

Why We Like to Drink: A Functional Magnetic Resonance Imaging Study of the Rewarding and Anxiolytic Effects of Alcohol

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People typically drink alcohol to induce euphoria or reduce anxiety, and they frequently drink in social settings, yet the effect of alcohol on human brain circuits involved in reward and emotion has been explored only sparingly. We administered alcohol intravenously to social drinkers while brain response to visual threatening and nonthreatening facial stimuli was measured using functional magnetic resonance imaging (fMRI). Alcohol robustly activated striatal reward circuits while attenuating response to fearful stimuli in visual and limbic regions. Self-ratings of intoxication correlated with striatal activation, suggesting that activation in this area may contribute to subjective experience of pleasure and reward during intoxication. These results show that the acute pharmacological rewarding and anxiolytic effects of alcohol can be measured with fMRI.

Key words: striatum; nucleus accumbens; alcohol; addiction; reward; amygdala

Introduction

Behind only tobacco use and obesity, alcohol use is the third most common lifestyle-related cause of death in the United States (Mokdad et al., 2004). People like to drink alcohol because of its ability to alter emotional states. Alcohol induces euphoria, relaxation, and disinhibition while reducing stress and anxiety. Consistent with human self-report, animal studies also suggest that alcohol produces a rewarding as well as an anxiolytic effect (Coop et al., 1990; Blanchard et al., 1993; Spanagel et al., 1995; Da Silva et al., 2005). Although its euphoric and stress-reducing effects have been known for centuries and are intuitively understood, how alcohol changes the function of human brain circuits has been explored only sparingly.

Where might alcohol recruit circuitry that regulates positive affect leading to euphoria? A critical area of interest is the ventral striatum (VS), which is recruited by reward-predictive stimuli (Knutson et al., 2001; Bjork et al., 2004). A variety of primary rewards activate this circuit, including fruit juice and water (Berns et al., 2001; O'Doherty et al., 2002; Pagnoni et al., 2002; McClure et al., 2003), as well as secondary rewards such as praise and money (for review, see Knutson and Cooper, 2005). Similarly, functional magnetic resonance imaging (fMRI) studies have shown striatal activation in response to drugs of abuse such as cocaine (Breiter et al., 1997) and nicotine (Stein et al., 1998). Although there have not yet been fMRI studies of the action of alcohol on reward circuits, positron emission tomography (PET)

studies demonstrate increased striatal glucose metabolism or blood flow in response to alcohol (Wang et al., 2000; Boileau et al., 2003; Schreckenberger et al., 2004). Accordingly, the mesocorticolimbic reward circuit is important in the development and maintenance of addiction (Koob et al., 1998).

How might alcohol affect circuitry that governs negative affect to decrease anxiety? Alcohol-mediated anxiolysis may result from disruption of threat detection circuitry. The amygdala in particular is critical in an attention allocation circuit that is recruited by stimuli that signal the requirement for an immediate behavioral response, such as fight or flight (LeDoux, 2003; Fitzgerald et al., 2006). Alcohol intoxication increases the incidence of aggression and social risk taking (Giancola and Zeichner, 1997; Corbin and Fromme, 2002; Giancola et al., 2002), perhaps by disrupting the amygdala-mediated differentiation between threatening and nonthreatening stimuli. Decreased differential response may increase approach while decreasing avoidance, thus facilitating social interaction.

The current study was designed to characterize the response of the brain to alcohol intoxication and emotional stimuli, and is the first fMRI study to examine acute pharmacological effects of alcohol on the neural circuitry underlying emotion. This study extends previous research by (1) using intravenous alcohol to minimize individual variability in alcohol pharmacokinetics and to maintain a steady-state of brain alcohol exposure, (2) using fMRI to measure the blood oxygenation level-dependent (BOLD) signal during alcohol administration, (3) presenting emotional facial stimuli, which allows the use of a general linear model (GLM) to examine main effects for alcohol and emotional cues as well as their interaction, and (4) collecting subjective measures of intoxication to correlate with BOLD signal.

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Materials and Methods

Participants. Twelve community-recruited healthy social drinkers (seven women) participated in this study. All participants underwent a complete medical and psychiatric evaluation, including clinical laboratory, radiological, and electrocardiogram examinations. Participants were excluded from the study if they had an abnormal physical exam or had laboratory values outside of normal ranges. Participants were given the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) and were excluded if they met criteria for alcohol or other substance dependency (excluding nicotine) at any time, or if they fulfilled DSM-IV criteria for a current axis-I psychiatric disorder. Participants were also excluded if they had never consumed at least two standard drinks of alcohol within 1 h, or if they reported to have a “facial flushing” response to the consumption of alcohol. They drank an average of 1.9 d per week (SD, 1.1) and an average of 3.6 drinks per drinking day (SD, 1.2).

Participants were all right handed (average age, 26.5 years; SD, 5.6) and none had ever had a head injury requiring hospitalization. They were instructed not to take any prescribed, non-prescribed, or over-the-counter medications in the 14 d period before the study visits. Additionally, participants were asked to abstain from alcohol for at least 3 d before each study visit. A urine sample was obtained from each participant during each study visit for a urine drug screen and for a pregnancy test in females.

Alcohol infusion procedure. Alcohol was infused as a 6% (v/v) solution in saline. The infusion rates were based on a physiologically based pharmacokinetic model for alcohol (Ramchandani et al., 1999), consisting of an exponentially increasing infusion rate from the start of the infusion until the target breath alcohol concentration (BrAC) of 0.08 g% was reached at 15 min, followed by an exponentially decreasing infusion rate to maintain (or “clamp”) the BrAC at the target level. This infusion-rate profile was computed using individualized estimates of the model parameters, which are based on the participant’s height, weight, age, and sex. This method has been used successfully in several studies of the pharmacokinetics and pharmacological effects of alcohol in humans (Kwo et al., 1998; Ramchandani et al., 1999, 2001, 2002; Blekher et al., 2002; Morzorati et al., 2002).

Experimental design. This study consisted of three infusion sessions on separate days, separated by at least 3 d. On each study session, participants reported to the National Institutes of Health Clinical Center Day Hospital where BrAC levels were measured and a urine drug screen and, in women, a urine pregnancy test were performed. An intravenous catheter was inserted in each forearm; one was used for the infusion of alcohol or saline and the other for the collection of blood samples.

The first study session (familiarization session) took place in the Clinical Center Day Hospital. Participants received an alcohol infusion over 45 min, to ensure that they tolerated the alcohol infusion without experiencing nausea or marked sedation, before undergoing the infusions in the fMRI scanner during the second and third sessions. Serial breathalyzer measurements were obtained every 3–5 min from the start of the infusion using the Alcotest 7410 handheld breathalyzer (Dräger Safety Diagnostics, Irving, TX), to ensure that the BrACs were within 0.01 g% of the target and to enable minor adjustments to the infusion rates to overcome errors in parameter estimation and experimental variability (Ramchandani et al., 1999; O’Connor et al., 2000). Subjective response to alcohol was measured using the Biphasic Alcohol Effects Scale (BAES) (Martin et al., 1993) and the modified Drug Effects Questionnaire (DEQ), (de Wit and McCracken, 1990), which were given before the

Table 1. Main effects of alcohol and emotion, and their interaction, on brain response

Region	Talairach coordinates			Activated volume (mm ³)	F value	p value
	x	y	z			
Alcohol						
Right putamen	23	5	6	5272	47.83	<0.0001
Left putamen	−23	−1	0	3824	52.76	<0.0001
Right parahippocampal gyrus	23	−45	−10	1568	23.04	<0.001
Left precuneus	−15	−43	40	1384	30.54	<0.001
Left anterior cingulate	−17	25	24	696	22.19	<0.001
Left superior temporal gyrus	−57	−5	4	560	24.22	<0.001
Emotion						
Left lingual gyrus	−23	−77	0	4160	30.88	<0.001
Right amygdala	17	−9	−2	3376	28.56	<0.001
Left superior temporal gyrus	−13	41	40	3208	24.82	<0.001
Right lingual gyrus	17	−85	−4	3088	22.57	<0.001
Right superior frontal gyrus	13	45	36	776	22.91	<0.001
Right anterior cingulate	3	31	−2	880	21.56	<0.001
Interaction						
Left insula	−41	−29	−2	8392	32.08	<0.001
Right lingual gyrus	29	−79	−4	6528	42.02	<0.0001
Left medial frontal gyrus	−29	35	22	5368	50.44	<0.0001
Right posterior cingulate	19	−63	16	2792	23.66	<0.001
Right inferior frontal gyrus	61	11	24	2168	30.78	<0.001
Right superior temporal gyrus	45	−19	0	2152	28.16	<0.001
Right middle frontal gyrus	31	41	20	1808	29.74	<0.001
Left posterior cingulate	−11	−57	12	1272	30.41	<0.001
Left thalamus	−9	−25	0	1248	31.62	<0.001
Left middle frontal gyrus	−29	35	22	1168	50.44	<0.0001
Left nucleus accumbens	−9	9	−8	633	34.11	<0.001

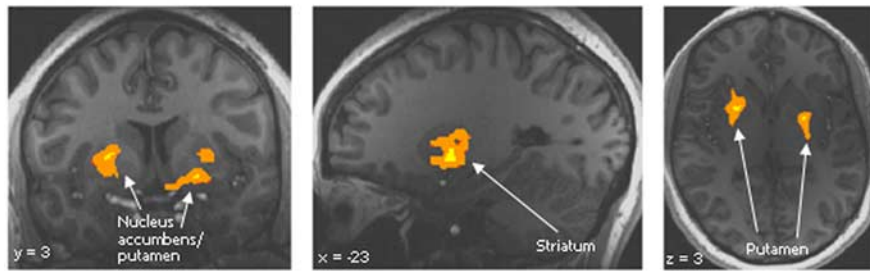
beginning of the infusion and every 10–15 min during the infusion. Mood ratings were obtained before the start and at the end of the infusion using the Positive and Negative Affect Scale (PANAS) (Watson et al., 1988). Blood samples (6 ml) were collected at three time points: before the start of the infusion, and at 15 and 45 min after the start of the infusion. After the infusion was completed, BrAC measurements were taken every 30 min. Participants were sent home in a taxi cab when their BrAC dropped to <0.02 g%.

On the second and third study sessions, participants received the infusions in the scanner. One of these infusions was saline (placebo) and one was alcohol, given in a double-blind, randomized order during sessions 2 and 3. On these days, after intravenous catheter insertion, participants were placed in the scanner. A nurse was present in the scanning room throughout the infusion.

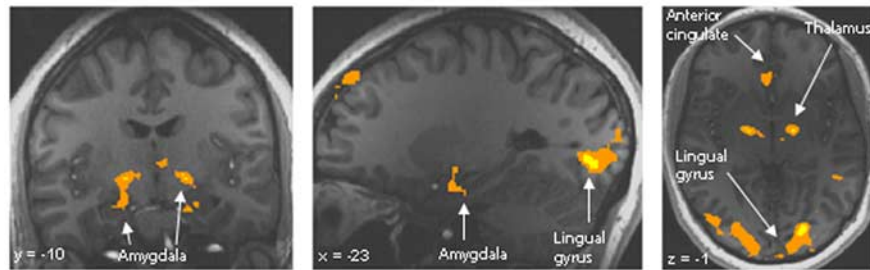
Structural scans were acquired as the infusion began. Target blood alcohol concentration (BAC) was expected to be achieved at 15 min, and emotional images were presented at 25 min as functional scans were acquired as described below. Participants were instructed to focus on the images, but no response was required. Blood samples (6 ml) were collected at three time points: before the start of the infusion, at 15 min after the start of the infusion, and at 45 min, when the infusion ended. The DEQ was given at baseline, and before and after the set of images. Participants also completed the PANAS before and after the scan. The total duration of the infusion was 45 min, after which participants were escorted from the scanner and immediately given a breathalyzer test. They were then transported to the clinical unit, where BrAC measurements were taken every 30 min. Participants were sent home in a taxi cab when their BrAC dropped to <0.02 g%.

Stimuli. Visual images from a series of standardized emotional facial expression (EFE) images (Matsumoto, 1988) were used in this study. Forty-five neutral and 45 fearful faces, as well as a nonemotional control crosshair condition that served as the interstimulus interval, were presented in an event-related design that lasted 8 min 30 s. The stimuli were each presented for 2 s, and the interstimulus interval ranged from 0 to 8 s. All stimuli were presented using a Linux laptop computer with in-house stimulus delivery software. They were projected using an Epson (Long Beach, CA) MP 7200 LCD projector onto a screen placed at the foot of the

A Main effect of alcohol intoxication



B Main effect of fearful faces



C Interaction between alcohol and facial emotion

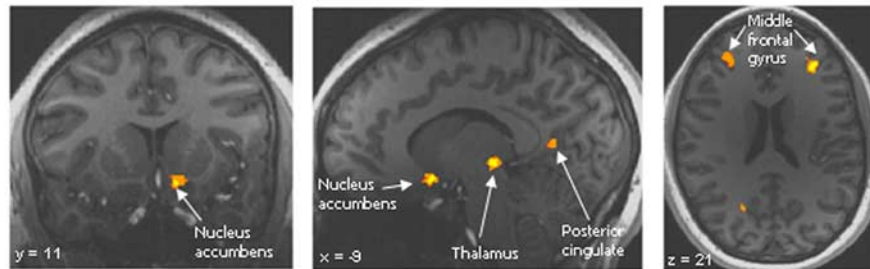


Figure 1. *A–C*, Main effect of alcohol (*A*), fearful facial emotion (*B*), and the interaction between them (*C*) on regional brain activation. Anatomical maps of *t* statistics were spatially normalized by warping to Talairach space and combined into a group map. Radiological convention is used to display left and right. A statistical map of the main effects of alcohol and facial emotion was computed by performing a voxelwise ANOVA of the event-related β coefficients calculated from the general linear model. In this three-factor mixed-model ANOVA, alcohol (alcohol or placebo) and emotion (fearful or neutral) were fixed factors, and subject was a random factor. Alcohol effects were seen primarily in striatal areas, whereas emotion effects were seen in limbic and visual processing areas. The color map represents the *t* score: in orange regions, $p < 0.01$, and in yellow regions, $p < 0.001$. For values, see Table 1.

MRI scanner bed and were viewed using a mirror mounted on the head coil.

fMRI acquisition. Imaging was performed using a 3T General Electric (Milwaukee, WI) MRI scanner with a 16-channel head coil. Thirty contiguous 5.0-mm-thick axial slices were acquired (in-plane resolution, 3.75×3.75 mm), providing whole-brain coverage including subcortical regions of interest such as the nucleus accumbens (NAcc), as well as the prefrontal cortex including the VMFC (ventromedial frontal cortex) and OFC (orbitofrontal cortex), together with limbic areas (amygdala), anterior cingulate and the paralimbic areas and thalamus. Whole-brain high-resolution coronal structural scans were collected using a T1-weighted magnetization-prepared rapid gradient echo pulse sequence, which facilitated localization and coregistration of functional data [voxel size, $0.859 \times 0.859 \times 1.2$ mm; matrix $256 \times 256 \times 124$; repetition time (TR), 100 ms; echo time (TE), 12 ms; field of view (FOV), 24 cm]. Functional scans were acquired using a T2*-sensitive echoplanar sequence that measure changes in BOLD contrast (210 volumes; TR, 2 s; TE, 30 ms; flip angle, 90° ; matrix, 64×64 ; in-plane matrix, 128; FOV, 24 cm; slice thickness, 5 mm. BOLD images were collected during the presentation of the stimuli. Because of the short duration of the run, we did not do any bandpass filtering or detrending of the data.

fMRI analysis. Analyses focused on changes in BOLD signal contrast (hereafter, activation) that occurred as the participants viewed the im-

ages after alcohol or placebo administration. Analyses were conducted using Analysis of Functional Neuroimages software (Cox, 1996). Echo-planar image volumes were preprocessed as follows: (1) voxel time series were interpolated to correct for nonsimultaneous slice acquisition within each volume (using sinc interpolation and the most inferior slice as a reference). (2) Volumes were corrected for motion in three-dimensional space. Motion-correction estimates indicated that no participant's head moved >1.0 mm in any dimension from one volume acquisition to the next. We imposed a 6 mm full-width half-maximum smoothing kernel in the spatial domain. (3) A mask was created so that all of the background values outside of the brain were set to zero. This allowed the calculation of the percentage signal change in each voxel. Statistical maps were generated for each individual separately by linear contrasts between the regressors of interest. The regressors of interest were the neutral and fearful EFE faces. Preprocessed time series data for each individual were then analyzed by multiple regression, which allowed covariation of variables related to head motion. The regression model consisted of the orthogonal regressors of interest and six regressors of no interest modeling residual motion after volume registration. Regressors of interest were convolved with a gamma-variate function that modeled a prototypical hemodynamic response before inclusion in the regression model (Cohen, 1997). Idealized signal time courses were time-locked to image onset.

Anatomical maps of *t* statistics were spatially normalized by warping to Talairach space (Talairach and Tournoux, 1988) and combined into a group map. Next, a statistical map of the main effects of alcohol and facial emotion was computed by performing a voxelwise ANOVA of the event-related β coefficients calculated from the general linear model (using inputs of the regression model). In this three-factor mixed-model ANOVA, drug (alcohol or placebo) and emotion (fearful or neutral) were fixed factors, and subject was a random factor. Linear contrasts were computed separately under the alcohol and

placebo conditions (alcohol: fearful vs neutral; and placebo: fearful vs neutral), as well as separately for each emotion type (neutral: alcohol vs placebo; and fearful: alcohol vs placebo) by performing voxelwise *t* tests between event-related β coefficients of each stimulus type. When reporting ANOVA results, a familywise error-rate correction (using a Monte Carlo simulation) was applied to rule out false positives. When computing familywise error-rate correction, statistical maps were resampled back into original voxel size. Clusters larger than five voxels at an individual voxel threshold level of $p < 0.001$ were considered significant. *t* statistics from the group maps were subsequently characterized by assessment of actual BOLD signal changes in volumes of interest.

Regions that have been implicated previously in either brain reward circuits (NAcc, putamen, and caudate) or emotional-visual circuits (amygdala, fusiform gyrus, and lingual gyrus) were characterized with volume-of-interest (VOI) analyses, in which time series signal data were analyzed. The VOIs were drawn as spheres with a radius of 5 mm, which was a small enough size to average signal data within the boundaries of small structures such as the NAcc and caudate, which were of a priori focus, and also allowed us to investigate the source of effects that were driving significant activations caused by alcohol, emotional valence, or interactions in other cortical regions *post hoc*. Signal data were extracted from the time series as follows: (1) the signal at each voxel was converted

Table 2. Brain activation by linear contrasts between each session and stimulus class

Region	Talairach coordinates			Volume (mm ³)	<i>t</i> -score	<i>p</i> value
	<i>x</i>	<i>y</i>	<i>z</i>			
Neutral: alcohol > placebo						
Left putamen	−23	−7	10	27504	8.57	<0.0001
Right putamen	23	3	0	11472	7.63	<0.0001
Right superior frontal gyrus	23	35	32	5392	5.56	<0.001
Right posterior cingulate	9	−49	24	12432	5.55	<0.001
Left lingual gyrus	−25	−65	−6	2312	4.69	<0.001
Left cingulate gyrus	−17	23	28	1992	4.75	<0.001
Neutral: placebo > alcohol ^a						
Fearful: alcohol > placebo						
Left putamen	−21	3	−4	448	7.53	<0.0001
Right superior temporal gyrus	49	−3	−10	456	5.19	<0.001
Fearful: placebo > alcohol						
Left lingual gyrus	−13	−79	−14	320	6.17	<0.0001
Left parahippocampal gyrus	−41	−33	−4	552	4.69	<0.001
Placebo: fearful > neutral						
Left amygdala	−21	−9	−14	3224	6.3	<0.0001
Right middle frontal gyrus	57	23	22	2784	6.05	<0.0001
Left parahippocampal gyrus	−21	−27	−4	728	5.64	<0.001
Right lingual gyrus	13	−91	6	7296	5.62	<0.001
Left lingual gyrus	−19	−85	2	3056	5.55	<0.001
Left fusiform gyrus	−37	−41	−12	5672	5.27	<0.001
Right anterior cingulate	9	13	−8	952	5.23	<0.001
Right insula	41	−25	−2	5440	4.9	<0.001
Right inferior frontal gyrus	45	−3	24	1744	4.89	<0.001
Left medial frontal gyrus	−21	37	24	1760	4.65	<0.001
Left medial frontal gyrus	−47	19	42	880	4.61	<0.001
Placebo: neutral > fearful ^a						
Alcohol: fearful > neutral ^a						
Alcohol: neutral > fearful						
Left thalamus	−19	−15	10	4544	5.22	<0.001

^aNo clusters detected.

to a (percentage) deviation from the mean for that voxel across the entire time series, (2) the signal was averaged by stimulus type and spatially translated into Talairach space, and (3) a mask was created consisting of the volume of interest through which each individual participant's data were extracted. These data were subject to ANOVA using the percentage signal change in each region as the dependent variable and alcohol (alcohol or placebo), emotion (fearful or neutral), and the interaction between them as the independent variables (package JMP-SAS; SAS Institute, Cary, NC). The *p* value for significance (two tailed) was set at 0.05. In cases of significant interactions, *post hoc t* tests were performed to evaluate differences between the conditions.

Correlational analysis. Coefficients of association were computed for the magnitude of change in the VOI measures versus subjective measures of intoxication, as measured by the DEQ. For these analyses, the VOI measure was a BOLD “change score,” calculated as the average percentage signal change to a stimulus class during the alcohol session minus the average percentage signal change to the same stimulus class during the placebo session. A positive change score indicates that the participant exhibited a larger response during the alcohol condition, and a negative score indicates a larger response during the saline condition. Analysis was conducted using BOLD signal change under the neutral condition because this was the emotion type that demonstrated striatal activation.

Results

Self-reported alcohol effects

All participants tolerated the infusion without complications. The average BrAC reached during the familiarization session was 0.070 g% (SD, 0.008). All participants reported both stimulation and sedation effects on the BAES during this session. We saw the

expected subjective effects of alcohol on the DEQ, with significant increases in high, intoxication, “feeling effects,” “liking,” the drug, and “wanting more” of the drug, compared with baseline. Participants reported peak ratings of intoxication and feeling high at 25 min after the start of the infusion.

During the scanning sessions, the average blood alcohol concentration was 0.0 g% on the placebo day, and 0.072 g% (SD, 0.009) at the end of the infusion on the alcohol day. Participants were asked to report subjective feelings of intoxication and high using the DEQ every 10 min during the scans. None of the participants reported feeling any alcohol effects on the placebo day, and during the alcohol day, they reported peak intoxication from 25 to 45 min after the start of the infusion.

Participants did not differ significantly in self-report of positive or negative affect, measured by the PANAS, between the alcohol and the placebo day either before or after the scan. On the alcohol day, there was no change in negative or positive affect from prescan to postscan, but on the placebo day, participants reported a decrease in positive affect from prescan to postscan (*p* = 0.003).

Neural activity

To test for the main effects of the alcohol and the facial emotion type, as well as the interaction between them, we used a GLM where alcohol (alcohol or placebo) and facial emotion (fearful or neutral) were fixed factors, and subject was a random factor. We found a significant main effect of alcohol intoxication on activation of VS across facial emotion types (Table 1, Fig. 1A). Activation was also significant in the right parahippocampal gyrus, left precuneus, left anterior cingulate, and left superior temporal gyrus. Conversely, we found a significant main effect of facial emotion regardless of alcohol administration in the right amygdala, bilateral lingual gyrus, left superior temporal gyrus, right superior temporal gyrus, and right anterior cingulate (Fig. 1B). Significant interactions between alcohol and facial emotion were seen in the several regions, including the left insula, right lingual gyrus, left nucleus accumbens, and bilateral middle frontal gyri (Fig. 1C). These interactions were characterized in *post hoc* volume of interest analyses (see Fig. 3).

During the placebo infusion, fearful faces (in contrast with neutral faces) activated the amygdala, insula, and parahippocampal gyrus, as well as visual processing areas, with no regions showing greater activations to the neutral compared with fearful faces (Table 2, Fig. 2A). In contrast, when participants were intoxicated, the fearful faces did not elicit a larger response than the neutral faces in any region.

Although we detected a main effect of alcohol intoxication in the striatum, this effect was primarily driven by the participants' reaction to neutral, but not fearful, stimuli. Neutral faces elicited ventral striatum activation when subjects were intoxicated, but not when they were sober (Fig. 2B). Fearful faces elicited increased activation in the left putamen, but in a much smaller and more ventral region than in the neutral face condition.

Volume-of-interest analysis

We characterized BOLD signal changes in VOIs that have previously been implicated in either brain reward circuits (e.g., NAcc, putamen, and caudate) or emotional–visual circuits (e.g., amygdala, fusiform gyrus, and lingual gyrus). Fearful faces elicited greater activation than neutral faces in the right-lateralized amygdala, fusiform gyrus, and lingual gyrus (Fig. 3). Alcohol main effects were not statistically significant in these regions (for values, see Table 3). The alcohol × facial emotion interaction effect

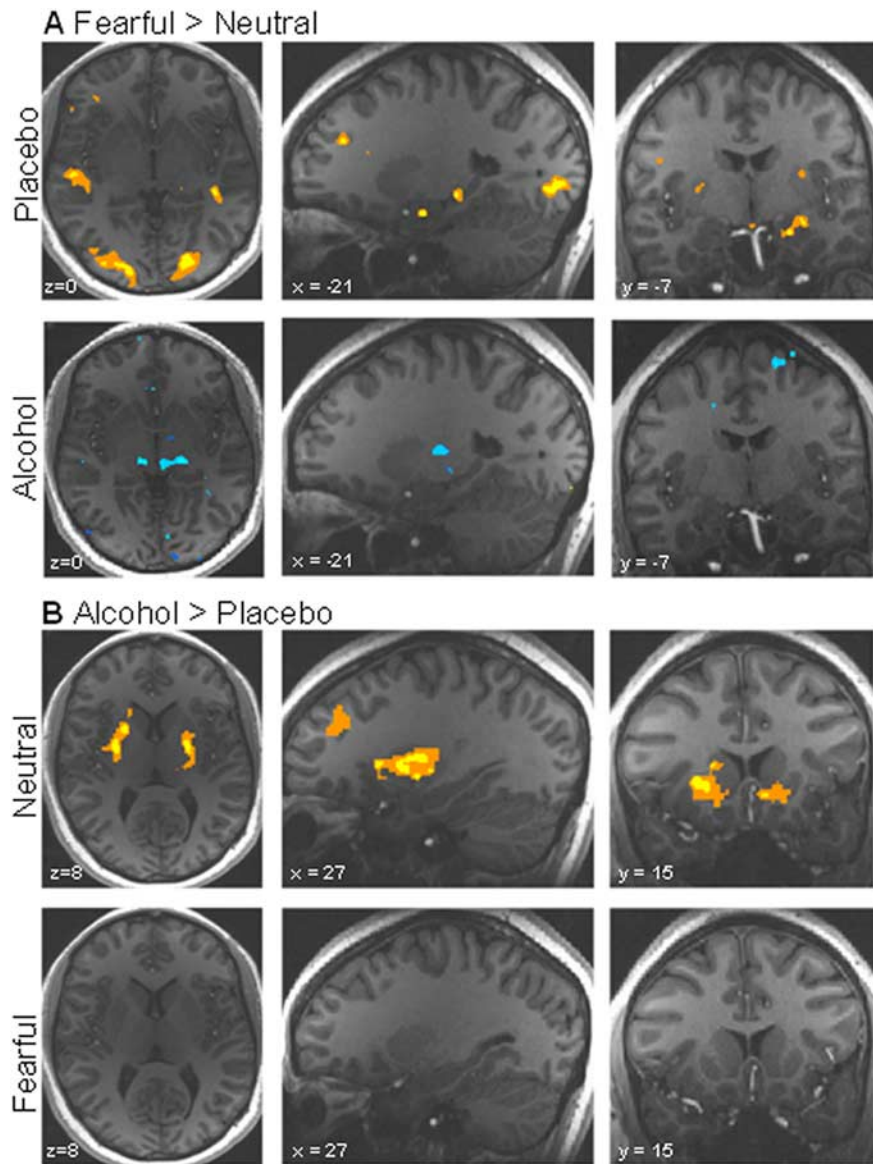


Figure 2. Linear contrasts between the alcohol and placebo condition under each emotion type (placebo: fearful > neutral; and alcohol: fearful > neutral), as well as linear contrasts between the fearful and neutral conditions separately under the alcohol and placebo conditions (neutral: alcohol > placebo; and fearful: alcohol > placebo). These contrasts were computed by performing voxelwise *t* tests between event-related β coefficients of each stimulus type. Radiological convention is used to display left and right. **A**, Linear contrast between fearful vs neutral faces in the placebo and the alcohol condition. Increased activation to negative faces is shown in yellow/orange ($p < 0.01$), whereas increased activation to neutral faces is shown in blue ($p < 0.01$). **B**, Linear contrast between alcohol and placebo in the neutral and fearful condition. Increased activation to alcohol is shown in yellow/orange ($p < 0.01$), whereas increased activation to placebo is shown in blue ($p < 0.01$). For values, see Table 2.

on amygdalar BOLD signal change reached trend level significance ($p = 0.08$). Pairwise simple effect *t* tests clarified this trend, demonstrating that whereas fearful faces activated amygdala significantly more than did neutral faces ($p < 0.05$) during placebo infusion (as seen in both the time-series linear contrast maps, and in the extracted VOI data), this effect was no longer significant ($p > 0.10$) during alcohol intoxication.

In the striatal VOIs, there were no main effects of emotion, but there were significant main effects of alcohol in the right NAcc, right caudate, right putamen, and left putamen, and significant interactions between alcohol and emotion in the left NAcc and the left caudate (Fig. 3; for values, see Table 3). In these two regions, *post hoc* one-way comparisons indicated significant

differences between the alcohol and the placebo condition when participants viewed the neutral faces, but no differences during the fearful face condition (Fig. 4A).

Association between self-reported intoxication and neural activity

There was a significant positive association between subjective ratings of intoxication and BOLD change scores in the neutral facial expression condition in the left NAcc ($r^2 = 0.467$, $p = 0.020$) and in the left caudate ($r^2 = 0.354$, $p = 0.045$). This indicates that participants who reported feeling more intoxicated showed a larger BOLD response to alcohol in these regions (Fig. 4B). Stepwise multiple regression indicated no effect of actual BAC levels, gender, or prescan mood ratings of negative or positive affect on BOLD activation. There was no correlation between subjective intoxication ratings and BAC levels, probably as a result of the minimal intersubject variability in BAC using our ethanol infusion method. We also did not find the session order to have a significant effect in any of our analyses.

Discussion

This study is the first to use fMRI to measure BOLD activation during intravenous alcohol infusion. The rapid intravenous administration of alcohol allowed us to achieve pharmacologically effective concentrations quickly, thus reducing acute adaptation and providing a clearer picture of the direct effects of alcohol. The results confirmed our expectation that alcohol would robustly activate striatal reward areas in the brain, especially the ventral striatum. Activation in the left NAcc and left caudate increased relative to baseline signal in conjunction with subjective ratings of intoxication. These findings confirm PET data indicating increased glucose utilization during alcohol administration in striatum (Wang et al., 2000; Boileau et al., 2003; Schreckenberger et al., 2004), and support Koob's (1992) hypothesis that all drugs of abuse activate the striatum.

The anxiolytic effect of alcohol in visual–emotional brain areas

Despite the use of alcohol in social settings, there have been no previous human imaging studies examining interactions between alcohol and emotional cues. A variety of nonimaging human studies have attempted to experimentally alter emotional states while administering alcohol or measuring alcohol intake (Gabel et al., 1980; Stritzke et al., 1996; Curtin et al., 1998; Schroder and Perrine, 2007), but these studies have not demonstrated a specific anxiolytic interaction between alcohol and emotional cues. Alco-

hol can have vastly different effects on emotion depending on factors such as the point on the blood alcohol concentration vs time curve, the individual's drinking history, and the dose of alcohol consumed (Levenson et al., 1980; Lukas et al., 1986; Turkkan et al., 1988; Giancola and Zeichner, 1997; Conrod et al., 2001; King et al., 2002). Very few studies have systematically controlled these factors.

Our analysis found that visual and limbic brain regions were sensitive to the effects of alcohol. Emotional facial expressions activated higher-order visual areas related to emotion, including lingual and superior temporal gyri as well as the affective division of the anterior cingulate, as has been previously reported in studies exploring the effects of emotional stimuli on brain activation (Devinsky et al., 1995; Phillips et al., 2003; Vuilleumier, 2005). This result is consistent with previous findings that recruitment of these regions is enhanced by emotionally valenced visual stimuli (Vuilleumier, 2005). Importantly, the increased response to the fearful faces that we observed in the placebo condition was abolished in the alcohol condition. This suggests that alcohol may have attenuated the increased sensitivity of the visual system and limbic areas to emotionally threatening stimuli, and this may in part account for the anxiolytic effect of alcohol. An alternative explanation involves the ability of alcohol to increase activation in dopamine terminal regions, including amygdala, during the viewing of neutral faces. This increase in amygdala BOLD signal during neutral face presentation decreases the difference in amygdala activity between fearful and neutral faces, making the amygdala less able to act as a detector of threatening stimuli. This may not only lead to anxiolysis, but may also trigger an increase in both approach and aggression in some individuals.

The rewarding effects of alcohol in striatal brain areas

More than a third of the volume of the striatum was activated by alcohol across emotional conditions. The VS, particularly the NAcc, is critical in the reward system of the brain (Robinson and Berridge, 1993; Koob and Nestler, 1997; Everitt and Wolf, 2002), and lesions in this brain region decrease the rewarding effects of many drugs of abuse (Di Chiara, 2000). The reinforcing effects of alcohol most likely involve multiple neurotransmitter systems, including the dopaminergic, opioidergic, glutamatergic, GABAergic, and serotonergic systems. The increase in

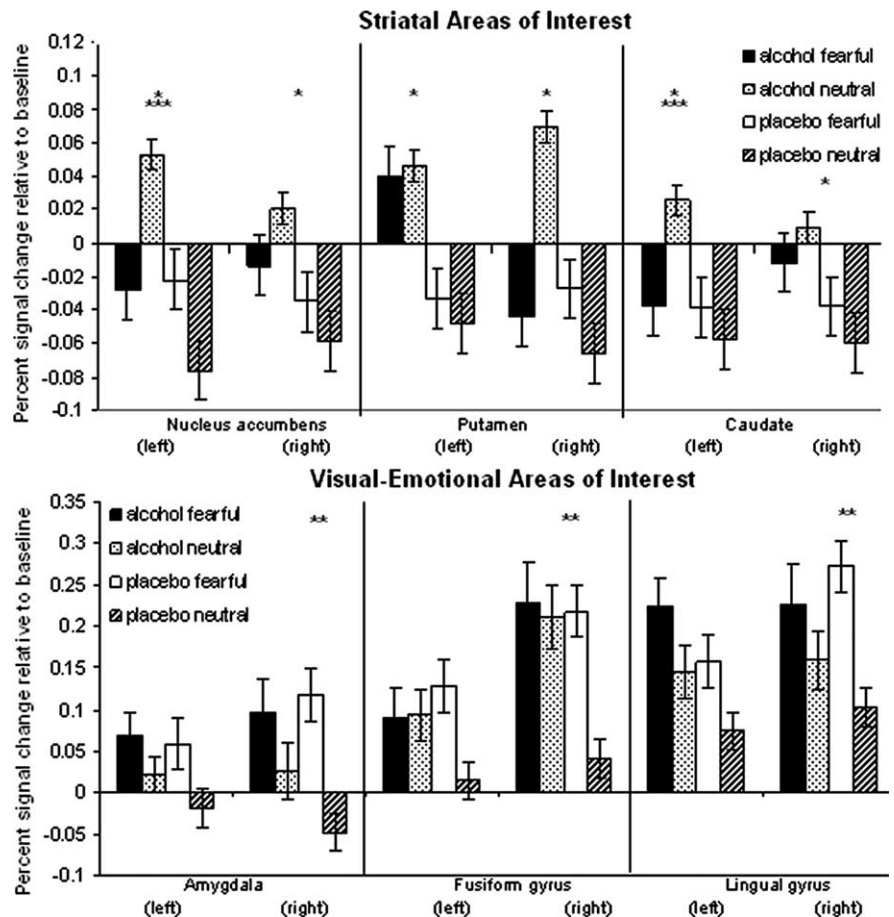


Figure 3. Percentage signal change in volumes of interest in each condition. Values were entered into the GLM to test for main effects of alcohol, emotion, and an interaction. *A significant main effect of alcohol; **a significant main effect of facial emotion; ***a significant interaction between alcohol and emotion. Striatal areas of interest showed significant alcohol effects, whereas visual–emotional areas showed significant effects of emotion. In the visual–emotional areas, alcohol decreased the difference between response to fearful and neutral faces. For values, see Table 3. Error bars indicate SEM.

Table 3. ANOVA results of volume-of-interest analyses in striatal and visual–emotional brain regions

Region	Alcohol	Emotion	Interaction
Striatal Regions			
Right NAcc (11, 10, -7)	$F = 6.09$ $p = 0.018$	NS	NS
Left NAcc (-11, 10, -7)	$F = 8.63$ $p = 0.005$	NS	$F = 10.53$ $p = 0.002$
Right putamen (24, 5, 6)	$F = 14.27$ $p = 0.0007$	NS	NS
Left putamen (-24, 5, 6)	$F = 15.11$ $p = 0.0004$	NS	NS
Right caudate (13, 17, -3)	$F = 6.07$ $p = 0.019$	NS	NS
Left caudate (-13, 17, -3)	$F = 7.64$ $p = 0.009$	NS	$F = 5.41$ $p = 0.027$
Visual–Emotional Regions			
Right amygdala (20, -5, -15)	NS	$F = 9.56$ $p = 0.004$	$F = 3.20$ $p = 0.083$
Left amygdala (-20, -5, -15)	NS	NS	NS
Right lingual gyrus (27, -79, -6)	NS	$F = 4.15$ $p = 0.049$	NS
Left lingual gyrus (-27, -79, -6)	NS	NS	NS
Right fusiform (29, -56, -8)	NS	$F = 4.3$ $p = 0.046$	$F = 3.86$ $p = 0.058$
Left fusiform (-29, -56, -8)	NS	NS	NS

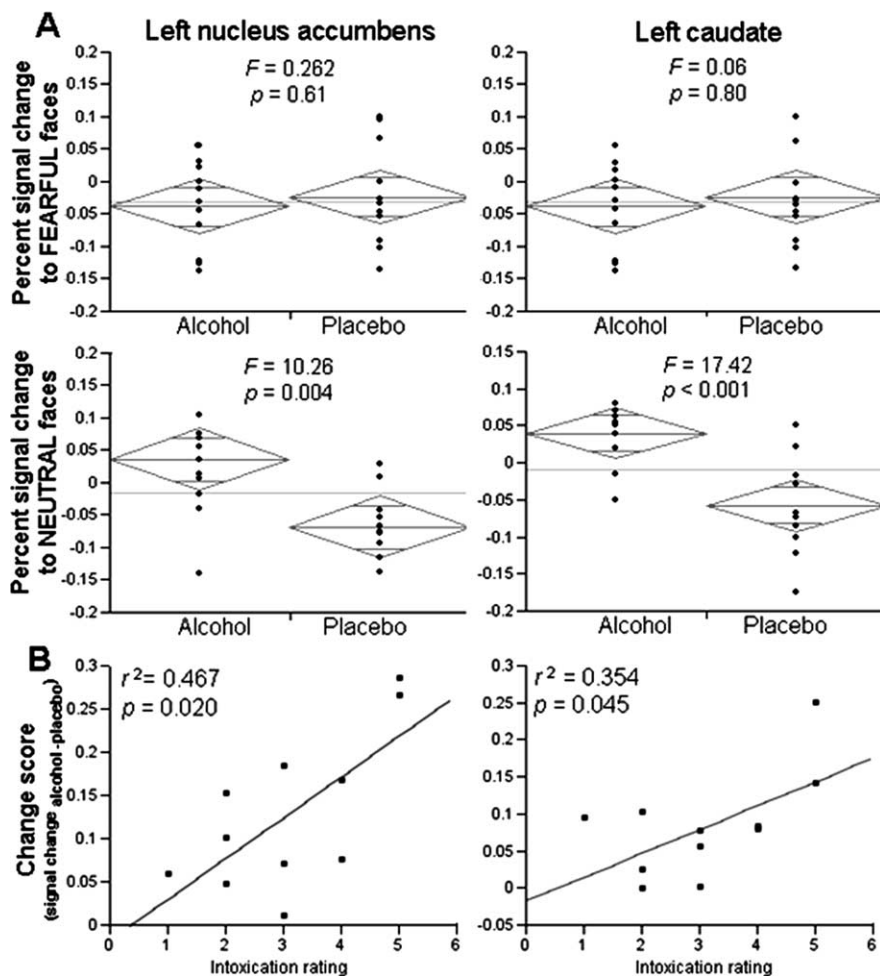


Figure 4. *A*, Where we observed significant interactions in the GLM (in the left NAcc and left caudate), we performed one-way ANOVAs. In these regions, there was a significant difference between the alcohol and the placebo condition when participants viewed the neutral faces, but no difference during the fearful face condition. *B*, A coefficient of association was computed between change scores, defined as percentage signal change (to the neutral faces) during the alcohol session minus percentage signal change (to the neutral faces) during the placebo session, and intoxication ratings measured by the DEQ. There was a significant association between change score and intoxication in the left NAcc and the left caudate.

BOLD signal in the striatum may result from the increased firing rate of dopaminergic neurons secondary to the disinhibitory effect mediated through GABAergic interneurons and a decrease in glutamate-related potassium currents in the ventral tegmental area (Pierce and Kumaresan, 2006). A recent review of animal pharmacological MRI suggests that NAcc dopamine release increases local BOLD signal via postsynaptic D1 receptor activation (Knutson and Gibbs, 2007).

Consistent with previous studies that have shown significant intersubject variability in subjective responses to alcohol at constant breath alcohol concentrations (Holdstock and de Wit, 1998, 2001), we did not find a correlation between subjective ratings of intoxication and actual BACs. We also did not find a correlation between BOLD response and actual BAC, which was not entirely unexpected given that the infusion method was designed to minimize the intersubject variability in BAC exposure. We did find a significant association between BOLD response in the NAcc and subjective perceptions of intoxication, suggesting that under conditions where the BAC is held constant, the intensity of the subjective feeling of intoxication is associated with VS activation.

In addition, our results suggest that alcohol-mediated striatal

activation can be modulated by negative emotional stimuli. The participants' decreased striatal activation when viewing fearful faces suggests that the threatening stimuli may have attenuated the rewarding effects of the alcohol in the striatum, suggesting that context and environment influence the intensity of activation during intoxication.

Conclusions and future directions

This study demonstrates robust activation in response to intravenous alcohol infusion in the VS, an area that is critical in the acquisition and maintenance of addictive behavior. We were able to correlate striatal activation with subjective ratings of intoxication, indicating that the BOLD change in this area is directly related to an individual's subjective experience of the effects of alcohol. Alcohol also modulates emotional processing in limbic and visual regions by decreasing the difference in activation between threatening and nonthreatening stimuli, which may contribute to both the anxiolytic properties of alcohol and to risky decision making during intoxication. The data also indicate an interaction between alcohol and fearful emotional stimuli, such that fearful stimuli decrease striatal activation.

Although this study is underpowered to assess gender differences, future studies should examine whether alcohol has different effects on emotion in men and women, as previous research has shown that gender does influence emotional processing. For example, Klein et al. (2003) found no significant differences in activation could be found between pleasant and unpleasant stimuli in men, but significantly more activation to unpleasant than pleasant cues in women. Furthermore, studies can assess gender differences in mood, striatal alcohol response, and any possible interactions between the subject's gender and the gender of the facial stimuli.

Future studies should also further explore the interaction between alcohol and emotion in alcohol-dependent patients and in individuals at risk for alcoholism. Previous studies have demonstrated differences between controls and alcohol-dependent patients (Heinz et al., 2007; Salloum et al., 2007), and between nonabusing adults with and without a family history of alcoholism (Glahn et al., 2007), in brain regions involved in the processing of emotional stimuli. None of these studies, however, has examined differences among these groups in the effects of acute alcohol administration. These studies could enhance our understanding of how the neural correlates of intoxication and emotion contribute to addiction and risky behavior while intoxicated. In addition, it is possible that attenuation of the alcohol-mediated striatal BOLD response could be used as a surrogate marker for the clinical effectiveness of medications being developed for the treatment of alcoholism.

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