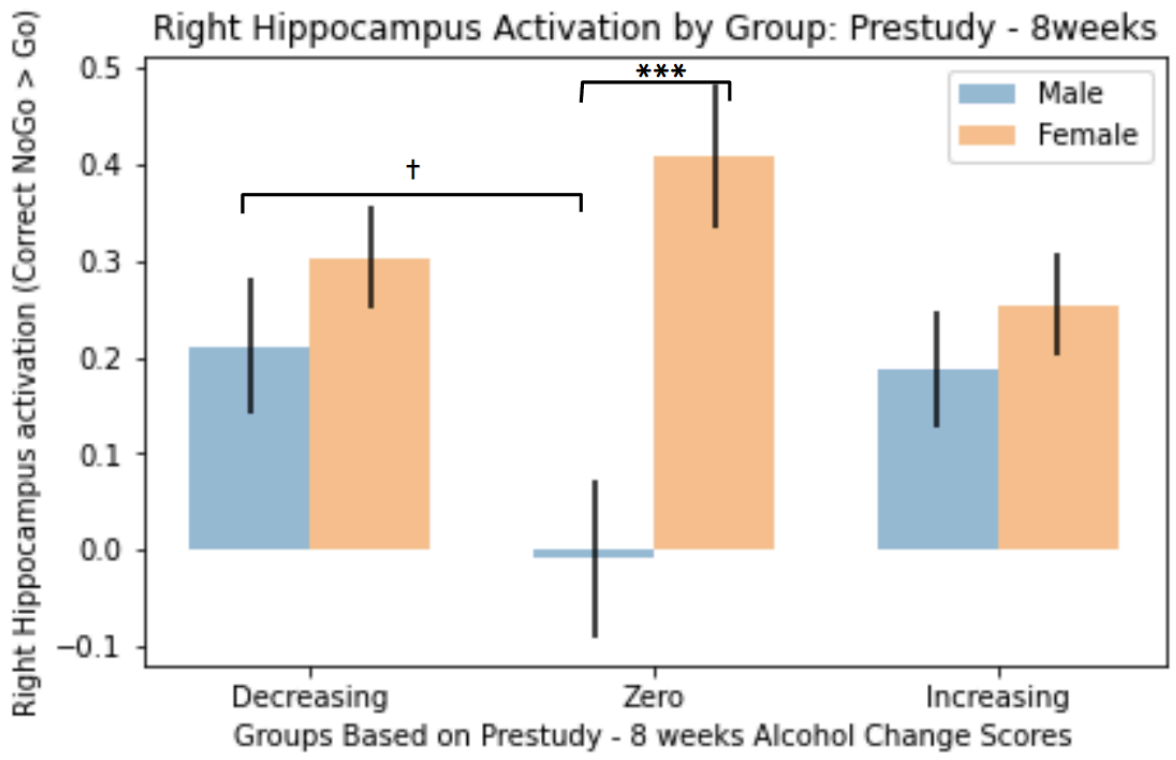

Figure 2. Mean right hippocampus activation separated by alcohol change group and sex for the 8 week timeframe. Error bars represent standard error of the mean; Zero = No Change Group. † p<0.10, *p<0.05 , ** p<0.01, ***p<0.001

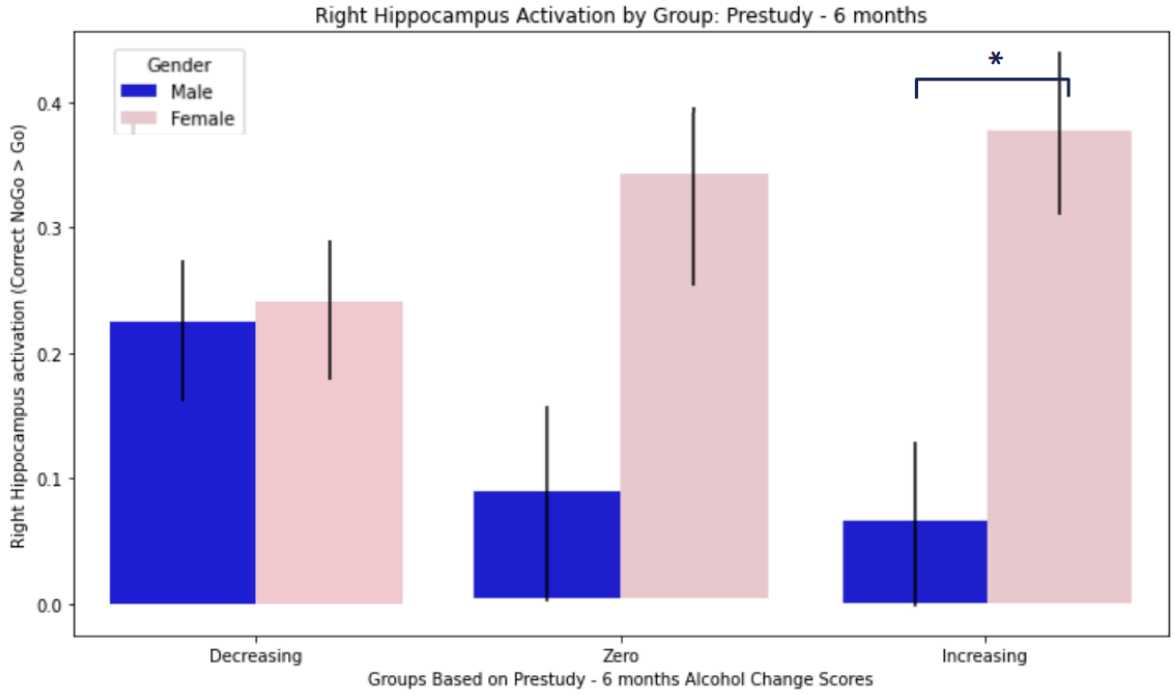

Figure 3. Mean right hippocampus activation separated by alcohol change group and sex for the 6 month timeframe. Error bars represent standard error of the mean; Zero = No Change Group. *p<0.05

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