ORIGINAL ARTICLE

Activation of Prefrontal Cortex and Anterior Thalamus in Alcoholic Subjects on Exposure to Alcohol-Specific Cues

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Background: Functional imaging studies have recently demonstrated that specific brain regions become active in cocaine addicts when they are exposed to cocaine stimuli. To test whether there are regional brain activity differences during alcohol cue exposure between alcoholic subjects and social drinkers, we designed a functional magnetic resonance imaging (fMRI) protocol involving alcohol-specific cues.

Methods: Ten non–treatment-seeking adult alcoholic subjects (2 women) (mean [SD] age, 29.9 [9.9] years) as well as 10 healthy social drinking controls of similar age (2 women) (mean [SD] age, 29.4 [8.9] years) were recruited, screened, and scanned. In the 1.5-T magnetic resonance imaging scanner, subjects were serially rated for alcohol craving before and after a sip of alcohol, and after a 9-minute randomized presentation of pictures of alcoholic beverages, control nonalcoholic beverages, and 2 different visual control tasks. During picture presentation, changes in regional brain activity were measured with the blood oxygen level–dependent technique.

Results: Alcoholic subjects, compared with the social drinking subjects, reported higher overall craving ratings for alcohol. After a sip of alcohol, while viewing alcohol cues compared with viewing other beverage cues, only the alcoholic subjects had increased activity in the left dorsolateral prefrontal cortex and the anterior thalamus. The social drinkers exhibited specific activation only while viewing the control beverage pictures.

Conclusions: When exposed to alcohol cues, alcoholic subjects have increased brain activity in the prefrontal cortex and anterior thalamus—brain regions associated with emotion regulation, attention, and appetitive behavior.

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SUBSTANCE-induced stimulation and craving are key features of developing and maintaining an addictive disorder. In those seeking treatment for an addiction, substance-related environmental stimuli and craving are clinically important because of their ability to trigger relapse.[1] Animal models of addiction consistently implicate key brain structures, such as the septum, amygdala, nucleus accumbens, and other regions that are part of the anterior paralimbic system.[2-5] Several recent functional imaging studies in cocaine addicts have shown that these structures as well as the prefrontal cortex are activated by cocaine stimuli.[6,7] There has been little brain imaging work done to date using alcohol, a more commonly abused substance, but one with an even greater burden on public health.[8]

Alcohol, compared with other substances of abuse, has benefits and liabilities with respect to functional brain imaging research.[8] Although with alcohol one can study easily both alcoholic and nonalcoholic control subjects (social drinkers), the degree of self-report of craving for alcohol is generally less than for other substances.[9] We sought to test whether individuals could experience alcohol craving inside the magnetic resonance imaging (MRI) scanner, and if so, whether the amount of craving differed between alcoholic subjects and matched social drinkers. Furthermore, independent of potential differences in self-reported alcohol craving, we wondered whether specific brain regions would be differentially activated in alcoholic subjects while viewing alcohol cues compared with neutral beverage cues, and whether this activation differed in magnitude or location from that in social drinkers. Based on results from animal studies and those reported in cue-induced brain-imaging studies done in cocaine subjects, we hypothesized that alcoholic subjects would have increased

SUBJECTS AND METHODS

SUBJECTS

Eleven non–treatment-seeking alcoholic subjects (3 women) (mean [SD] age, 31.7 [11.2] years) and 13 social drinking controls (5 women) (mean [SD] age, 30.7 [9.4] years) were initially recruited at least 12 days after participation in another alcohol-related study[11] and offered $100 to participate in the fMRI study. The intent was to generate a usable data set of 10 matched pairs. Thus, social drinkers were recruited based on age and gender to match each previously scanned alcoholic subject. One alcoholic subject and 1 social drinker had large movement artifact (>3 mm), and their scans were not used for further analysis. Therefore, from these initial 11 scans, 10 non–treatment-seeking alcoholic subjects had usable data (2 women) (mean [SD] age, 29.9 [9.9] years). These subjects met *DSM-IV*[12] criteria for current alcohol dependence, including criterion 4 (persistent desire or unsuccessful efforts to cut down or control drinking), and drank an average of 7 standard drinks per drinking day. Exclusion criteria included meeting *DSM-IV* criteria for any other substance abuse dependency disorder or any other Axis 1 disorder, and the inability to remain alcohol-free for at least 1 day. Subjects were given a urine drug screen to detect other substances of abuse and were not included if the drug screen was positive. They were recruited through advertisements in the local community (including newspaper, restaurant, and radio advertisements), signed written informed consent approved by the Medical University of South Carolina Institutional Review Board, and were screened using the Structured Clinical Interview for the *DSM-IV*[13] Additionally, 13 age- and sex-matched healthy adults who did not have a substance or alcohol abuse problem were recruited from the same study.[11] Of the fMRI scans from these 13, 10 were deemed both usable (no excessive movement) and matched the alcohol cohort on a pairwise basis (2 women) (mean [SD] age, 29.4 [8.9] years). All subjects were medication-free for a minimum of 12 days before scanning. All subjects underwent a Breathalyzer test on the morning of the study and immediately before the MRI procedure and were not scanned if there was any detection of alcohol or any evidence of alcohol withdrawal.

PROCEDURES

On the day of the MRI scan, subjects were rated using the following instruments: Beck Depression Inventory,[14] Beck Anxiety Inventory,[15] Revised Clinical Institute Withdrawal Assessment Scale for Alcohol,[16] Obsessive-Compulsive Drinking Scale,[17,18] a timeline followback for drinking in the past 90 days,[19] and a 5-item visual analog alcohol craving scale. All scans were performed between 6 and 10 PM.

Alcohol and nonalcohol beverage picture cues were drawn primarily from the Normative Appetitive Picture System (**Figure 1**).[20] To avoid repeating the same stimuli during the scanning sequence, additional similar pictures (27 of the 58 total) were selected from advertisements in several contemporary magazines (eg, *Glamour*, *Cigar Aficionado*) and scanned on a flatbed scanner. Visual control pictures were then created from the alcohol pictures in Adobe Photoshop (Adobe Systems Inc, San Jose, Calif) by various distortion effects (eg, blurring, smoothing), resulting in pictures that matched the alcohol cues in color and hue but lacked any object recognition. A 9-minute script for stimulus presentation was created in Superlab 1.68 (Cedrus Corp, San Pedro, Calif) on a Power Macintosh computer consisting of six 90-second epochs. Each epoch contained three 24-second blocks: 1 block each of alcohol (ALC), nonalcohol beverage (BEV), and visual control pictures (VIS) and one 18-second rest (REST) (cross-hair). Each 24-second block consisted of 5 individual pictures, each displayed for approximately 4.8 seconds. The 6 ALC blocks were each specific to a beverage type (beer, wine, or liquor), with 2 blocks per type. To control for time and order effects, the order of the individual pictures, the blocks within the epoch, and the epochs were all randomized. In addition, a 10-minute relaxation script was created, consisting of 20 scenic pictures drawn from the International Affective Picture System,[21] each displayed for 30 seconds. These pictures were displayed during MRI scanning setup, tuning sequences and structural scan before the actual functional imaging study. The computer was connected to an MRI-compatible nonferromagnetic projector, which displayed the pictures on an MRI-compatible translucent screen placed at their feet on the scanner gantry. Subjects wore prism glasses, which enabled them to view the screen while supine and in the MRI scanner.

On the evening of the scan, subjects completed self-assessment questionnaires (Beck Depression Inventory and Beck Anxiety Inventory) and were escorted into the MRI suite. They were fitted with prism glasses and a small plastic tube was placed in the corner of their mouth (for giving a sip of the subject's alcoholic beverage of choice as a taste cue but producing negligible blood alcohol levels) in a procedure similar to that used by Modell and Mountz.[10] After subjects were positioned in the scanner, they were checked to ensure that they could view the cues. During initial scanner tuning and structural scanning, subjects were shown the relaxation pictures. For the fMRI sequence, subjects were initially rated while in the magnet for alcohol

activation in prefrontal cortex and anterior paralimbic structures during alcohol-specific cue presentations. To test this hypothesis, we used functional MRI (fMRI) to image neural activity during alcohol cue presentation in non–treatment-seeking alcoholic subjects and a control sample of social drinkers. Immediately before subjects viewed the images, they were given a sip of alcohol to maximize the interest in alcohol cues, following on the study cited by Modell and Mountz,[10] who used this same method.

RESULTS

CRAVING INDEXES

The average self-reported urge to drink alcoholic beverages on a 0 to 100 visual analog scale is shown for each group before and after the sip of alcohol, during the picture viewing (rated retrospectively), and then at the completion of the 9-minute study (**Figure 2**). At all time points, alcoholic subjects had a higher self-report of urge

craving and anxiety level using visual analog scales, and were then given a sip of their preferred beverage and rated again. They were then shown 9 minutes of alternating visual cues concurrent with blood oxygen level–dependent image acquisition (Figure 1). Subjects were retrospectively rated for their beverage craving during the different stimuli (alcohol and nonalcohol beverage), and were taken out of the scanner. A Breathalyzer test was performed and they were given instructional material about the hazards of drinking, which they read during a 1-hour waiting period after the completion of the scan. They were then allowed to leave.

MRI IMAGE ACQUISITION

Subjects wore earplugs and head movement was restricted using inflatable cushions. Magnetic resonance imaging scans were performed in a Picker Edge 1.5-T MRI scanner (Marconi, Cleveland, Ohio) with actively shielded magnet and high-performance whole-body gradients. An initial high-resolution, 142-slice, 1-mm-thick, sagittal T1-weighted scan was acquired for later volumetric and coregistration analysis and to ensure that there were no large infarctions or tumors. A structural scan was then taken consisting of 15 coplanar coronal slices (5-mm-thick/2-mm gap) centered around the septum as determined on a sagittal scout image. After more tuning, the cue-induction paradigm was performed while also acquiring blood oxygen level–dependent-weighted coronal scans in the exact plane as before using a gradient echo, echo-planar fMRI sequence (flip angle, 90°; echo time, 40 milliseconds; repetition time, 3000 milliseconds; field of view, 27.0 cm; fifteen 5-mm-thick slices; and gap, 2.0 mm, with frequency selective fat suppression).

DATA ANALYSIS

Subject demographics (**Table 1**) and clinical rating scales were compared between groups using analysis of variance with post hoc *t* tests. Craving ratings during the fMRI procedure were analyzed using mixed-design analysis of variance, with group as the between-subjects factor and time as the repeated measure. Magnetic resonance imaging scans were transferred into ANALYZE format and then further processed on Sun workstations (Sun Microsystems, Palo Alto, Calif). Scans were checked using MEDx 3.0 (Sensor Systems Inc, Sterling, Va) for movement across runs, and then were coregistered to a mean image using automatic image registration.[22] For all subjects, movement across the 9-minute study was less than 3 mm in all 3 axes.

Functional images were analyzed using 2 separate techniques—a within-subject technique that involved no spatial distortion, and a group analysis involving transformation into a common brain atlas. Both methods produced similar results, with alcoholic subjects activating more brain regions during presentation of the alcohol cues. Only the spatially transformed group analysis results are described.

Scans were checked using MEDx for movement across runs, and were then motion corrected for movement if greater than 2 mm but less than 3 mm. Scans with less than 2-mm movement were not corrected for motion. There were 2 subjects (1 alcoholic subject and 1 social drinker) with greater than 4-mm movement in the initial 24 studies who were not included for final data analysis. Two alcoholic subjects required motion correction for movement of approximately 2.5 mm, which was corrected to a maximum movement of approximately 1.5 mm.[22] We then only used a subject's coregistered data for data analysis if it showed less than 2-mm movement in all planes after coregistration. After corrections for motion, we spatially transformed each subject's scans into the Talairach Atlas and performed within-individual analyses as well as averaging brain activity at each time point by group and performing within-group and between-group comparisons of brain activity across conditions.

Using the Statistical Parametric Mapping 99 module[23] in MEDx 3.0, we transformed and spatially normalized,[23] and transformed (input voxel dimensions, $2.1 \times 2.1 \times 7$ mm, to output voxel dimensions, $3 \times 3 \times 3$ mm) and smoothed (6×3 mm) the data. We next intensity-masked (40%) and intensity-normalized each person's data. At this stage, we performed a within-subject analysis of each person's brain activity while viewing the different cues. To test for group differences (alcoholic subjects and social drinkers) across the tasks, we generated a mean group image of brain activity at each time point. Thus, using the Tool Command Language scripting capabilities within MEDx 3.0, we averaged (for alcoholic subjects and social drinkers separately) all subjects' functional data to generate group data at each of the 180 time points.

Using Statistical Parametric Mapping statistics in MEDx 3.0 on the group data, we then performed a cluster analysis (2-tailed *z* map threshold of $P<.01$, and spatial extent threshold of $P<.05$) to find brain regions where the group showed statistically more blood oxygen level–dependent-fMRI signal during the alcohol cue condition than during the control beverage cues.[24] We assumed an uncorrected F threshold UFp>.99 to preserve as many voxels as possible for the cluster analysis. Only clusters showing a statistical weight (spatial extent threshold) of $P<.05$ were considered to be significantly activated. We used a delayed boxcar model, employed a high-pass filter to remove signal drift, cardiac and respiratory effects, and other low-frequency artifacts, and temporally smoothed the data.

to drink alcohol (craving) ($F_{1,18}=10.20$, $P=.005$) than social drinkers. In addition, craving ratings for the entire sample tended to show a modest, yet significant, increase over the course of the cue-induction procedures ($F_{3,54}=3.18$, $P=.03$)

BRAIN ACTIVITY ANALYSIS

Brain regions that significantly differed across conditions within each group are listed in **Table 2** and are depicted in **Figure 3**. We discuss them here in ascending order of specificity for addressing the issue of differential specific brain activation between alcoholic subjects and social drinkers.

GENERAL NONSPECIFIC ACTIVATION

As would be expected, both groups showed areas of significant increases while viewing the visual control images (complex color shapes) compared with the rest

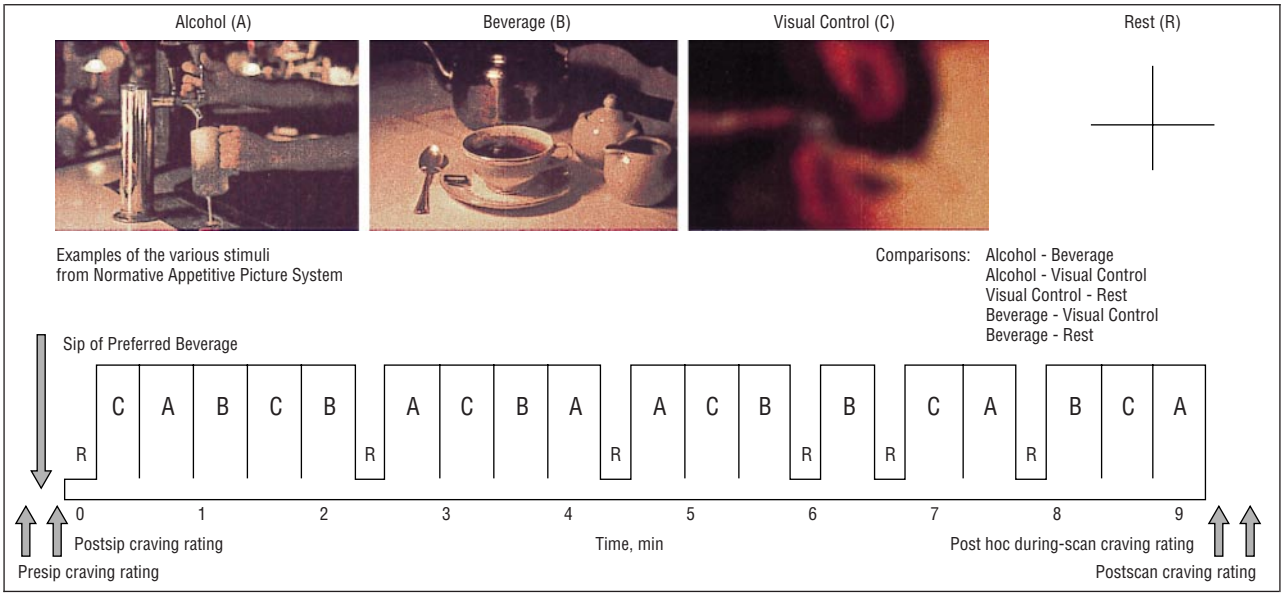

Figure 1. *Representative stimuli and a diagram of the functional magnetic resonance imaging alcohol-induction paradigm.*

Table 1. Subject Demographics*

	Alcoholic Subjects Mean (SD)†	Social Drinkers, Mean (SD)†
Sex, No.		
Female	2	2
Male	8	8
Age, y	29.9 (9.9)	29.4 (8.9)
Alcohol Dependence Scale‡§	11.6 (5.8)	1.4 (1.9)
Days since last drink	3.4 (2.2)	6.8 (9.2)
Standard drinks/drinking day‖¶	7.4 (3.9)	2.0 (1.2)
Drinking days, %‖	73.1 (19.6)	15.2 (12.4)
CIWA-Ar#	1.8 (2.0)	0.6 (0.7)
Beck Anxiety Inventory	2.4 (3.7)	0.9 (1.4)
Beck Depression Inventory‡	4.1 (4.7)	0.8 (0.8)
OCDS‖**	11.1 (5.1)	2.0 (1.9)

**CIWA-Ar indicates Revised Clinical Institute Withdrawal Assessment Scale; OCDS, Obsessive-Compulsive Drinking Scale.*
†Unless otherwise indicated.
‡P<.005.
§A score of 10 to 20 is considered mild to moderate alcohol dependence.
‖P<.001.
¶A standard drink is considered 1.5 oz of 80 proof, 12 oz of beer, or 4 oz of wine.
#Significant alcohol withdrawal is rated as 10 or greater.[13]
***Alcoholic subjects usually score 7 or greater.[14,15]*

(crosshair) images—largely in the anterior temporal and prefrontal cortex. The amount of voxels (655 for alcoholic subjects and 685 for social drinkers) that met the significance threshold was similar across the 2 groups. (Note that we did not acquire blood-flow data from the primary or secondary visual cortex.)

COMPARISONS OF BEVERAGE CUES WITH THE CROSSHAIR "RESTING" CONTROL

The alcohol group had no significant increases when viewing the nonalcohol beverage cues compared with the resting crosshair control. In contrast, the social drinkers had significant increases in 3 clusters—the cerebellum, the medial temporal cortex, and the prefrontal cortex.

Both groups displayed increases in brain activity when viewing the alcohol cues compared with the resting control images. Alcoholic subjects had increased activity in the anterior thalamus and bilateral prefrontal cortex. The control subjects showed increased activity in the medial temporal lobes and the right prefrontal cortex.

COMPARISONS OF BEVERAGE CUES WITH THE NONOBJECT VISUAL CONTROLS

These comparisons control for differences in color, pitch, and hue, and theoretically, the only thing that differs across this comparison are the identifiable objects (eg, beer mugs, coffee cups). Neither group had significant activations in the alcohol cues minus visual control comparison. There were no areas of significantly increased activity in the alcoholic subjects when comparing brain activity while viewing beverage cues compared with while viewing the visual controls. In contrast, the social drinkers had increased activity in the left prefrontal cortex with this comparison.

DIRECT COMPARISON OF ACTIVITY DURING ALCOHOL BEVERAGE CUES MINUS NONALCOHOL BEVERAGE CUES

This comparison is the most important and directly tests the study hypothesis. It directly compares the summation of all potential brain activity generated by the neutral (control) beverage cues and subtracts this from all the potential brain activity generated by the alcohol beverage cues. Theoretically, the brain regional activity remaining should be specifically related to the alcohol-specific content of the pictures.

There was no increased activity in this comparison in the social drinkers. In contrast, the alcohol group had increased activity in the thalamus and the prefrontal cortex.

COMMENT

To our knowledge, this is the first report to use fMRI to investigate the brain regions associated with visual cues for alcohol. The results demonstrate that it is possible to combine fMRI and short time domains (24 seconds) to evaluate alcohol cue-induced brain activity in both alcoholic subjects and social drinkers. The brain regions that are activated by alcoholic subjects while viewing alcohol cues are in the anterior paralimbic system (thalamus) or cortical regions that are known to connect with this system. This anterior paralimbic cortex has long been associated with regulating appetitive behavior and emotion. These findings are likely important in understanding the neural aspects of craving and alcohol addiction. However, this initial study suffers from several limitations that bear on the interpretation of results.

In this study, we had a relatively small sample size of mildly dependent non–treatment-seeking alcoholic subjects. Although we employed conservative approaches in the data analysis, and performed 2 distinct sets of data analysis, which generated convergent results (only the second analysis results are presented here), this study needs replication with larger samples.

The regions activated in this study should not be interpreted as correlates of craving per se, but rather as brain areas that activate in alcoholic subjects during alcohol cue presentation. Thus, these results should not necessarily be construed as implying that these regions are causing, or mediating (enhancing or diminishing) craving. Directly proving that these regions (prefrontal cortex and anterior thalamus) actually mediate craving could be approached in several ways. One could more closely temporally link variations in subjective craving with specific regional activity changes. For example, in ongoing work, we are measuring subjective craving in real time during fMRI scanning and cue presentation, and plan to perform analyses directly investigating changes in regional brain activity that temporally correlate with subjective craving for alcohol. Alternatively, one could modify regional brain activity, either pharmacologically (eg, naltrexone) or with a physical intervention (eg, transcranial magnetic stimulation), and see if this directly changes both regional brain activity and craving.

Because our blood oxygen level–dependent fMRI method repeatedly switched from control to task, we employed 1 standard set of visual cues and did not tailor the specific cues to each individual as has been done in some other craving and imaging studies. Individualized cues may increase the degree of craving, while sacrificing the generalizability of the task and control. While the majority of the visual alcohol cues used in this study have been standardized and tested in the Normative Appetitive Picture System,[20] to our knowledge they have not been used previously in alcoholic subjects during functional brain imaging. Interestingly, while using taste stimulation alone, Modell and Mountz[10] reported increased blood flow (by single-photon emission computed tomography imaging) in the basal ganglia, which correlated with the level of craving.[10] Whether taste cues and visual cues of alcohol differentially stimulate different brain regions is open to further study. Our goal in this initial study was to maximally stimulate with several alcohol cues (taste and visual) to enhance our chances of detecting a brain activation effect. Our choice of control tasks (neutral beverages) was designed to mimic all visual aspects of the alcohol-specific cues. While alcohol beverage cues induced an urge to drink (craving) in some subjects, all alcoholic subjects started from a higher baseline of craving, which may have provided a "ceiling effect" on craving stimulation. Interestingly, some social drinking subjects reported craving for the nonalcoholic beverage pictures.

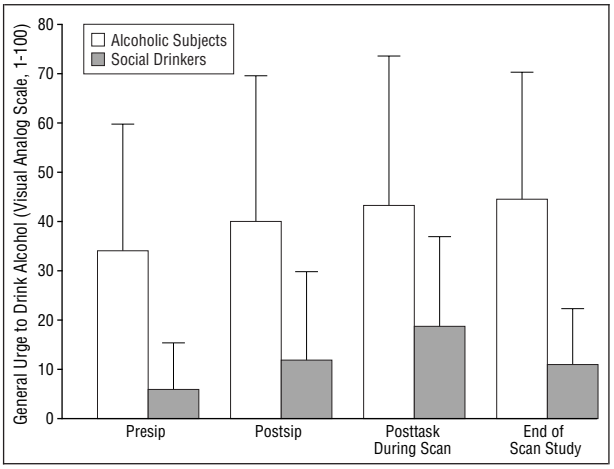

Figure 2. *Mean craving ratings and SEM before, during, and after scanning.*

One might argue that the differences seen in this study might represent, simply, directed attention. Although the cingulate and dorsolateral prefrontal cortex are involved in selective attention, no studies of selective attention have found anterior paralimbic activation.[9,25,26] Nevertheless, future studies employing this paradigm along with a control study of selective attention would help differentiate the regions activated in this study from those commonly seen in mere selective attention. It would nevertheless continue to be significant that specific brain regions are involved in the enhanced "selected attention" for alcohol found in alcohol-dependent individuals. Cue-based research in addiction focuses on the evaluation of stimulus-generated physiological and psychological effects that may initiate a drinking bout or cause relapse. The "selected attention" paid to alcohol cues by alcoholic subjects may be the basis for the maintenance of alcohol dependence or the triggering of a relapse drinking episode.[1]

Finally, we only imaged the anterior third of the brain and do not have data about changes in the visual cortex, which might be useful in interpreting some of the control tasks. While confining the brain regions under investigation helps to reduce the chance of a type II error, we cannot make statements about changes in brain regions where we did not scan.

Some subjects had recently (within the last month) participated in a clinical laboratory study testing opiate antagonist effects on alcohol intake (8 days of ingestion). Regardless of whether they had received active or placebo medication in that short trial, many alcohol subjects were drinking and craving less at the time of the

Table 2. Brain Regions Activated by Group and by Condition*

Regions†	*P*	No. of Voxels in Cluster	Cluster *z* Score	*x, y, z* Talairach Coordinates
Alcohol-Beverage				
Alcoholic subjects				
Anterior thalamus	*.02*	*167*	*5.3*	*0, –6, 3*
Left midfrontal gyrus‡	.07	134	3.98	–57, 21, 30
Social drinkers				
Alcohol-Visual				
Alcoholic subjects				
Social drinkers				
Beverage-Visual				
Alcoholic subjects				
Social drinkers				
Left midfrontal gyrus‡	.08	89	5.01	–24, 36, 36
Alcohol-Rest				
Alcoholic subjects				
Anterior thalamus	*.002*	*439*	*6.28*	*0, –6, 3*
Left midfrontal gyrus‡	*.02*	*200*	*4.74*	*–63, –3, 24*
Right midfrontal gyrus‡	.10	116	4.08	48, –3, 42
Social drinkers				
Left inferomedial temporal lobe§	*.003*	*262*	*6.43*	*–33, –27, –27*
Right inferomedial temporal lobe§	*.004*	*246*	*5.37*	*33, –30, –24*
Right prefrontal cortex‖	.13	79	3.88	48, 6, 33
Right orbitofrontal cortex¶	.12	80	3.77	45, 33, –18
Beverage-Rest				
Alcoholic subjects				
Social drinkers				
Right cerebellum	*.02*	*116*	*5.65*	*33, –30, –27*
Left temporal lobe	*.006*	*220*	*5.59*	*–33, –27, –27*
Right prefrontal lobe		*420*	*4.59*	*54, 21, 21*
Visual-Rest				
Alcoholic subjects				
Left prefrontal lobe	*.003*	*354*	*4.43*	*–45, 3, 33*
Right prefrontal lobe	*.03*	*188*	*4.2*	*36, 30, –18*
Left prefrontal lobe	.11	113	3.77	–3, 57, –12
Social drinkers				
Left temporal lobe	*.006*	*83*	*6.18*	*–33, –27, –27*
Left prefrontal lobe	*.02*	*159*	*4.93*	*–30, 39, –15*
Left temporal lobe	.09	88	4.41	–45, –9, –24
Right prefrontal lobe	.06	102	4.24	63, –6, 30
Left prefrontal lobe	.01	174	4.01	–42, 21, 21
Right frontal lobe	.13	79	3.7	24, –12, 36

**All regions shown meet overall cluster significance of extent of* $P<.05$ *(corrected for multiple comparisons). Clusters shown in italics also have a height value of* $P<.05$.

†*As reported by Alan Evans, PhD, McConnell Brain Imaging Centre, Montreal Neurological Institute, Montreal, Quebec.*

‡*Indicates the dorsolateral prefrontal cortex, Brodmann area 9.*

§*Indicates Brodmann areas 20 or 28.*

‖*Indicates Brodmann areas 4 or 9.*

¶*Indicates Brodmann area 11.*

fMRI procedure than in their natural prestudy state.[11] While no medication had been ingested for at least 12 days before the scan, the participation in this prior trial might have masked even more stark differences in cue-induced regional brain activity between the alcoholic subjects and social drinkers.

This study has several important findings. It seems that the confining nature of the MRI scanner and the loud noises did not prevent us from performing alcohol cue stimulation. With both forms of image data analysis, alcoholic subjects had much more brain activation than social drinkers when exposed to alcohol-specific cues. Furthermore, the specific regions activated during alcohol-specific cues in alcoholic subjects are the prefrontal cortex and the anterior thalamus. Although the exact definition of *craving* is hotly disputed, it likely involves appetite drives and emotional changes like arousal. In this light, the brain regions activated by alcoholic subjects during alcohol cue stimulation may participate in these behaviors.

Differences in the regions activated in the current study and those reported in cocaine abusers may be caused by several important variables. These variables may be related to the abused substance, the stimulation paradigm, or the scanning methods. Despite these differences, the current study results overlap with previous im-

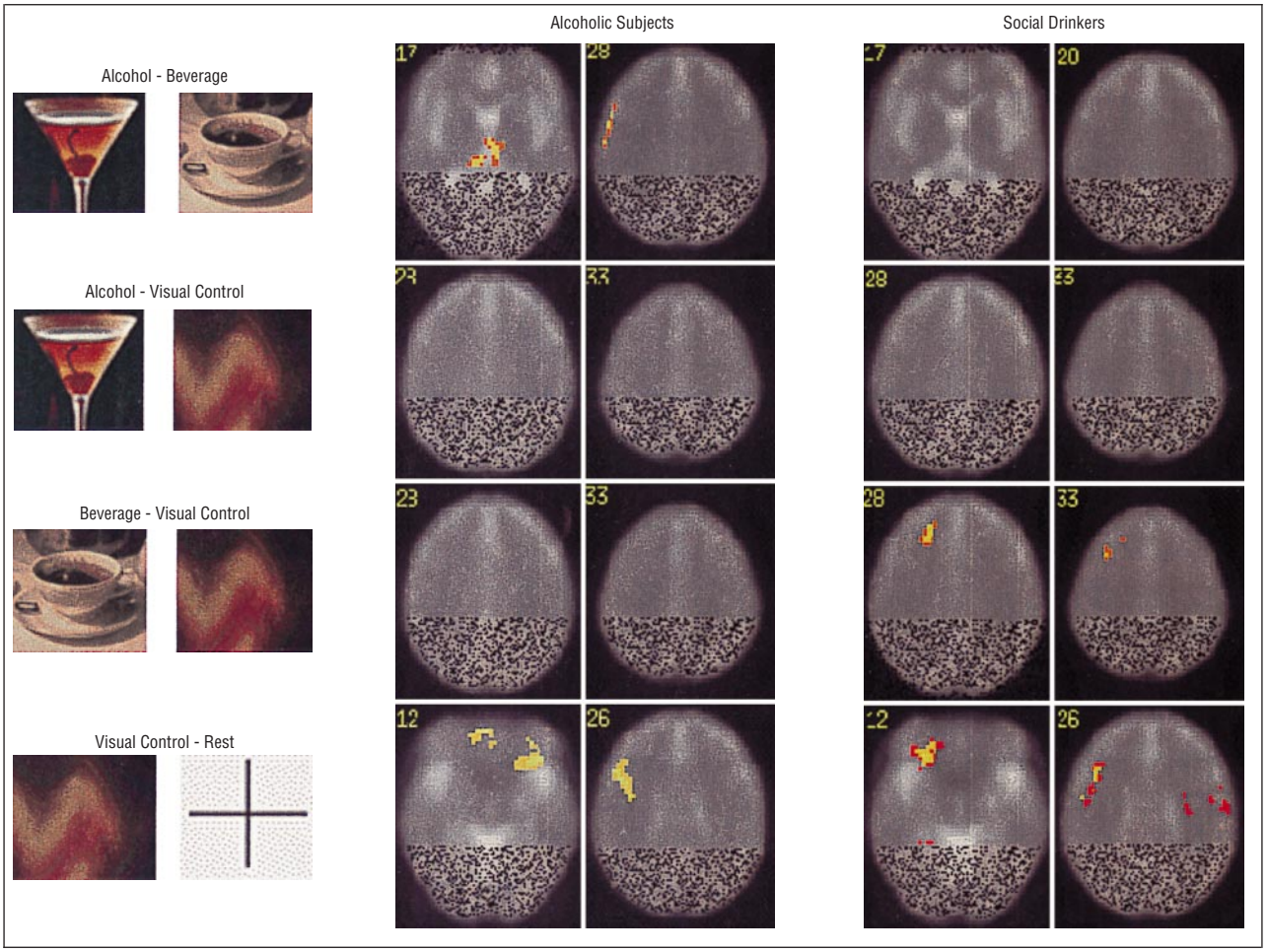

Figure 3. *Within-group Standard Parametric Mapping data by contrast. Brain regions that are significantly increased in one task compared with another are depicted in color for each group (alcoholic subjects [left] and social drinkers [right]) on representative transverse structural magnetic resonance imaging scans. Posterior brain regions that were not imaged and for which there are no dates are shaded in black. The threshold for determining significance is an extent cluster threshold of* $P<.05$. *The top row shows brain regions significantly increased while viewing alcohol cues compared with the beverage cues at the level of the anterior commisure (AC) (left image, 17; and 30 mm above the AC line, 28). The next 2 rows depict brain activity while viewing the alcohol or beverage cues compared with the visual control at 30 and 36 mm above the AC–posterior commisure (AC-PC) line. Note that only the social drinkers have significant increases in activity in the nonalcohol beverage contrast. The bottom row shows significant brain activity by group in the contrast of looking at the nonobject visual control compared with a "rest" task of viewing a cross. Note that both groups have increased activity across this comparison both 12 mm below and 28 mm above the AC-PC line. These results in the bottom row suggest that the group differences seen in the other contrasts are not a function of the failure of either group in general to activate the brain.*

aging studies in cocaine users, which used scripted cue-induced craving in cocaine subjects. For instance, Grant and colleagues,[6] using visual presentations that are similar in design to the current study, found increased activation of the dorsolateral prefrontal cortex in cocaine subjects while viewing cocaine stimuli. Childress and colleagues[7] examined brain activity in 14 detoxified cocaine users and 6 healthy controls during presentation of cocaine-related videos. There was increased activation in the anterior cingulate and amygdala during the cocaine cues in the cocaine users but no differential activation of the dorsolateral prefrontal cortex, thalamus, cerebellum and visual cortex between cocaine users and controls. Maas and colleagues[27] used fMRI to measure brain activity in 6 subjects with a history of crack cocaine use and 6 matched controls. The cocaine-using group had significantly increased activity in the anterior cingulate and left dorsolateral prefrontal cortex while viewing drug-related scenes.

Only more alcohol cue-induced brain imaging studies in alcoholic subjects will provide data to address the sensitivity and specificity of brain regional activation.

This study suggests that changes in brain activity caused by tasting alcohol and viewing alcohol cues can be measured by an fMRI procedure. Alcoholic subjects, compared with social drinking controls, report higher rates of craving at baseline, after a taste of alcohol and while viewing alcohol-related cues. During alcohol cue presentations, alcoholic subjects have specific activation in the anterior thalamus and the prefrontal cortex. Future work is warranted to determine if this paradigm might be useful to better understand the pathophysiology of craving and addiction, to evaluate potential anticraving medications, or to predict relapse.

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