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Journal

Alcoholism: Clinical and Experimental Research, 48(4)

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Publication Date

2024-04-01

DOI

10.1111/acer.15279

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Author manuscript

Alcohol Clin Exp Res (Hoboken). Author manuscript; available in PMC 2025 April 01.

Published in final edited form as:

Alcohol Clin Exp Res (Hoboken). 2024 April ; 48(4): 612–622. doi:10.1111/acer.15279.

Sex differences in alcohol's effects on fronto-amygdalar functional connectivity during processing of emotional stimuli

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Abstract

Background: Amygdala function underlying emotion processing has been shown to vary with an individuals' biological sex. Expanding upon functional magnetic resonance imaging (fMRI) findings reported previously where a low level of response was the focus, we examined alcohol and sex effects on functional connectivity between the amygdala and other brain regions. The central hypothesis predicted that sex would influence alcohol's effects on frontal-limbic functional circuits underlying the processing of negative and positive facial emotions.

Methods: Secondary analyses were conducted on data from a double-blind, placebo controlled, within-subjects, cross-over study in 54 sex-matched pairs (N=108) of 18- to 25-year-old individuals without an alcohol use disorder at baseline. Participants performed an emotional faces fMRI processing task after placebo or approximately 0.7 mL/kg of ethanol. Psychophysiological interaction analyses examined functional connectivity between the amygdala with other brain regions.

Results: Significant alcohol-by-sex interactions were found when processing negatively-valenced faces. Intoxicated men exhibited decreased functional connectivity between the amygdala and ventral and dorsal anterior cingulate, angular gyrus, and middle frontal gyrus whereas connectivity was increased in inebriated women. There was also a main sex effect where women exhibited decreased functional connectivity in the middle insula compared with men regardless of alcohol or placebo condition. For happy faces, main effects of both sex and alcohol were observed. Women exhibited decreased amygdala functional connectivity in right inferior frontal gyrus compared with men. Both men and women exhibited increased functional connectivity in the superior frontal gyrus in response to alcohol versus placebo.

Conclusions: Alcohol's effects on amygdala functional circuits underlying emotional processing vary with sex. Women had higher functional connectivity than men following exposure to a moderate dose of alcohol which might indicate that women can better process affectively-laden stimuli when intoxicated.

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Keywords

Functional Connectivity; fMRI; Alcohol; Facial Expressions; Sex Differences

Introduction

Decades-long gender gaps in women's and men's drinking patterns have narrowed in the United States such that what was once a five-fold, male-to-female preponderance in alcohol use disorder (AUD) prevalence has dwindled to a less than two-fold difference (Grant et al., 2017). Some of the gender convergence in problematic drinking is being driven by young women whose past month alcohol use and reports of drunkenness have eclipsed men's (Agabio et al., 2016, Grant et al., 2017). The increased drinking among female emerging adults is alarming, in part, because of sex differences in alcohol's distribution and metabolism (McCaul et al., 2019). The higher blood alcohol concentrations attained per an equivalent dose of alcohol in women compared with men contribute to more negative health outcomes (Jones, 2019, Karaye et al., 2023). Thus, heavy drinking women with AUD are more prone to develop several alcohol-related diseases than their male counterparts including cirrhosis of the liver and cardiomyopathy (McCaul et al., 2019, White, 2020).

Some of alcohol's effects on the brain may also be sex-specific. For example, in alcohol-naïve adolescents with a family history of AUD, heavy drinking is associated with lower cortical volume and thickness in boys whereas the opposite pattern is observed in girls (Tapert and Eberson-Shumate, 2022). As aging occurs, heavy drinking young adults generally exhibit greater thinning of the dorsolateral prefrontal cortices compared with light drinking controls; however, the magnitude of this effect is greater in men than women (Mann et al., 2005, Medina et al., 2008). Adult women also appear more vulnerable than men to the damaging effects of alcohol on the brain, including volumetric loss in fronto-limbic regions despite, on average, having fewer years of drinking and consuming less alcohol in their lifetime (Nixon et al., 2014).

In some instances, alcohol's sex-specific effects may interact with brain regions exhibiting a degree of sexual dimorphism. Of relevance to the present study is alcohol's effects on prefrontal cortical - limbic system pathways that mediate emotion regulation. In particular, the amygdala in the limbic system is a sexually dimorphic brain region that plays a key role in emotional processing (Alarcón et al., 2015). The amygdala is typically engaged when viewing emotionally salient images and/or faces, reflecting its central connectivity to visual, subcortical, and cortical regions of the brain that are needed to decode and detect emotional cues required for social interactions (Pessoa and Adolphs, 2010, Fusar-Poli et al., 2009). Structural magnetic resonance imaging (MRI) studies have found sex differences in the volume of the amygdala with men having higher volumes than women (Ruigrok et al., 2014). Functional MRI (fMRI) studies on amygdala activation during the viewing of emotional human faces generally report involvement of several additional brain regions, in addition to the amygdala, including the prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, as well as areas in the temporal, parietal, and occipital lobes (Preckel et al., 2019, Fusar-Poli et al., 2009). Regarding sex differences, men typically have greater

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regional activation than women during passive viewing of emotional faces (Fusar-Poli et al., 2009, Sergerie et al., 2008). Further, women generally are more accurate at recognizing and expressing affective states than men, while men react faster during facial affective decision-making (Mann et al., 2005). These findings support a need for greater understanding of the neurobiology of sex differences regarding alcohol effects in order to better elucidate potential sex differences in biological targets for prevention and treatment of AUD and other drug use disorders (Sinha et al., 2022).

The PFC-limbic pathways are particularly sensitive to intoxicating doses of alcohol (Sullivan and Pfefferbaum, 2005), potentially due to overlap with stress pathophysiology (Logrip et al., 2018, Peltier et al., 2019). Studies comparing men with women have found that sex moderates the effects of heavy drinking on brain function in PFC-limbic pathways as measured with fMRI, with men having greater regional activation than women in the medial PFC, inferior and middle frontal gyri, and caudate during an emotion processing task (Padula et al., 2015). Additionally, in an MRI resting-state functional connectivity study, men showed a stronger relationship between decreased amygdala-dorsal ACC connectivity and problem drinking compared to women (Hu et al., 2018). However, neuroimaging studies have not routinely accounted for potential sex differences (Lind et al., 2017). As such, sex differences are generally understudied and findings of sex-dependent effects on neuronal responses are inconsistent across studies. Further, even fewer studies have examined sex differences in functional connectivity between brain regions linked with the sexually dimorphic amygdala -- an ideal region in which to examine the differential effects of alcohol between men and women.

The fMRI-based emotional matching paradigms first introduced by Hariri et al. (Hariri et al., 2002, Hariri et al., 2000) are emotional reactivity paradigms that reliably activate the amygdala (Preckel et al., 2019, Foland-Ross et al., 2010). Participants are asked to match the affective state of faces standardized to portray either negatively valenced affective states, such as anger and fear, or positively valenced affective states, such as happiness. Decoding facial affect is vital when interacting with one’s social environment and successful navigation of social interactions that are important for mental and physical health. Paramount to such efforts is the ability to resolve the nature of socially ambiguous information, that is, social inputs that do not provide enough information about social actions to take such as behaviorally incongruent facial expressions.

Impairments in decoding basic and complex emotional facial expressions have been consistently reported in individuals with AUD, even during periods of lengthy abstinence (Bora and Zorlu, 2017, Le Berre, 2019, Castellano et al., 2015). As a potential *forme fruste* of this phenomenon, and using a modified Hariri paradigm of angry, fearful, and happy faces, we reported functional connectivity differences between low and high responders to alcohol in amygdala-based connections. A low level of response (LR) to alcohol was associated with lower functional connectivity in PFC-amygdala regions (McKenna et al., 2022). Although we did not find sex differences in the connectivity patterns of low- versus high-LR participants, we speculated that attenuated connectivity among low LR individuals when processing emotional faces may contribute to an impaired ability to recognize alcohol intoxication in social situations and appraise emotional states. While research has focused on

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the contributions of a cortico-limbic circuit supporting emotion processing in the emergence of AUD risk (e.g., Glahn et al., 2007), how social drinking women and men differ in their brain response while intoxicated is not known. At a time when alcohol misuse is on the rise, and binge drinking and AUD rates have substantially increased in women (Grant et al., 2017), there is a major gap in understanding the mechanisms and processes that specifically increase risks for the onset and development of AUD in women compared with men. Given that AUD is a heterogeneous disorder, elucidating sex-specific neuroimaging biomarkers underlying emotion processing could aid in developing sex-specific novel interventions.

The aim of the present study was to focus on an integrative perspective of the brain using amygdala-based functional connectivity analyses to investigate sex differences in response to alcohol with a modified Hariri paradigm in a sample of young social drinkers without AUD. This sample allowed us to examine potential sex-dependent functional connectivity changes in response to alcohol before more chronic alcohol use leads to significant neuroadaptive changes (Clapp et al., 2008) or changes neurobiology as observed during AUD (Gilpin and Koob, 2008). Once an individual has AUD it is more difficult to determine if any variable, including fMRI patterns, are caused by heavy drinking. Further, the vast majority of drinkers do not have AUD and we aimed to understand important information on sex differences among this population. Specifically, we employed generalized psychophysiological interactions (gPPI), a technique that examines the task-modulated connectivity between a seed region (e.g., the amygdala) and the whole brain (O'Reilly et al., 2012, McLaren et al., 2012). Hypothesis 1 predicts that the effect of modest alcohol intoxication would differentially impact PFC-amygdala functional connections in men and women such that women would have lower amygdala-frontal cortical connectivity values compared to men during the placebo condition. Hypothesis 2 predicts that women would have greater amygdala-frontal cortical connectivity values compared with men while under the influence of alcohol. That non-AUD women would have greater fronto-amygdalar connectivity compared to men under the influence of alcohol might indicate that women can better process affectively-laden stimuli when intoxicated.

Methods

Participants:

We conducted secondary analyses on a dataset of 216 MRI scanning sessions from 108 individuals (54 male and 54 female participants) extracted from a study first reported by Paulus et al. (2012). A detailed explanation of the methodological approach is discussed in both the original Paulus et al. (2012) study and our more recent functional connectivity paper (McKenna et al., 2022). Briefly, as part of the original UCSD Institutional Review Board-approved study, a survey was distributed to randomly selected 18 – 25-year-old European American and White Hispanic students at the University of California, San Diego. Information on demography, substance use, and DSM-IV psychiatric disorders was collected using standardized self-report instruments (Bucholz et al., 1994). Exclusion criteria included: 1) left-handed; 2) history of brain trauma or epilepsy; 3) history of alcohol or drug dependence; 4) current major psychiatric disorder; 5) was pregnant at time of MRI; 6) and

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had irremovable body metal. Participants were matched on demography, level of response to alcohol, drinking frequency and quantity, as well as tobacco and cannabis use.

Following screening and an in-lab alcohol challenge reported elsewhere (Paulus et al., 2012), two MRI sessions were scheduled approximately one week apart. Alcohol and placebo MRI sessions were carried out in a random order where participants drank either alcohol (0.75 mL/kg for men and 0.70 mL/kg for women) over a 10-minute period while instructed and monitored to drink consistently throughout time and to consume the entire contents. The alcoholic beverage was given as a 20% by volume solution in a room-temperature carbonated beverage, or placebo and was consumed before undergoing MRI. The modified Hariri emotional face-processing task was presented to participants in the MRI scanner 60 minutes post-beverage consumption during placebo and alcohol fMRI sessions, a time close to the peak BrAC during the average alcohol session. This protocol produced approximately equivalent BrACs across sexes (Baraona et al., 2001).

Task:

The modified version of the Hariri emotional face-processing task (Hariri et al., 2005, Paulus et al., 2005) is a block design involving a 5 second presentation of a target face and two probe faces, with instructions to match the probe and emotional expression of the target by pressing one of two buttons on response box. There were a total of 12 blocks consisting of six trials in each block with a total task time of 512 seconds. Each emotion condition (angry, fearful, or happy faces) and a sensorimotor control condition were presented in three separate blocks in a pseudorandom order. The control condition involved vertical or horizontal ovals or circles with instructions to match the shape of the probe to the target. The task began with an 8-second fixation period and had interspersed 12-second fixation periods between each block. We recorded accuracy and reaction time during the task to confirm the task was carried out correctly (i.e., above chance levels). A further detailed description of the task paradigm is presented in McKenna et al. (2022).

Image Acquisition:

Scanning was conducted at the UC San Diego Center for Functional Magnetic Resonance Imaging on a 3.0 Tesla GE CXK4 Magnet equipped with eight high-bandwidth receiver head coil. A sagittal high-resolution T1-weighted anatomical scan was acquired using a spoiled gradient recalled sequence (field of view = 25 cm; matrix = 192 × 256; 172 sagitally acquired slices 1-mm thick; repetition time = 8 msec; echo time = 3 msec; flip angle = 12°). An eight-channel brain array coil was used to axially acquire T2*-weighted echo-planar images (EPIs) (field of view = 23 cm, matrix = 64 × 64, 30 slices 2.6-mm thick, gap = 1.4mm, repetition time = 2000 msec, echo time = 32 msec, flip angle = 90°).

Image Processing:

We used the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996) to process imaging data and conduct statistical analyses. First, structural T1-weighted images were stripped of the skull and extraneous tissue and warped into Talairach-Tournoux atlas space using a 12-parameter affine transformation. EPI scans were each visually inspected for scanner artifacts and motion across time. In order to correct for small movements over time,

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image repetitions were registered to a selected base volume in the middle of the time series. Six motion parameters from this step were used in subsequent linear regression analyses of individual data to control for spin history effects (Friston et al., 1996). EPI data were transformed into the participant's anatomical space and aligned to standard space using the previously computed anatomical transformation matrix, and smoothed with a 4-mm FWHM Gaussian kernel. Deconvolution analysis of the fMRI time series was conducted using general linear models (GLMs) where the reference vectors for the task conditions were convolved with the hemodynamic response function. Estimated motion parameters and linear, quadratic, and cubic trends were included as nuisance variables. The resulting output used in out functional connectivity analyses were beta coefficient maps representing the mean change in percent BOLD signal for each condition versus baseline.

Statistical Analyses:

Identical statistical analytic methods were used in our prior report on LR and described in detail there (McKenna et al., 2022). Briefly, anatomical-defined seeds in the left and right amygdala were used for gPPI analyses. Seed regions were chosen using Neurosynth (https://neurosynth.org/), a meta-analytic tool for selecting fMRI activation coordinates from a database of studies (Yarkoni et al., 2011). We reviewed coordinates from studies using emotional face processing tasks to elicit amygdala activation. Based on this review, we created a 5-mm sphere around the coordinates X = −26, Y = 6, Z = −14 and resampled to the template space of our EPI scans. Visual inspection ensured that the derived seeds were anatomically constrained to the amygdala. For each participant, the BOLD signal time series was extracted for each seed and polynomial trends removed. The task hemodynamic response function was estimated using a one parameter gamma model and a deconvolution of each seed's time series was calculated. PPI regressor interaction terms for each condition of the task were computed by multiplying the mean time series of the de-convolved seed with the condition vector of interest, and then convolved with a gamma basis function. In this way the effects of angry, fearful, or happy conditions on effective connectivity (relative to control condition) were estimated and subsequently analyzed at the group level (i.e., sex differences).

Group analyses involved separate voxel-wise GLMs for each bilateral amygdala seed to compare functional connectivity between men and women. The GLMs were composed of PPI regressors, the physiological regressor (seed time series), psychological regressors (task condition regressors), and nuisance variables (the motion regressors from the prior individual-level analyses). Left and right amygdala seed connectivity with other brain areas were examined separately in whole-brain analyses. Between-group differences were estimated using mixed-effects ANOVAs where the within-subject factor was alcohol condition and the between-subject factor was sex. A cluster threshold approach was used to determine significant clusters of activation by estimating the noise in our fMRI volumes with AFNI program 3dFWHMx with -acf option to better estimate the auto-correlation function in our fMRI data using a mixed-models approach (Gaussian plus a mono-exponential function). Cluster thresholding involved two steps using 3dClustSim in AFNI. First, a voxel-level primary threshold was used to define clusters by retaining significant voxels at a $p = 0.01$ threshold. Second, a cluster-level threshold, measured in

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units of contiguous voxels, was determined at a p = 0.01 level. This two-step process controlled the family-wise error rate at p = 0.01. This estimation set the minimum volume for a significant cluster in our analyses at 448 μL or seven contiguous significant $4mm^3$ voxels consistent with published methodologies in controlling type I and II error in fMRI research (Caparelli et al., 2019).

Results

Demographic Characteristics and Task Performance:

Table 1 shows the characteristics of men and women participants. Pairwise comparisons of men and women did not reveal any sex differences, thus, we did not covary for these variables in our statistical models. Men and women had similar reaction times after placebo and alcohol for angry, fearful, and happy faces. Accuracy was above chance levels (p's < 0.001) suggesting the participants were able to attend to the task regardless of emotional or beverage conditions.

Functional Connectivity Results:

We examined potential sex differences in amygdala functional connectivity during the alcohol and placebo conditions separately for left and right amygdala seeds. Table 2 presents clusters with a significant (i.e., minimum cluster of 448 μL at p ≤ 0.01) sex, alcohol, or sex-by-alcohol interaction effects for each task condition (i.e., fearful, angry, and happy faces). Specifically, the table lists brain regions, associated Brodmann area [a cytoarchitectural organization system (Brodmann, 1909)], peak activation, Talairach coordinates, and volume for each significant cluster. The pattern of functional connectivity main effects for exemplar regions is presented in Figure 1. Interaction effects for exemplar regions are presented in Figure 2. ANCOVA models covarying for LR to alcohol were also ran for all significant clusters. Consistent with our prior report, (McKenna et al. 2022) we did not find any significant interaction effect between LR and sex in our results. An evaluation of the potential impact of sex differences in BrAC curves from the oral alcohol challenge using ANOCVA models covarying for BrAC at 60 minutes (the BrAC timepoint closest to when the Hariri task was given) did not reveal any significant main effects or interactions with sex in our results.

Sex Main Effects: As illustrated in Table 2 and Figure 1, during processing of angry faces, using the left amygdala seed, a main effect of sex was found such that men had greater increases in functional connectivity compared to women in the middle insular region during both the placebo and alcohol conditions. Similarly, during processing of happy faces, men had greater increases in functional connectivity as compared to women in the inferior frontal gyrus during both the placebo and alcohol conditions.

Alcohol Main Effects: For both men and women, during happy faces, increased functional connectivity was observed following alcohol administration compared to placebo (see Table 2 and Figure 1). The increased functional connectivity was observed among the right amygdala seed and the left superior frontal gyrus, left middle insula, and right postcentral gyrus.

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Sex-by-Alcohol Interactions: As depicted in Table 2 and Figure 2, while processing angry faces, and within the right ventral anterior cingulate, decreased functional connectivity was observed with the left amygdala following alcohol compared with placebo in men, but increased connectivity following alcohol was found in women. Similarly, decreased functional connectivity was observed with the right amygdala following alcohol compared with placebo in male individuals, but increased connectivity following alcohol was found in women within the right dorsal anterior cingulate.

Interactions while processing fearful faces were characterized as a decreased functional connectivity with left amygdala following alcohol as compared to placebo in male individuals, but increased connectivity following alcohol in women in right angular gyrus. Also, during fearful faces, using the right amygdala seed, interactions were characterized as decreased functional connectivity following alcohol versus placebo in men, but increased connectivity following alcohol in women in bilateral medial and left middle frontal gyri, right dorsal anterior and dorsal posterior cingulate gyri, left posterior cingulate gyrus, left middle insula, right angular gyrus, left postcentral gyrus, right caudate, and left putamen. Notably, these were all patterns similar to the interactions observed during the processing of angry faces.

Discussion

The primary goal of this study was to expand upon our previous findings (McKenna et al., 2022) demonstrating that in young social drinkers, alcohol's effects on amygdala-based functional circuits underlying facial affect matching varied independently with LR to alcohol. Focusing this time on potential sex differences in emotional processing, and as predicted in hypothesis 1, we found that women demonstrated lower amygdala-frontal cortical functional connectivity compared to men during the placebo condition across all three emotionally-valence conditions. We also observed a main effect of sex when processing angry and happy faces during both placebo and alcohol conditions. Thus, compared with men, women exhibited markedly decreased contralateral functional connectivity between the left amygdala seed and right middle insula for fearful faces, and right inferior frontal gyrus for happy faces. These findings are consistent with other reports that men exhibit increased bilateral amygdala activity than do women (Fusar-Poli et al., 2009, Sergerie et al., 2008), perhaps reflecting their need to work harder than women to decode emotions (Thompson and Voyer, 2014).

When interpreting these findings, it is important to consider that differences in regional activation and functional connectivity patterns depend upon the nature of the task and the novelty of the stimulus. For example, in men more than women, amygdala activation is attenuated with repeated presentations of the same stimulus, perhaps due to greater connectivity between the amygdala and medial frontal regions that inhibit amygdala activation (Andreano et al., 2014, Lungu et al., 2015). Alcohol may interfere with this process, leading to greater frontal lobe involvement to inhibit amygdala activation. Interestingly, the main effect of alcohol observed in the present study was limited to connections between the right amygdala and lateral postcenteral gyrus, as well as the contralateral insular cortex and superior frontal gyrus. These focal effects suggest that

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alcohol itself may not impact all amygdala-based functional networks and other functional networks should be examined in future studies. For example, among heavy drinkers, functional neuroimaging studies have found that brain areas in the salience network, including the insula and anterior cingulate cortex (ACC), or regions associated with reward processing, such as the ventral striatum, are activated by alcohol-related cues (Seo et al., 2011, Heinz et al., 2009, Wrase et al., 2007).

Consistent with hypothesis 2, we observed several sex-by-alcohol interactions in fronto-amygdalar functional connectivity. When moderately intoxicated, women exhibited increased fronto-amygdalar functional connectivity compared to men while processing negatively-valenced faces. Specifically, when processing angry faces, alcohol increased functional connectivity between the contralateral right ventral anterior cingulate and the left amygdala seed region in women, whereas in men under the influence, functional connectivity between these brain regions was decreased. A similar sex-by-alcohol interaction was observed for the right amygdala seed region and its functional connectivity with the unilateral right dorsal anterior cingulate cortex region; men's functional connectivity decreased, while women's functional connectivity increased, when under the influence of alcohol. Similar to the processing of angry faces, women and men exhibited differential patterns of functional connectivity when viewing fearful faces under the influence of alcohol versus placebo. Specifically, functional connectivity between the contralateral right angular gyrus and left amygdala seed region increased in women after imbibing alcohol while the opposite pattern was observed in men. This same pattern was observed in functional connectivity between the right amygdala seed region and a plethora of regions including bilateral medial and middle frontal gyri; lateral anterior and posterior cingulate cortex, caudate, superior and inferior parietal lobe; contralateral posterior cingulate, postcentral gyrus, putamen, and insular cortex.

The brain regions demonstrating a sex-by-alcohol interaction in the present study overlap with brain areas activated and reported by other investigators who used similar emotional processing paradigms. For example, others have found involvement of the ventrolateral and medial PFC, inferior frontal cortex, ACC, insula, superior temporal sulcus, temporal gyrus, superior parietal lobe, and caudate when processing facial emotions (Preckel et al., 2019, Sergerie et al., 2008, Fusar-Poli et al., 2009). Additionally, these regions, especially the PFC, ACC, and amygdala, are altered by alcohol use. For example, one study found that men with AUD had lower activation compared with men without AUD in frontal regions, whereas women with AUD had greater activation than women without AUD in superior frontal and supramarginal gyri in response to happy and aversive stimuli (Sawyer et al., 2019). Interestingly, we did not observe any sex-by-alcohol interactions while processing happy faces. While meta-analyses of fMRI studies have shown that the amygdala is involved in processing both negative and positive emotions, negative-valence emotional material appears to have particularly strong effects on amygdala reactivity (Morris et al., 1996). Engagement of amygdala-based networks in response to negative emotions may have greater salience for action, such as potential threat, to prepare an individual to react quickly (Fernandes Jr et al., 2013, Sinke et al., 2012). In support of this idea, we found the largest number of interaction effects when participants were presented with fearful faces, a negatively charged emotion that indicates potential danger. Positive emotions

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represent the converse, allowing psychological growth and well-being (Fredrickson, 2001). Our findings suggest that alcohol moderates underlying sex differences in functional connectivity through differential responses to negatively-valence emotions, which may be more amygdala-dependent than processing positive emotions.

The mechanisms underlying sex differences in neuronal functional networks are complex and not fully understood. Sex differences in human brain structure and function are likely due to interactions between social, genetic, and hormonal factors (Cosgrove et al., 2007, McCarthy and Arnold, 2011). Most research into sex differences has focused on sex steroid hormones on brain development. For example, convergent findings suggest that sex hormones influence the size and function of the amygdala, with prenatal androgens appearing particularly important (Beltz et al., 2023). There is also evidence that sex hormones affect gray matter volume, especially during adolescence (Bramen et al., 2012). Finally, there is evidence for both endogenous and exogenous effects of sex hormones on the adult brain, particularly with how estrogen effects the frontal lobes (Maki and Resnick, 2001).

In viewing the current results, it is important to keep some limitations in our research protocol in mind. First, participants were well educated European-American university students without an AUD, and it is not clear whether the current results generalize to other groups. Second, reflecting the fact that laterality findings are unclear in many fMRI studies of emotion processing (Davidson and Irwin, 1999), we did not have formal hypotheses on laterality and analyzed the combination of both the left and right amygdala seeds and their respective connectivity patterns. Thus, future work will need to further evaluate the importance of laterality influencing connectivity patterns associated with sex. Third, to better simulate the way that people consume alcohol in real-life situations, including oral stimulation and the relatively slow rise in BrAC values, our paradigm used oral alcohol as opposed to intravenous (IV) alcohol administration. Oral dosing is a common, affordable, and portable method and is useful when subjective experiences of alcohol are part of the research question, but as compared to IV administration, the oral approach might produce greater inter-individual variability in BrAC values (Cyders et al., 2020). However, as demonstrated in data presented by Paulus et al., (2012) and others (e.g., Schuckit, 2018) when the alcohol administration paradigm controls for the rate of drinking, percent body water, as well as recent drinking and drug use, blood alcohol levels within males and within females are remarkably similar across participants. In addition, when the current analyses examined the effect of BrAC at 60 minutes (the timepoint closest to when the Hariri task was given) by covarying for BrAC at 60 minutes in our analyses no effect on functional connectivity patterns were observed. Nonetheless, MRI studies using IV alcohol dosing methods would be powerful to control the alcohol concentrations in the brain at a steady state measure changes in fMRI patterns. With regards to our analytic plan, Woo et al. (2014) and others have suggested that a more stringent voxel-level primary threshold of $p = 0.001$ in cluster threshold approaches. This would reduce the possibility of large activation clusters and improve confidence in inferences about specific locations. However, importantly, the primary threshold level should be chosen *a priori* to reduce potential bias towards findings in brain regions investigators want to find. We sought to control the family-wise error rate at 0.01 consistent with a large body

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of neuroimaging studies on alcohol effects and power analyses based on that literature in our original analytic plan from which these data are derived in an *a priori* manner. As demonstrated in our Results and Figures, we observed medium to large effects sizes using this approach suggesting meaningful findings in anatomically constrained regions of interest. Nonetheless, future replication studies that use more stringent thresholds to better elucidate functional networks that differ between sexes in response to alcohol are needed. Lastly, there are physiological effects when consuming alcohol that directly impact the BOLD signal, such as cerebral blood flow changes (Courtney et al., 2019). With advances in neuroimaging methodologies, studies are being done isolating mechanisms that drive BOLD signal changes observed in the literature including blood flow, volume, and oxygenation. Our analyses did not covary these physiological effects and included multiple comparisons across hemispheres. Replication studies integrating multi-modal imaging with mode advance echo-planer collection techniques are needed to confirm our findings and expand upon them to better understand whether brain regions demonstrating sex differences are predictive of future alcohol problems and onset of AUD. Finally, we used shapes as our control condition, as opposed to neutral faces which may offer additional important information on emotion processing.

In conclusion, findings suggest that sex-specific brain pathways differentially modulate emotional processing responses in women and men. Women exhibited higher functional connectivity than men in cortico-amygdalar circuits subserving emotion processing following a moderate dose of alcohol. That women had higher functional connectivity than men following exposure to a moderate dose of alcohol might indicate women are more capable than men to synchronize signaling across these specific brain regions to process affective stimuli when intoxicated. Changes in the evaluation of emotional, especially aversive, stimuli, play a crucial role in the transition to AUD or alcohol relapse (Maleki and Oscar-Berman, 2019; Witkiewitz et al., 2015). Future prospective research is needed to understand if sex differences in emotional processing among social drinkers predicts subsequent problematic drinking behavior and onset of AUD in the future, as opposed to sex differences that develop as a result of chronic heavy drinking.

Acknowledgements and Disclosures:

Funding for this project was provided by NIAAA grant award #s 1R21 AA027634 and RO1 AA021162. Drs. McKenna's and Anthenelli's writing of this manuscript was supported, in part, by National Institute on Drug Abuse (NIDA) grant award #s UO1 DA041731 and UO1 DA051077, and by the University of California, Office of the President, Tobacco-Related Disease Research Program Award #T29IP0379. Dr. Anthenelli and the Pacific Treatment and Research Center receive additional research support from Pfizer, Inc. and Embera NeuroTherapeutics, Inc.

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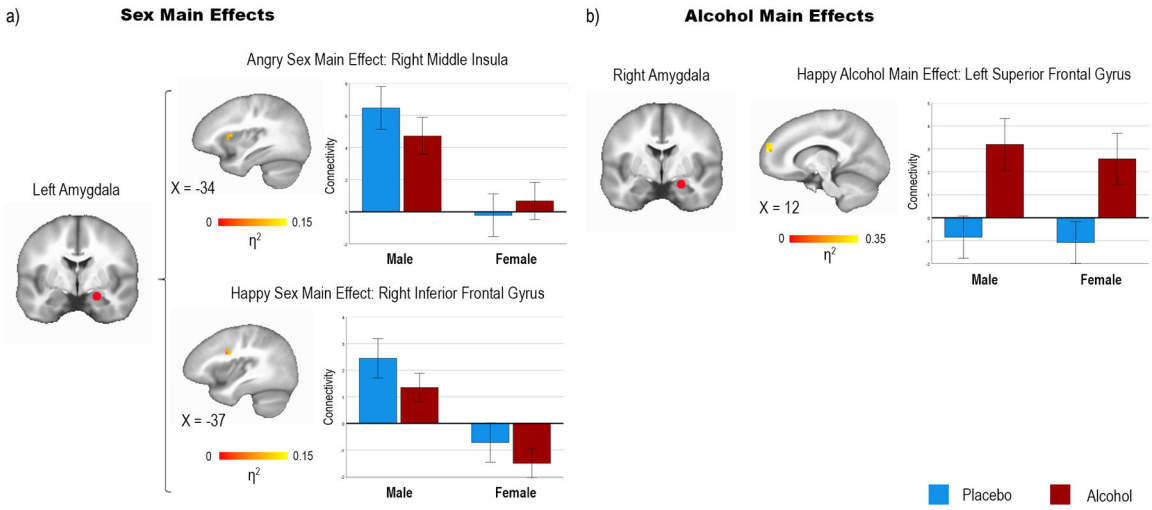

Figure 1.

Regions showing significant main effects of sex (female vs. male) and alcohol (alcohol vs. placebo) during processing of angry, fearful, and happy faces. Footnote: Images are displayed in the neurological convention. X coordinates are provided to show which sagittal plane is being depicted. Bar graphs depict extracted measures of connectivity (PPI parameter estimates) within each group. Error bars indicate standard error of the mean.

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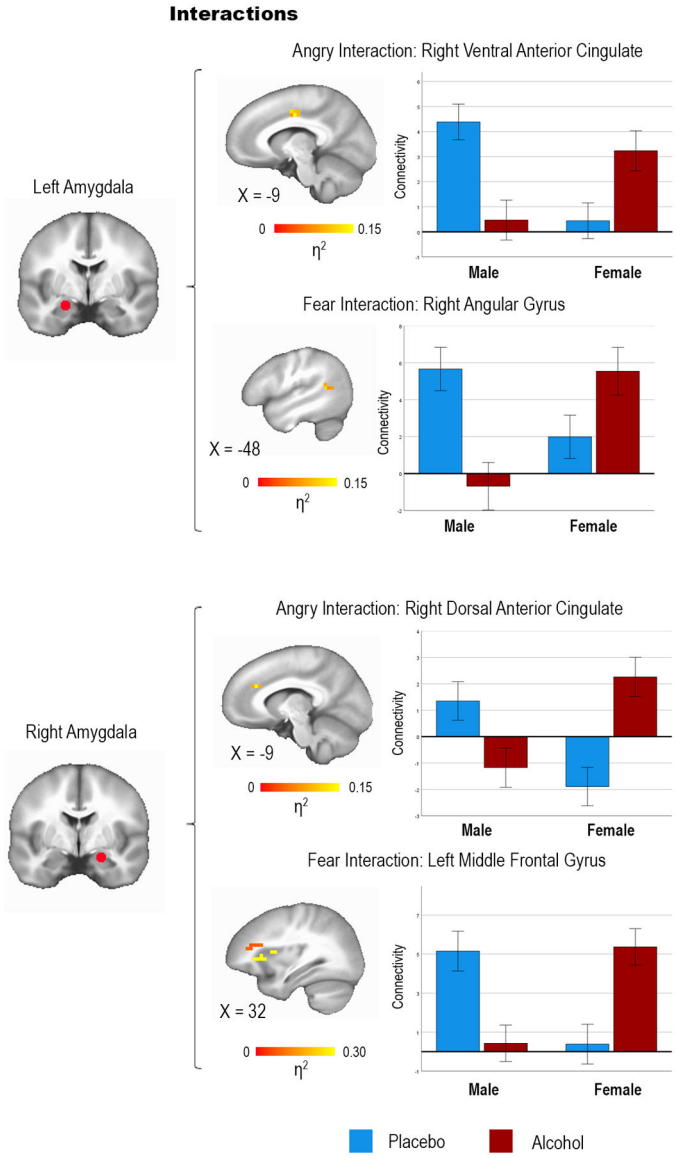

Figure 2.

Regions showing significant Sex-by-Alcohol interaction effects during processing of angry, fearful, and happy faces. Footnote: Images are displayed in the neurological convention. X coordinates are provided to show which sagittal plane is being depicted. Bar graphs depict extracted measures of connectivity (PPI parameter estimates) within each group.

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Table 1.

Characteristics of Women and Men Participants

	Women (n=54)	Men (n=54)	p-value[c]
Age (yrs)	19.8 (1.5)	19.9 (1.5)	0.72
Yrs of Education Completed	13.6 (1.2)	13.6 (1.1)	0.90
Body Mass Index	22.7 (3.4)	23.3 (3.5)	0.34
Days/Months Used Alcohol[a]	6.0 (3.7)	7.5 (5.6)	0.11
Usual Drinks/Occasion[a]	3.5 (1.6)	3.6 (2.0)	0.72
% Ever Used Tobacco	60.7 %	53.8 %	0.47
% Regular Tobacco User[b]	5.4 %	3.8 %	0.71
% Ever Used Cannabis	60.7 %	55.8 %	0.60
Lifetime Cannabis Use Occasions	23.4 (70.3)	32.8 (96.1)	0.57
BrAC at 60 Minutes (mg/dL)	0.06 (0.01)	0.06 (0.01)	0.81

Values given are mean (standard deviation), unless otherwise indicated.

BrAC: Breath Alcohol Concentration; LR Level of Response.

[a]Data for prior 6 months.

[b]Regular user defined as smoking a total of 100 cigarettes in lifetime.

[c]p-values for Independent Sample T-tests or chi-square tests.

Alcohol Clin Exp Res (Hoboken). Author manuscript; available in PMC 2025 April 01.

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Table 2.

Results of whole-brain PPI analyses examining sex and alcohol conditions for angry, fearful, and happy faces

					Talairach Coordinates[a]		
Emotion	**Seed Region**	**Region Name**	**BA(s)**	**Volume (μL)**	**x**	**y**	**z**
Sex Main Effects							
Angry	Left Amygdala	R Middle Insula	13	448	−42	−15	8
Happy	Left Amygdala	R Inferior Frontal Gyrus	6	448	−38	−3	32
Alcohol Main Effects							
Happy	Right Amygdala	L Middle Insula	13	448	42	1	12
		R Postcentral Gyrus	43	448	−54	9	16
		L Superior Frontal Gyrus	9	448	18	−55	28
Sex-by-Alcohol Interactions							
Angry	Left Amygdala	R Ventral Anterior Cingulate Gyrus	24	640	−10	9	40
Angry	Right Amygdala	R Dorsal Anterior Cingulate Gyrus	32	448	−10	−31	28
Fear	Left Amygdala	R Angular Gyrus	39	448	−46	57	12
Fear	Right Amygdala	L Middle Frontal Gyrus	46	960	42	−31	24
		B Medial Frontal Gyrus	6	832	2	5	52
		R Caudate	--	768	−18	−23	0
		R Dorsal Anterior Cingulate Gyrus	32	768	−18	−39	8
		L Posterior Cingulate	29	640	2	53	8
		R Dorsal Posterior Cingulate Gyrus	31	640	−14	25	40
		L Postcentral Gyrus	2	640	50	21	40
		R Superior Parietal Lobule / Precuneus	5, 7	640	−18	49	56
		L Putamen	--	576	22	−11	−4
		L Middle Insula	13	576	46	−3	12
		L Middle Insula	13	448	38	−19	4
		R Angular Gyrus	39	448	−46	57	12
		R Middle Frontal Gyrus	8	448	−2	−15	52

Results for corrected p-value ≤ 0.01. PPI: psychophysiological interaction; BA: Brodmann area; LR: level of response; L: left; R: right; B: bilateral

[a]Talairach coordinates refer to peak effects within the cluster