Published in final edited form as:

Alcohol Clin Exp Res. 2020 November ; 44(11): 2212–2224. doi:10.1111/acer.14465.

A Distinct Neurophenotype of Fearful Face Processing in Alcohol Use Disorder With and Without Comorbid Anxiety

Nicole MacIvane, MA^{1,*}, Samantha J. Fede, PhD^{1,*}, Emma E. Pearson, BA¹, Nancy Diazgranados, MD², Reza Momenan, PhD^{1,*}

¹Clinical NeuroImaging Research Core, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, United States, 20892

²Office of the Clinical Director, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, United States, 20892

Abstract

Background—Individuals with alcohol use disorder (AUD) can present with comorbid anxiety symptoms, and often have deficits in emotional processing. Previous research suggests brain response is altered during facial affect recognition tasks, especially in limbic areas, due to either AUD or anxiety symptomology; however, the impact of both AUD and clinically significant anxiety symptoms during these tasks has not yet been examined.

Methods—In this study, we investigated neural activation differences during an emotional face-matching task. Participants (N = 232) underwent fMRI scanning, as part of a larger study. Three groups were investigated: individuals with diagnosed AUD and elevated anxiety traits (AUD +ANX, n=90), individuals with diagnosed AUD but non-clinically significant levels of anxiety (AUD-ANX, n=39) and healthy controls (HC, n=103).

Results—Our results illustrate distinct neurophenotypes of AUD, where individuals with comorbid anxiety symptomology have blunted emotional face processing while those with singular AUD are hyperresponsive.

Conclusions—This suggests AUD with anxiety symptomology may have a unique neurobiological underpinning, and treatment and intervention should be tailored to individual constellations of symptoms.

Keywords

alcohol use disorder; anxiety; fear; face processing; fMRI

* Corresponding author at: Clinical NeuroImaging Research Core, 10 Center Drive (Bldg. 10, Rm. 1-5435), Bethesda, MD, United States, 20892-1108; Phone: (301) 451-6972; rezam@nih.gov.

*These authors contributed equally to the manuscript

Declaration of Interest

All authors report no direct or indirect conflicts of interest.

Data Availability

Upon request.

Introduction

Alcohol Use Disorder and Anxiety—

Alcohol Use Disorder (AUD), a substance use disorder consisting of increased use of alcohol over an extended period of time resulting in mild to severe negative functional, psychological, and biological outcomes (American Psychiatric Association, 2013), is increasing in prevalence in the United States, with 12.7% of adults affected at some point in their lifetime (Grant et al., 2015). Addiction, including AUD, is thought to be comprised of three interconnected processes: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (Koob & Volkow, 2016). The withdrawal/negative affect stage often manifests in patients as negative affect along with symptoms of anxiety, irritability, dysphoria and increased reactivity to stress (Heilig et al., 2010). The magnitude of stress and negative affect, including anxiety, has direct implications on AUD treatment outcomes, as it often leads to increased craving and susceptibility to relapse (Sinha et al., 2007).

In the brain, the negative affect stage of AUD is associated with altered functioning of the extended amygdala (Heimer and Alheid, 1991), which in turn disrupts communications in large brain networks that use the amygdala as a hub (ie, afferently from thalamic, hippocampal and sensory association areas; efferently to hypothalamus and striatum; reciprocally to the medial prefrontal cortex (mPFC; LeDoux, 2007)). Withdrawal and stress lead to increased activation of these connections along the hypothalamo-pituitary-adrenal (HPA) axis, releasing hormones associated with elevated anxiety and stress response (Heilig and Koob, 2007, Koob, 2008, Koob and Kreek, 2007). Additionally, the amygdala's bottom-up connections to limbic areas such as the insula, mPFC, anterior and posterior cingulate (ACC/PCC) are thought to underlie emotional decision making (Clark et al., 2008), and are associated with craving (Naqvi and Bechara, 2009) and relapse outcomes (Sinha et al., 2007).

Comorbid anxiety disorders are common in AUD (Grant et al., 2004), and develop either independently or as a result of chronic alcohol use problems (Kushner et al., 2005). Anxiety disorders exacerbate and maintain symptoms of AUD in a feed-forward cycle (Smith and Randall, 2012) that interferes with treatment of both AUD (Book et al., 2009, Smith and Book, 2010, Kushner et al., 2005) and the anxiety disorder (Bruce et al., 2005). This often leads to a more persistent and distressing disorder, with greater risk of relapse (Driessen et al., 2001). Similar to AUD, anxiety is also associated with altered activation of the extended amygdala and broader limbic network of the insula, mPFC, hippocampus and ACC (Shin and Liberzon, 2009, Wilcox et al., 2016), where additional stress increases activation of the limbic HPA and release of stress hormones (Heim and Nemeroff, 2001, Liberzon and Martis, 2006).

AUD & Anxiety's effects on presentation of emotional faces—

The brain's response to emotional faces is clinically relevant to both anxiety and AUD. Visual processing of emotional faces is a means through which information about the emotional state of others or possible threats in the environment are evaluated. For individuals with AUD, deficits in emotional face processing have been linked to greater severity of

interpersonal problems and risk of relapse (Kornreich et al., 2002), longer length of heavy drinking periods (Valmas et al., 2014), and may predict treatment outcomes (Charlet et al., 2014). Individuals with anxiety disorders and high trait anxiety show differential patterns of facial emotion recognition and matching (Demenescu et al., 2010, Surcinelli et al., 2006, Ball et al., 2012, Dickie and Armony, 2008, Bishop et al., 2004a, Phan et al., 2006).

Emotional face processing is associated with the activation of brain areas relevant to both AUD and anxiety, namely the extended amygdala, insula, mPFC, ACC and hippocampus. Studies consistently report the role of the amygdala in facial processing; for example, individuals with no substance use or anxiety disorders show an increase in bilateral amygdala activity when perceiving fearful and other negative emotional faces (Hariri et al., 2002b, Marinkovic et al., 2009, Bishop et al., 2004a), and sometimes also neutral faces (Fusar-Poli et al., 2009, Wright and Liu, 2006). Although other regions are less consistently implicated, the insula, mPFC, ACC, hippocampus, and fusiform gyrus are also thought to be involved in emotional face processing (Phillips et al., 1997, Schienle et al., 2002, Fusar-Poli et al., 2009, Morris et al., 1996, Marinkovic et al., 2009, Phan et al., 2004, Posamentier and Abdi, 2003, Blair et al., 1999, Wright and Liu, 2006, Dolan et al., 1996).

Acute alcohol intoxication alters brain activity in fronto-limbic areas during face processing. In social drinkers, the bilateral insula and right amygdala show decreased activity to fearful and angry faces when intoxicated (Padula et al., 2011, Sripada et al., 2011). Face processing during acute intoxication can also predict risk of developing AUD; in one study, increased activation of the insula predicted future problems with alcohol up to 5 years later (Schuckit et al., 2016). In drinkers with mild alcohol problems, negative face-related activation in the amygdala and its connectivity with the right orbitofrontal cortex was decreased after alcohol administration, suggesting altered recruitment of the frontal cortex (Gorka et al., 2013).

The chronic effects of heavy alcohol use on the neural correlates of face processing are less consistent. For example, one study found dampening of the hippocampus and amygdala across positive and negative emotional faces as well as emotion and modality specific effects in the prefrontal cortex (Marinkovic et al., 2009); another found that individuals with AUD have greater activation in the amygdala when viewing happy faces, greater activation in the fusiform when viewing fearful faces, decreased middle frontal gyrus activity when viewing negative faces, and emotion-specific hypo and hyper activity in the insula and ACC/vmPFC (Salloum et al., 2007). AUD related processing differences have also been found in other regions. During processing of negative facial emotions, individuals with AUD had elevated activity in the ACC and reduced activity in bilateral fusiform gyrus, occipital gyrus, middle frontal gyrus, and cerebellum (Charlet et al., 2014). However, some studies show no differences between individuals with and without AUD in limbic regions (Wilcox et al., 2016).

One explanation for these apparent inconsistencies in findings on facial emotion processing in individuals with AUD could be heterogeneity of the disorder itself (Litten et al., 2015). For example, one study found that women with AUD, but not men, had facial emotion processing deficits (Lewis et al., 2019), and that emotion processing deficits were more

severe in individuals with AUD and polysubstance use (Lewis et al., 2020). Another found that only in combination with individual differences in anxiety and sensation seeking did alcohol related effects on neural emotion processing prospectively predict AUD (Shakra et al., 2018).

Anxiety on its own is also associated with atypical processing while viewing emotional faces. The insula and amygdala of individuals with higher anxiety often show hyperactivation in neural response to negatively valenced emotional faces, which increases with self-reported anxiety symptoms (Wilcox et al., 2016, Stein et al., 2007, Ball et al., 2012, Somerville et al., 2004, Bishop et al., 2004b). In the prefrontal cortex, individuals with higher anxiety often show decreasing activation in lateral areas to negative and neutral faces, but increased activation in the mPFC in response to positively valenced faces. The ACC also shows differential patterns of activation across areas, with hypoactivation in ventral ACC (vACC) but hyperactivation in dorsal ACC (dACC) and subgenual cingulate areas.

Current Study—

Individuals with AUD are more likely than the general population to have anxiety (Grant et al., 2015). However, higher anxiety may be particularly related to a phenotype of AUD associated with specific patterns of drinking (e.g., drinking as a coping mechanism), since it varies by severity in AUD (Novak et al., 2003). Although some research into negative valance processing suggests that in individuals with AUD, anxiety symptomology is related to greater activation in the parahippocampal gyrus (Gilman and Hommer, 2008), there is a paucity of research exploring how brain function differs during negative facial emotion processing in individuals with AUD and anxiety. This is particularly important given findings that consideration of anxiety in alcohol and substance use treatment may improve outcomes (Wolitzky-Taylor et al., 2018). Moreover, understanding the impact of anxiety on AUD related emotion processing may help to explain the heterogeneity in findings on the topic.

Here, we aim to understand how AUD and anxiety in combination impact neural functioning during the presentation of fearful faces. To do this, we collected hemodynamic response data during a face-matching task in three groups: healthy controls (HC), individuals with AUD and little or no anxiety symptomology (AUD-ANX), and those with both AUD and anxiety traits (AUD+ANX). We expected to replicate the main effects of previous studies using similar face-matching tasks. Given the similar patterns of neural changes associated with AUD and anxiety, we hypothesized that individuals with both (AUD+ANX) would differ more greatly from the healthy control group than the AUD-ANX group, reflecting an additive effect of the two sets of symptomology. Since this is the first study, to our knowledge, to examine this, we took an exploratory approach to localizing these differences, though we expected to see alterations in the frontal, cerebellar, paralimbic, occipital/parietal and insula regions elicited by processing of facial emotions. An alternative hypothesis is that the AUD+ANX group would show a different pattern of neural activation from both the AUD-ANX group and HC group in these areas, reflecting a distinct neurophenotype of AUD with anxiety features.

Materials and Methods

Participants—

All participants (N = 232) were enrolled in studies at the National Institutes of Alcohol Abuse and Alcoholism. Participation was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. After providing separate written informed consent, participants completed a screening protocol and a MRI scan. Participants were divided into three groups based on AUD diagnosis and anxiety levels: those with AUD and high levels of anxiety (AUD+ANX, n= 90), those with AUD and without high levels of anxiety (AUD-ANX, n= 39), and healthy control volunteers without AUD or anxiety (HC, n= 103). See Table 1 for demographic information on the sample. Individuals were excluded if they had neurological disorders, had a positive urine drug screen, or had MRI contraindications.

Measures—

AUD status was determined based on diagnosis via the Structured Clinical Interview for the DSM-5 (SCID; First et al., 2015). The SCID was conducted by trained research and clinical staff as part of the screening protocol. In some cases where the SCID-5 was unavailable, a SCID-IV diagnosis of alcohol dependence or abuse was used instead (First et al., 1997). Scores on the Alcohol Use Disorder Identification Test (AUDIT) were used to quantify AUD severity for supplementary analyses (Saunders et al., 1993).

Anxiety status was determined based on scores on the Trait subscale of the State Trait Anxiety Inventory (STAI-T; Spielberger et al., 1983). The STAI-T is a self-report scale consisting of 20 items about anxiety feelings “in general”. Participants respond by indicating how often they experienced those feelings, ranging from 1: “almost never” to 4: “almost always”. Scores range from 20–80; a score of 40 or higher is considered clinically significant anxiety (Knight et al., 1983). We used that cut-off to define our AUD+/-ANX groups.

Image Acquisition—

All participants underwent scanning on a Siemens 3T Skyra Magnetic Resonance Imaging (MRI) machine at the NIH Clinical Center in Bethesda, MD. While in the scanner, they completed a face-matching task to measure emotional face processing. This scan was acquired using an echoplanar-imaging pulse sequence (TR: 2000 msec, TE: 30 msec, flip angle: 90°, FOV: 24 × 24 cm, 38mm slice thickness, 36 slices, multi-slice mode: interleaved). The structural scan was acquired using a T1-MPRAGE sequence (TR: 1900 msec, TE: 3.09 msec, flip angle: 10°, FOV: 24 × 24 cm, 1 mm slice thickness, 144 slices, multi-slice mode: single shot).

Face Matching Task—Processing of emotional faces was measured following a modified version of the procedures described in Hariri et al., 2002. During this task, participants viewed a target picture and two additional pictures, all demonstrating the same facial emotion; participants were instructed to select the picture that matched the target face exactly by pressing the corresponding button. Six types of pictures were shown: 1) angry

faces, 2) sad faces, 3) fearful faces, 4) happy faces, 5) neutral faces, and 6) shapes (i.e., no faces). Images were part of the Pictures of Facial Affect (POFA) image set (Ekman and Friesen, 1976). An exemplar of the fearful face and shape task conditions, as seen by participants, is available as Supplemental Figure 1. There were two interleaved blocks of each picture type. Prior to each block, instructions were presented for two seconds for subjects to “match shapes” or “match faces”. Each block contained 6 images of the same type, displayed for 5 seconds with no inter-stimulus interval, for a total of 30 seconds per block. Male and female faces were equally represented. The task was presented using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurojobs.com).

Statistical Analysis—

Preprocessing—The fMRI data was processed on a single-subject basis using AFNI version 17.00.00 (Cox, 1996) using the following pipeline. First, 3dDespike was applied to smooth spikes in signal over the time course. Next, time courses were shifted for each voxel to be aligned to the same temporal origin by detrending then interpolating the time series. Volumes across the time series were then aligned to the base volume and to the skull-stripped anatomy of the subject, then warped to standard Talairach space using a non-linear warping procedure. Finally, each volume was blurred with a 4-mm full-width at half maximum Gaussian smoothing kernel. TRs where the motion derivative value was 0.3 or higher were censored from future analysis and stimuli onset times were regressed to identify signal associated with each condition, with demeaned motion parameters and their derivatives regressed to remove variance associated with movement. Subjects with greater than 30% of trials censored ($n = 22$) were removed from group analyses; these subjects would have fallen into AUD+ANX ($n = 10$), AUD-ANX ($n = 9$), and HCV groups ($n = 3$). An additional $n=9$ subjects were removed for other reasons (i.e., did not meet criteria for either AUD or HCV groups, did not complete or do the MRI scan portion of the study, scan data did not save properly etc.); the sample description and descriptive statistics do not include any of these removed individuals.

Whole Brain Analysis—To address our hypotheses, task data was analyzed at the whole brain level using multivariate modeling (3dMVM) in AFNI. Our hypotheses covered a wide selection of regions, so this whole-brain analytical approach was deemed more appropriate than a region of interest analysis. The full MVM (group [AUD+ANX, AUD-ANX, HC] x condition [Fearful Faces, Neutral Faces, Shapes]) was run to examine overall significance for all main effects and interactions; age, sex, and years of education were included as covariates. Then, conditions of interest were modeled using general linear tests and related to participant groups. Our conditions of interest were (across all subjects and for each group comparison of *i*) AUD+ANX – AUD-ANX, *ii*) AUD+ANX – HC, *iii*) AUD-ANX – HC: 1) *Fearful Faces* > *Shapes*, 2) *Fearful Faces* > *Neutral Faces*). Condition of interest 1 served to isolate fearful face processing generally, while condition of interest 2 served to isolate circuits associated specifically with fear. Results were thresholded at a voxel-wise threshold of $p < 0.001$ and a cluster-size threshold of $k = 9$ to control for multiple comparisons at a level of $\alpha < 0.05$. This was calculated using autocorrelation function (ACF) estimates of blur calculated at the end of the preprocessing pipeline using 3dFWHMx in AFNI. The average

of these estimates across subjects was then used as input to determine the cluster size threshold at a voxel-wise threshold of $p < 0.001$ using 3dClustSim in AFNI.

For the purposes of evaluating replication, we evaluated whether clusters of neural engagement we found engaged during the contrast of fearful face processing compared to shapes corresponded to those identified in previous meta-analysis of this facematching task (Fusar-Poli et al., 2009). To do so, we examined the whole-brain statistical maps of this contrast across subjects and determined whether hemodynamic response passing whole-brain significance thresholds was detected in our data at the coordinates previously reported by Fusar-Poli et al.

Following whole brain analysis, beta values were extracted from significant clusters and plotted by group and task condition for interpretation purposes. These plots were generated using R version 3.4.2 (R Core Team, 2017). In supplementary analyses, contrast values in these clusters were examined within AUD groups only to explore whether these effects were driven by the linear relationships between AUD severity (AUDIT), trait anxiety (STAI) or the interactions between these two variables, or if instead differences between AUD+/-ANX were reflective of distinct neurophenotypes. We ran Pearson's correlations to quantify these relationships; p 's are reported for completeness and as guidance for relative significance. However, it should be noted that these tests are exploratory and p -values are likely inflated since the selection of these clusters was informed by previous statistical tests. Scatter plots illustrating each of these tests are available as Supplemental Figure 2.

Results

Behavioral Results-

Behavioral results are reported covarying age, sex, and years of education in the model. During the review of behavioral results, several subjects ($n = 8$) had outlying behavioral performance (i.e., had less than 50% correct matching); these individuals were not included in the behavioral analysis. See Table 2 for means and standard deviations for the remaining subjects, broken down by group and condition. There was no significant group by condition effect on either response time or matching accuracy.

There was a significant effect of task condition on response time ($F(2, 660) = 41.730$, $p < 2e-16$) and matching accuracy ($F(2, 660) = 3.213$, $p = 0.0409$). Tukey post-hoc tests indicated that participants matched shapes more quickly than neutral ($p < 0.0000002$) or fearful ($p < 0.0000001$) faces, and neutral faces more quickly than fearful ones ($p = 0.0009$). Participants also matched fearful faces more accurately than either neutral faces or shapes, though the post-hoc tests were marginally significant (versus neutral: $p = 0.057$; versus shapes: $p = 0.096$).

There was also a significant effect of group on matching accuracy ($F(2, 660) = 4.647$, $p = 0.0099$). Specifically, the AUD-ANX group had higher matching accuracy than the control group ($p = 0.00989$). There was no effect of group on response time.

Main Effects-

There was widespread neural engagement in processing of *Fearful Faces > Shapes* (see Supplemental Figure 3A). See Supplementary Table 1 for a full list of cluster peaks for each contrast and comparison of regions identified in previous meta-analyses of this task (Supplemental Table 2). *Fearful Faces > Neutral Faces* also engaged distinct neural correlates (Supplemental Figure 3B).

Group by Condition Effects-

There was a significant difference between AUD+ANX and HC in both contrasts. Specifically, AUD+ANX had increased activation of the temporoparietal junction (TPJ; $x = 42, y = -53, z = 11, T = -4.394, k = 10$) when exposed to fearful faces, but also hyperactivity of the supplementary motor area (SMA; $x = -4, y = 27, z = 53, T = 4.298, k = 10$) when exposed to neutral faces (see Figure 1). There was also a significant difference between AUD-ANX and HC in the contrast of *Fearful Faces > Shapes*. Specifically, AUD-ANX had increased engagement in a cluster near the supramarginal gyrus ($x = -32, y = -39, z = 21, T = -3.895, k = 9$) when exposed to fearful faces, while HC had deactivation (see Figure 2). Betas for contrasts in these regions suggest that the differential findings for comparisons between HC and each group were not driven linearly by AUD severity, trait anxiety, or the simple multiplication of the two (see Table 3).

In individuals with AUD, anxiety traits had a significant effect of neural activity in the cerebellum ($x = 17, y = -78, z = -42, T = -4.288, k = 9$) and inferior frontal gyrus (IFG; $x = 56, y = 24, z = 0, T = -3.956, k = 9$) in the contrast of *Fearful Faces > Neutral Faces*. Specifically, AUD-ANX engaged both these regions when viewing fearful faces while AUD +ANX was not reactive to fearful faces in these regions (see Figure 3). We examined associations between STAI, AUDIT, and neural response in individuals with AUD only. In the cerebellum, there was a continuous, inverse relationship between hemodynamic response and STAI ($r = -0.325$), AUDIT ($r = -0.157$), and their interaction ($r = -0.248$) where the difference in neural processing during fearful faces compared to neutral became smaller or more negative in individuals with higher trait anxiety and more severe AUD along a continuous (rather than dichotomous) trajectory. A clear association between STAI, AUDIT or their interaction and neural response to fearful faces was not observed in the IFG (see Table 3).

Discussion

In this study, we used a face-matching task during fMRI to measure the underlying neural dynamics associated with fearful face processing. In particular, we examined differences in those processes between individuals with AUD in combination with or in absence of trait anxiety symptoms, as well as how these individuals differed from control participants without AUD. Across subjects, we largely replicated previous studies of the neural correlates of fearful face processing versus visual shape processing. However, we found that individuals with AUD had small but significant differences from healthy controls volunteers in level of neural engagement in the TPJ and SMA, and moreover, that neural correlates of fearful face processing in these regions, as well as in the IFG, were influenced by anxiety

traits in a non-additive fashion. On the other hand, the engagement of the cerebellum was inversely related to the interaction between trait anxiety and AUD severity in a linear fashion. In total, we find more support for our alternative hypothesis, that AUD with anxiety features is a distinct neurophenotype, though patterns of activity in certain regions may reflect an additive effect of the two disorders instead.

During viewing of fearful faces, all individuals engaged the frontal gyrus, cerebellum, temporal gyrus, occipital/fusiform gyrus, and amygdala. These regions are consistent with those thought to drive the mechanism of emotional face processing. Perception of faces starts in regions across the occipital gyrus and in facial recognition areas including the fusiform gyrus and temporal gyrus. This perception is modulated through reciprocal connections to the amygdala and prefrontal cortex. The amygdala plays a role in recognition of emotions and in addition to the frontal cortex, triggers association of related knowledge and learned behavioral response (Adolphs, 2002). The amygdala likely aids in this emotional processing through connections to limbic and frontal areas (Clark et al., 2008). The cerebellum also has a more general role in facial and emotion processing, consistent with evidence that this extended “limbic cerebellum” region is essential for affect regulation and emotional experience (Schmahmann, 2000, Turner et al., 2007).

Individuals with AUD but without comorbid anxiety symptoms had greater engagement of the right pars triangularis portion of the IFG during processing of fear compared to AUD individuals with high levels of anxiety, who had a reduction of engagement of that region compared to processing of neutral expressions. A similar pattern was seen for the pre-SMA region, functionally connected to the IFG (Obeso et al., 2013). Our findings reflect a double dissociation where AUD individuals without comorbid anxiety have hyper-reactivity to fear while those with higher anxiety fail to distinguish between neutral and fearful faces. The pars triangularis plays an important role in object recognition and labeling (Naeser et al., 2011); previous work has also shown that inhibition of response to emotional face cues in particular has been associated with increased IFG (and response inhibition in general, through connection with the pre-SMA), perhaps suggesting an effortful control of hyper-response in individuals with AUD but without anxiety (Schulz et al., 2009). On the other hand, studies have found that pars triangularis structural atrophy in schizophrenia is associated with poor recognition of angry faces (Maat et al., 2016), and that individuals with panic disorder have lower cortical thickness in the pars triangularis (Kang et al., 2017), consistent with the lack of distinction between emotional face processing in individuals with both AUD and anxiety traits here.

Findings on the association between AUD and facial emotion recognition have been generally heterogeneous up to this point, though there is more support for individuals with AUD and other SUDs having worse recognition than controls (Castellano et al., 2015). A dissociable neurophenotype underlying response to emotional face processing in AUD subgroups would go a long way towards explaining these observed inconsistencies. Moreover, it has important treatment implications since worse emotional facial recognition is predictive of relapse and treatment drop out in AUD (Rupp et al., 2017); if this is instead driven by subtypes of AUD with more anxiety having more severe outcomes, the need to properly assess and treat underlying anxiety symptomatology is doubly important.

Altered social cognition could also be indicated by our findings of hyperactivity in the TPJ (Boehme et al., 2015). In the right TPJ, individuals with AUD and comorbid anxiety traits had greater activity than healthy controls during fearful face processing. The TPJ, though involved in understanding the emotions of others via theory of mind, attention reorienting, and attribution of beliefs to others (Mitchell, 2007, Geng and Vossel, 2013), has also been associated with inward versus outward focus in response to aversive pictures and stronger emotional response in individuals with social anxiety (Boehme et al., 2015, Gaebler et al., 2014). Given the lack of linear association between trait anxiety and engagement of the TPJ in individuals with AUD, and a similar (though non-significant) hyperactivity in the AUD without anxiety group, anxiety is unlikely to drive this observed group difference. The role of the TPJ in addiction is less well established. Individuals with AUD have impaired affective theory of mind (Bora and Zorlu, 2017, Schmidt et al., 2016), but some initial work has found hyperactivity of the TPJ during negative emotionality in chronic cocaine users (Albein-Urios et al., 2014), consistent with the findings here. It is possible that TPJ hyperactivity in AUD is also driven by inward focus, similar to anxiety, resulting in less emotion recognition but increased negative emotionality.

In the cerebellum, a simpler multiplicative effect of AUD and anxiety was observed, where trait anxiety and AUD severity, and their interaction, was associated with decreased engagement of a Crus II posterior cerebellar cluster during fear processing. Rather than traditional sensorimotor functions, the posterior lobe of the cerebellum is implicated in higher level cognitive and emotional processes (Schmahmann, 2019). Cerebellar structure atrophy has been regularly implicated associated with anxiety (Evans et al., 2008) and chronic alcohol use (Oscar-Berman and Marinkovic, 2007), and alcohol induced cerebral damage has been shown to cause disruption of a variety of cognitive and affective behaviors (Fitzpatrick et al., 2008). Crus II in particular is a subregion of the cerebellum involved in cognitive/emotional processes including language and mental rotation, partially through connection with the prefrontal cortex (Stoodley and Schmahmann, 2009, Stoodley et al., 2012), with particular hyperactivity in response to negative rather than positive emotional faces (Schraa-Tam et al., 2012). Atrophy in this region has been previously implicated in impaired social communication and interaction in autism spectrum disorders (Riva et al., 2013). Despite this, our results are somewhat inconsistent with the literature finding cerebellar hyperactivity in anxiety disorders (Moreno-Rius, 2018). Our results may reflect a distinct neural feature of the effect of alcohol on anxiety-related cerebellar function; for example, the previously discussed blunted emotion recognition process may correspond to reduced anticipation or aversive responsivity. However, it may also reflect the functional heterogeneity of the cerebellum.

Unexpectedly, we did not find a main effect of condition including the insula, thalamus, and putamen, failing to replicate previous studies of emotional face-matching that found alterations in activity of these regions. There may be several reasons for this. Our task differed from the classic design (i.e., Hariri et al., 2002) in that our stimuli included positive (Happy), neutral, and additional negative (Sad, Angry) faces in addition to Fearful Faces, though we did not include those stimuli in our analysis. The neural correlates of facial emotion processing are not consistent across emotion types (Fusar-Poli et al., 2009), so inclusion of these stimuli may have attenuated the emotional impact of fearful faces. Our

task was also an implicit facial emotion processing task, while previous studies considered multiple study designs; for example, Fusar-Poli et al. illustrated that inferior frontal gyrus regions were more commonly elicited in explicit rather than implicit emotion processing tasks (2009).

It is also important to note that despite our exploration of the whole brain for effects of AUD and anxiety, we found a small number of regions with an effect of this comorbidity. Though of the two explanations hypothesized *a priori*, a distinct neurophenotype fits better than an additive effect of AUD and anxiety, it is also possible that the effects of AUD and anxiety on the brain are simply not large or widespread enough to fit either. Still, we argue for the cautious adoption of the distinct neurophenotype interpretation as the best of available options. The idea of a simple null effect is unlikely, since, as reviewed in the introduction, we know that both AUD and anxiety are consistently associated with altered neural emotion processing, though the exact localization or size of these effects varies. On the other hand, we know that standard control for false-positives inflates false-negative rate, particularly when it comes to small effects. That, rather than actual null effects, likely explains the lack of detection of the group by condition interaction effects, which we can expect to be small in most cases. Indeed, if we adjust this threshold to favor smaller but more widespread effects, we see the size of the reported clusters (and a few additional clusters) expand to cover larger portions of the brain; qualitatively, these patterns of response remain distinct across groups, consistent with our interpretation.

There is a last alternative hypothesis: that the impacts of AUD and anxiety are compensatory. This hypothesis, though not anticipated *a priori*, could explain why differences between the HC and AUD-ANX groups were not detected in the HC and AUD +ANX comparison, but it could not explain the reverse (i.e., that differences observed in the HC and AUD+ANX contrast were not seen in the HC and AUD-ANX) or the AUD group differences that were not also visible in the HC contrasts. Moreover, the most important implication of our findings for AUD treatment is the importance of approaching AUD with anxiety features as a whole rather than treating anxiety as a piecemeal add-on. Even if this compensatory hypothesis were true, the impact on treatment strategy would be the same.

The combined effects of anxiety symptomology and AUD are important to study across sex and gender, especially since women are more likely to suffer from anxiety disorders in general (Bandelow and Michaelis, 2015). We included sex as a covariate here; moreover, we modelled supplementary models with the contrast of males > females to identify any significant differences in the group by task interactions we were interested in. Previous studies find significant gender differences in brain function and structure (e.g., Wager et al., 2003; Ruigrok et al., 2014); in our study, we observed no significant findings of sex. It is possible we were not adequately powered for multiple 3-way ANOVAs, particularly with small numbers in certain cells (e.g., $n = 11$ female AUD-ANX). Examining results from each group separately, we observed differences in neural activation only between the AUD +ANX and AUD-ANX groups in males, whereas females showed differences between all three groups (HC, AUD+ANX, and AUD-ANX). Additionally, areas of differing neural activity occurred in both males and females in traditionally high-order cognitive structures (i.e. superior frontal, angular, and middle temporal gyri), suggesting potential sex differences

in higher-order cognition in the context of AUD, anxiety, and emotional face stimuli; this comparison needs to be formally tested.

We also covaried for age and education. To determine the impact these had on the model, we ran supplementary Pearson's correlations of the betas for each of the significant clusters. TPJ betas in the contrast of Fearful Faces and Shapes were correlated with age ($r = 0.118$, $p = 0.07$) and education ($r = -0.141$, $p = 0.03$). Age and education were not significantly correlated with neural response in other significant clusters. The AUD+ANX group, which had greater engagement in this contrast, had higher age and lower education than the control group; since this was in the same direction as the observed effect, it is possible including these covariates attenuated the effect of group (AUD+ANX > HCV) in the TPJ.

Limitations—

We did not have a full anxiety-group x AUD-group x condition design, which may be needed to definitively rule out the possibility that trait anxiety alone rather than the effect of anxiety in combination with AUD is driving the findings we report for our AUD+ANX group. It may also be the case that some individuals would have been better characterized as individuals with an anxiety disorder, and secondary AUD. However, our primary goal was to examine differences between those individuals with AUD who do or do not have comorbid anxiety symptomology, regardless of etymology. Our results serve to emphasize the importance of considering anxiety during treatment or research of individuals with AUD. Even if the patterns of neural activity associated with our higher anxiety level group is not specific to individuals with comorbid AUD, it does not take away from the ability to apply these insights to better understand neural alterations in individuals with AUD.

Our anxiety grouping was based on trait anxiety symptomology rather than specific diagnosis (i.e., on the SCID). This was intentional; since our primary focus in this study was individuals with AUD, we wanted to be sure to capture symptomology in these individuals regardless of whether it met diagnostic criteria for a specific anxiety disorder. Still, our findings should be applied to the comorbid diagnosis of AUD and various anxiety disorders cautiously. As demonstrated in Table 1, only 30% of the AUD+ANX group had a formal diagnosis of an anxiety disorder, while 7% of the AUD-ANX group had such a diagnosis.

To explore this issue in a post-hoc analysis, we recoded the groupings based on SCID diagnosis. The results of the comparisons between HCV and either AUD group were substantively the same as in the STAI based analysis, though the preSMA and supramarginal gyrus cluster size dropped below the whole brain multiple comparisons threshold. However, there was no indication of the IFG and cerebellum results in the AUD+/-ANX comparison. Interestingly, this diagnosis-based grouping was characterized by a smaller distinction between the groups in trait anxiety (mean $STAI_{\text{anxiety diagnosis}} = 53.56$; mean $STAI_{\text{no anxiety diagnosis}} = 41.80$) than grouping based on the STAI (see Table 1). Indeed, the AUD group *without* an anxiety diagnosis had an average trait level about the clinical cut-off (Knight et al., 1983). For this reason, it is possible that the effect on the brain of this small variation in anxiety is simply too small to detect with our sample size, rather than representing a true contradiction of our original results. It may also be that trait anxiety symptomology (STAI) is a more useful measure for understanding the impact of anxiety

when the primary patient diagnosis is AUD, or that STAI measures some feature distinct from true clinical anxiety measured by the SCID. Regardless, one should keep in mind the distinction between STAI and SCID measurements of anxiety when considering this report.

Our AUD groups differed on features other than anxiety. The AUD+ANX group had more severe AUD, 45% of our AUD+ANX group but only 5% of the AUD-ANX had some current depression diagnosis, and comorbid substance use was more common in the AUD+ANX group. These group differences are not surprising; individuals with more severe AUD are more likely to have major depression or anxiety (Lai et al., 2015). At the same time, anxiety and depression symptoms are comorbid in 85–90% of cases (Gorman, 1996). Because these features are inherently related to the construct of interest, it was not appropriate to statistically control for them. Thus we are limited in our ability to say the AUD+/-ANX effects are due to anxiety *only*. However, as demonstrated in Supplemental Figure 3, only the cerebellum effect had a significant correlation with AUDIT score, and even that was more highly correlated with the interaction between AUDIT and anxiety traits. Qualitatively, depression also did not appear to be driving the anxiety results in the significant clusters; grouping individuals by comorbid depression diagnosis increases the standard deviation of group averages, and attenuated or even reversed patterns of engagement and relative deactivation (Supplemental Figure 4).

Our emotional face processing task was implicit; it did not ask participants to identify the emotion, just to match the faces displaying said emotions. It was possible to accomplish this without recognizing facial emotions; more problematically, we have no way of examining whether our groups differed behaviorally on recognition of emotions. We interpret the pattern of neural findings here as suggesting anxiety and alcohol related impacts on processes related to emotion recognition; this interpretation is driven by the previous literature on emotion processing in AUD and anxiety samples, as reviewed in the introduction and previously in our discussion of the findings. However, it could be that our participants have intact socioemotional cognition, and thus, patterns of neural results could reflect positive, compensatory processes. Our interpretation would be best supported by explicit behavioral data on emotion recognition performance in our sample specifically; moreover, such an interpretation would not detract from a distinct neurophenotype of AUD with anxiety, though it would impact some of the treatment implications.

Conclusions—

In this study, we investigated how AUD in combination with or in absence of anxiety symptomology was associated with neural response during a face emotion processing fMRI task. Across regions previously found to be engaged by face processing, we found that AUD individuals with and without anxiety traits have differential patterns of engagement. This underlines the importance of considering individual differences in the heterogeneous disorder of AUD. This lesson is particularly relevant for treatment and understanding of disease trajectories; individuals with AUD who have comorbid anxiety symptoms may be the highest risk for relapse. Future research should consider whether combined anxiety and AUD treatment is adequate or if AUD with anxiety features is a specific phenotype that needs to be treated as greater than the sum of its parts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank our patients and participants of the National Institutes on Alcohol Abuse and Alcoholism at the National Institutes of Health Clinical Center in Bethesda Maryland for their cooperation in this study.

Support: This research was supported by the National Institutes on Alcohol Abuse and Alcoholism/National Institutes of Health intramural research funding ZIA-AA000125 to the Clinical NeuroImaging Research Core (PI: R. Momenan).

References

- ADOLPHS R (2002) Neural systems for recognizing emotion. *Current opinion in neurobiology*, 12, 169–177. [PubMed: 12015233]
- ALBEIN-URIOS N, VERDEJO-ROMÁN J, ASENSIO S, SORIANO-MAS C, MARTÍNEZ-GONZÁLEZ JM & VERDEJO-GARCÍA A (2014) Re-appraisal of negative emotions in cocaine dependence: Dysfunctional corticolimbic activation and connectivity. *Addiction biology*, 19, 415–426. [PubMed: 22978709]
- AMERICAN PSYCHIATRIC ASSOCIATION (2013) Diagnostic and statistical manual of mental disorders (DSM-5®), American Psychiatric Pub.
- BALL TM, SULLIVAN S, FLAGAN T, HITCHCOCK CA, SIMMONS A, PAULUS MP & STEIN MB (2012) Selective effects of social anxiety, anxiety sensitivity, and negative affectivity on the neural bases of emotional face processing. *Neuroimage*, 59, 1879–1887. [PubMed: 21920442]
- BANDELOW B & MICHAELIS S (2015) Epidemiology of anxiety disorders in the 21st century. *Dialogues in clinical neuroscience*, 17, 327. [PubMed: 26487813]
- BISHOP SJ, DUNCAN J, BRETT M & LAWRENCE AD (2004a) Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. *Nature neuroscience*, 7, 184. [PubMed: 14703573]
- BISHOP SJ, DUNCAN J & LAWRENCE AD (2004b) State anxiety modulation of the amygdala response to unattended threat-related stimuli. *Journal of Neuroscience*, 24, 10364–10368. [PubMed: 15548650]
- BLAIR R, MORRIS JS, FRITH CD, PERRETT DI & DOLAN RJ (1999) Dissociable neural responses to facial expressions of sadness and anger. *Brain*, 122, 883–893. [PubMed: 10355673]
- BOEHME S, MILTNER WHR & STRAUBE T (2015) Neural correlates of self-focused attention in social anxiety. *Social Cognitive and Affective Neuroscience*, 10, 856–862. [PubMed: 25326038]
- BOOK SW, THOMAS SE, DEMPSEY JP, RANDALL PK & RANDALL CL (2009) Social anxiety impacts willingness to participate in addiction treatment. *Addictive Behaviors*, 34, 474–476. [PubMed: 19195794]
- BORA E & ZORLU N (2017) Social cognition in alcohol use disorder: a meta-analysis. *Addiction*, 112, 40–48. [PubMed: 27287050]
- BRUCE SE, YONKERS KA, OTTO MW, EISEN JL, WEISBERG RB, PAGANO M, SHEA MT & KELLER MB (2005) Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. *American Journal of psychiatry*, 162, 1179–1187. [PubMed: 15930067]
- CASTELLANO F, BARTOLI F, CROCAMO C, GAMBA G, TREMOLADA M, SANTAMBROGIO J, CLERICI M & CARRÀ G (2015) Facial emotion recognition in alcohol and substance use disorders: a meta-analysis. *Neuroscience & Biobehavioral Reviews*, 59, 147–154. [PubMed: 26546735]
- CHARLET K, SCHLAGENHAUF F, RICHTER A, NAUNDORF K, DORNHOF L, WEINFURTNER CE, KÖNIG F, WALASZEK B, SCHUBERT F & MÜLLER CA (2014) Neural activation during processing of aversive faces predicts treatment outcome in alcoholism. *Addiction biology*, 19, 439–451. [PubMed: 23469861]

- CLARK L, BECHARA A, DAMASIO H, AITKEN M, SAHAKIAN B & ROBBINS T (2008) Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. *Brain*, 131, 1311–1322. [PubMed: 18390562]
- COX RW (1996) AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical research*, 29, 162–173. [PubMed: 8812068]
- DEMENESCU LR, KORTEKAAS R, DEN BOER JA & ALEMAN A (2010) Impaired attribution of emotion to facial expressions in anxiety and major depression. *PloS one*, 5, e15058. [PubMed: 21152015]
- DICKIE EW & ARMONY JL (2008) Amygdala responses to unattended fearful faces: Interaction between sex and trait anxiety. *Psychiatry Research: Neuroimaging*, 162, 51–57.
- DOLAN RJ, FLETCHER P, MORRIS J, KAPUR N, DEAKIN J & FRITH CD (1996) Neural activation during covert processing of positive emotional facial expressions. *Neuroimage*, 4, 194–200. [PubMed: 9345509]
- DRIESSEN M, MEIER S, HILL A, WETTERLING T, LANGE W & JUNGHANS K (2001) The course of anxiety, depression and drinking behaviours after completed detoxification in alcoholics with and without comorbid anxiety and depressive disorders. *Alcohol and Alcoholism*, 36, 249–255. [PubMed: 11373263]
- EKMAN P & FRIESEN WV (1976) *Pictures of Facial Affect*, Consulting psychologists Press.
- EVANS KC, WRIGHT CI, WEDIG MM, GOLD AL, POLLACK MH & RAUCH SL (2008) A functional MRI study of amygdala responses to angry schematic faces in social anxiety disorder. *Depression and anxiety*, 25, 496–505. [PubMed: 17595018]
- FIRST M, SPITZER R, WILLIAMS J & GIBBON M (1997) Structured clinical interview for DSM-IV (SCID), 1997. American Psychiatric Association, Washington, DC.
- FIRST M, WILLIAMS J, KARG R & SPITZER R (2015) Structured clinical interview for DSM-5—Research version (SCID-5 for DSM-5, research version; SCID-5-RV). Arlington, VA: American Psychiatric Association.
- FITZPATRICK LE, JACKSON M & CROWE S (2008) The relationship between alcoholic cerebellar degeneration and cognitive and emotional functioning. *Neuroscience & Biobehavioral Reviews*, 32, 466–485. [PubMed: 17919727]
- FUSAR-POLI P, PLACENTINO A, CARLETTI F, LANDI P, ALLEN P, SURGULADZE S, BENEDETTI F, ABBAMONTE M, GASPAROTTI R & BARALE F (2009) Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of psychiatry & neuroscience*.
- GAEBLER M, DANIELS JK, LAMKE J-P, FYDRICH T & WALTER H (2014) Behavioural and neural correlates of self-focused emotion regulation in social anxiety disorder. *Journal of psychiatry & neuroscience: JPN*, 39, 249. [PubMed: 24690369]
- GENG JJ & VOSSEL S (2013) Re-evaluating the role of TPJ in attentional control: contextual updating? *Neuroscience & Biobehavioral Reviews*, 37, 2608–2620. [PubMed: 23999082]
- GILMAN JM & HOMMER DW (2008) Modulation of brain response to emotional images by alcohol cues in alcohol-dependent patients. *Addiction Biology*, 13, 423–434. [PubMed: 18507736]
- GORKA SM, FITZGERALD DA, KING AC & PHAN KL (2013) Alcohol attenuates amygdala-frontal connectivity during processing social signals in heavy social drinkers: a preliminary pharmacofMRI study. *Psychopharmacology*, 229, 141–154. [PubMed: 23584670]
- GORMAN JM (1996) Comorbid depression and anxiety spectrum disorders. *Depression and anxiety*, 4, 160–168. [PubMed: 9166648]
- GRANT BF, GOLDSTEIN RB, SAHA TD, CHOU SP, JUNG J, ZHANG H, PICKERING RP, RUAN WJ, SMITH SM & HUANG B (2015) Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA psychiatry*, 72, 757–766. [PubMed: 26039070]
- GRANT BF, STINSON FS, DAWSON DA, CHOU SP, DUFOUR MC, COMPTON W, PICKERING RP & KAPLAN K (2004) Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the national epidemiologic survey on alcohol and related conditions. *Archives of general psychiatry*, 61, 807–816. [PubMed: 15289279]

- HARIRI AR, MATTAY VS, TESSITORE A, KOLACHANA B, FERA F, GOLDMAN D, EGAN MF & WEINBERGER DR (2002a) Serotonin transporter genetic variation and the response of the human amygdala. *Science*, 297, 400–403. [PubMed: 12130784]
- HARIRI AR, TESSITORE A, MATTAY VS, FERA F & WEINBERGER DR (2002b) The amygdala response to emotional stimuli: a comparison of faces and scenes. *Neuroimage*, 17, 317–323. [PubMed: 12482086]
- HEILIG M, EGLI M, CRABBE JC & BECKER HC (2010) Acute withdrawal, protracted abstinence and negative affect in alcoholism: are they linked? *Addiction biology*, 15, 169–184. [PubMed: 20148778]
- HEILIG M & KOOB GF (2007) A key role for corticotropin-releasing factor in alcohol dependence. *Trends in neurosciences*, 30, 399–406. [PubMed: 17629579]
- HEIM C & NEMEROFF CB (2001) The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biological psychiatry*, 49, 1023–1039. [PubMed: 11430844]
- HEIMER L & ALHEID GF 1991 Piecing together the puzzle of basal forebrain anatomy. The basal forebrain. Springer.
- KANG E-K, LEE KS & LEE S-H (2017) Reduced cortical thickness in the temporal pole, insula, and pars triangularis in patients with panic disorder. *Yonsei medical journal*, 58, 1018–1024. [PubMed: 28792148]
- KNIGHT RG, WAAL-MANNING HJ & SPEARS GF (1983) Some norms and reliability data for the State-Trait Anxiety Inventory and the Zung Self-Rating Depression scale. *British Journal of Clinical Psychology*, 22, 245–249. [PubMed: 6640176]
- KOOB G & KREEK MJ (2007) Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *American Journal of Psychiatry*, 164, 1149–1159. [PubMed: 17671276]
- KOOB GF (2008) A role for brain stress systems in addiction. *Neuron*, 59, 11–34. [PubMed: 18614026]
- KOOB GF & VOLKOW ND (2010) Neurocircuitry of addiction. *Neuropsychopharmacology*, 35, 217–38. [PubMed: 19710631]
- KOOB GF & VOLKOW ND (2016) Neurobiology of addiction: a neurocircuitry analysis. *The Lancet Psychiatry*, 3, 760–773. [PubMed: 27475769]
- KORNREICH C, PHILIPPOT P, FOISY M-L, BLAIRY S, RAYNAUD E, DAN B, HESS U, NOËL X, PELC I & VERBANCK P (2002) Impaired emotional facial expression recognition is associated with interpersonal problems in alcoholism. *Alcohol and alcoholism*, 37, 394–400. [PubMed: 12107044]
- KUSHNER MG, ABRAMS K, THURAS P, HANSON KL, BREKKE M & SLETTEN S (2005) Follow-up study of anxiety disorder and alcohol dependence in comorbid alcoholism treatment patients. *Alcoholism: Clinical and experimental research*, 29, 1432–1443.
- LAI HMX, CLEARY M, SITHARTHAN T & HUNT GE (2015) Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990–2014: A systematic review and meta-analysis. *Drug and Alcohol Dependence*, 154, 1–13. [PubMed: 26072219]
- LEDoux J (2007) The amygdala. *Current biology*, 17, R868–R874. [PubMed: 17956742]
- LEWIS B, GARCIA CC, BOHAN R & NIXON SJ (2020) Impact of polysubstance use on social and non-affective cognitive performance among treatment-seeking individuals with alcohol use disorders. *Addictive Behaviors*, 106, 106359. [PubMed: 32109774]
- LEWIS B, PRICE JL, GARCIA CC & NIXON SJ (2019) Emotional face processing among treatment-seeking individuals with alcohol use disorders: investigating sex differences and relationships with interpersonal functioning. *Alcohol and Alcoholism*, 54, 361–369. [PubMed: 30796771]
- LIBERZON I & MARTIS B (2006) Neuroimaging studies of emotional responses in PTSD. *Annals of the New York Academy of Sciences*, 1071, 87–109. [PubMed: 16891565]
- LITTEN RZ, RYAN ML, FALK DE, REILLY M, FERTIG JB & KOOB GF (2015) Heterogeneity of alcohol use disorder: Understanding mechanisms to advance personalized treatment. *Alcoholism: Clinical and Experimental Research*, 39, 579–584.

- MAAT A, VAN HAREN NE, BARTHOLOMEUSZ CF, KAHN RS & CAHN W (2016) Emotion recognition and theory of mind are related to gray matter volume of the prefrontal cortex in schizophrenia. *European Neuropsychopharmacology*, 26, 255–264. [PubMed: 26711688]
- MARINKOVIC K, OSCAR-BERMAN M, URBAN T, O'REILLY CE, HOWARD JA, SAWYER K & HARRIS GJ (2009) Alcoholism and dampened temporal limbic activation to emotional faces. *Alcoholism: Clinical and Experimental Research*, 33, 1880–1892.
- MITCHELL JP (2007) Activity in right temporo-parietal junction is not selective for theory-of-mind. *Cerebral cortex*, 18, 262–271. [PubMed: 17551089]
- MORENO-RIUS J (2018) The cerebellum in fear and anxiety-related disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 85, 23–32. [PubMed: 29627508]
- MORRIS JS, FRITH CD, PERRETT DI, ROWLAND D, YOUNG AW, CALDER AJ & DOLAN RJ (1996) A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature*, 383, 812. [PubMed: 8893004]
- NAESER MA, MARTIN PI, THEORET H, KOBAYASHI M, FREGNI F, NICHOLAS M, TORMOS JM, STEVEN MS, BAKER EH & PASCUAL-LEONE A (2011) TMS suppression of right pars triangularis, but not pars opercularis, improves naming in aphasia. *Brain and Language*, 119, 206–213. [PubMed: 21864891]
- NAQVI NH & BECHARA A (2009) The hidden island of addiction: the insula. *Trends in neurosciences*, 32, 56–67. [PubMed: 18986715]
- NOVAK A, BURGESS ES, CLARK M, ZVOLENSKY MJ & BROWN RA (2003) Anxiety sensitivity, self-reported motives for alcohol and nicotine use, and level of consumption. *Journal of anxiety disorders*, 17, 165–180. [PubMed: 12614660]
- OBESO I, ROBLES N, MUÑOZ-MARRÓN E & REDOLAR-RIPOLL D (2013) Dissociating the role of the pre-SMA in response inhibition and switching: a combined online and offline TMS approach. *Frontiers in human neuroscience*, 7, 150. [PubMed: 23616761]
- OSCAR-BERMAN M & MARINKOVIC K (2007) Alcohol: Effects on neurobehavioral functions and the brain. *Neuropsychology Review*, 17, 239–257. [PubMed: 17874302]
- PADULA CB, SIMMONS AN, MATTHEWS SC, ROBINSON SK, TAPERT SF, SCHUCKIT MA & PAULUS MP (2011) Alcohol attenuates activation in the bilateral anterior insula during an emotional processing task: a pilot study. *Alcohol and alcoholism*, 46, 547–552. [PubMed: 21665869]
- PHAN KL, FITZGERALD DA, NATHAN PJ & TANCER ME (2006) Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biological psychiatry*, 59, 424–429. [PubMed: 16256956]
- PHAN KL, WAGER TD, TAYLOR SF & LIBERZON I (2004) Functional neuroimaging studies of human emotions. *CNS spectrums*, 9, 258–266. [PubMed: 15048050]
- PHILLIPS ML, YOUNG AW, SENIOR C, BRAMMER M, ANDREW C, CALDER AJ, BULLMORE ET, PERRETT DI, ROWLAND D & WILLIAMS SC (1997) A specific neural substrate for perceiving facial expressions of disgust. *Nature*, 389, 495. [PubMed: 9333238]
- POSAMENTIER MT & ABDI H (2003) Processing faces and facial expressions. *Neuropsychology Review*, 13, 113–143. [PubMed: 14584908]
- R CORE TEAM 2017 R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing.
- RIVA D, ANNUNZIATA S, CONTARINO V, ERBETTA A, AQUINO D & BULGHERONI S (2013) Gray matter reduction in the vermis and CRUS-II is associated with social and interaction deficits in low-functioning children with autistic spectrum disorders: a VBM-DARTEL Study. *The Cerebellum*, 12, 676–685. [PubMed: 23572290]
- RUIGROK AN, SALIMI-KHORSHIDI G, LAI M-C, BARON-COHEN S, LOMBARDO MV, TAIT RJ & SUCKLING J (2014) A meta-analysis of sex differences in human brain structure. *Neuroscience & Biobehavioral Reviews*, 39, 34–50. [PubMed: 24374381]
- RUPP CI, DERNTL B, OSTHAUS F, KEMMLER G & FLEISCHHACKER WW (2017) Impact of social cognition on alcohol dependence treatment outcome: poorer facial emotion recognition predicts relapse/dropout. *Alcoholism: Clinical and Experimental Research*, 41, 2197–2206.

- SALLOUM JB, RAMCHANDANI VA, BODURKA J, RAWLINGS R, MOMENAN R, GEORGE D & HOMMER DW (2007) Blunted rostral anterior cingulate response during a simplified decoding task of negative emotional facial expressions in alcoholic patients. *Alcoholism: Clinical and Experimental Research*, 31, 1490–1504.
- SAUNDERS JB, AASLAND OG, BABOR TF, DELAFUENTE JR & GRANT M (1993) DEVELOPMENT OF THE ALCOHOL-USE DISORDERS IDENTIFICATION TEST (AUDIT) - WHO COLLABORATIVE PROJECT ON EARLY DETECTION OF PERSONS WITH HARMFUL ALCOHOL-CONSUMPTION .2. *Addiction*, 88, 791–804. [PubMed: 8329970]
- SCHIENLE A, STARK R, WALTER B, BLECKER C, OTT U, KIRSCH P, SAMMER G & VAITL D (2002) The insula is not specifically involved in disgust processing: an fMRI study. *Neuroreport*, 13, 2023–2026. [PubMed: 12438918]
- SCHMAHMANN JD (2000) The role of the cerebellum in affect and psychosis. *Journal of Neurolinguistics*, 13, 189–214.
- SCHMAHMANN JD (2019) The cerebellum and cognition. *Neuroscience Letters*, 688, 62–75. [PubMed: 29997061]
- SCHMIDT T, ROSER P, JUCKEL G, BRÜNE M, SUCHAN B & THOMA P (2016) Social cognition and social problem solving abilities in individuals with alcohol use disorder. *Journal of clinical and experimental neuropsychology*, 38, 974–990. [PubMed: 27456035]
- SCHRAA-TAM CKL, RIETDIJK WJR, VERBEKE WJMI, DIETVORST RC, VAN DEN BERG WE, BAGOZZI RP & DE ZEEUW CI (2012) fMRI Activities in the Emotional Cerebellum: A Preference for Negative Stimuli and Goal-Directed Behavior. *The Cerebellum*, 11, 233–245. [PubMed: 21761197]
- SCHUCKIT MA, SMITH TL, PAULUS MP, TAPERT SF, SIMMONS AN, TOLENTINO NJ & SHAFIR A (2016) The ability of functional magnetic resonance imaging to predict heavy drinking and alcohol problems 5 years later. *Alcoholism: Clinical and Experimental Research*, 40, 206–213.
- SCHULZ KP, CLERKIN SM, HALPERIN JM, NEWCORN JH, TANG CY & FAN J (2009) Dissociable neural effects of stimulus valence and preceding context during the inhibition of responses to emotional faces. *Human brain mapping*, 30, 2821–2833. [PubMed: 19086020]
- SHAKRA MA, LEYTON M, MOGHNIEH H, PRUESSNER J, DAGHER A & PIHL R (2018) Neurobiological correlates and predictors of two distinct personality trait pathways to escalated alcohol use. *EBioMedicine*, 27, 86–93. [PubMed: 29292030]
- SHIN LM & LIBERZON I (2009) The Neurocircuitry of Fear, Stress, and Anxiety Disorders. *Neuropsychopharmacology*, 35, 169.
- SINHA R, SINHA R, LI CSR, SINHA R & LI CSR (2007) Imaging stress- and cue-induced drug and alcohol craving: association with relapse and clinical implications. *Drug and Alcohol Review*, 26, 25–31. [PubMed: 17364833]
- SMITH JP & BOOK SW (2010) Comorbidity of generalized anxiety disorder and alcohol use disorders among individuals seeking outpatient substance abuse treatment. *Addictive Behaviors*, 35, 42–45. [PubMed: 19733441]
- SMITH JP & RANDALL CL (2012) Anxiety and alcohol use disorders: comorbidity and treatment considerations. *Alcohol research: current reviews*.
- SOMERVILLE LH, KIM H, JOHNSTONE T, ALEXANDER AL & WHALEN PJ (2004) Human amygdala responses during presentation of happy and neutral faces: correlations with state anxiety. *Biological psychiatry*, 55, 897–903. [PubMed: 15110733]
- SPIELBERGER CD, GORSUCH RL, LUSHENE R, VAGG P & JACOBS G (1983) *Manual for the state-trait anxiety inventory* Consulting Psychologists Press. Palo Alto, CA.
- SRIPADA CS, ANGSTADT M, MCNAMARA P, KING AC & PHAN KL (2011) Effects of alcohol on brain responses to social signals of threat in humans. *Neuroimage*, 55, 371–380. [PubMed: 21122818]
- STEIN MB, SIMMONS AN, FEINSTEIN JS & PAULUS MP (2007) Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *American Journal of Psychiatry*, 164, 318–327. [PubMed: 17267796]
- STOODLEY CJ & SCHMAHMANN JD (2009) Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. *Neuroimage*, 44, 489–501. [PubMed: 18835452]

- STOODLEY CJ, VALERA EM & SCHMAHMANN JD (2012) Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. *Neuroimage*, 59, 1560–1570. [PubMed: 21907811]
- SURCINELLI P, CODISPOTI M, MONTEBAROCCI O, ROSSI N & BALDARO B (2006) Facial emotion recognition in trait anxiety. *Journal of anxiety disorders*, 20, 110–117. [PubMed: 16325118]
- TURNER BM, PARADISO S, MARVEL CL, PIERSON R, PONTO LLB, HICHWA RD & ROBINSON RG (2007) The cerebellum and emotional experience. *Neuropsychologia*, 45, 1331–1341. [PubMed: 17123557]
- VALMAS MM, MOSHER RUIZ S, GANSLER DA, SAWYER KS & OSCAR-BERMAN M (2014) Social cognition deficits and associations with drinking history in alcoholic men and women. *Alcoholism, clinical and experimental research*, 38, 2998–3007.
- WAGER TD, PHAN KL, LIBERZON I & TAYLOR SF (2003) Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. *Neuroimage*, 19, 513–531. [PubMed: 12880784]
- WILCOX CE, POMMY JM & ADINOFF B (2016) Neural circuitry of impaired emotion regulation in substance use disorders. *American Journal of Psychiatry*, 173, 344–361. [PubMed: 26771738]
- WOLITZKY-TAYLOR K, NILES AN, RIES R, KRULL JL, RAWSON R, ROY-BYRNE P & CRASKE M (2018) Who needs more than standard care? Treatment moderators in a randomized clinical trial comparing addiction treatment alone to addiction treatment plus anxiety disorder treatment for comorbid anxiety and substance use disorders. *Behaviour research and therapy*, 107, 1–9. [PubMed: 29800622]
- WRIGHT P & LIU Y (2006) Neutral faces activate the amygdala during identity matching. *Neuroimage*, 29, 628–636. [PubMed: 16143545]

Figure 1: Neural differences between AUD+ANX and Controls during Fearful Face Processing
Notes: Top Panel) Whole-brain images centered on significant cluster in the group (Control > AUD+ANX). Warm and cool colors represent positive and negative T-values, respectively. Images thresholded at $p < 0.001$, $k = 9$. Bottom Panel) Plots generated for visualization purposes from betas extracted from clusters identified in the whole-brain analysis. Bars represent means; error bars represent standard errors. Abbreviations: AUD- Alcohol Use Disorder; ANX- Anxiety; TPJ- temporoparietal junction; SMA- Supplementary Motor Area.

Figure 2: Neural differences between AUD-ANX and Controls during Fearful Faces > Shape processing

Notes: Closest gray matter to cluster corresponding to the supramarginal gyrus. Top Panel) Whole-brain images centered on significant cluster in the group (Control > AUD-ANX). Cool colors represent negative T-values. Images thresholded at $p < 0.001$, $k = 9$. Bottom Panel) Plots generated for visualization purposes from betas extracted from clusters identified in the whole-brain analysis. Bars represent means; error bars represent standard errors. Abbreviations: AUD- Alcohol Use Disorder; ANX- Anxiety.

Figure 3: Neural differences in AUD+/- ANX during Fearful > Neutral Face processing
Notes: Left Panel) Whole-brain images centered on significant cluster. Cool colors represent negative T-values. Images thresholded at $p < 0.001$, $k = 9$. Right Panel) Plots generated for visualization purposes from betas extracted from clusters identified in the whole-brain analysis. Bars represent means; error bars represent standard errors. A) Peak at $x = 17$, $y = -78$, $z = -42$. B) Peak at $x = 56$, $y = 24$, $z = 0$. Abbreviations: IFG- Inferior frontal gyrus; AUD- Alcohol Use Disorder; ANX- Anxiety.

Table 1.

Sample Description

	Group		
	<i>AUD+ANX</i>	<i>AUD-ANX</i>	<i>HC</i>
N	90	39	103
%Male	65.56	71.8	44.66
%Smoker	52.81	46.15	3.88
%Current / Past Anxiety Disorder	30.34 / 35.96	7.69 / 5.13	1.96 / 2.94
%Current / Past Depression	44.94 / 42.70	5.13 / 17.95	1.96 / 4.90
Race/Ethnicity			
% <i>Hispanic / Latinx</i>	7.87	10.26	12.62
% <i>American Indian / Alaska Native</i>	1.12	0.00	0.00
% <i>Asian</i>	2.25	0.00	8.74
% <i>Black / African-American</i>	30.34	53.85	41.75
% <i>White</i>	50.56	43.59	38.83
% <i>More than One Race</i>	11.24	0.00	4.85
% <i>Unknown or Not Reported</i>	4.49	2.56	5.83
Age	41.74 (11.11)	39.90 (12.59)	36.08 (11.14)
Years of Education	13.51 (2.95)	13.97 (2.82)	16.22 (2.92)
AUDIT	36.72 (13.89)	21.36 (8.09)	3.31 (3.89)
STAI-T	52.46 (8.26)	30.26 (5.40)	29.23 (8.51)
Drinks per Day	14.52 (8.66)	9.63 (5.99)	2.09 (1.83)
Number of Drinking Days (Last 90 Days)	69.39 (25.13)	69.97 (20.79)	15.49 (15.76)
Number of Other SUDs *	1.36 (1.33)	0.62 (1.27)	0.04 (0.31)

Notes: Values are reported as mean (standard deviation). AUDIT: Alcohol use disorder identification test; STAI-T: State Trait Anxiety Inventory - Trait; SUD: Substance use disorder.

* The most common current SUD comorbidities were cannabis (14% / 3% / 0%) and stimulant (15% / 3% / 1%).

Table 2.

Behavioral performance on face matching task by group

		Overall	AUD+ANX	AUD-ANX	HC
Fearful Faces					
RT	mean	1.27	1.30	1.27	1.25
	sd	0.30	0.35	0.29	0.26
Accuracy	mean	0.99	0.99	1.00	0.99
	sd	0.03	0.03	0.00	0.03
Neutral Faces					
RT	mean	1.18	1.19	1.15	1.18
	sd	0.30	0.30	0.27	0.31
Accuracy	mean	0.98	0.99	1.00	0.97
	sd	0.06	0.03	0.01	0.08
Shapes					
RT	mean	1.04	1.03	1.05	1.05
	sd	0.24	0.22	0.23	0.25
Accuracy	mean	0.98	0.99	0.99	0.98
	sd	0.04	0.02	0.02	0.06

Notes: Abbreviations- RT: Response Time; sd: standard deviation; AUD: Alcohol use disorder; ANX: anxiety symptoms; HC: healthy controls

Table 3.

Associations between neural correlates of fearful face processing and continuous measures of anxiety/AUD in individuals with AUD

Region	AUDIT	STAI	AUDxSTAI
Cerebellum	-0.223 *	-0.325 ***	-0.305 ***
Supramarginal Gyrus	0.081	0.003	0.061
Pre-SMA	-0.049	-0.033	-0.057
TPJ	-0.061	-0.065	-0.059
IFG	-0.062	-0.068	-0.046

Notes: Numbers reported are Pearson's correlation values for the association between contrast betas in the identified region and the variable indicated. Lines highlighted in gray use values corresponding to the significant Fearful Faces > Shapes contrast; other lines correspond to the significant Fearful > Neutral Faces contrast.

Significance indicated as follows:

⁺
p < 0.10

*
p < 0.05

**
p < 0.01

p < 0.001.

Abbreviations: SMA- Supplementary Motor Area; TPJ- Temporoparietal Junction; IFG- Inferior Frontal Gyrus; AUD- Alcohol Use Disorder; AUDIT- AUD Identification Test; STAI- State Trait Anxiety Inventory. Interaction between AUD and STAI indicated in right-most column.