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Low versus high level of response to alcohol affect amygdala functional connectivity during processing of emotional stimuli

Benjamin S. McKenna, Ph.D.[1,2], **Robert M. Anthenelli, M.D.**[1], **Tom L. Smith, Ph.D.**[1], **Marc A. Schuckit, M.D.**[1]

[1]Department of Psychiatry, University of California, San Diego, Health Sciences, La Jolla, California, 92093

[2]VA San Diego Healthcare System, San Diego, California, 92161

Abstract

Background: Low levels of response (low LR) to alcohol predict heavy drinking and alcohol problems. Functional magnetic resonance imaging (fMRI) studies of emotion processing have demonstrated low LR individuals exhibit lower activation in task-related brain regions following both placebo and alcohol administration but the studies did not examine functional brain networks that might contribute to the phenomena. The current study expands upon those earlier results by evaluating if functional connectivity differences between the amygdala and other brain regions modulated by emotional face processing are likewise associated with LR. Based on the prior study, we hypothesized that low LR will be related to lower functional connectivity in fronto-amygdalar functional circuits underlying processing of emotional stimuli.

Methods: Secondary analyses were conducted on data from a double-blind, placebo controlled, within-subjects, cross-over study in 108 18-to-25-year-old low and high LR sex matched pairs without an alcohol use disorder at baseline. Participants performed modified emotional faces processing tasks after placebo or approximately 0.7 mL/kg of ethanol. Psychophysiological interaction analyses examined functional connectivity between left and right amygdala and related brain circuits using LR-by-alcohol general linear models. The data included 54 sex-matched pairs with 216 fMRI scans comprising alcohol and placebo conditions.

Results: Compared with individuals with high LR, low LR subjects demonstrated lower functional connectivity between the amygdala and the frontal lobes, insula, and parietal regions, respectively, while processing angry and happy faces. Interactions showed lower connectivity following alcohol in low LR and higher connectivity in high LR groups.

Conclusions: Low LR individuals demonstrated lower functional connectivity both with placebo and in response to a modest ethanol dose. Attenuated connectivity among low LR individuals when processing emotional faces may contribute to an impaired ability to recognize alcohol intoxication in social situations and impaired ability to make appraisals of angry and happy emotions irrespective of consuming alcohol.

Corresponding Author: Benjamin S McKenna, Pacific Treatment and Research Center @ UC San Diego, 3252 Holiday Court, Suite 200, La Jolla, CA 92037, U.S.A., bmckenna@health.ucsd.edu, Telephone: 858-534-8817, Fax: 858-534-9410.

Keywords

Functional Connectivity; fMRI; Alcohol; Emotional Stimuli; Level of Response

Introduction

The low level of response (low LR) to alcohol is one of several aspects of an alcohol response that have been shown to relate to concurrent or future heavy drinking, alcohol problems and alcohol use disorders (AUD) (King et al., 2011, King et al., 2014, Newlin and Renton, 2010, Schuckit, 2018). The low LR was initially shown through alcohol challenges to characterize drinkers at higher risk for AUD where, at similar blood alcohol levels and similar drinking histories, those at higher AUD risk demonstrated lower intensities of reaction to alcohol for subjective feelings of intoxication and levels of alcohol-induced increases in body sway (Schuckit and Gold, 1988, Monteiro et al., 1991, Ehlers et al., 1995, Pedersen and McCarthy, 2009). The low LR phenomenon was also demonstrated to relate to higher AUD risk using a retrospective measure of the number of drinks needed across up to four effects (Schuckit et al., 1997, Daeppen et al., 2000, Chung and Martin, 2009).

The lower alcohol responses associated with the low LR also relate to biological differences beyond subjective feelings (Schuckit, 2009, Heath et al., 1999, Kalu et al., 2012, Schuckit et al., 2017, Schuckit and Smith, 2017, Schuckit et al., 2014) and are genetically influenced (Schuckit, 2018). The biological markers associated with the low LR included several aspects of central nervous system (CNS) functioning such as lower alcohol-related changes in adrenocorticotropic hormone (ACTH), background cortical electroencephalogram measures of alpha rhythm patterns, and event-related potential P3 wave latency (Schuckit and Gold, 1988, Ehlers et al., 2001, Schuckit et al., 1988).

The finding that aspects of the low LR were observed in CNS measures led to a search for brain mechanisms that might contribute to the lower intensity of alcohol response. One series of studies compared functional magnetic resonance imaging (fMRI) blood oxygen-level dependent (BOLD) signal results following alcohol and placebo beverages during cognitive tasks in up to 60 matched pairs of individuals with high and low LRs to alcohol (Paulus et al., 2012, Schuckit et al., 2012, Trim et al., 2010). As summarized in the most recent of those papers (Paulus et al., 2012), although the LR groups were similar on their performance on an emotional face recognition task, those with low LRs demonstrated lower BOLD responses in processing different types of facial affect relative to a control condition in task-relevant brain regions such as the insula and anterior cingulate. Those results were seen during fMRI sessions with alcohol and during sessions with placebo. Those findings suggest that, compared with matched high LR subjects, individuals with low LR potentially required greater activation in relevant brain regions, including the middle and inferior frontal gyri, cingulate, and insula, to process emotion-laden faces. Subsequent follow up of these subjects demonstrated that aspects of the fMRI patterns added significantly to the alcohol challenge-based measure of low LR in predicting future heavier drinking and alcohol problems (Schuckit et al., 2016). The authors concluded that those results indicate

that the low LR to alcohol phenomenon might relate to problems recognizing more subtle effects of some modest sensory inputs, including modest levels of intoxication.

The ability to decode facial affect is important when assessing one's immediate social environment. This process provides valuable information regarding others' internal affective state, enabling behavioral adaptation according to others' thoughts and intentions, steps that facilitate social interactions in daily life. Impairments in decoding basic and complex emotional facial expressions of others have been consistently reported in individuals with AUD, even when they are sober (Castellano et al., 2015; Bora & Zorlu, 2017), and AUD is associated with difficulties in emotional processing (Le Berre, 2019). Such deficits might impede emotional self-regulation and social interactions (Le Berre, 2019).

While there is evidence that individuals with AUD have emotional processing deficits, less is known about whether the observed deficits are sequela of chronic alcohol consumption or if they predate heavy drinking in a manner potentially associated with a LR phenotype. Evidence that such findings might predate heavy drinking come from reports of lower activation in middle temporal and inferior frontal gyri in response to an emotion-based psychological test (Hill et al., 2007), and attenuated amygdala activation to faces expressing fear in young individuals with AUD relatives (Glahn et al., 2007). In addition, youth at high-risk for substance use disorders have been found to exhibit greater activation in medial prefrontal, precuneus, and occipital cortices on an angry / anxious facial emotion recognition matching task compared with low-risk, family history-negative individuals (Hulvershorn et al., 2013). Taken together, these differences suggest impaired affective processing in non-heavy drinking individuals at high familial risk for AUD.

The amygdala is a central structure in the limbic system that is associated with affective, stress and reward processing in coordination with the prefrontal cortex (PFC) (Morris et al., 1998, Phillips et al., 1998, Phillips et al., 2003, Breiter and Rosen, 1999, Wade et al., 2017). The emotional face matching paradigm of Hariri et al. (Hariri 2000; 2002) is a widely used neuroimaging procedure designed to activate the amygdala. The original version was limited to negative emotions like fear and anger, and modifications of the paradigm have been developed that include positive emotional stimuli (e.g., happy faces) that can be used in neuroimaging experiments of reward (Fredrickson, 2001; Rademacher et al., 2010). Positive emotions activate additional brain regions including the ventrolateral and medial PFC, the insula, and inferior frontal gyrus (Greening et al., 2014; Perry et al., 2012). Overall, these findings support the need to examine different emotional stimuli separately because different brain regions might react differently to negative (e.g., fearful) versus positive (e.g., happy) emotions.

Recent fMRI studies have begun to examine functional integration, or connectivity, between brain regions by using statistical techniques that examine relationships among two or more regions represented by distinct fMRI BOLD time-series analyses (Friston, 2002). Positive functional connectivity between regions is thought to reflect patterns of synchronous activity or increased communication. One might hypothesize that differences in connectivity between brain regions might be related to the LR group differences reported in the Paulus et al. paper, as connectivity analyses better capture underlying functional brain networks as

opposed to isolated regional brain activation. In the case of the functional networks involved in recognition of emotions expressed in pictures of faces, it is likely that the connections between the cortex and subcortical limbic regions, including the amygdala, are critically important. (Reynolds and Zahm, 2005, Friston, 2002).

There is a growing literature documenting disrupted PFC-amygdala connections of the fronto-limbic pathways in response to alcohol (O'Daly et al., 2012, Gorka et al., 2013, Gilman et al., 2012, Sripada et al., 2011, Gilman et al., 2008). Specifically, Gorka et al. (2013) examined functional connectivity between the PFC and amygdala in a two-session (alcohol vs. placebo), double-blind, within-subjects cross-over pilot fMRI study of 12 heavy social drinkers during the same emotional processing task used by Paulus et al. (2012). These authors reported that during the processing of a broad range of emotional stimuli including angry, fearful, and happy faces, alcohol significantly reduced functional coupling between the amygdala and orbital frontal cortex differentially depending on the facial emotion presented (Gorka et al., 2013). Another study examined resting-state functional connectivity in 83 non-AUD alcohol drinkers and found a positive association between increased alcohol misuse scores with decreased amygdala-dorsal anterior cingulate cortex connectivity (Hu et al., 2018). These data indicate that the underlying processing of emotional signals required to detect a potential threat in the environment and make an appropriate response are altered while intoxicated. However, neither of these protocols included a measure of the LR to alcohol, a phenotype associated with future heavy drinking and alcohol problems.

This manuscript presents the results of secondary analyses of amygdala-based functional networks using data from the fMRI dataset reported in Paulus et al., (2012). These new analyses used generalized psychophysiological interactions (gPPI), a technique that allows for the examination of connectivity between two brain areas as a specific function of the task of interest. gPPI was developed to allow for the use of more than two task conditions in the same model while also improving model fit (O'Reilly et al., 2012, McLaren et al., 2012). The evaluations were centered around two hypotheses. Hypothesis 1 is based on observations from fMRI studies of young individuals who did not have an AUD history prior to testing (Paulus et al., 2012) where regional BOLD differences were observed during placebo (non-alcohol) conditions. This prediction states that compared with high LR individuals, those with less intense response to modest alcohol doses (i.e., low LR) will demonstrate lower levels of functional connectivity between the amygdala and PFC when processing emotion-laden faces. Further, we predict negatively-valenced emotions (angry and fearful faces) will elicit a greater decrease in connectivity relative to positively-valenced emotions (happy faces). Given prior studies demonstrating changes to brain functional connectivity following alcohol administration, Hypothesis 2 states that low LR individuals will have lower levels of functional connectivity following alcohol for negatively-valenced emotions (angry and fearful faces) compared with high LR individuals.

Methods

Participants:

In the original study from which the current data were extracted (Paulus et al., 2012), a survey was distributed to randomly selected 18 – 25-year-old European American and white Hispanic students at the University of California, San Diego, using methods approved by the UCSD Institutional Review Board. This questionnaire gathered information on demography, substance use, and DSM-IV psychiatric disorders using questions extracted from the Semi-Structured Assessment for the Genetics of Alcoholism interview (Bucholz et al., 1994). To be included in the fMRI protocol described below, subjects were limited to those who were: 1) right-handed; 2) had no history of brain trauma or epilepsy; 3) no history of alcohol or drug dependence; 4) no current major psychiatric disorder; 5) were not pregnant; 6) and had no irremovable body metal.

A laboratory-based alcohol challenge was then used to establish an individual's LR. After confirming zero baseline breath alcohol concentrations (BrACs), subjects drank alcohol (0.75 mL/kg for men and 0.70 mL/kg for women) over a 10 minute period given as a 20% by volume solution in a room-temperature carbonated beverage, a protocol that produced approximately equivalent BrACs across sexes (Baraona et al., 2001). We used a median split on self-report scores from the Subjective High Assessment Scale (Schuckit and Gold, 1988) during the alcohol challenge to determine low vs. high LR in both the prior study (Paulus et al. 2012) and the present secondary analysis of those data. Once the LR status was confirmed through the initial alcohol challenge, two MRI sessions were scheduled on non-consecutive days within one week of each other whenever possible. Alcohol and placebo sessions were carried out in an MRI scanner where participants received, in random order, the same alcohol dose as in the laboratory session or placebo in sessions that included the Hariri emotional face recognition task (Hariri et al., 2005, Paulus et al., 2005).

Complete data required for functional connectivity analyses were available from 216 fMRI scans across placebo and alcohol challenge sessions for 108 individuals. The subjects were comprised of 54 pairs of low- and high-LR participants who were matched on sex, demography, drinking frequency and usual quantities, as well as tobacco and cannabis use. The data presented here were extracted from the Hariri emotional face recognition task, which was presented to participants in the MRI scanner 60 minutes post-beverage consumption during placebo and alcohol fMRI sessions. The task was measured at a time close to the peak BrAC during the average alcohol session. At this point of the alcohol session the alcohol levels were similar in the LR groups.

Task:

We used a modified version of the Hariri emotional face-processing task (Paulus et al., 2005, Hariri et al., 2005). Participants were presented with a target face and two probe faces for 5 seconds, with instructions to match the probe and emotional expression of the target by pressing a button in a block-design. Each block had six consecutive trials where faces were either angry, fearful, or happy. Additionally, a sensorimotor control condition was used where vertical or horizontal ovals or circles were presented for six consecutive

trials in block with instructions to match the shape of the probe to the target. Each block of emotion condition and the sensorimotor control condition were presented three times in a pseudorandomized order. The task began with an 8 second fixation period and had interspersed 12-second fixation periods between each block. There were 18 trials (3 blocks of 6 trials) for each condition yielding 512 seconds total task time. Figure 1 illustrates the timing of the task with examples from the first two blocks (angry faces followed by the control condition). We recorded accuracy and reaction time during the task to confirm the task was carried out correctly (i.e., above chance levels).

Image Acquisition:

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

Image Processing:

The Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996) was used for preprocessing data and gPPI analyses. All T1-weighted images were skull-stripped and warped into Talairach-Tournoux atlas space using a 12 parameter affine transformation. Next, functional data were visually inspected for scanner artifacts. To correct for small movements over time, image repetitions were registered to a selected base volume via AFNI's 3dvolreg program. The time series of the motion parameters were used in the linear regression analysis of individual data to control for spin history effects (Friston et al., 1996). Functional data were then transformed into the participant's anatomical space and aligned to standard space using the previously computed anatomical transformation matrix, and smoothed with a 4-mm FWHM Gaussian kernel. Deconvolution analysis of the fMRI time series data was conducted using AFNI's 3dDeconvolve algorithm. The general linear models (GLMs) used reference vectors for the task conditions (i.e., angry, fearful, and happy) convolved with the hemodynamic response function. Estimated motion and linear, quadratic, and cubic trends were also included as nuisance variables. The resulting model generated scaled beta coefficient maps representing the mean percent BOLD signal change for each condition of the task relative to baseline.

Statistical Analyses:

Functional connectivity analyses were conducted using gPPI with anatomical-defined seeds in the left and right amygdala. Seed regions were chosen using Neurosynth (https://neurosynth.org/), a meta-analytic tool for selecting fMRI activation coordinates from a database of studies (Yarkoni et al., 2011), where we examined studies using tasks of emotional faces to elicit amygdala activation. Specifically, we created a 5-mm sphere around the coordinates X = −26, Y = 6, Z = −14 and resampled to the template space of our fMRI

scans. Visual inspection of these seeds ensured that they were anatomically constrained to the amygdala using the Talairach-Tournoux atlas. For each participant, the average time series of the BOLD signal was extracted for each seed, and trends were removed. A one parameter gamma model was used to estimate the hemodynamic response function of the task and a deconvolution of the seed's time series with this function was calculated using the 3dTfitter AFNI program yielding scaled coefficients. PPI regressor interaction terms for each condition of the Hariri task were computed by multiplying the mean time series of the de-convolved seed with the condition vector of interest, and then convolved with a gamma basis function using the AFNI program Waver.

Separate voxel-wise GLMs were conducted for each bilateral amygdala seed. Each GLM contained the PPI regressors, the physiological regressor (seed time series), the psychological regressors (i.e., task condition regressors), and nuisance variables (i.e., the motion regressors from the prior fMRI analysis). Each seed's connectivity with other brain areas was examined separately. Whole-brain between-group differences in functional connectivity were estimated using mixed-effects ANOVAs with the AFNI 3dANOVA3 program where the within-subject factor was alcohol / placebo condition and the between-subjects' factor was Low / High LR. We applied a cluster correction to guard against identifying false positive areas for potential functional connectivity differences. Specifically, we estimated the noise in our fMRI volumes using 3dFWHMx in AFNI and used that information to apply a cluster-size threshold of $\alpha = 0.01$ for a given voxel-wise threshold of $\alpha = 0.01$ to protect our α at a 0.01 level using the 3dClustSim AFNI program. Using this approach, the minimum volume for a significant cluster in our analyses was set at 448 μL or seven contiguous significant voxels.

Results

Demographic Characteristics:

As shown in Table 1, demographic and substance use characteristics were similar across LR groups. Pairwise comparisons for each LR group did not reveal any sex differences across low LR or high LR groups. However, pairwise comparisons for each sex did reveal that more low LR women had ever used tobacco and marijuana in their lifetime compared with high LR women.

Task Performance:

As reported in the Paulus et al. (2012) paper described above, both low and high LR groups, as well as men and women, had similar reaction times after placebo and alcohol for angry, fearful, and happy faces. Also, accuracy was above chance levels (p's < 0.001) suggesting the participants were able to attend to the task regardless of emotional or alcohol/placebo conditions.

Functional Connectivity Results:

Connectivity analyses were carried out examining LR groups during the alcohol and placebo conditions using left and right amygdala seeds. Clusters showing significant (i.e., minimum cluster of 448 μL at $p \leq 0.01$) LR, alcohol, or LR-by-alcohol interaction effects in functional

connectivity differences in response to fearful, angry, and happy faces are described below and detailed in Table 2. Specifically, the table lists brain regions, associated Brodmann area (a cytoarchitectural organization system (Brodmann, 1909), peak activation, Talairach coordinates, and volume for each significant cluster. Figure 2 illustrates the pattern of functional connectivity main effects for exemplar regions, while Figure 3 illustrates the pattern of functional connectivity interaction effects for exemplar regions. For all significant clusters we also ran ANCOVA models covarying for sex and did not find any significant effect of sex in our results.

Main Effects of LR: During angry faces, using the left amygdala seed, the differences between low and high responders illustrate that low LR participants had lower functional connectivity in several cortical regions compared with high LR participants in both placebo and alcohol conditions. This was observed in the left medial frontal gyrus, bilateral ventral anterior cingulate, bilateral posterior cingulate, and left supramarginal gyrus. Using the right amygdala seed, the main effects of LR during processing of angry faces were identical to left amygdala such that low LR participants had diminished functional connectivity as compared to high LR participants in both placebo and alcohol conditions in the bilateral posterior cingulate. In contrast, during happy faces, significant effects were observed only with the right amygdala seed where, opposite to the LR main effects pattern observed for angry faces, low LR participants had greater functional connectivity compared with high LR participants in the right dorsal anterior cingulate gyrus and right caudate.

Main Effects of Alcohol: For both low and high LR groups, during happy faces increased functional connectivity was observed following alcohol administration compared with placebo. The increased functional connectivity was observed between the right amygdala seed and the left superior frontal gyrus and left middle insula brain regions.

LR-by-Alcohol Interactions: During angry faces, within the right precuneus, lower functional connectivity was observed with the left amygdala following alcohol compared with placebo in low LR individuals, but increased connectivity following alcohol was found in high LR individuals. Interactions during processing of happy faces were characterized as a decrease in functional connectivity with right amygdala following alcohol as compared to placebo in low LR individuals, but increased connectivity following alcohol in high LR individuals in left middle frontal gyrus regions; a pattern similar to the interaction observed during angry faces.

Predicting Future Alcohol Problems: Given that we had 5-year follow-up data on these participants (Schuckit et al., 2016), we conducted *post hoc* exploratory regression analyses examining if regions with significant functional connectivity differences predicted a change 5-years later in drinking quantity (defined as usual number of drinks when consuming alcohol) or the subsequent development of alcohol problems (defined as number of DSM-IV alcohol use disorder criteria symptoms endorsed) in low vs. high LR individuals. Two regions during the placebo condition significantly predicted an increase in alcohol problems for low LR participants: 1) the right dorsal anterior cingulate gyrus during happy faces ($p=0.010$); and 2) the bilateral posterior cingulate gyrus during angry faces ($p=0.017$).

For both regions, greater decreases in amygdalar functional connectivity during placebo was associated with an increase in future alcohol problems.

Discussion

The main goal of these analyses were to expand upon the findings of Paulus et al. (2012) by evaluating LR group differences in functional connectivity. This is the first demonstration of differences in connectivity between low and high LR individuals, results that might help explain why drinkers with low LRs might require greater cognitive effort to perform optimally on some tasks. Consistent with our hypotheses, in the current analyses the most prominent patterns found were attenuation of amygdala connectivity with cortical regions in low LR participants, both during placebo and in response to alcohol, relative to high LR participants while viewing angry faces. Additionally, comparing alcohol and placebo sessions, low LR individuals exhibited decreased functional connectivity in response to alcohol, whereas high LR individuals showed increased functional connectivity while viewing both angry and happy faces. The present findings add to the regional brain changes originally reported by Paulus et al. (2012). While those authors found no difference in amygdala regional activation patterns across LR groups, we found several differences in functional connectivity with the amygdala that varied depending on the valence (e.g., negative vs. positive emotion) of facial affect being decoded. Thus, BOLD signal changes in the cortex in response to an emotional processing task in low versus high LR individuals might reflect aberrant functional connectivity in cortico-amygdalar circuits.

These functional connectivity differences were observed in relatively highly functioning individuals from a nonclinical sample, some of whom carried an enhanced risk for alcohol problems through a low LR but none of whom had yet developed an AUD. Along with a growing body of evidence that the low LR phenotype is characterized by CNS differences relative to their high LR peers (Paulus et al., 2012, Ehlers et al., 2001, Schuckit et al., 1988), these emotional processing data suggest that low LR individuals may have an altered neurobiological process in which they recognize some negative or positive social cues through decoding facial affect. It is also possible that given the pattern of brain regions in the frontal lobe, anterior cingulate, and insular cortex that showed altered amygdala functional connectivity, as well as regional BOLD signal changes in the insula, low LR individuals may have an impaired ability to recognize intoxication, or the rewarding aspects of alcohol, in social situations.

Functional connections between the amygdala and cortical regions play important roles in processing human emotions. For example, connections between the PFC and amygdala facilitate the cortex’s top-down regulation (Kanske et al., 2011, Ochsner et al., 2002) in decoding emotional stimuli (Adolphs, 2002), allowing appraisals based on affective information to moderate goal-directed behaviors (Iidaka et al., 2011, Pessoa, 2010). PFC-amygdala functional interactions are reciprocal and likely necessary to process socially-based emotional signals to generate an emotional response (Ghashghaei et al., 2007, Davidson and Irwin, 1999). Additionally, connections between the amygdala and insular cortex have been shown to be involved in the interoceptive processes involved in recognizing intoxication (Campbell and Lawrence, 2021, Reynolds and Zahm, 2005). That finding

supports our interpretation that low LR individuals may have an impaired ability to recognize the effects of alcohol at the moderate doses used in our challenge paradigms.

It is interesting to note that the findings of low LR-related lower connectivity between the amygdala and cortical region pathways observed with angry faces were not seen in the reaction to fearful faces. While similar in that both are negatively-valenced emotions, fearful and angry emotional responses regulate the stress response in specific adaptive ways with different biological profiles. For example, when responding to a psychosocial stressor (i.e., the Trier Social Stress Test), angry reactions to stress lead to greater increases in cortisol over time but not to elevations in pro-inflammatory cytokines. In contrast, fear reactions to stressors lead to increases in pro-inflammatory cytokines over time and decreased cortisol (Moons et al., 2010). Therefore, our findings of altered functional connectivity needed to process anger in low LR individuals are consistent with the perspective that distinct emotional experiences trigger specific adaptive biological processes.

Another finding of interest relates to happy faces. Here, we also observed an opposite main effect pattern such that low LR participants had greater functional connectivity between the amygdala and anterior cingulate as compared to high LR participants across both placebo and alcohol. Positive emotions often elicit activation in the brain's reward circuitry and future studies should examine if the LR group patterns related to happy faces are also related to future problematic drinking and the development of AUD.

Regional brain differences, especially in the anterior insula and frontal gyrus, predicted future problems with alcohol five years later in this sample (Schuckit et al., 2016). In our *post hoc* exploratory analyses, lower cingulate-amygdala functional connectivity during the placebo condition among low LR individuals significantly predicted an increase in alcohol problems five years later. Given the exploratory nature of these analyses, and that we did not correct for multiple tests, caution should be applied in interpretation of these *post hoc* findings. Nonetheless, they do suggest that LR-specific functional MRI findings may be predictive of future alcohol problems and additional research is needed in this area.

In viewing the current results, it is important to keep some limitations in our research protocol in mind. First, the participants were all relatively stable and functional European American university students, and it is not clear whether the current results generalize to other groups. Second, consistent with the results reported by Paulus et al (2012) and most of our prior papers, in order to place LR into a more useful clinical context LR was evaluated as a dichotomy, and examination of LR-derived scores as a continuous variable may yield additional findings. Third, reflecting the fact that laterality findings are unclear in many fMRI studies of emotion (Davidson and Irwin, 1999), we analyzed the combination of both the left and right amygdala seeds and their respective connectivity patterns. Thus, future work will need to further evaluate the importance of laterality influencing connectivity patterns associated with the low LR. Fourth, our analyses focused on the whole amygdala and not amygdalar subregions, and future work will be needed to expand upon the analyses presented here (Alarcón et al., 2015, NeuroImage). Fifth, there are physiological effects when consuming alcohol that directly impact the BOLD signal, such as cerebral blood flow changes (Courtney et al., 2019). With advances in neuroimaging methodologies, future

studies can be done isolating mechanisms that drive BOLD signal changes observed in the literature including blood flow, volume, and oxygenation. Sixth, only 18 trials per emotional face were used in the current protocol yielding a task time of 512 seconds, which may have limited statistical power given concerns for task-based fMRI reliability. Future work should expand upon this task to include more trials for improved power and signal reliability. Seventh,, gPPI analyses are correlational and therefore directionally between the amygdala and other regions cannot be inferred. Future studies on dose-dependent effects of alcohol are needed to make causal inferences and it would be interesting to examine other important brain regions as gPPI seeds. Finally, regarding the *post-hoc* exploratory analyses linking some of the functional connectivity findings with the development of future alcohol problems, these results should be considered tentative until tested more directly in future research.

In summary, building upon prior findings of regional brain LR group fMRI differences in frontal and insular cortices (Paulus et al., 2012), we demonstrate that low LR individuals have amygdala connectivity differences relative to high LR individuals. These findings add to a growing body of fMRI studies that show regional brain characteristics in low LR individuals (Paulus et al., 2012, Trim et al., 2010, Schuckit et al., 2012) and demonstrate how amygdala-dependent functional connections may play a role in those characteristics. Attenuated connectivity among low LR individuals may contribute to an impaired ability to recognize developing alcohol intoxication in social situations and impaired ability to make appraisals of angry and happy emotions irrespective of consuming alcohol.

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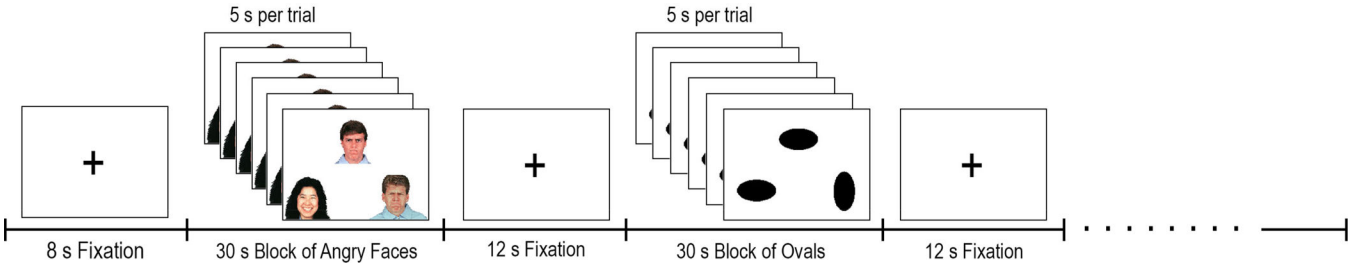

Figure 1.

Example of first two blocks of the task. Each emotion condition and the oval shape control condition are presented in three separate blocks in a pseudorandom order with a fixation cross presented between blocks. s = seconds.

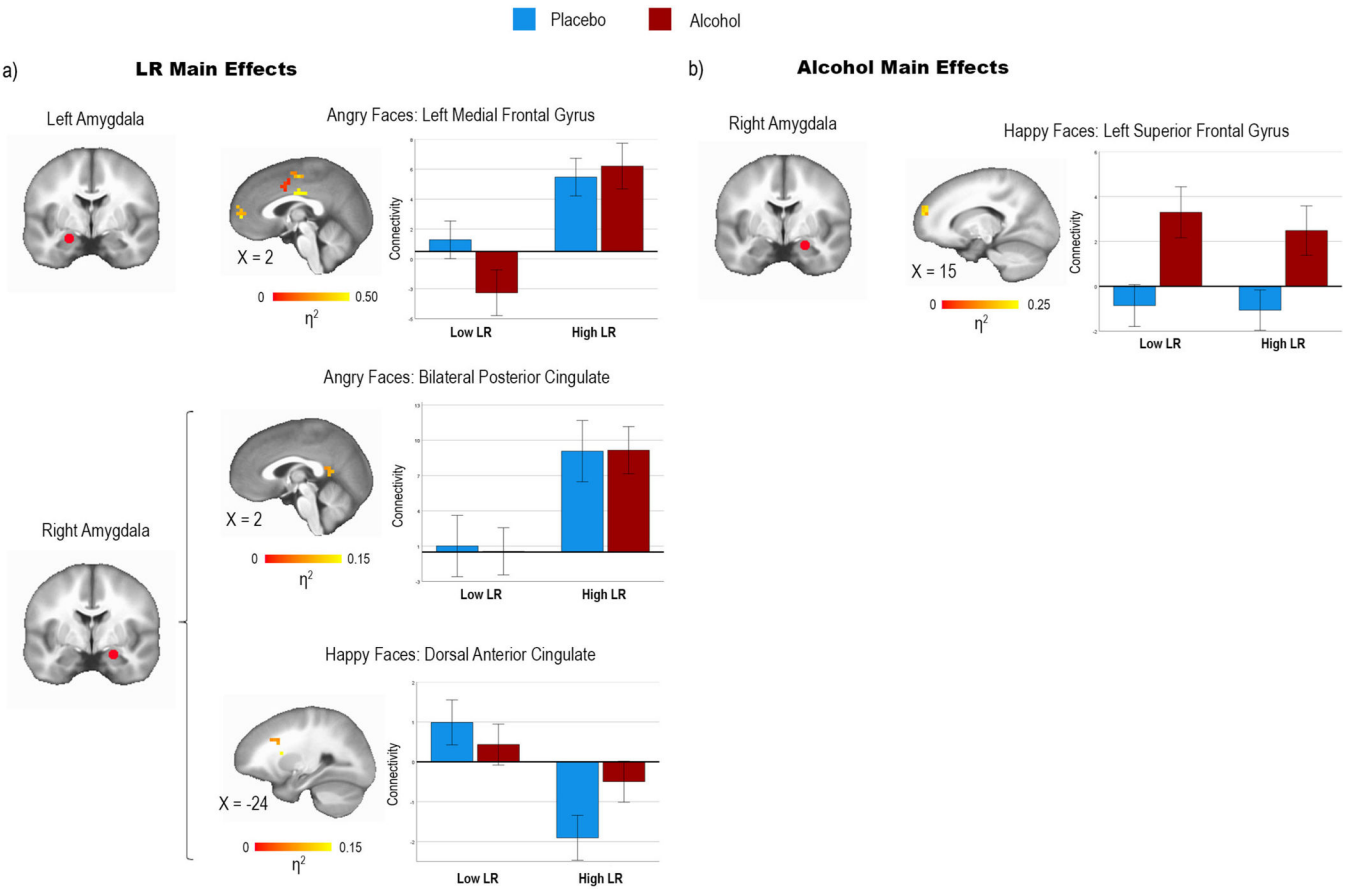

Figure 2.

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

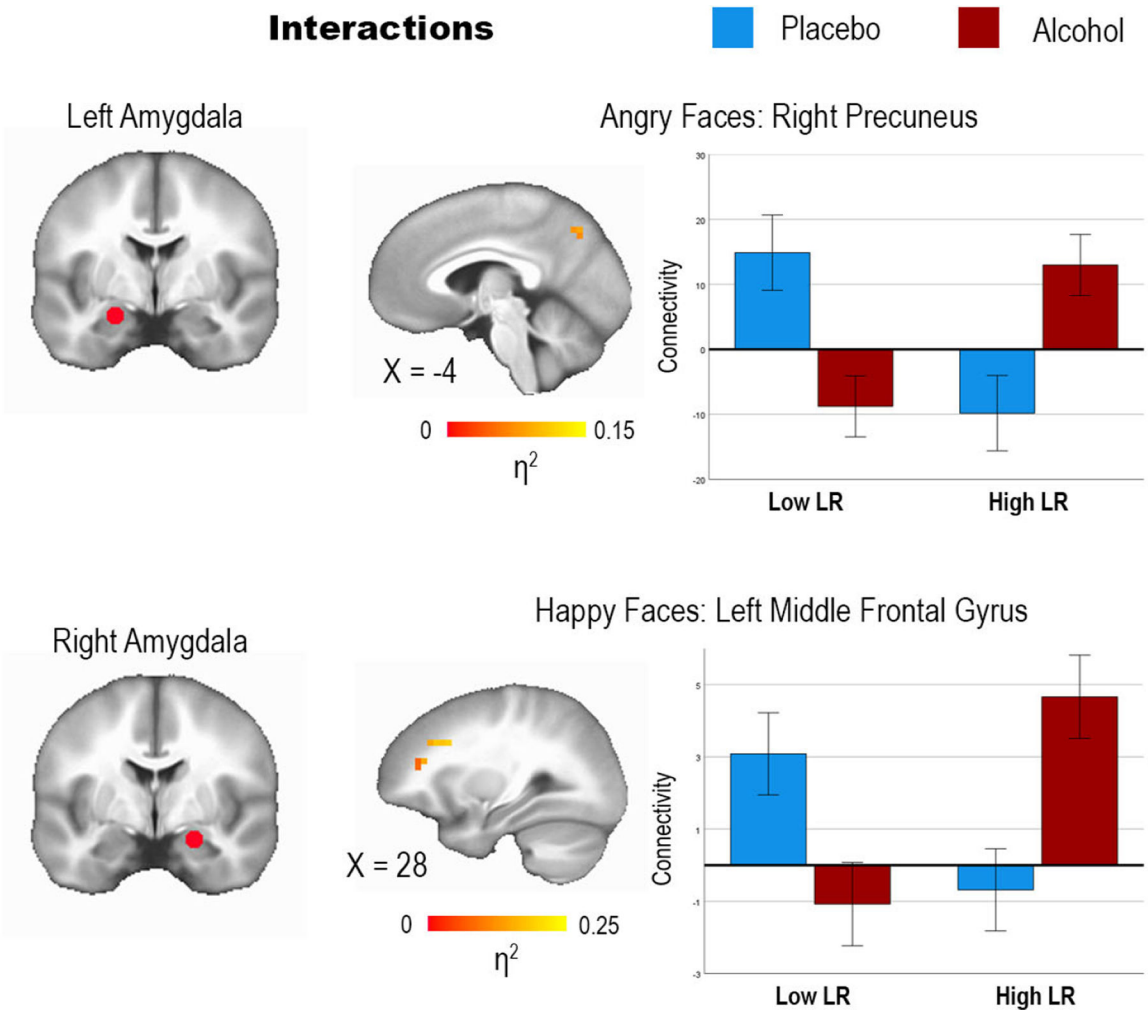

Figure 3.

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

Table 1.

Characteristics of Women and Men with High and Low level of response (LR) to alcohol

	Low LR Women (n=27)	High LR Women (n=27)	Low LR Men (n=27)	High LR Men (n=27)	p-value[c]
Age (yrs)	19.9 (1.3)	19.8 (1.6)	19.7 (1.6)	20.2 (1.4)	0.61
Yrs of Education Completed	13.7 (1.1)	13.6 (1.3)	13.6 (1.1)	13.7 (1.1)	0.94
Body Mass Index	22.7 (2.9)	22.6 (3.8)	23.6 (3.7)	23.0 (3.3)	0.72
Days/Months Used Alcohol[a]	6.7 (3.5)	5.4 (3.7)	7.9 (5.4)	7.0 (5.9)	0.26
Usual Drinks/Occasion[a]	3.8 (1.3)	3.2 (1.8)	4.1 (2.1)	3.1 (1.8)	0.11
% Ever Used Tobacco	78 %[d]	52 %[d]	59 %	48%	0.06
% Regular Tobacco User[b]	0 %	11 %	0 %	8 %	0.15
% Ever Used Cannabis	78%[d]	48 %[d]	59 %	52 %	0.08
Lifetime Cannabis Use Occasions	23.0 (33.5)	23.9 (93.1)	37.4 (108.6)	27.8 (82.4)	0.92
BrAC at 60 Minutes (mg/dL)	0.06 (0.01)	0.06 (0.01)	0.06 (0.01)	0.06 (0.01)	0.35

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

BrAC: Breath Alcohol Concentration; LR Level of Response.

[a]Data for prior 6 months.

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

[c]p-values for between-subject ANOVAs or Kruskal-Wallis test.

[d]Significant LR difference (p=0.012) for women

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Table 2.

Results of whole-brain PPI analyses examining level of response and alcohol/placebo conditions for angry, fearful, and happy faces

Emotion	Seed Region	Region Name	BA(s)	Volume (μL)	Talairach Coordinates[a]		
					x	y	z
LR Main Effects							
Angry	Left Amygdala	B Ventral Anterior Cingulate	24	1344	2	−3	40
		L Postcentral Gyrus / Supramarginal Gyrus	2, 40	1280	54	21	20
		L Medial Frontal Gyrus	6	1152	2	5	56
		L Medial Frontal Gyrus	10	1024	2	−55	4
		L Supramarginal Gyrus	40	960	38	45	32
		B Posterior Cingulate	23	512	2	17	32
Angry	Right Amygdala	B Posterior Cingulate	29	512	2	49	12
Happy	Right Amygdala	R Dorsal Anterior Cingulate Gyrus	32	576	−14	−19	32
		R Caudate	--	512	−18	−11	12
Alcohol Main Effects							
Happy	Right Amygdala	L Middle Insula	13	448	42	1	12
		L Superior Frontal Gyrus	9	448	18	−55	28
LR-by-Alcohol Interactions							
Angry	Left Amygdala	R Precuneus	7	448	−2	65	44
Happy	Right Amygdala	L Middle Frontal Gyrus	10	512	34	−39	20
		L Middle Frontal Gyrus	9	512	26	−35	32

Results shown are limited to those achieving a threshold corrected p-value ≤ 0.01 for functional connectivity between each amygdalar seed and brain region. PPI: psychophysiological interaction; BA: Brodmann area; LR: level of response; L: left; R: right; B: bilateral

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