Alcohol Attenuates Amygdala-Frontal Connectivity During Processing Social Signals in Heavy Social Drinkers: A Preliminary Pharmaco-fMRI Study

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Abstract

Rationale—Convergent evidence shows that alcohol exerts its effects on social behavior via modulation of amygdala reactivity to affective stimuli. Given that affective processing involves dynamic interactions between the amygdala and the prefrontal cortex (PFC), alcohol's effects are likely to extend beyond regional changes in brain activity to changes that manifest on a broader functional circuit level.

Objective—The current study examines alcohol's effects on functional connectivity (i.e., 'coupling') between the amygdala and the PFC during the processing of socio-emotional stimuli using functional magnetic resonance imaging (fMRI).

Methods—In a randomized, double blind, placebo-controlled, within-subjects cross-over design, twelve heavy, social drinkers performed an fMRI task designed to probe amygdala response to socio-emotional stimuli (angry, fearful, and happy faces) following acute ingestion of alcohol or placebo. Functional connectivity between the amygdala and PFC was examined and compared between alcohol and placebo sessions using a conventional generalized psychophysiological interaction (gPPI) analysis.

Results—Relative to placebo, alcohol reduced functional coupling between the amygdala and the right orbitofrontal cortex (OFC) during processing of both angry and fearful faces. Alcohol also reduced functional coupling between the amygdala and left OFC during processing of happy faces.

Conclusions—These preliminary findings suggest that alcohol's effects on social behavior may be mediated by alternations in functional connectivity between the amygdala and OFC during processing of emotional faces.

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Keywords

alcohol; amygdala; functional connectivity; social threat

Introduction

Alcohol is known to affect both affective states and social behavior (Armeli et al. 2003; Giancola et al. 2009; Kushner et al. 1996). Moreover, alcohol's ability to modulate affective states is widely considered a key motivational factor underlying drinking behavior (Baker et al. 2004; Cooper et al. 1995; Khantzian 1997; Levenson et al. 1980). Numerous theoretical models indicate that alcohol use brings perceived and/or actual relief from negative affective states (e.g., stress, anxiety), thereby reinforcing drinking behavior and increasing the likelihood of future alcohol use (Baker et al. 2004; Khantizan 1997). Acutely, alcohol intoxication reduces subjective and physiological responses to stress (Hefner and Curtin 2012; Kushner et al. 1996; Moberg and Curtin 2009; Sayette et al. 1992), reduces social inhibition, and increases the propensity to act aggressively towards others (Bushman and Cooper 1990; Chermack and Giancola 1997). Given these findings, identifying mechanisms that underlie modulation of negative affective states and social behavior by alcohol use is of the utmost public health significance. Yet, relatively little is known regarding the neural processes that mediate this association.

Functional magnetic resonance imaging (fMRI) studies have begun to examine the acute effects of alcohol on processing social stimuli with negative valence. Initial work by Gilman and colleagues (2008, 2011) examining the effects of alcohol on neural response to fearful and neutral faces indicates that intravenous alcohol administration results in attenuated BOLD activity in the amygdala during the viewing of fearful faces and also enhanced activity in striatal reward circuits to neutral faces in social drinkers. Unexpectedly, these authors also found that alcohol increased amygdala activity to neutral faces, concluding that alcohol may exert its anxiolytic effects by reducing the amygdala's ability to detect threatening information and/or by attenuating amygdala reactivity to threat (Gilman et al. 2008). Using the Emotional Face Assessment Task (EFAT) to probe amygdala activity to threat (angry and fearful faces), a prior study by our group also demonstrated that alcohol attenuated amygdala reactivity to threat-related faces (but not happy faces) in heavy, social drinkers (Sripada et al. 2011). These findings suggest that alcohol may mediate its anxiolytic effects by down-regulating the brain's response to signals of threat, consistent with a large body of human and animal literature noting the importance of the amygdala in negative affective processing (Adolphs 2002; LeDoux 2000; Phan et al. 2002; Phelps 2004).

While the amygdala is clearly a viable target region for alcohol's anxiolytic effects, the generation, expression and modulation of emotion involves dynamic interactions between emotion-evoking regions such as the amygdala and its relation to other brain areas such as the prefrontal cortex (PFC), in the context of mediating change in affect regulation and in social behavior (Goldin et al. 2008; Harenski and Hamann, 2006; Kanske et al. 2011; Ohira et al. 2006). Existing neuroimaging research has shown that frontal control regions such as the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), dorsal medial prefrontal cortex (DMPFC), and ventrolateral prefrontal cortex (VLPFC) are engaged during the recognition and regulation of emotion (Beauregard et al. 2001; Ochsner et al. 2002, 2004; Levesque et al. 2003; Phan et al. 2005) and during social cognition and social interaction (Beer et al. 2003; Gallager and Frith 2003; Mitchell et al. 2006). Importantly, engagement of these regions during processing of affective stimuli is associated with the modulation of amygdala activity (Beauregard et al. 2001; Ochsner et al. 2002; Phan et al. 2005; Urry et al. 2006). Data from our lab has shown that in response to negative affect,

there is increased connectivity between the amygdala and the PFC, specifically the anterior cingulate cortex (ACC), medial prefrontal cortex (MPFC), inferior frontal gyrus (IFG), OFC, and DLPFC (Banks et al. 2007; Prater et al. 2012). These findings are consistent with other studies which have also reported increased connectivity between the amygdala and PFC during social decision-making and interpretation of facial cues (Adolphs 2002; Blair et al. 1999; Iidaka et al. 2011; Nomura et al. 2004). Anatomical tracing studies have also shown that the amygdala has strong reciprocal connections with frontal regions, including the OFC, VLPFC, and DMPFC (Amaral and Price 1984; Ghashghaei and Barbas 2002; Ghashghaei et al. 2007). Taken together, these data suggest that alcohol may affect socio-emotional processing and behavior by altering the functional interactions between the amygdala and PFC (Hariri et al. 2003; Forbes and Grafman 2010; Frith and Frith 2007; Meyer-Lindenberg et al. 2005; Ochsner et al. 2004; Stein et al. 2007).

Consistent with this speculation, studies have demonstrated that individuals with alcohol use disorders have disrupted patterns of functional connectivity (Chanraud et al. 2011; Courtney et al. 2012; O'Daly et al. 2012; Rogers et al. 2012). For example, Courtney et al. (2012) found that greater alcohol dependence severity was associated with weaker functional connectivity within fronto-striatal pathways during a response inhibition task, while Pitel et al. (2012) demonstrated aberrant hippocampal and cerebellar connectivity during a social associative learning task. Relevant to the current study, in response to fearful faces alcoholic patients with multiple detoxifications have been shown to exhibit decreased connectivity between the amygdala and globus pallidus, and the insula and prefrontal regions including the ACC, OFC, and VLPFC (O'Daly et al. 2012). These data lend support to the hypothesis that alcohol may disrupt functional interactions between neural regions; however, the acute effects of alcohol on functional connectivity during socio-emotional processing are still unknown.

The current study aimed to test this hypothesis with a novel analysis of fMRI data collected during our previous study (Sripada et al. 2011). The study utilized a two-session (placebo vs. alcohol), double blind, within-subjects cross-over design. Our analyses indicated that alcohol consumption diminished amygdala reactivity to social signals of threat (angry and fearful faces), without affecting amygdala reactivity to non-threat signals (happy faces; Sripada et al. 2011). In the present study, we employed a generalized form of context-dependent physiological interaction analyses (gPPI; McLaren et al. 2008), which allows for more than two conditions to be modeled independently and has greater sensitivity and specificity than standard PPI methods (McLaren et al. 2012). Given these above results, we examined functional connectivity between the amygdala and the PFC as a function of emotional stimuli (angry, fearful, and happy faces) and condition (placebo and alcohol), using the amygdala as the seed region. We hypothesized that alcohol would reduce amygdala connectivity to these broad areas within the PFC during processing of angry and fearful faces, relative to placebo.

Methods

Participants

Sample descriptive information are provided in Table 1. The sample consisted of twelve healthy, right-handed volunteers. Individuals were selected to meet criteria for heavy social drinking consistent with our prior studies (King et al. 2002, 2009), defined as consuming 10 standard alcoholic drinks per week with one to five weekly "binge" drinking episodes (5+ drinks per occasion for men; 4+ drinks for women; NIAAA 2005a, SAMHSA 2005). The rationale for recruiting a group of heavy social drinkers included both ethical concerns (e.g., avoid potential alcohol withdrawal) and scientific considerations (e.g., non-dependent social drinkers exhibit heightened alcohol reward without excessive sedative effects; King et

al. 2002, 2011). Most notably, Gilman et al. (2011) recently reported that heavy problematic drinkers demonstrate amygdala hypoactivation in response to threatening faces across both placebo and alcohol conditions and thus, exhibit differences in alcohol-induced neural responding relative to social drinkers. Approximately 50% of interested participants screened by phone were eligible for the in-laboratory assessment; all candidates attending the in-person screening were accepted into the study, one of whom withdrew prior to the first session.

Participants were excluded from the study if they met lifetime criteria for any major Axis I (except alcohol abuse) or Axis II psychiatric disorders according to the Structured Clinical Interview for DSM-IV (SCID-IV Patient Edition; First et al. 1995). Individuals were also excluded if they were taking medications, had a history of neurological or medical illness as confirmed by medical examination, or had liver enzyme tests out of the normal range for aspartate aminotransferase and alanine transaminase. All participants provided written informed consent, as approved by the Institutional Review Board. All baseline breathalyzer tests were negative for alcohol upon arrival to the sessions, confirming compliance with study abstinence instructions on testing days.

Procedure

The study protocol has been described in detail elsewhere (see Sripada et al. 2011). In brief, the current study was a two-session, double-blind, placebo-controlled, within-subjects design. Prior to each session, participants were instructed to abstain from alcohol, recreational drugs, and any psychoactive medications for at least 48 hours, as well as caffeine, food, and cigarette smoking for 3 hours. Upon arrival, the subject underwent abstinence verification, consumed a low-fat snack (20% daily calories), and acclimated to the laboratory.

Approximately 45-minutes after arrival, participants were served a beverage and a small placebo gel capsule containing dextrose. To reduce alcohol expectancies, the Alternative Substance Paradigm (Conrad et al. 2012) was employed in which participants were told that the beverage or capsule might contain alcohol, a stimulant, a sedative, a placebo, or some combination of those substances. In actuality, the beverage contained either a high dose of alcohol (ALC; 0.8 g/kg; 16% volume alcohol) or placebo (PBO; 0.0 g/kg; 1% volume ethanol as a taste mask).

The beverages were prepared with flavored drink mix, a sucralose-based sugar substitute, water, and the appropriate dose of 190-proof ethanol based on body weight and were consumed through a straw in a lidded, opaque cup to conceal potential scent cues. Women received an 85% dose to adjust for total body water differences (Frezza et al. 1990; Sutker et al. 1983). Total beverage volumes for placebo and alcohol were identical (mean 472 mL; range 297-581 mL) and based on the participants' body weight. Consumption of the beverage occurred within a 13-minute interval and was timed such that the upcoming fMRI task would concur with expected peak breath alcohol concentration (Epstein et al. 2007; King et al. 2002, 2011). Immediately following beverage consumption, the participant was escorted into the scanning room, underwent fMRI preparation and structural MRI, and completed the EFAT (described below). The end of the task occurred approximately 65-minutes after alcohol ingestion. Prior to consumption of the alcohol or placebo beverage, participants completed the Biphasic Alcohol Effects Scale (BAES; Martin et al. 1993; Rueger et al. 2009), which was repeated 75-minutes later. Notably, the EFAT followed a visual stimulus processing task involving smoking and non-smoking images as part of a larger experiment, the results of which have previously been published (King et al. 2010). BrAC levels for the session have been previously published (Sripada et al. 2011) and followed the expected time-course (average BrAC at 75-min, 90-min, 120-min, 150-min,

and 180-min post alcohol ingestion = 0.090, 0.085, 0.076, 0.069, 0.060). Of note, we did not assess BrAC while participants were in the scanner and therefore we do not have exact BrAC values during the EFAT task. Alcohol ingestion increased to an average of 0.091 ($\pm$ 0.014) % 75-minutes after initiation of beverage consumption with a slow elimination phase over the next few hours. Once participants' BrAC was below 0.04% and they displayed no overt signs of intoxication (NIAAAb), they were discharged from the study and given a vehicle service ride to their home and instructed not to drive or operate machinery for at least 12-hours.

Emotional Face Assessment Task (EFAT)

The EFAT task has previously been described in detail (see Phan et al. 2008). The EFAT and variants of the task have been shown to reliably and robustly engage the amygdala (Hariri et al. 2002; Kirsch et al. 2005; Paulus et al. 2005). In brief, participants viewed three faces (one on the top of the screen and two on the bottom) and were asked to select one of the two faces on the bottom of the screen that expressed the same emotion as the target face on the top of the screen. The identity of all three faces was always different and an equal number of male and female faces were presented. The target face and the congruent probe face always displayed one of three expressions (angry, fearful, or happy) and the other (i.e., incongruent) probe face always displayed a neutral expression. The face photographs were selected from the validated stimulus set from Gur et al. (2002). The angry, fearful, and happy target faces were presented in separate blocks and a total of three blocks of each target expression were presented. Importantly, no target stimuli were repeated within or across blocks. In addition, there were also blocks in which participants similarly matched simple geometric shapes (i.e., circles, rectangles, or triangles). This 'control' task was included to maintain attention and allow limbic brain responses to return to baseline. The paradigm consisted of eighteen 20-seconds blocks: 9 blocks of matching emotional faces, interleaved with 9 blocks of matching shapes (blocks occurred back-to-back without intervening fixation), counterbalanced across two runs for a total task time of 6-minutes. Each task block contained four sequential matching trials, 5-seconds each. Participants made responses by pressing the left or right response buttons with their dominant hand. These responses also provided a measure of participants' response accuracy and reaction time.

Brain Imaging

Functional MRI was performed on a 3T GE magnetic resonance scanner which acquired functional images (i.e., blood oxygenated level-dependent [BOLD]) from 30 axial, 5-mm-thick slices using a T2*-sensitive gradient echo reserve spiral acquisition sequences (repetition time, 2000 ms; echo time, 25 ms; 64×64 matrix; 24 cm field of view; flip angle, 77), optimized to minimize susceptibility artifacts in the amygdala (Stenger et al. 2000). This was followed by a high-resolution, T1-weighted volumetric anatomical scan (three-dimensional magnetization-prepared rapid gradient echo) for anatomical localization.

Functional MRI Data Analyses

Data from all 12 participants met criteria for high quality and scan stability with minimum motion correction (i.e., 3 mm or less displacement in any one direction) and thus were included in subsequent analyses. Functional data were analyzed using Statistical Parametric Mapping software (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK) using similar previously published methods (e.g., Rabinak et al. 2011). Images were spatially realigned to correct for head motion, warped to standardized Montreal Neurological Institute (MNI) space using the participant's mean functional image, resampled to 2 mm^3 voxels, and smoothed with an 8 mm^3 kernel to minimize noise and residual differences in gyral anatomy. The general linear model (GLM) was applied to the time series, convolved with the canonical hemodynamic response function (HRF; Friston et al. 1995) and with a 128

second high-pass filter. Condition effects were modeled with box-car regressors representing the occurrence of each block type. Effects were estimated at each voxel, and for each subject. Individual contrast maps (statistical parametric maps [SPMs]) were then analyzed at the second level in a random-effects statistical model (Holmes and Friston 1998).

The current analysis intended to examine angry and fearful faces separately given that prior work has suggested that different facial expressions may convey different messages about the 'source' of threat (e.g., direct threat from angry faces, indirect threat from fearful faces) and may differentially engage the amygdala, insula, ACC and MPFC (Fusar-Poli et al. 2009) and elicit qualitatively different behavioral responses (Pichon et al. 2009; Whalen et al. 2001). Angry faces often signal to the observer to modify his/her own behavior, while fearful faces typically signal danger in the environment (Fridlund 1994; Whalen 1998), which may be differentially sensitive to alcohol's effect on amygdala-PFC connectivity. Of note, earlier studies examining the effects of alcohol on neural responses to threat had either used fearful faces only (Gilman et al. 2008, 2011) or had collapsed across fearful and angry faces (Sripada et al. 2011). Therefore, examining the threat conditions separately will extended these previous findings.

To examine functional coupling between the amygdala and other areas of the brain during placebo (PBO) vs. alcohol (ALC) in the context of processing social signals of threat, we used a generalized form of context-dependent psychophysiological interaction analyses (gPPI; http://brainmap.wisc.edu/PPI, McLaren et al. 2008). The use of gPPI allowed us to model each condition (i.e., angry, fearful, happy, and shapes) independently. We chose to define functionally-derived amygdala seeds of interest (SOIs) as activation clusters that exhibited a significant modulation by alcohol. In other words, in order to facilitate interpretations, we only chose to examine the effects of alcohol on amygdala functional connectivity if there was a main effect of ALC (vs. PBO) on amygdala activation to angry/fearful faces in the primary analysis, as shown by a paired-sample t-test contrasting PBO against ALC. We considered activations that survived $p < 0.005$ (uncorrected; Lieberman and Cunningham, 2009) for between-session contrast t-maps as significant. In-order to clarify the direction of differences (or lack thereof), we also extracted BOLD signal responses (i.e., parameter estimates, β weights [arbitrary units, a.u.]) from 10mm spheres surrounding peak activations within the amygdala from each session (ALC, PBO) and emotion (angry, fearful, and happy) separately. Using conventional gPPI methods, the de-convolved time series from these functionally-derived spherical SOIs around the group peak activation voxel within the amygdala (identified in the above analyses) was extracted for each subject to create the physiological variable. Next, the condition onset times for angry faces, fearful faces, happy faces, and shapes were separately convolved with the canonical HRF for each condition, creating the psychological regressors. The interaction terms (PPIs) were then computed by multiplying the time series from the psychological regressors (angry/fearful/happy) with the physiological variable. To examine the effect of the interaction terms, activity within the amygdala was regressed on a voxel-wide basis against the interaction, with the physiological and psychological variables serving as regressors of interest. The individual contrast images were then entered into a 2nd-level random effects analysis in which drug effects (ALC > PBO; PBO > ALC) were investigated using paired-sample t-tests, in order to identify which areas, if any, exhibited a difference in functional connectivity with the amygdala between PBO and ALC sessions. For a whole-brain analysis, we set the significance at $p < 0.005$ (uncorrected) with a cluster extent threshold of greater than 20 contiguous voxels (volume $> 160mm^3$) to balance between Type I and Type II errors consistent with prior fMRI studies of drug effects on amygdala-frontal connectivity (Kobiella et al. 2010; Labuschagne et al. 2010; Lieberman and Cunningham 2009; Parent et al. 2011).

Results

Behavioral Results

The behavioral results from the EFAT task have been previously published (Sripada et al. 2011). Results ($n = 7$; 5 participants missing button-press data) indicated that participants were more accurate ($F_{(1,6)} = 12.79$, $p = 0.012$) and responded quicker ($F_{(1,6)} = 27.44$, $p = 0.002$) during the non-threat conditions compared with the threat conditions. There were no differences between the ALC and PBO sessions on task accuracy or response time [(beverage: accuracy: $F_{(1,6)} = 2.54$, $p = 0.162$), response time: $F_{(1,6)} = 0.65$, $p = 0.452$) beverage × condition: accuracy: $F_{(1,6)} = 0.89$, $p = 0.383$, response time: $F_{(1,6)} = 0.81$, $p = 0.403$)].

Imaging Results

We observed two main effects of alcohol on amygdala activation. First, activation of *right* amygdala to angry faces ([22, -4, -26]; $Z = 3.67$; $p < 0.005$) was greater on PBO than ALC (Figure 1a). *Post hoc* extraction showed that the amygdala activation to angry faces on PBO was absent on ALC (Figure 1b) and that there were no differences in activation to happy faces on PBO and ALC in this same region. Second, activation of *left* amygdala to fearful faces ([-24, -4, -18]; $Z = 3.33$; $p < 0.005$) was greater on PBO than ALC (Figure 2a). *Post hoc* extraction showed that amygdala activation to fearful faces on PBO was deactivated on ALC (Figure 2b) and that there were no differences in activation to happy faces on PBO and ALC in this same region. From these main effects, we chose a right amygdala SOI for angry faces and a left amygdala SOI for fearful faces to conduct our planned gPPI analyses.

gPPI analyses during angry faces (> shapes) indicated that activity in the right amygdala exhibited greater connectivity with right orbitofrontal cortex (OFC; [30, 22, -22]; $Z = 3.60$, $p < 0.001$, uncorrected) during PBO relative to ALC (Figure 1c). Analyses during fearful faces (> shapes) indicated that activity in the left amygdala exhibited greater connectivity with a similar area localized to the right OFC ([30, 34, -16], $Z = 3.42$, $p < 0.001$) during PBO relative to ALC (Figure 2c). In both instances, *post hoc* comparisons of extracted gPPI parameter estimates (a.u.) indicated greater amygdala-OFC connectivity on PBO than on ALC, albeit with trend level significance from left amygdala seed (right amygdala: $t_{(11)} = 3.22$, $p < .01$; left amygdala: $t_{(11)} = 2.06$, $p = .06$; Figure 1d and 2d).

Post hoc analyses showed that alcohol-induced changes in amygdala activation were not significantly correlated with changes in amygdala-OFC functional connectivity (PBO vs. ALC) when processing fearful faces ($r = .24$, $p = .46$) or angry faces ($r = -0.07$, $p = .84$).

Results also indicated during angry faces (> shapes), activity in the right amygdala exhibited greater connectivity with the right superior frontal gyrus (SFG, [18, 20, 62], $Z = 3.04$, $p < 0.005$) and the left middle frontal gyrus (MFG, [-32, -10, 66], $Z = 3.03$, $p < 0.005$) during ALC relative to PBO. Other brain regions outside the PFC that demonstrated effects of ALC (>PBO) on amygdala connectivity are shown for completeness in Table 2. In addition, although there were no main effects of alcohol on amygdala activation to happy faces, we conducted exploratory *post-hoc* gPPI analyses during happy faces (> shapes) using the same left and right amygdala seed regions. These results are displayed in Table 3.

Discussion

Recently, it has been postulated that alcohol's ability to modulate affect may be mediated by attenuation of threat processing in the amygdala (Gilman et al. 2008, 2011; Sripada et al. 2011). Given that emotional processes involve dynamic interactions between the amygdala and regions of the PFC (Ochsner et al. 2004; Stein et al. 2007) there are likely important

alterations in functional interactions between these regions that underlie alcohol's effects. The current study was the first to our knowledge to examine alcohol's effects on functional connectivity between the amygdala and the PFC during the viewing of socio-emotional stimuli using gPPI analyses (McLaren et al. 2012). Our results indicated that during the processing of angry and fearful faces (examined separately), alcohol significantly reduced functional coupling between the amygdala and the right OFC relative to placebo. However, these preliminary findings are not specific to threatening faces, as results also indicated that alcohol reduced connectivity between the amygdala and left OFC during processing of happy faces. Alcohol's effects on amygdala-OFC connectivity may therefore be broad and extend to non-threatening social stimuli. These findings are noteworthy given that previous research has demonstrated that the OFC has direct, dense projections to the amygdala (Ghashghaei et al. 2007; Porrino et al. 1981; Amaral and Price 1984), and that the amygdala-OFC network is implicated in the expression and modulation of anxiety (Blackmon et al. 2011; Rauch et al. 2006).

Reduced amygdala-OFC connectivity during alcohol intoxication likely has important influences on processing of socio-emotional signals. A large body of evidence indicates that the amygdala and OFC work together to decode and represent affective information (see Murrary and Izquierdo 2007 for a review). Specifically, the amygdala is thought to detect and recognize the valence of affective stimuli and then feed forward this information to the OFC to guide goal-directed behavior (Bechara et al. 2000; Blair 2007). Animal and human research suggests that these functional interactions are reciprocal and necessary to process the threat value of a stimulus and subsequently generate an emotional response (Ghashghaei et al. 2007; Price 2003). In the present study, alcohol significantly attenuated amygdala reactivity to threat signals *and* reduced amygdala-OFC connectivity. Moreover, our results indicated that these alcohol-induced effects are not be dependent, as changes in amygdala activity were not correlated with changes in amygdala-OFC connectivity. Thus, it is plausible that during acute alcohol intoxication, stimuli that typically signal threat are not perceived as salient due to dampened amygdala reactivity and/or reduced interactions between the amygdala and OFC. This diminished perception of threat salience may then further lead to reduced negative affect and/or decreased scanning of the environment for threatening cues.

Importantly, the aforementioned interpretation of the present findings is consistent with numerous theoretical models of alcohol use, which broadly posit that alcohol dampens negative affect via disruption of attention and appraisal processes (Curtin et al. 2001; Hull 1987; Steele and Josephs 1990; Sayette 1993). Although there have been some mixed findings within the literature, accumulating evidence over the past several decades have supported aspects of these theories. For instance, Sayette and colleagues (2001) have demonstrated that alcohol's anxiolytic effects are more robust when alcohol consumption occurs prior to stimulus presentation and thus, prior to threat appraisal, rather than when drinking occurs in response to a stressor. In addition, a series of studies by Curtin and colleagues (Moberg and Curtin 2009; Hefner and Curtin 2012), provides evidence to suggest that when threat stimuli are well-defined and unambiguous (i.e., temporally predictable cues that reliably signal threat), alcohol does not modulate affective responding. Thus, extant theoretical and empirical evidence indicate that alcohol exerts its anxiolytic effects by disrupting the perception of threat salience, which the current study suggests may be mediated by reduced functional amygdala-OFC connectivity.

Reduced amygdala-OFC activity during alcohol intoxication may also have important implications for emotion regulation processes. In addition to determining the affective salience of threat stimuli, converging lines of evidence indicate that interactions between the amygdala and OFC are instrumental in the modulation and expression of emotion (Ochsner

et al. 2002; Levesque et al. 2003; Ochsner et al. 2004; Phan et al. 2005). For instance, emotion regulation strategies such as appraisal and suppression have repeatedly been shown to be associated with amygdala-OFC interactions (Schaefer et al. 2002; Urry et al. 2006), and evidence indicates that the extent of the functional coupling between these regions predicts successful emotion modulation (Banks et al. 2007). Therefore, reduced amygdala-OFC coupling in the context of affective stimuli may contribute to many of the well-known dysregulated emotional and behavioral consequences of alcohol use including increased risk-taking (Burian et al. 2002; Morris and Albery 2001), aggression (Bushman and Cooper 1990; Parrott et al. 2003), and impaired inhibitory control (Marczinski et al. 2005; de Wit 2000). This is a potentially important avenue for future research and studies are needed to delineate the consequences of alcohol's effects on amygdala-OFC connectivity.

Functional connectivity between the amygdala and two other PFC regions involved in emotion regulation processes were also found to be affected by alcohol in the present study (Banks et al. 2007; Kim et al. 2007; Oshner et al. 2002). More specifically, our findings indicated that alcohol enhanced coactivation between the right amygdala and the right SFG and left MFG during the processing of angry faces. This increase in functional connectivity may reflect compensatory processes such that the SFG and MFG were recruited to help the amygdala decode socio-emotional information during alcohol intoxication. The MFG and SFG have been shown to play a role in attentional influences on visual processing (Barceló et al. 2000; Chawla et al. 1999) and threat detection and evaluation (Han et al. 2008), which may have been used to compensate for alcohol's deleterious effects on amygdala reactivity and/or amygdala-OFC connectivity. However, because these frontal regions have indirect connections to the amygdala (Ghashghaei et al. 2007) it is difficult to interpret these patterns of coactivation and future studies are needed to delineate the consequences of these findings.

One of the secondary aims of the present study was to explore whether alcohol had similar effects on amygdala-PFC connectivity during angry and fearful faces. Interestingly, there is a growing literature suggesting that the OFC and amygdala play critical roles in regulating aggressive emotions (Davidson et al. 2001; Saddoris et al. 2005), and that clinical populations characterized by high levels of aggression (e.g., psychopathy, borderline personality disorder) exhibit abnormal amygdala-OFC connectivity (Blair 2003; Tebartz van Elst et al. 2003). Further, a meta-analysis by Murphy and colleagues (2003) indicates that the OFC may be more activated during the processing of anger stimuli relative to other emotions. Our current findings indicate that alcohol was associated with reduced amygdala-OFC coactivation during processing of socio-emotional stimuli . However, the strength of this effect (i.e., Z-score value) appears to be slightly more robust in response to angry faces in a qualitative comparison to fearful and happy faces

Given that alcohol affects multiple neurotransmitter systems in the brain including glutamate, GABA, dopamine, serotonin, and acetylcholine (Chastain 2006; Nutt and Peters 1994), it is likely that there are key neurochemical mechanisms underlying processing of socio-emotional stimuli during alcohol intoxication. For instance, research suggests that many of alcohol's anxiolytic effects are primarily mediated via direct and indirect increases in GABAergic synaptic transmission, particularly in the extended amygdala (Buck 1996; Criswell and Breese, 2005; Hyytia and Koob 1995; Koob 2003, 2004; Kumar et al., 2009; Weiner and Valenzuela, 2006), and that administration of benzodiazepines (drugs with similar neurochemical effects as alcohol on GABA neurotransmission) dampens amygdala reactivity (Arce et al. 2006; Paulus et al. 2005). Importantly, the OFC has projections to several alcohol-induced pro-GABAerigc regions including the amygdala and the nucleus accumbens (Nie et al. 2004; Ray and Price 1993; Roberto et al. 2004), suggesting that alcohol may affect the transmission of GABA in the amygdala and OFC individually and the amygdala-OFC circuit. Evidence also suggests that increased dopamine release during

alcohol intoxication may relate to the present findings, as a large body of evidence indicates that the mesolimbic dopamine system is implicated in anxiety (de la Mora et al. 2005; Diaz et al. 2011; Talalenko et al. 1994), and that dopamine levels in the amygdala have been shown to be associated with amygdala and amygdala-PFC processing of aversive stimuli (Kineast et al. 2008).

While the results extend prior findings on alcohol's acute disruption of neurocognitive circuits during processing of emotional stimuli, there are a few limitations worth noting. First, the current findings come from a small sample and also would not withstand correction for multiple comparisons and thus, are preliminary. Second, although a within-subjects study, the sample size was small, which likely reduced statistical power to detect gPPI effects elsewhere in the PFC and limited our ability to conduct sub-analyses on individual differences (e.g., gender). Similarly, the EFAT task included a low number of trials which may have also limited statistical power. Future research is needed to replicate the present findings in the OFC and investigate effects in other areas. Third, all participants in the current study were heavy social drinkers and it is unclear whether the current pattern of results apply to individuals that are less and/or more frequent (e.g., dependent) drinkers. Fourth, gPPI analyses are correlational and therefore directionality between the amygdala and OFC cannot be inferred. Future studies on dose-dependent effects of alcohol are needed to make causal inferences. Likewise, future studies are needed to determine whether alcohol's affective effects are mediated by attenuating amygdala reactivity and/or disrupting amygdala-OFC functional connectivity. The specificity of the present findings to threat stimuli or socio-emotional more broadly also requires further investigation. Lastly, the functional relevance of alcohol's effects on amygdala-OFC connectivity remain unclear and future tests to link these effects on functional (e.g., behavioral, affective, cognitive) outcomes are needed.

In sum, the results of the present study extend the literature on the acute effects of alcohol on human processing of affective stimuli and suggest that alcohol attenuates amygdala reactivity and reduces amygdala-OFC connectivity during the processing of emotional faces. These neural effects of alcohol may serve to impair the perception and appraisal of the salience of social signals of threat, and contribute to alcohol-associated harm during intoxicated states. Given this pattern of results, psychological and pharmacological treatments targeting this pathway may be a valuable for alcohol prevention or harm-reduction interventions.

Acknowledgments

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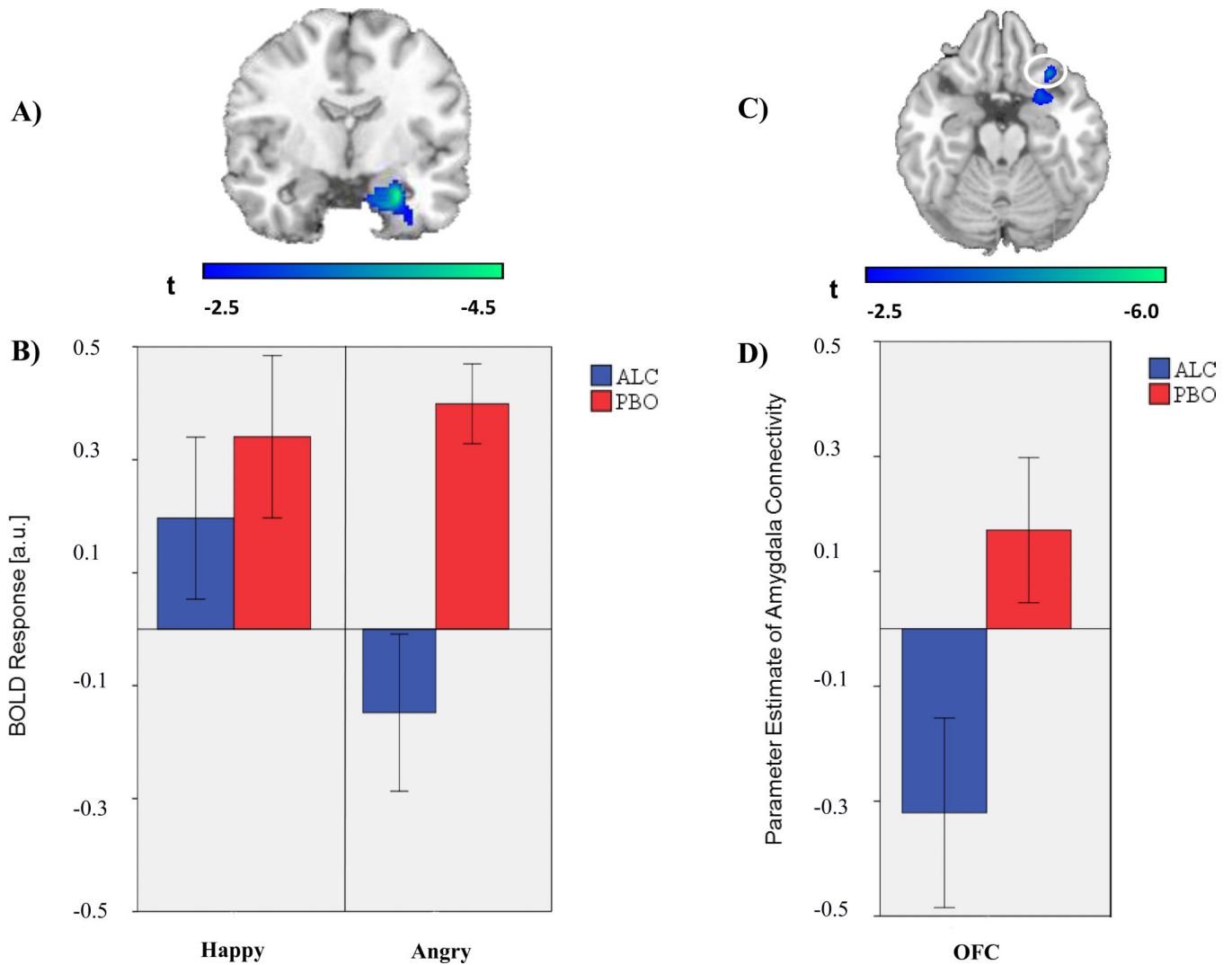
Fig. 1.
(A) Voxel-wise statistical *t*-map displayed on a canonical brain; Activation difference shown in relation to the amygdala anatomically derived region of interest (ROI); Color scale reflects *t*-score. (B) Bar graphs illustrating extracted BOLD responses from the anatomical right amygdala ROI during happy faces (> shapes) and angry faces (> shapes) for the alcohol and placebo conditions; ALC = alcohol condition; PBO = placebo condition (C) Voxel-wise statistical *t*-map displayed on a canonical brain; Color scale reflects *t*-score. (D) Bar graph illustrating extracted parameter estimates of right amygdala-right OFC connectivity during angry > shapes for the alcohol and placebo condition.
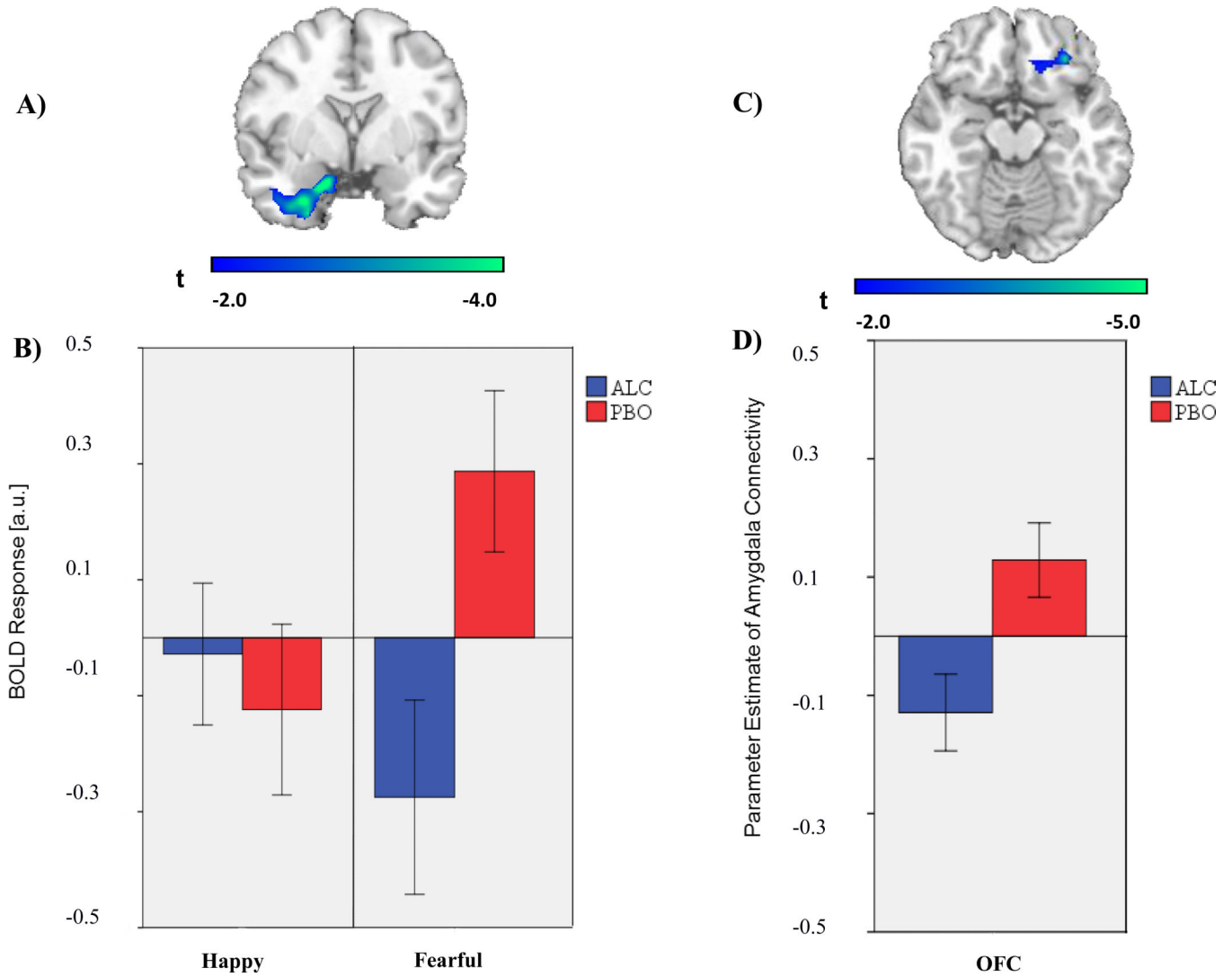
Fig. 2.
(A) Voxel-wise statistical *t*-map displayed on a canonical brain; Activation difference shown in relation to the amygdala anatomically derived region of interest (ROI); Color scale reflects *t*-score. (B) Bar graphs illustrating extracted BOLD responses from the anatomical left amygdala ROI during happy faces (> shapes) and fearful faces (> shapes) for the alcohol and placebo condition; ALC = alcohol condition; PBO = placebo condition (C) Voxel-wise statistical *t*-map displayed on a canonical brain; Color scale reflects *t*-score. (D) Bar graph illustrating extracted parameter estimates of left amygdala-right OFC connectivity during fearful > shapes for the alcohol and placebo condition.

Table 1

Participant Demographics and Clinical Characteristics

Demographics	Mean (*SD*) or %
Age (years)	23.2 (1.8)
Sex (% male)	83.3%
Race (% Caucasian)	66.7%
Education (years)	15.7 (1.2)
Alcohol Use	
Lifetime diagnosis of DSM-IV alcohol abuse	91.7%
Lifetime diagnosis of DSM-IV alcohol dependence	0%
AUDIT total score	12.3 (4.5)
Alcohol drinking days per month	13.2 (7.1)
Drinks per drinking day	6.7 (3.5)
Binges[a] in last month	7.8 (3.4)
Maximum number of drinks on one occasion in last month	13.5(7.7)
Days since last alcohol use	3.8 (1.7)
Range of days since last alcohol use	1.6 - 6.7
Cigarette Use	
Daily smokers	0.0%
FTND total score	0.08 (0.1)
Cigarettes smoked in last month	14.7 (7.1)
Cigarettes smoked per smoking day	4.3 (2.8)
Illicit Drug Use	
Used cannabis within the past 30 days	8.3%
Used any other illicit drug in past 30 days	0.0%
Psychiatric Symptoms	
Depressive Symptoms- BDI total score	3.6 (4.2)
Anxiety Symptoms- STAI-Trait total score	52.8 (3.1)

Note.

AUDIT = Alcohol Use Disorders Identification Test (Babor et al. 1989); BDI = Beck Depression Inventory (Beck et al. 1961); STAI-Trait = State-Trait Anxiety Scale, Trait Anxiety subscale (Spielberger et al. 1970)

[a]A binge is defined as consuming 5 or more drinks for men, 4 or more for women, on one occasion.

Table 2

Results of Whole-brain gPPI Analyses with the Amygdala as the Seed Region for Angry and Fearful Faces (>Shapes)

Seed Region	Emotion	Contrast	Region Name	MNI Coordinates			Voxels	Z-score
				X	Y	Z		
Right Amygdala	**Angry**	**PBO > ALC**	R Orbitofrontal Cortex	30	22	-22	26	3.60
			R Olfactory Region	24	10	-20	49	3.18
		ALC > PBO	L Postcentral Gyral	-2	-38	80	275	3.98
			R Sub-Gyral	34	-48	4	92	3.94
			L Lateral Ventricle	-30	-58	6	378	3.84
			L Extra-Nuclear	-20	-50	22	36	3.74
			L Middle Temporal Gyrus	-62	-64	8	45	3.55
			L Cuneus	0	-98	-2	51	3.46
			L Insula	-32	-40	20	58	3.44
			L Lingual Gyrus	-12	-84	-20	465	3.36
			R Middle Temporal Gyrus	60	-32	-18	37	3.30
			R Middle Occipital Gyrus	34	-96	10	73	3.26
			R Declive	18	-66	-20	120	3.10
			R Superior Frontal Gyrus	18	20	62	32	3.04
			L Middle Frontal Gyrus	-32	-10	66	77	3.03
			L Culmen	-8	-42	-28	39	2.98
			L Precuneus	-2	-48	52	27	2.80
Left Amygdala	**Fear**	**PBO > ALC**	L Precentral Gyrus	-22	-26	74	151	3.75
			R Superior Frontal Gyrus	14	-14	80	59	3.69
			L Fastigium	-8	-50	-28	47	3.44
			R Orbitofrontal Cortex	30	34	-16	22	3.42
			R Temp Inferior Cortex	66	-40	-18	34	3.11
			R Sub-Gyral	52	-32	-14	33	3.10
			L Supp Motor Area	-6	-14	58	225	3.05
		ALC > PBO	None					

Note. gPPI= generalized psychophysiological interaction; MNI = Montreal Neurological Institute; results at $p < .005$, uncorrected; >20 voxel minimum.

Table 3

Results of Exploratory Whole-brain gPPI Analyses with the Amygdala as the Seed Region for Happy Faces (>Shapes)

Seed Region	Emotion	Contrast	Region Name	MNI Coordinates			Voxels	Z-score
				X	Y	Z		
Right Amygdala	**Happy**	**PBO > ALC**	L Inferior Frontal Gyrus	-48	42	14	108	3.05
			R Cerebellar Tonsil	18	-40	-48	32	3.02
			L Cerebellar Tonsil	-46	-52	-42	20	3.00
		ALC > PBO	L Calcarine	4	-98	-2	602	4.31
			L Sub-lobar	-18	-30	16	132	3.94
			L Cerebelum Crus II	-34	-80	-34	252	3.29
			L Cuneus	-24	-78	10	100	3.28
			R Paracentral Lobule	6	-44	80	69	3.25
			R Cerebelum	8	-48	-16	31	3.17
			R Fusiform	50	-66	-18	76	3.12
			L Sub-Gyral	-32	-36	22	22	2.93
			R Inferior Temporal Gyrus	62	-34	-18	25	2.85
Left Amygdala	**Happy**	**PBO > ALC**	R Fusiform Gyrus	18	-94	-22	38	3.60
			L Precuneus	0	-50	58	50	3.56
			L Orbitofrontal Cortex	-42	48	-12	59	3.31
			L Medial Frontal Gyrus	-8	-10	54	42	3.08
			L Inferior Occipital Gyrus	-32	-86	-18	35	3.02
			R Cerebelum	30	-50	-30	87	3.02
			L Cerebelum	-16	-36	-46	29	2.97
		ALC > PBO	None					

Note. gPPI= generalized psychophysiological interaction; MNI = Montreal Neurological Institute; results at *p* < .005, uncorrected; >20 voxel minimum.