COGNITIVE ASPECTS

Alcohol Attenuates Activation in the Bilateral Anterior Insula during an Emotional Processing Task: A Pilot Study†

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Abstract — Aims: Alcohol acutely reduces agitation and is widely used in social situations, but the neural substrates of emotion processing during its intoxication are not well understood. We examine whether alcohol’s social stress dampening effect may be via reduced activity in the cortical systems that subserve awareness of bodily sensations, and are associated with affective distress. Methods: Blood oxygen level-dependent activation was measured through 24 functional magnetic resonance imaging sessions in 12 healthy volunteers during an emotional face-processing task following ingestion of a moderate dose of alcohol and a placebo beverage. Results: Results revealed that bilateral anterior insula response to emotional faces was significantly attenuated following consumption of alcohol, when compared with placebo (clusters >1472 μl; corrected P < 0.05). Conclusion: Attenuated response in the anterior insula after alcohol intake may explain some of the decreased interoceptive awareness described during intoxication.

INTRODUCTION

Alcohol is the most commonly used and misused intoxicant in the USA, with 69% of 21-25 year olds having consumed this drug in the past year (Johnston et al., 2005; SAMHSA, 2006). Drinking occurs for a variety of reasons including alteration of emotional states and reduction of anxiety (Sayette, 1993), thus acting as a ‘social lubricant’ (Monahan and Lannoniti, 2000) by reducing social fears and facilitating interpersonal interaction. However, intoxication from alcohol has been linked to affective lability and impairment of behavioral control (Vogel-Sprott et al., 2001) and decreases in attention, cognitive control, memory and error processing (Bartholow et al., 2003; Cabson et al., 2003). Although the positive and negative effects of alcohol are well studied, the neural substrates underlying the changes emotional processing after alcohol consumption have not been well established.

In a prior study investigating the emotional processing effects of another depressant drug, lorazepam, our group found significant deactivations in the bilateral insula and amygdala perhaps as a reflection of reduced interoceptive monitoring, i.e. the sensing and evaluation of sensory information coming from the inside of the body (Paulus et al., 2005). The insula is an important brain region for processing emotional and physiological states and the resulting awareness of emotional feelings (Craig, 2003). Prior research suggests that the insula may also be integral in experiencing the intoxicating effects of alcohol, perhaps through the attenuation of insular response to affective stimuli with resulting altered emotional processing (Gilman et al., 2008). Furthermore, insular functioning appears to be related to alcohol and drug-induced craving and relapse (Tapert et al., 2004; Naqvi et al., 2007). The insula and amygdala also demonstrate excessive response in anxiety disorders, with the insula showing particularly large activation in individuals with panic disorder (Etkin and Wager, 2007). Regarding alcohol, functional magnetic resonance imaging (fMRI) studies using acute alcohol administration have revealed both significant patterns of activation and deactivation to cognitive tasks in task-related regions (Calhoun et al., 2004; Paulus et al., 2006), while imaging during alcohol withdrawal, a condition characterized by increased anxiety, has demonstrated increased activation in the insula during a cue reactivity task, potentially showing increased physiological distress (Myrick et al., 2004).

The aim of this study was to expand on prior results to test the hypothesis that acute alcohol administration attenuates the neural substrates of affective arousal during emotional processing. Specifically, we predicted attenuated activation in the bilateral insula and amygdala after a moderate dose of alcohol, when compared with placebo as measured by blood oxygen level-dependent (BOLD) response to a well-validated face-processing task.

METHODS

Participants

Twelve healthy non-smoking social drinkers (five females) aged 19–29 (mean = 23.2, SD = 2.4) participated in the study, which was approved by the Human Research Protection Program at the University of California, San Diego. Based on questions extracted from the Semi-Structured Assessment for the Genetics of Alcoholism interview (SSAGA; Hesselbrock et al., 1999), eligible participants indicated no history of alcohol or drug dependence, and had no medical, psychiatric or neurological disorders and all tested negative for illicit substances using a standard urine toxicology screen. Non-pregnancy status of females was established with a urine pregnancy test, and a zero breath alcohol concentration (BrAC) prior to the start of the experiment was confirmed for all subjects (Intoximeter, St. Louis, MO, USA).
**Procedures**

Prior to the fMRI scan, participants completed questionnaires detailing medical, psychiatric and substance use histories, and were instructed to complete the Subjective High Assessment Scale (SHAS; Schuckit, et al., 1997a, b) to rate the perceived level of response to alcohol. This measure evaluated how they were feeling regarding the effects on a 36-point Likert scale for each of 13 items. At baseline, subjects were instructed to circle a score of zero for each item, and to be mindful of the questions so as to differentiate feelings of alcohol from other attributes (e.g. baseline sleepiness).

All individuals completed two sessions where they received an alcohol or a placebo beverage in a random order. Alcohol was given as 0.75 ml/kg of 95% laboratory ethanol for males, and 0.68 ml/kg for females, mixed with caffeine-free, room temperature diet soda and typically resulted in BrAC between 0.06 and 0.08 gm/dl (Schuckit et al., 1997a, b), this combined with precise timing of alcohol administration was designed to result in relatively consistent BrAC values across all subjects during the experiment. The alcohol beverage consisted of 20% ethanol, with the remainder being non-caffeinated, sugar free soda. The placebo beverage was the caffeine-free, room temperature diet soda with ethanol rubbed onto the lid of the thermos and in a small reservoir in the straw, so that the participant would smell and taste alcohol but not ingest enough to change blood levels. The beverage in both conditions was consumed over 8 min in a solid-colored thermos designed to disguise its contents. The protocol followed this rigid time course to ensure tight experimental control across all participants (Schuckit et al., 1997a, b). BrAC and SHAS ratings were obtained at 13 and 27 min after drinking commencement to obtain alcohol effect measures; at 30 min, fMRI began.

Subjects were tested on a slightly modified version of the Hariri Emotion Face Assessment Task (Hariri et al., 2000) given ~60 min after drink consumption as part of a larger multi-task protocol. During each 5-s trial, the subject was presented with a target face or shape at the top and two probe faces or shapes on the bottom of the screen, and was instructed to match the probe with the same emotional expression or shape as the target by pressing the appropriate button. A total of twelve blocks were presented. Each block consisted of six consecutive trials during which the target face was angry, fearful or happy or a shape (Ekman et al., 1983), with each target face or shape remaining constant for the whole block. During the emotional faces, the foil was the voxel-wise normalized relative signal change (% signal change). Spatial smoothing using a filter with full-width half maximum (FWHM) of ~1–2 voxels (i.e. 3–6 mm) has been reported to yield the highest detection power (Skudlarski et al., 1999). Thus, % signal change data were smoothed with a 6 mm FWHM kernel and transformed into standard (Talairach) coordinates defined on the anatomical MR image.

**Image acquisition**

MR images were obtained with a 3T CXK4 scanner (General Electric, Milwaukee, WI, USA) with an 8-channel head array coil. During the task, T2-weighted echo-planar imaging (EPI) was collected (repetition time = 2000 ms, echo time = 32 ms, 64 × 64 matrix, 30 2.6 mm axial slices with 1.4 mm gap, 256 repetitions). At this in-plane resolution and with a fast time to repeat of 2 s, the scanner could accommodate slices thickness down to 4 mm, which is equivalent to slices of 2.6 mm with a 1.4 gap. This has been shown to provide better signal in the amygdala, while still being able to obtain full-brain coverage (Merboldt et al., 2000; Robinson et al., 2004). A T1-weighted image (repetition time = 8 ms, echo time = 4 ms, flip angle = 12°, field of view = 256 × 256, 1 mm³ voxels) was obtained for anatomical reference.

**Data processing**

All processing of structural and functional images was done with the Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). EPI intensity images were co-registered to the 128th image and three motion parameters (roll, pitch and yaw) from each subject’s time series were used as nuisance regressors to correct for head motion. Four orthogonal regressors of interest temporally indicated presentation of: (a) happy faces, (b) angry faces, (c) fearful faces and (d) shapes (circle/oval) control condition. Additionally, an average of all face conditions was created to account for task-related activation. Each 0–1 regressor was convolved with a gamma variate function modeling a prototypical hemodynamic response to shift the regressor according to the hemodynamic delay (6–8 s) and accounted for temporal characteristics of the hemodynamic response (typically 12–16 s). The convolved time series was normalized and used as a regressor of interest, then was entered along with a motion regressor into the AFNI program 3dDeconvolve to determine the height of each regressor for each subject. The key dependent variable was the voxel-wise normalized relative signal change (signal change). Spatial smoothing using a filter with full-width half maximum (FWHM) of ~1–2 voxels (i.e. 3–6 mm) has been reported to yield the highest detection power (Skudlarski et al., 1999). Thus, % signal change data were smoothed with a 6 mm FWHM kernel and transformed into standard (Talairach) coordinates defined on the anatomical MR image.

**Statistical analysis**

Planned comparisons using contrasts for repeated measures designs were performed for only bilateral amygdala and insula, as confirmatory analysis for the a priori hypothesis. The voxel-wise % signal change data were entered into a mixed-model analysis of variance with task contrast (face type versus shape matching condition) and dose (placebo or alcohol) as fixed factors, and subjects as a random factor. In addition, a whole-brain analysis determined whether alcohol affected non-hypothesized areas, as an exploratory analysis. Activation clusters corrected for multiple comparisons using an a priori P < 0.05 per voxel threshold and a volume mask >1472 µl, as determined by the AFNI program AlphaSim (Ward, 2000). Then mean activation for each cluster was imported into SPSS 14.0 (Chicago, IL, USA).

Behavioral analyses were carried out with SPSS 14.0. A repeated measures multivariate ANOVA, with condition (placebo or alcohol) as the within-subjects factor, was used to analyze the behavioral measures and neural activation.
patterns. Behavioral measures are reported as an interaction between condition and task block.

RESULTS

Effects of alcohol on BrAC and SHAS
BrAC and SHAS ratings were collected at 27 min after drinking, just prior to entering the scanner. BrACs reached 0.070 on average (SD = 0.017) and subjective ratings of the effects of alcohol (SHAS7) were 8.40 for the alcohol condition (SD = 8.18). SHAS ratings for the placebo condition were not collected.

Task performance effects of alcohol
Subjects responded faster to shapes than to faces, and faster to happy compared with angry or fearful faces ($F(3,33) = 60.21$, $P < 0.01$), but there was no effect of facial emotion on response accuracy ($F(3,33) = 2.33$, $P = 0.09$; Table 1). Alcohol had no significant effect on reaction time ($F(1,11) = 0.01$, $P = 0.91$) or accuracy ($F(1,11) = 0.12$, $P = 0.73$) overall, or on reaction time ($F(3,33) = 0.55$, $P = 0.65$) or accuracy to the target faces or the sensorimotor control condition ($F(3,33) = 0.36$, $P = 0.78$; see Fig. 1).

fMRI response
The task significantly activated the right insula ($t = 4.29$, $P = 0.001$), left insula ($t = 3.74$, $P = 0.003$), right amygdala ($t = 4.66$, $P = 0.001$) and left amygdala ($t = 2.89$, $P = 0.015$) as subjects viewed faces across all conditions relative to viewing shapes (Table 2). While activation did not differ between the three face emotions of angry, fear and happy ($F(3,33) = 2.07$, $P = 0.15$), alcohol had an effect on insula activation ($F(1,11) = 10.83$, $P < 0.007$), attenuating activation in the right ($t = −3.17$, $P = 0.009$) and left ($t = −3.26$, $P = 0.008$) insula compared with placebo (Table 3). However, there was no significant alcohol effect on right ($t = 0.20$, $P = 0.85$) or left ($t = −0.65$, $P = 0.53$) amygdala activation. Furthermore, alcohol did not differentially influence activation to the

<p>| Table 1. Hariri Emotion Face Assessment Task descriptive statistics of performance (accuracy and latency) during alcohol and placebo conditions |
|-------------------------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Accuracy (%) M (SD)</th>
<th>Latency (s) M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Alcohol</td>
<td>Placebo</td>
</tr>
<tr>
<td>Shapes</td>
<td>97.20 (3.80)</td>
<td>97.70 (3.70)</td>
</tr>
<tr>
<td>Happy</td>
<td>99.10 (3.20)</td>
<td>99.10 (2.20)</td>
</tr>
<tr>
<td>Fear</td>
<td>96.80 (4.40)</td>
<td>96.60 (6.00)</td>
</tr>
<tr>
<td>Angry</td>
<td>97.60 (4.50)</td>
<td>99.10 (2.20)</td>
</tr>
</tbody>
</table>
target face or the sensorimotor control condition ($F(3,33) = 0.70, P = 0.50$; Fig. 2), and did not affect brain response to faces in the amygdala.

**DISCUSSION**

The main finding of this study was that an acute moderate dose of alcohol resulted in attenuation of bilateral insula activation during the Hariri Emotion Face Assessment Task, in contrast to placebo activation patterns. The effect of alcohol on BOLD response to emotional face processing was specific to the insula; response differences were not observed in the amygdala, as had been hypothesized, nor in any other brain region, a finding that differs from previous research (Gilman et al., 2008). Although the amygdala has repeatedly been implicated in processing emotional or affective information (Pessoa et al., 2010), previous studies suggest that acute alcohol may not exert its strongest effects directly on the amygdala during emotion processing (Gilman et al., 2008). Further, the insular functioning effect was equivalent across

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**Table 2. Brain regions showing significant (t-statistics) BOLD response to Hariri Emotion Face Assessment Task during the placebo condition, based on limbic-masked analyses**

<table>
<thead>
<tr>
<th>Location</th>
<th>t-value</th>
<th>Volume (µl)</th>
<th>x a</th>
<th>y a</th>
<th>z a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right insula</td>
<td>4.29</td>
<td>4800</td>
<td>36</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Left insula</td>
<td>3.74</td>
<td>3904</td>
<td>−36</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Right amygdala</td>
<td>4.66</td>
<td>1600</td>
<td>24</td>
<td>−6</td>
<td>−14</td>
</tr>
<tr>
<td>Left amygdala</td>
<td>2.89</td>
<td>704</td>
<td>−24</td>
<td>−8</td>
<td>−12</td>
</tr>
</tbody>
</table>

aBased on Talairach co-ordinates.

**Table 3. Brain regions showing significant differences in BOLD response to Hariri Emotion Face Assessment Task following a moderate dose of alcohol relative to placebo, based on whole-brain analyses (volume threshold >1472 µl, voxel-wise $P < 0.05$)**

<table>
<thead>
<tr>
<th>Location</th>
<th>t-value</th>
<th>Volume (µl)</th>
<th>x a</th>
<th>y a</th>
<th>z a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left insula</td>
<td>−3.26</td>
<td>1920</td>
<td>−30</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Right insula</td>
<td>−3.16</td>
<td>1856</td>
<td>36</td>
<td>8</td>
<td>15</td>
</tr>
</tbody>
</table>

aBased on Talairach co-ordinates.

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Fig. 2. Alcohol versus placebo for all faces minus shapes contrast in a whole-brain analysis (A). Bar graphs are shown for the all faces minus shapes (B) as well as angry versus shapes (C), fearful versus shapes (D) and happy versus shapes (E). The y-axis shows percent signal change, and the x-axis shows drug condition and left and right insula.
emotion types (fearful, angry and happy faces). As no differences in task accuracy or response latency were observed, the blunted insular response may suggest reduced interoceptive awareness during emotional processing when under the influence of a moderate dose of alcohol.

Increased insula activation relates to various trait measures of affective distress such as anxiety (Simmons et al., 2006; Stein et al., 2007), harm avoidance (Paulus et al., 2003) and intolerance of uncertainty (Simmons et al., 2008). In addition, several studies have shown that the anticipation of aversive events involves the insular cortex. For example, brain areas activated by anticipation of aversive pictures include dorsal amygdala, anterior insula, dorsal anterior cingulate cortex, right dorsolateral prefrontal cortex and right posterior orbitofrontal cortex (Simmons et al., 2004; Nitschke et al., 2006). This network of activation in relation to the anticipation of aversive stimuli extends to other modalities such as monetary losses (Samanez-Larkin et al., 2008), conditioned stimulus predicting an aversive stimulus (Marschner et al., 2008) and the expectation of pain (Ploghaus et al., 1999). Moreover, insula activation is an important processing area for the affective elements of an individual’s pain experience in subjects with depression (Giesecke et al., 2005; Strigo et al., 2008). Some have argued that the insula and anterior cingulate are relatively more sensitive to the expectation of unpleasant stimuli relative to expecting pleasant or neutral stimuli (Herwig et al., 2007). Finally, uncertainty or ambiguity is an important aspect of anticipatory processing. Thus, it is not surprising that the degree to which an individual is sensitive to uncertainty correlates positively with activation in bilateral insula during affective ambiguity (Simmons et al., 2008).

Unpredictable stimulus presentations have been linked to brain activity in the anterior insula (Carlsson et al., 2006). The insula is also involved in modulating autonomic arousal (Critchley et al., 2004) and connecting visceral changes to facial emotion processing (Critchley et al., 2004). Taken together, these data suggest that the insula plays an important role in processing the anticipation and subjective experience of aversive stimuli across a number of different modalities. Furthermore, insular functioning appears to be related to alcohol and drug-induced craving and relapse (Tapert et al., 2004; Naqvi et al., 2007). Our finding of alcohol-attenuated neural response to all facial emotions in the insula may relate to reduced anticipatory processing of potentially aversive events or of events that are judged to be potentially aversive following moderate alcohol consumption. However, alcohol has been associated with better discrimination of positive stimuli (happy faces), and this may be due to suppression of these interoceptive systems allowing positive stimuli to be more readily processed via disinhibition (Steele and Southwick 1985; Kano et al., 2003). This is the first study to our knowledge that examined the neural mechanisms of positive or happy affective processing following a moderate dose of alcohol; therefore future studies are needed to replicate these results. In the current pilot study, the acute effect of alcohol on the insula may be related to its anxiolytic and pro-social effects (Gilman et al., 2008). However, future study will need to examine this relationship more directly.

The present study is limited by a small sample size, the restriction to Caucasian race, the modest age range and the relatively intelligent participants selected from a college population. Additional caveats include the reliance on estimation of blood alcohol concentration during the scan session by controlling the time after drinking when the task was administered instead of exact BrAC, the relatively narrow focus of the fMRI regressions evaluated, the absence of a direct placebo manipulation check and the lack of data on cerebral perfusion, which could potentially account for alcohol condition findings. Future studies should address these limitations, as well as attempt to address within subject longitudinal data including blood alcohol concentration to understand the interaction of time by alcohol.

In summary, this preliminary study suggests that reduced insula activation may be one source of decreased interoceptive awareness that is often described during moderate intoxication. Future studies may determine if the degree of interoceptive attenuation relates to the risk for an alcohol use disorder. Knowledge of the effects of alcohol on affective information processing may provide new clues as to why alcohol is used and misused, and may help clarify the positively and negatively reinforcing mechanisms of alcohol.

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