Modulation of brain response to emotional images by alcohol cues in alcohol-dependent patients

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ABSTRACT

Alcohol is often used to modulate mood states. Alcohol drinkers report that they use alcohol both to enhance positive affect and to reduce dysphoria, and alcohol-dependent patients specifically state reduction of negative affect as a primary reason for drinking. The current study proposes that alcohol cues may reduce negative affect in alcoholics. We used functional magnetic resonance imaging to examine brain activation in response to combination images that juxtaposed negative or positive International Affective Picture System (IAPS) images with an alcohol or non-alcohol-containing beverage. We found that in the absence of the alcohol cue, alcoholics showed more activation to negative than to positive images and greater activation than controls to negative images. When the IAPS images were presented with the alcohol cue, there was a decreased difference in activation between the positive and negative images among the alcoholics, and a decreased difference in response to the negative images between controls and alcoholics. Additionally, in the neutral-beverage conditions, anxiety ratings significantly predicted activation in the right parahippocampal gyrus but did not predict activation when the alcohol cues were presented. In conclusion, the alcohol cues may have modulated cortical networks involved in the processing of emotional stimuli by eliciting a conditioned response in the alcoholics, but not in the controls, which may have decreased responsiveness to the negative images.

Keywords   Addiction, affect, alcoholism, drug cues, emotion, fMRI

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INTRODUCTION

People often use drugs of abuse to regulate mood states, especially negative moods (Thorberg & Lyvers 2006). Alcohol drinkers report that they use alcohol both to enhance positive affect (PA) and to reduce dysphoria (Cooper *et al.* 1995; Kassel, Jackson & Unrod 2000), and alcohol-dependent patients specifically state reduction of negative affect (NA) as a primary reason for drinking (Woody, Urshel & Alterman 1992). In addition, treatment-seeking alcoholic patients often suffer from co-morbid psychiatric disorders, including major depression, dysthymia, phobias, anxiety and panic disorders (Hesselbrock, Meyer & Keener 1985; Black, Winokur & Nasrallah 1987; Powell *et al.* 1987; Ross, Glaser & Germanson 1988; Herz *et al.* 1990; Tomasson & Vaglum 1995). Thorberg & Lyvers (2006) found that mood self-regulation is impaired in substance abusers and suggested that this impairment may predispose to substance abuse and addiction.

Compared with healthy individuals, patients suffering from depression, phobias, anxiety disorders and panic disorders show an attentional bias towards negative stimuli compared with positive or neutral stimuli (Mathews, Ridgeway & Williamson 1996; Bradley, Mogg & Lee 1997; Spector, Pecknold & Libman 2003; Lang & Sarmiento 2004). A similar attentional bias has been noted among alcoholics. In a study by Stormark *et al.* (2000) using the Stroop task, alcohol-dependent patients showed a bias towards negative emotional words. This bias could be related to co-morbid psychiatric disorders, alcoholism itself or a combination of both.

In addition to biased attention to negative stimuli, patients with substance abuse problems have an attentional bias towards drug-related cues. This has been reported in individuals with alcohol (Stetter *et al.* 1995; Bauer & Cox 1998; Cox, Yeates & Regan 1999; Stormark *et al.* 2000; Sharma, Albery & Cook 2001; Townshend & Duka 2001; Cox *et al.* 2002; Ryan 2002), cocaine (Rosse *et al.* 1993, 1997; Franken, Kroon & Hendriks 2000a;

Table 1 Demographic characteristics of study groups.

Characteristics	Alcoholics (n = 12)	Controls (n = 12)
Age, mean (SD)	41.83 (8.39)	38.08 (6.97)
Years of education	13.79 (2.49)	17.41 (1.88)
Average number of drinking days/month	27.25 (5.66)	3.09 (2.25)
Average number of drinks/drinking day	15.5 (9.32)	2.27 (1.62)
Number of co-morbid drug abusers[a]	8	0
Number of patients with Axis I disorders	10	0
Mood disorder	4	0
Anxiety disorder	4	0
Number of patients with Axis II disorders	3	0

All categories differ significantly between groups ($P < 0.05$) except for age; [a]drugs of abuse included cocaine (seven patients), cannabis (six), sedatives (two), opioids (two), amphetamine (one) and hallucinogens (one). All patients reported alcohol dependence as their primary complaint.

Franken *et al.* 2000b), opiate (Franken *et al.* 2000b; Lubman *et al.* 2000), marijuana (Field 2005) and nicotine (Gross, Jarvik & Rosenblatt 1993; Johnsen *et al.* 1997; Franken *et al.* 2000b) dependence, as well as among caffeine users (Yeomans *et al.* 2005). Robinson & Berridge (1993) suggest that stimuli associated with drugs of abuse become particularly salient and therefore 'grab attention' more than non-drug-related stimuli. Drug cues have motivational significance because they predict a rewarding event to substance abusers and therefore tend to dominate attentional resources.

This attentional bias to drug cues can be shown using brain imaging techniques. Several imaging studies have shown that specific brain regions are more highly activated by drug and alcohol-associated cues compared with neutral cues in drug users (Grant *et al.* 1996; Maas *et al.* 1998; Breiter & Rosen 1999; Childress *et al.* 1999; Garavan *et al.* 2000; Braus *et al.* 2001; George *et al.* 2001; Schneider *et al.* 2001; Wexler *et al.* 2001). Alcoholics show increased activation to visual alcohol cues in the anterior thalamus, prefrontal cortex (George *et al.* 2001) and ventral putamen, (Braus *et al.* 2001), and a study using alcohol odors reported increased activity among alcoholics in the right amygdala, hippocampus and cerebellum (Schneider *et al.* 2001).

We used functional magnetic resonance imaging (fMRI) to examine brain activation in response to combination images that juxtaposed negatively and positively valenced emotional images with alcohol and non-alcohol beverages in both hospitalized alcoholics and healthy non-alcoholics. This study tests the hypotheses that alcoholics will show more activation in limbic regions and in the visual ventral processing stream to negative images than positive images, and that a higher-order emotion valence by beverage-type interaction will be evident where alcohol cues will modulate the response to negative images in alcoholics but not in control participants. We also hypothesized that patients with higher anxiety

scores would show increased activation to negative pictures, and this effect may also be modulated by the alcohol cues.

METHODS

Participants

Twelve community-recruited healthy controls and 12 males with alcohol dependence participated. Alcoholics were recruited from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) inpatient unit at the Clinical Center of the National Institutes of Health (NIH) in Bethesda, MD. We excluded patients with a history of delirium tremens or gross neurological disorders, an IQ less than 80, or who demonstrated signs of dementia or Korsakoff's disease. Patients did not have a history of head injury or any serious alcohol-related medical disorders. All participants were assessed with the Structured Clinical Interview for DSM-IV, which confirmed that each patient met criteria for alcohol dependence. Patients were scanned 3 weeks after admission.

Healthy community-recruited age-matched male participants with no history of significant medical illness or psychiatric disorders were included for comparison. All participants were right-handed and had normal or corrected-to-normal vision. All participants provided written informed consent to participate in the study, which was approved by the NIH Neuroscience Institutional Review Board.

Participant demographic characteristics are provided in Table 1.

Visual stimulation and task

Visual images were chosen from the International Affective Picture System (IAPS) (Lang, Bradley & Cuthbert 1995). Fifty-five high-arousal negative pictures and 55 high-arousal positive pictures were presented. These pic-

Positive Alcohol   Positive Non-Alcohol

Figure 1 Examples of the four classes of stimuli. Half of the beverage cues were presented to the left of the International Affective Picture System image, and half were presented on the right

Negative Alcohol   Negative Non-Alcohol

tures were paired with pictures of alcoholic beverages and non-alcoholic beverage pictures (i.e. milk, orange juice). The IAPS pictures and the beverage pictures appeared simultaneously, side-by-side (see Fig. 1 for examples). Scrambled images were used as the control condition and were displayed during the interstimulus interval (ISI). The scrambled images were derived from the IAPS images using a script that introduced a random phase shift into Fast Fourier Transformations of each image, which preserved overall brightness and color but did not contain recognizable features. The ISI ranged from 0 to 15 seconds. The pictures were presented in random order in one run lasting 9 minutes and 30 seconds.

Stimuli were presented using a Linux laptop computer with in-house stimulus delivery software. They were projected using an Epson MP 7200 LCD projector (Epson America, Inc., Long Beach, CA) onto a screen placed at the foot of the MRI scanner bed and were viewed using a mirror mounted on the head coil. Each stimulus presentation lasted 800 milliseconds. Data suggest that a quick glimpse of emotionally relevant stimuli appears sufficient to tune the brain for selective perceptual processing (Schupp *et al.* 2004). Participants were instructed to attend to the pictures. Participants were also asked to rate their mood on a five-point scale using the PA and NA scales (Watson, Clark & Tellegen 1988) at baseline and immediately following each scan.

fMRI acquisition

Imaging was performed using a 3-T General Electric MRI scanner (General Electric, Milwaukee, WI, USA) and 16-channel head coil. In-plane resolution was 3.75×3.75 mm. Functional scans were acquired using a T2*-sensitive echoplanar sequence with a repetition time (TR) of 400 milliseconds, echo time (TE) of 40 milliseconds and flip equal to 30°. We collected five 5.0-mm axial slices with a 1.0-mm gap drawn from the base of the orbitofrontal cortex upward to the level approximately at the base of the mid-corpus callosum, which allowed us to image most of the temporal and ventral frontal lobe as well as the ventral visual stream. Five slices was the maximum number we could collect at a TR of 400 milliseconds, which was chosen because it allowed for selective filtering of noise due to the cardiac cycle (Rio *et al.* 2006). A total of 1430 volumes were collected. Structural scans were acquired using a T1-weighted magnetization-prepared rapid gradient echo sequence (TR, 100 milliseconds; TE, 7 milliseconds; flip, 90°), which facilitated localization and coregistration of functional data.

fMRI analysis

Analyses focused on changes in blood-oxygenation level-dependent (BOLD) signal contrast (hereafter, activation) that occurred as the participants viewed the positive and negative pictures and the beverage cues. Analyses were conducted using Analysis of Functional Neuroimages software (Cox 1996).

Echoplanar image volumes were preprocessed as follows: (1) voxel time series were interpolated to correct for non-simultaneous 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; and (3) we created a mask so that all of the background values outside of the brain were set to zero so that we could calculate the percentage signal change in each voxel.

Statistical maps were generated for each individual separately by linear contrasts of combinations of the four regressors of interest. The four regressors of interest were (1) positive IAPS image with alcohol cue; (2) positive IAPS image with non-alcoholic beverage cue; (3) negative IAPS image with alcohol cue; and (4) negative IAPS image with non-alcoholic beverage cue. Preprocessed time-series data for each individual were then analyzed by multiple regression, which allowed covariation of variables related to head motion and scanning run. The regression model consisted of the four regressors of interest and six regressors of no interest modeling residual motion. 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 representing each of these regressors of interest were spatially normalized by warping to Talairach space and combined into a group map.

We then calculated a statistical map of the differences in activation within groups for each contrast (negative versus positive IAPS image with non-alcoholic beverage cue, negative versus positive IAPS image with alcohol cue, alcohol versus non-alcohol cue with negative IAPS image, and alcohol versus non-alcohol cue with positive IAPS image) by performing voxel-wise *t*-tests of the event-related β coefficients calculated from the general linear model (using inputs of the regression model). We also ran between-subjects *t*-tests to test for differences between alcoholics and controls for each of the four inputs. These single-factor ANOVAs compared normalized event-related β weights. We applied a family-wise error-rate correction (using a Monte Carlo simulation) to rule out false positives resulting from the large number of multiple comparisons inherent in voxel-wise studies. Activated voxels were part of a contiguous cluster of sufficient size (6 voxels, or ≥ 506 mm^3) to obtain a corrected type I error rate of less than 0.05.

Post hoc analysis: Volume of Interest (VOI)

Differences between groups in event-related signal changes in specific regions were characterized with VOI analyses, in which time-series signal data from the same brain coordinates in both groups were analyzed. The three regions we selected were the right amygdala (coordinates:

25, −12, −9), the right parahippocampal gyrus (32, −9, −11) and the right lingual gyrus (22, −77, −3), which are regions that have been implicated in emotional image processing (Vuilleumier 2005). The VOIs were drawn as spheres with a radius of 5 mm. Signal data were extracted from the time series as follows: (1) signal at each voxel was converted to a (percentage) deviation from the mean for that voxel across the entire time series; (2) signal was averaged by stimulus type and spatially translated into Talairach space; and (3) impulse response functions were estimated by generating a 20-TR (or 8.0-second) time course following the presentation of each of the four conditions. We used a repeated-measures MANOVA to examine the effect of the independent variable of group diagnosis (alcoholic or control) on the dependent variable of mean percent signal change in each condition (package JMP-SAS; SAS Institute, Cary, NC, USA).

Anxiety ratings

Alcohol-dependent patients were given the Comprehensive Psychopathological Rating Scale (Svanborg & Asberg 1994) within 5 days of their fMRI scan.

RESULTS

Self-report affect ratings

There were no significant differences in PA between controls and alcoholics before or after the scan. Alcoholics scored higher on NA than controls before the scan (alcoholics: mean = 13, SD = 3.5; controls: mean = 10.09, SD = 0.30; $P = 0.013$) but showed no difference in NA after the scan. Neither group showed a difference in PA or NA between prescan and postscan.

Brain activation analysis

Within-group comparisons

Brain regions that differed significantly between conditions within the alcoholics are depicted in Fig. 2. There were no significant differences between conditions detected in controls (data not shown).

Comparison 1: Negative versus positive IAPS images paired with non-alcoholic beverage cues. This direct linear comparison provided an examination of the response to the positive and negative images in the absence of alcohol cues (i.e. in the presence of non-alcoholic beverage cues). Brain regions that differed significantly are shown in Table 2. Alcoholics showed more activation to negative images than positive images in 10 distinct clusters. The largest clusters were found in the bilateral insula, inferior frontal gyri (IFG), lingual gyri, parahippocampal gyri and
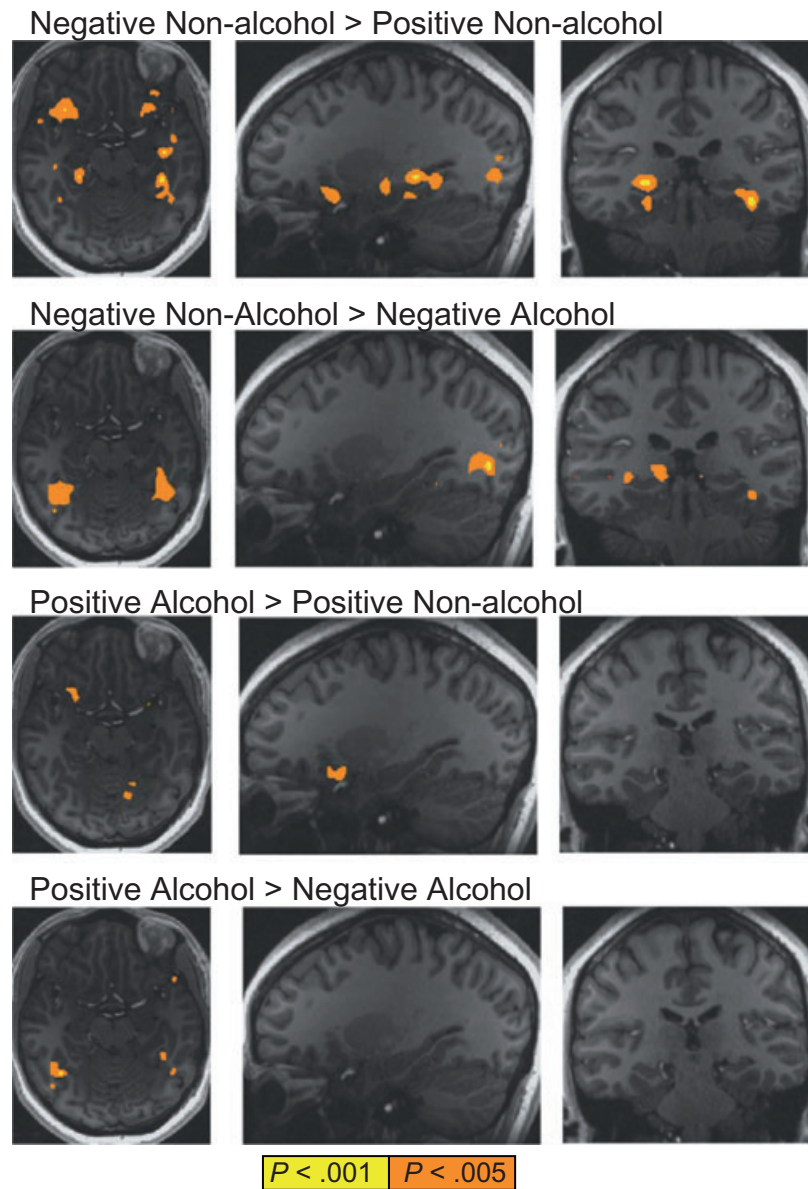
Negative Non-alcohol > Positive Non-alcohol

Negative Non-Alcohol > Negative Alcohol

Positive Alcohol > Positive Non-alcohol

Positive Alcohol > Negative Alcohol

Figure 2 Linear contrasts of regional brain activation in alcoholics. Group statistical maps are superimposed upon a T1 structural image in Talairach space. Clusters ≥ 6 contiguous voxels (*P* < 0.05 corrected) are considered significant. The color scale reflects the *P*-value

$P < .001$ $P < .005$

Table 2 Negative versus positive International Affective Picture System images paired with non-alcohol beverage cues (negative non-alcohol > positive non-alcohol).

Group	Brain region	Talairach coordinates			Activated volume (mm³)	t-score	P (uncorrected)
		x	*y*	*z*			
Alcoholics	Left insula	−41	−23	−8	5231	4.72	< 0.001
	Right inferior frontal gyrus	41	19	−8	4556	4.47	< 0.001
	Left lingual gyrus	−19	−45	−2	3122	5.39	< 0.001
	Right medial temporal gyrus	45	−49	4	2700	5.54	< 0.001
	Right insula	41	−15	−2	2616	3.56	< 0.005
	Right parahippocampal gyrus	23	−34	−2	2194	4.66	< 0.001
	Right lingual gyrus	19	−71	4	2194	4.19	< 0.005
	Left inferior frontal gyrus	−34	23	−8	1856	3.50	< 0.005
	Left parahippocampal gyrus	−38	−34	−14	1688	4.75	< 0.001
	Right thalamus	8	−8	−2	1097	3.83	< 0.005
Controls	No clusters detected						

Table 3 Non-alcohol versus alcohol cues paired with negative International Affective Picture System images (negative non-alcohol > negative alcohol).

Group	Brain region	Talairach coordinates			Activated volume (mm³)	t-score	P (uncorrected)
		x	y	z			
Alcoholics	Left inferior temporal gyrus	−45	−64	−2	4050	5.55	< 0.001
	Right lingual gyrus	23	−75	−2	3712	6.51	< 0.0001
	Left fusiform gyrus	−45	−56	−8	3628	4.35	< 0.005
	Right fusiform gyrus	45	−53	−8	2025	4.33	< 0.005
	Left lingual gyrus	−19	−45	−2	1941	4.17	< 0.005
	Left medial occipital gyrus	−23	−86	4	1856	4.58	< 0.001
	Right medial occipital gyrus	38	−75	4	1688	3.44	< 0.005
	Right thalamus	11	−30	−2	759	3.56	< 0.005
Controls	No clusters detected						

Table 4 Positive versus negative International Affective Picture System images paired with alcohol cues (positive alcohol > negative alcohol).

Group	Brain region	Talairach coordinates			Activated volume (mm³)	t-score	p (uncorrected)
		x	y	z			
Alcoholics	Right middle occipital gyrus	30	−83	−8	1688	4.96	< 0.001
	Left lingual gyrus	−26	−79	−2	1688	4.71	< 0.001
	Right inferior occipital gyrus	34	−71	−2	1603	4.54	< 0.001
	Right fusiform gyrus	38	−53	−14	1519	3.44	< 0.005
	Left parahippocampal gyrus	−38	−38	−8	1181	3.72	< 0.005
	Right inferior temporal gyrus	45	−45	−8	928	3.64	< 0.005
	Right lingual gyrus	11	−79	−2	844	5.20	< 0.001
	Left medial occipital gyrus	−41	−68	−2	759	4.20	< 0.005
Controls	Left medial occipital gyrus	−30	−86	4	1097	3.56	< 0.005

right medial temporal gyrus (MTG). Control subjects did not show increased activation to negative relative to positive images in any region.

Comparison 2: Non-alcoholic versus alcoholic beverage cues paired with negative images. This comparison, shown in Table 3, directly tested how alcohol cues modulated the response to negative images in alcoholics and controls. Alcoholic patients had higher activation to the negative images paired with the non-alcohol cues compared with those paired with alcoholic beverage cues in eight clusters. The largest clusters to show increased activation were in the left inferior temporal gyrus, bilateral lingual gyri, bilateral fusiform gyri and bilateral medial occipital gyri (MOG). Control participants did not show any differences in activation to negative images with the non-alcohol compared with alcohol cues.

Comparison 3: Alcoholic versus non-alcoholic beverage cues paired with positive images. This comparison tested whether the alcohol cues modulated positive emotional processing. Alcoholics showed higher activation to positive images paired with the alcohol cues relative to non-alcohol cues in the bilateral IFG, right culmen and the left parahippocampal gyrus, and decreased activation in the bilateral inferior occipital gyrus (IOG). Control participants showed higher activation to the positive images with alcohol cues relative to non-alcoholic cues in the right parahippocampal gyrus and left superior temporal gyrus.

Comparison 4: Positive versus negative images paired with alcoholic beverage cues. This comparison tested how the alcohol cues themselves affected valence-specific response to positive and negative images. Alcoholics showed higher activation to the positive than to negative IAPS images paired with alcohol cues in eight clusters, shown in Table 4. The largest clusters were found in the bilateral MOG, lingual gyri, IOG, right fusiform gyrus and left parahippocampal gyrus. Controls showed higher activation to positive than to negative images in the left IOG.

Between-group comparisons

Brain regions that differed significantly across conditions between alcoholics and controls are shown in Table 5 and depicted in Fig. 3.

Negative images with non-alcoholic beverage cues. This comparison examined how response to negative images, in the absence of alcohol cues, differed between alcoholics and controls. Alcoholics demonstrated more activation than controls in six clusters. The largest clusters were found in the left hippocampus, bilateral parahippocampal gyri and right lingual gyrus. There were no clusters in which the alcoholics had less activation than controls.

Negative images with alcoholic beverage cues. In this comparison, we examined how alcoholics compared with controls when viewing negative images in the presence of alcohol cues. In contrast to the large differences between alcoholics and controls when their brain responses to negative images with non-alcoholic beverage cues were compared, alcoholics and controls differed much less when the negative images were paired with alcohol cues. Alcoholics showed more activation only in the right MTG. Controls displayed higher activation than alcoholics in the left lingual gyrus and the fusiform gyrus.

Positive image with neutral beverage cue. In this comparison, alcoholics showed less activation than controls in eight clusters, including the right MTG, right IFG, left insula and right hypothalamus. There were no areas where alcoholics had more activation than controls.

Positive image with alcoholic beverage cue. When viewing positive images with alcohol cues, alcoholics showed less activation than controls in the right hippocampus. There were no areas where alcoholics had more activation than controls.

VOI analysis

In each analysis, we ran a repeated-measures MANOVA, using group (control or alcoholic) as a between-subject factor and condition (negative IAPS–alcohol beverage, negative IAPS–neutral beverage, positive IAPS–alcohol beverage and positive IAPS–neutral beverage) as the within-subjects factor.

Right amygdala

We found a significant group effect in the amygdala ($F_{3,23} = 27.08$, $P < 0.0001$). We did not find a significant within-subject effect of condition, indicating that the alcoholics showed an increased response in the amygdala relative to controls in each of the conditions.

Right parahippocampal gyrus

In the right parahippocampal gryus, we found an effect of group ($F_{3,23} = 4.958$, $P = 0.037$) and condition ($F_{3,23} = 3.51$, $P = 0.035$) but no significant interaction. Alcoholics showed an increased response relative to controls, but the groups did not significantly differ across conditions.

Right lingual gyrus

We did not find any significant effects in the lingual gyrus.

Correlation between anxiety and percent signal change in the right parahippocampal gyrus (alcoholic patients only)

In the negative IAPS–non-alcoholic beverage condition, anxiety self-ratings significantly correlated with activation in the right parahippocampal gyrus ($r^2 = 0.44$; $P = 0.02$) (Fig. 4). In the negative alcohol condition, anxiety did not predict signal change. In the positive non-alcohol condition, there was a significant effect of anxiety ($r^2 = 0.51$; $P = 0.01$). Anxiety did not correlate with signal change in the positive alcohol condition. Correlations were not significant in the amygdala or the lingual gyrus.

DISCUSSION

There are three main findings of this study. First, in the absence of the alcohol cues (positive and negative IAPS–neutral beverage conditions), alcoholics showed significantly more activation to negative than to positive images. The greater activation to threatening images was located in the ventral, object-related visual processing stream and in the insular cortex. Alcoholics also showed greater activation than controls to negative images. Second, when the images were presented with the alcohol cues, there was a decrease in the difference in activation between the positive and negative images among the alcoholics, and a decrease in the difference in response to the negative images between controls and alcoholics. The presence of alcohol images reduced the increased activation to negative images among alcoholics in the hippocampus, parahippocampal and lingual gyri, so that the alcoholics' activation was more similar to that of the controls. Third, in the IAPS–neutral beverage conditions, anxiety ratings among the alcoholics predicted activation in the right parahippocampal gyrus, but self-reported anxiety did not predict activation when the alcohol cues were presented with the images.

Table 5 Brain regions that differ significantly between alcoholics and controls in each condition.

| Condition	Comparison	Brain region	Talairach coordinates			Activated volume (mm^3)	t-score	P (uncorrected)
			x	y	z			
Negative non-alcohol	Alcoholics > controls	Left hippocampus	−34	−30	−8	1856	3.84	< 0.001
		Right lingual gyrus	19	−79	−2	1350	3.69	< 0.005
		Left parahippocampal gyrus	−38	−34	−14	759	3.58	< 0.005
		Right thalamus	19	−26	4	675	3.12	< 0.005
		Right lingual gyrus	23	−79	−8	506	3.20	< 0.005
		Right inferior occipital gyrus	34	−79	−2	506	3.43	< 0.005
	Controls > alcoholics	No clusters detected						
Negative alcohol	Alcoholics > controls	Right middle temporal gyrus	64	−34	−8	506	3.41	< 0.005
	Controls > alcoholics	Left lingual gyrus	−8	−75	−2	928	3.54	< 0.005
		Right fusiform gyrus	41	−41	−14	506	3.14	< 0.005
Positive non-alcohol	Alcoholics > controls	No clusters detected						
	Controls > alcoholics	Right medial temporal gyrus	60	−30	−2	1519	3.45	< 0.005
		Right inferior frontal gyrus	30	19	−14	844	3.32	< 0.005
		Left insula	−41	−15	−8	675	3.48	< 0.005
		Right hypothalamus	11	−4	−2	591	3.32	< 0.005
		Left inferior frontal gyrus	−23	15	−14	506	4.25	< 0.001
		Left superior temporal gyrus	−41	0	−14	506	3.37	< 0.005
		Right medial temporal gyrus	53	−38	−2	506	3.22	< 0.005
		Right middle temporal gyrus	8	−11	−8	506	3.26	< 0.005
Positive alcohol	Alcoholics > Controls	No clusters detected						
	Controls > alcoholics	Right hippocampus	26	−26	−14	591	3.32	< 0.005
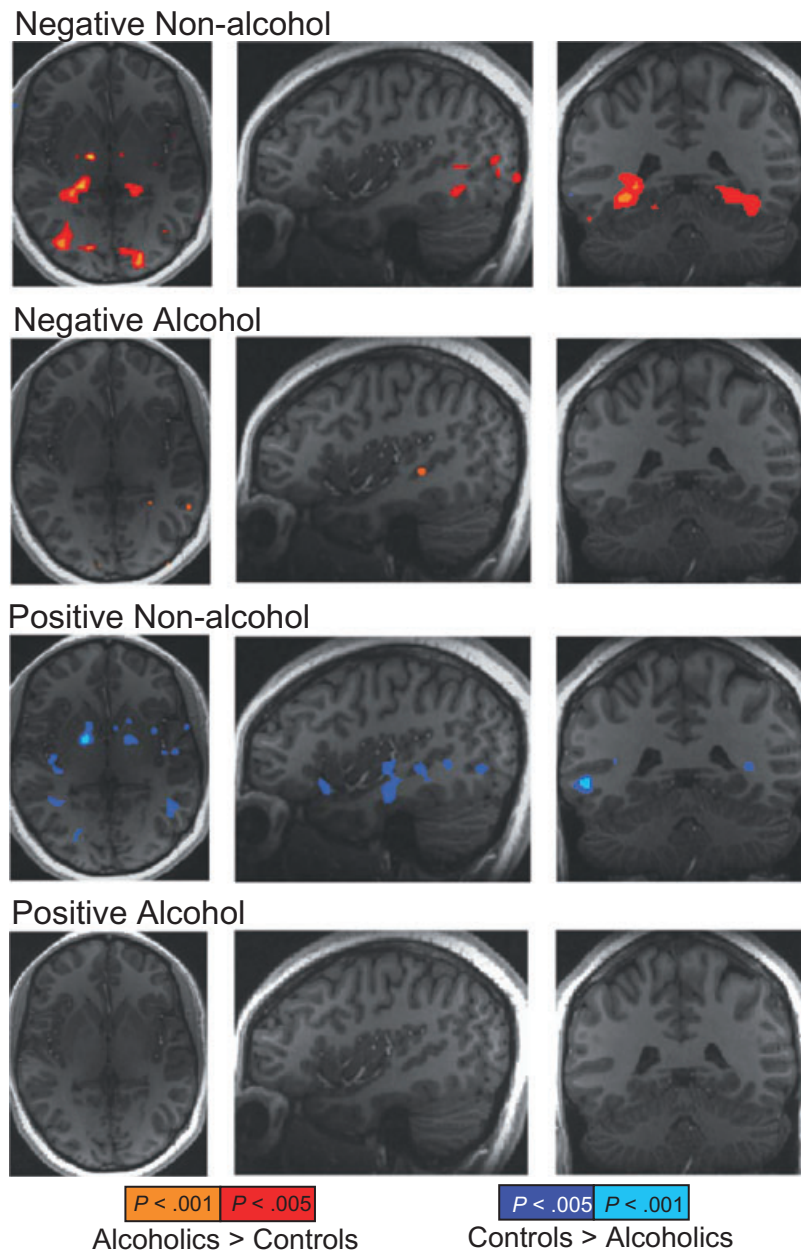
Figure 3 Between-group differences in regional brain activation in response to each condition. Yellow-orange regions indicate more activation in the alcoholics, while blue regions indicate more activation in controls. Group statistical maps are superimposed upon a T1 structural image in Talairach space. For each condition, *t*-tests were conducted between groups. The color scale reflects the *P*-value

Increased activation to negative images in alcoholics

Many studies have shown that visual processing is enhanced by emotion (see Vuilleumier 2005 for review). Imaging studies of healthy controls have shown that both positive and negative emotional images elicit robust activation in both early and late visual processing areas (Lane, Chua & Dolan 1999). We found increased activity in alcoholics to negative images in many cortical regions along the ventral visual stream, including the hippocampus, parahippocampal gyrus, fusiform gyrus and lingual gyrus. Neurons in the amygdala have direct monosynaptic projections to all occipital and temporal levels in the visual system, which suggests that the amygdala can modulate processing at all stages of the visual stream (Amaral, Behniea & Kelly 2003). When we used a VOI approach to examine activation in the amygdala, we found that alcoholics had a higher level of BOLD in amygdala than the non-alcoholics. This suggests that among alcoholics the amygdala is more responsive to meaningful visual images in general, but the increased visual stream activation to negative images suggests that the increased amygdala activity may specifically affect the processing of threatening images. In this study, control participants did not show robust differences between activation to negative and positive images, most likely because of our selection of high-arousal images of each valence.
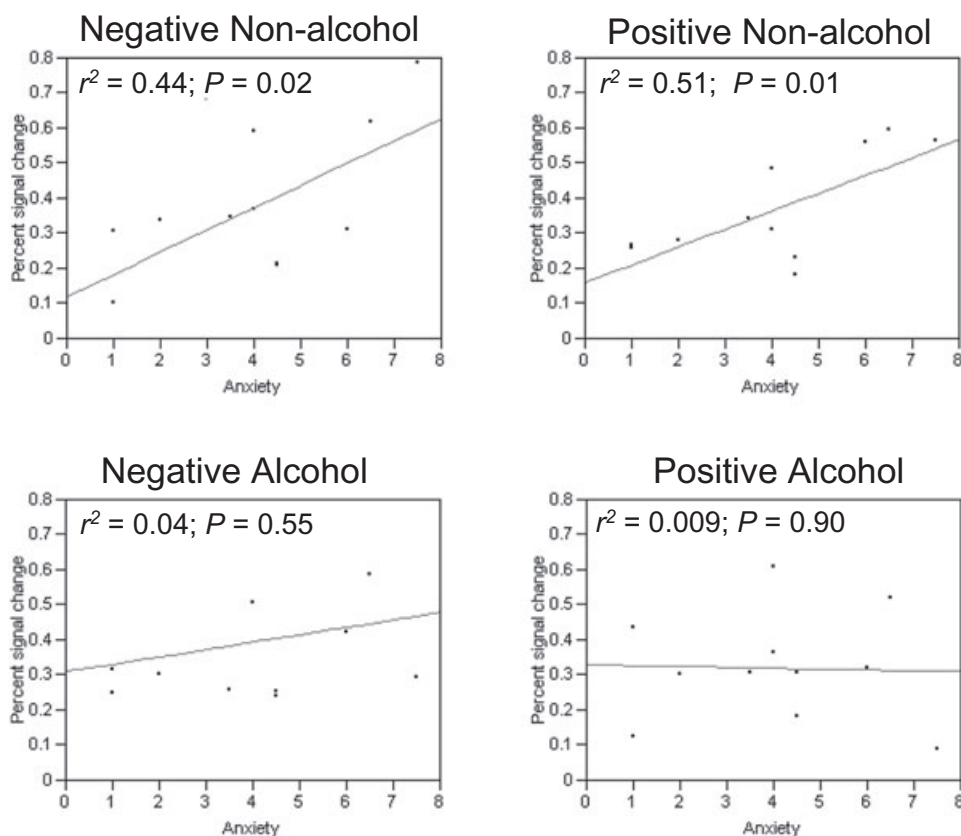
Negative Non-alcohol

$r^2 = 0.44$; $P = 0.02$

Positive Non-alcohol

$r^2 = 0.51$; $P = 0.01$

Negative Alcohol

$r^2 = 0.04$; $P = 0.55$

Positive Alcohol

$r^2 = 0.009$; $P = 0.90$

Figure 4 Positive correlations between percent signal change in the right parahippocampal gyrus and anxiety scores in alcohol-dependent patients. Correlations were significant in the negative non-alcohol ($r^2 = 0.44$; $P = 0.02$) and positive non-alcohol ($r^2 = 0.51$; $P = 0.01$) condition, but not in the negative alcohol ($r^2 = 0.04$; $P = 0.55$) or positive alcohol ($r^2 = 0.009$; $P = 0.90$) condition

Modulation of brain response to emotional images by alcohol cues

The attenuated response to the negative images in the presence of alcohol cues we observed among the alcoholics could be a function of cognitive interference, in which processing of one stimulus impedes simultaneous processing of another stimulus (van den Heuvel *et al.* 2005). Among alcoholics, beverage cues may have become 'attention grabbing' stimuli (Robinson & Berridge 1993) and may have competed with the negative images for limited attentional resources in a way that would not occur among control participants. It is also possible that alcoholics may associate alcohol cues with the positive, rewarding or anxiolytic properties of alcohol, and this could, in part, explain the attenuation of the response to the negative images.

Correlation of activation of the right parahippocampal gyrus with anxiety scores

We found that the alcohol cues modulated brain activity in several areas, but consistently in the parahippocampal gyrus. The parahippocampal gyrus has multiple direct connections with the hippocampus and the amygdala, and many studies implicate this region in the processing of both visual–spatial information (Burgess, Maguire & O'Keefe 2002; Henson 2005; Sommer *et al.* 2005) and intense emotional images (Surguladze *et al.* 2006). The correlation between parahippocampal response to emotional images and anxiety scores suggests that anxious patients may have a greater response to both positive and negative images. Fox *et al.* (2001) demonstrated that highly anxious individuals were unable to rapidly disengage visual attention away from threatening stimuli and it is possible that anxious alcoholics may require a particularly salient competing stimulus, such as an alcohol cue, in order to shift attention.

A limitation of this study is the absence of eye-tracking data that could determine the location of gaze of the participants during the simultaneous presentation of the IAPS image and the beverage cue. We are currently running eye-tracking studies in order to relate cue-based differences in brain activation to concomitant changes in attention allocation. We verified that all participants had a strong visual response in primary visual areas, indicating that their attention was engaged by the stimuli.

In summary, our study is the first to demonstrate a reduction in brain response to negative images in the presence of drug cues among drug users. Because alcoholics report that they use alcohol to blunt the effects of painful, threatening or fearful emotions (Woody *et al.* 1992), our ability to measure this phenomenon in the brain may be of considerable value in the development of medications for the treatment of alcoholism. It should be possible not only to measure anxiolytic actions of putative treatments but also to determine if a treatment can reduce the ability of alcohol cues themselves to blunt the expression of brain states underlying fear.

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