

# Neural Response to Alcohol Stimuli in Adolescents With Alcohol Use Disorder

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**Background:** Cue reactivity studies in alcohol-dependent adults have shown atypical physiological, cognitive, and neural responses to alcohol-related stimuli that differ from the responses of light drinkers. Cue reactivity and its neural substrates are unclear in youth. We hypothesized that teens with alcohol use disorder would show greater brain response than nonabusing teens to alcohol images relative to neutral beverage images in limbic and frontal brain regions.

**Methods:** We tested the hypotheses in a cross-sectional functional magnetic resonance imaging study. Adolescents aged 14 to 17 were recruited from local high schools. Teens with alcohol use disorders (n=15) and demographically similar infrequent drinkers (n=15) met strict exclusion criteria (no left-handedness or neurological, other psychiatric, or other substance use disorders). Diagnoses were determined by means of structured and semistructured clinical interviews. Subjects were shown pictures of alcoholic and nonalcoholic beverage advertisements during blood oxygen level-dependent functional magnetic resonance imaging. Self-

reports of craving were obtained before and after cue exposure.

**Results:** Teens with alcohol use disorders showed substantially greater brain activation to alcoholic beverage pictures than control youths, predominantly in the left anterior, limbic, and visual system areas ( $P < .05$ ; cluster threshold, 515  $\mu$ L). The degree of brain response to the alcohol pictures was highest in youths who consumed more drinks per month and reported greater desires to drink.

**Conclusions:** These results confirm previous studies by demonstrating an association between the urge to drink alcohol and blood oxygen use in areas of the brain previously linked to reward, desire, positive affect, and episodic recall. This study extends this relationship to adolescents with relatively brief drinking histories using visual alcohol stimuli, and suggests a neural basis for response to alcohol advertisements in youths with drinking problems.

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**D**RUG CRAVING is often described as the subjective experience of an intense desire for an addictive substance.<sup>1,2</sup> It may occupy cognitive resources and influence substance use decisions,<sup>3</sup> but it is difficult to measure objectively. Cue reactivity is an observable correlate of craving<sup>4</sup> that has been demonstrated in alcohol-dependent adults<sup>5-7</sup> through physiological changes such as increased heart rate or salivation on exposure to alcohol-related words, pictures, scents, tactile cues, or imaginal stimuli.<sup>6,8,9</sup> Alcohol-dependent adults show difficulty shifting attention away from alcohol-related stimuli,<sup>10</sup> and, consequently, substance cues can interfere with the deployment of effective coping responses.<sup>11,12</sup> Although cue reactivity has not been studied in adolescents, substance-dependent youths

show difficulty implementing coping skills when substance cues are salient.<sup>13</sup>

Knowledge about the neural systems subserving cue reactivity and craving has expanded recently.<sup>14</sup> Alcohol-dependent adults given small amounts of alcohol showed increased blood flow in the right caudate nucleus that was positively correlated with self-reports of alcohol craving.<sup>15</sup> Left prefrontal<sup>16-19</sup> and bilateral orbitofrontal cortices<sup>17,20-24</sup> have commonly activated in response to substance cues among adults. Some studies have reported bilateral activation changes in the amygdala,<sup>16,17,21,22</sup> but more have shown a left and bilateral anterior cingulate response that correlates with craving.<sup>16-18,20-22,25</sup> The reward-related nucleus accumbens appears responsive to substance cues and is related to craving reports, bilaterally<sup>16,25</sup> and on the left,<sup>20</sup> although some studies could not precisely localize this small region. In the first functional

**Table 1. Characteristics of Adolescent Participants\***

	AUD Group (n = 15)	Controls (n = 15)	P Value
Female, No. (%)	6 (40)	6 (40)	>.99
Age	16.96 (0.78)	16.35 (1.02)	.08
School grades completed	10.27 (0.96)	9.73 (0.80)	.11
WISC-III Vocabulary scaled score	12.53 (2.85)	12.93 (2.28)	.68
Parent annual salary, ×\$1000	101.93 (67.26)	71.33 (29.21)	.12
White, No. (%)	14 (93)	11 (73)	.14
Family history negative, No. (%)†	6 (40)	6 (40)	>.99
CBCL externalizing T score	44.78 (4.77)	45.08 (7.65)	.91
CBCL internalizing T score	44.19 (5.49)	42.68 (4.11)	.43
Beck Depression Inventory total score	5.29 (5.11)	2.20 (2.83)	.06
Spielberger State Anxiety T score‡	45.84 (8.67)	37.24 (4.51)	.002
Sleepiness before scanning§	3.00 (1.20)	2.67 (1.40)	.49
Sleepiness after scanning§	3.87 (1.41)	3.67 (1.35)	.69
No. of drinks per month	49.80 (28.54)	0.73 (2.05)	<.001
Alcohol abuse/dependence symptoms, past 3 months	2.53 (1.36)	0.00 (0.00)	<.001
Alcohol withdrawal symptoms, past 3 months	2.47 (1.64)	0.00 (0.00)	<.001
DAQ reinforcement score	2.48 (1.06)	0.86 (0.10)	<.001
DAQ strong desire score	1.28 (0.35)	0.81 (0.00)	<.001
DAQ mild desire score	2.55 (0.77)	0.73 (0.09)	<.001

Abbreviations: AUD, alcohol use disorder; CBCL, Child Behavior Checklist; DAQ, Desires for Alcohol Questionnaire; WISC-III, Wechsler Intelligence Scale for Children-III.

\*Unless otherwise indicated, data are expressed as mean (SD).

†Indicates no first- or second-degree biological relative with alcohol or other drug abuse or dependence.

‡Normed to high school sample for each sex.

§Scoring is described in the "State Measures" subsection of the "Methods" section.

magnetic resonance imaging (fMRI) study of pictorial alcohol cues, George and colleagues<sup>19</sup> reported a thalamic and left prefrontal response to alcoholic relative to nonalcoholic beverage pictures (hereafter referred to as alcohol and nonalcohol pictures, respectively) among alcohol-dependent adults compared with matched control subjects. Our group previously studied brain responses of women aged 18 to 25 years to alcohol- and nonalcohol-related words.<sup>26</sup> Alcohol-dependent young women demonstrated significantly more blood oxygen level-dependent (BOLD) response than controls during alcohol word presentation relative to neutral words in the anterior cingulate, left prefrontal cortex, bilateral insular gyri, and subcallosal cortex, which houses the nucleus accumbens. However, group differences were relatively modest.<sup>26</sup>

To summarize, a sizable literature reports that adults with substance use disorders demonstrate atypical reactions to stimuli that have been conditioned to addictive substances.<sup>27</sup> However, the brain regions reported to subservise cue reactivity have been somewhat inconsistent, due in part to differing imaging techniques, stimuli, and populations, as previously reviewed.<sup>26</sup> Cue-induced brain changes have not been studied in adolescents, although substance-dependent youths report substantial levels of craving,<sup>28</sup> posttreatment relapses among adoles-

cents are associated with exposure to substance-related cues,<sup>29</sup> and youths report exposure to alcohol cues through advertising an average of 30 times per month.<sup>30</sup> To assess the neural substrates of cue reactivity in youth, we studied adolescents aged 14 to 17 years, used pictures instead of words to more directly elicit cue reactivity, and used personally relevant alcohol stimuli. It was hypothesized that adolescents with alcohol use disorders (AUDs) would exhibit more brain activity in response to alcohol cues relative to teens without drinking problems, particularly in anterior cingulate, prefrontal, orbitofrontal, and subcallosal cortices. In addition, we hypothesized that desires to drink would correlate with levels of activation.

## METHODS

### PARTICIPANTS

Recruitment flyers were distributed at local high schools. When a teen telephoned in response, a brief interview preliminarily ascertained eligibility, then the legal guardian was asked exclusionary questions. After a description of the study, written informed consent and assent, approved by the University of California–San Diego Institutional Review Board, were obtained from parents and adolescents. The teen was administered a 90-minute detailed screening interview, including the Family History Assessment Module screener,<sup>31</sup> to assess family history of substance use and psychiatric diagnoses. We used the Customary Drinking and Drug Use Record<sup>32</sup> to assess substance use and abuse/dependence criteria, and the Diagnostic Interview Schedule for Children to assess adolescent psychiatric diagnoses.<sup>33</sup> The same measures were administered to the parent by a separate interviewer for corroboration. In cases of discrepancies, additional data were obtained or data were coded to represent the lower level of functioning or presence of problems.

Exclusionary criteria were a history of a *DSM-IV* psychiatric or substance disorder other than AUD, neurological illness, head trauma with loss of consciousness for longer than 2 minutes, serious medical problems and learning disability; current use of medications that could affect the central nervous system; smoking more than 4 cigarettes per day; significant maternal drinking during pregnancy ( $\geq 4$  drinks per occasion or  $\geq 7$  drinks per week); family history of bipolar I or psychotic disorders; inadequate English skills; sensory problems; left-handedness; and irremovable metal on the body. Because of high comorbidity with substance use disorders,<sup>34,35</sup> teens meeting criteria for conduct disorder ( $n=2$ ) were not excluded.

Participants with AUD ( $n=15$ ) met current *DSM-IV* criteria for alcohol abuse or dependence, and normal controls ( $n=15$ ) had very limited experience with alcohol or other drugs. Each group contained 6 girls and 9 boys with an average age of 16 years, mostly from upper middle-class families (**Table 1**). Based on neuropsychological tests administered the day of scanning, participants in both groups were above average intellectually. Youths with AUD typically drank 6 drinks each weekend night and had met criteria for alcohol abuse ( $n=7$ ) or dependence ( $n=8$ ) for 1 to 2 years. Youths with AUD reported higher levels of depressed mood and nervousness before scanning than controls, although all were in the reference range except 1 participant with AUD (Beck Depression Inventory score, 19; Spielberger Anxiety T score, 64). After excluding this participant, groups had similar Beck Depression Inventory scores. Subjects with AUD still showed more anxiety, although within the normal range (Spielberger Anxiety T score, 44).

## MEASURES

### Structured Clinical Interview

Teens and parents were administered a structured clinical interview<sup>36</sup> by separate psychometrists covering demographic, medical, academic, family, and social functioning information. Parents were asked about the teen's developmental history and familial socioeconomic status<sup>37</sup> and administered the Child Behavior Checklist.<sup>38</sup>

### Substance Use and Diagnoses

Substance involvement and use disorder diagnoses were assessed with the Customary Drinking and Drug Use Record,<sup>32</sup> which collects lifetime and past 3-month information on alcohol, nicotine, and other drug use and assesses *DSM-IV* abuse and dependence criteria,<sup>39,40</sup> withdrawal symptoms, and other negative consequences of substance use. Strong psychometric properties have been demonstrated in adolescents.<sup>32,41</sup> The Timeline Follow-back<sup>42</sup> provided substance use patterns for the previous 30 days. All participants submitted urine samples for drug toxicologic screening.

### Neuropsychological Testing

A 2-hour neuropsychological test battery was administered by a trained psychometrist (A.D.S.). The battery covered attention, working memory, learning and memory, and executive, visuospatial, and language functioning. General intellect was estimated with the Wechsler Intelligence Scale for Children-III Vocabulary subtest,<sup>43</sup> which correlates highly with full-scale IQ.<sup>43,44</sup>

### State Measures

The Beck Depression Inventory<sup>45</sup> and state scale of the Spielberger State-Trait Anxiety Inventory<sup>46</sup> assessed mood at the time of scanning. The Stanford Sleepiness Scale measured alertness immediately before and after scanning with self-reported ratings (1 indicates alert; 7, almost asleep).<sup>47</sup>

### Drinking Urge

Alcohol craving was evaluated immediately before and after scanning with a 100-mm visual analog scale for rating the urge to drink<sup>48</sup> and the Desires for Alcohol Questionnaire (DAQ).<sup>49</sup> The DAQ yields the following 3 factors: reinforcing effects, strong desires to drink, and mild desires to drink.

## PROCEDURES

Several days before scanning, participants were asked for their preferred alcoholic and nonalcoholic beverage brands and what brands they had consumed in the past year to guide individualized beverage picture selection. Participants were asked to abstain from alcohol and other drugs for at least 48 hours before imaging. The most recent drinking reported was 72 hours before scanning, and no withdrawal symptoms were reported or evident in any participant the day of scanning. All imaging sessions occurred on Thursdays from 8 to 10 PM to maximize recovery from weekend binge drinking and maintain consistent circadian influence across subjects. Once subjects arrived for the single assessment session, Breathalyzer (Intoximeter, Inc, St Louis, Mo) and urine samples were collected for drug toxicologic screening and, for girls, pregnancy screening. No participant had a measurable breath alcohol concentration, and only 1 participant, who had disclosed recent marijuana use (3 days before), had positive findings in a urine sample.

Teens underwent assessment by a trained bachelor-level psychometrist of the same sex (E.H.C. or A.D.S.). Throughout scheduling and the assessment session, adolescents were told about the imaging procedures and the importance of keeping as still as possible during scanning. This was emphasized again just before scanner entry by the MRI technologist. After lying in the scanner, a soft cloth was placed on the participant's forehead, which was then taped to the head coil to minimize head motion, and a response box was placed in the subject's right hand.

The scanning protocol consisted of high-resolution structural imaging (inversion-recovery-prepared, T1-weighted, sagittally acquired 3-dimensional spiral fast spin echo<sup>50</sup>; 16 interleaves; echo-train length, 8; repetition time, 2000 milliseconds; inversion time, 700 milliseconds; echo spacing, 15.6 milliseconds; echo time, 15.6 milliseconds; field of view, 240 mm; in-plane resolution, 0.9375 × 0.9375 mm; through-plane resolution, 1.328 mm; 128 continuous slices; acquisition time, 8 minutes 36 seconds) and axially-acquired T2\*-weighted spiral gradient recall echo imaging (repetition time, 3000 milliseconds; echo time, 40 milliseconds; flip angle, 90°; field of view, 240 mm; 20-21 axial slices covering the whole brain; slice thickness, 7 mm; reconstructed in-plane resolution, 1.875 × 1.875 mm; 138 repetitions; acquisition time, 6 minutes 54 seconds). Spiral imaging was used because it helps reduce the effects of motion on time series acquisitions.<sup>51,52</sup>

During fMRI data collection, an alcohol pictures task was administered. This task sequentially presented 20 alcohol and 20 nonalcohol pictures matched by color, visual complexity, and presence of people. The images were selected from a bank of more than 200 advertisements scanned from youth-oriented popular magazines (eg, *Rolling Stone*, *Spin*, *Sports Illustrated*, and *Cosmopolitan*) or downloaded from the Internet. A personalized set of images was selected for each adolescent, on the basis of his or her alcoholic and nonalcoholic beverage preferences and experiences, to ensure familiarity with the stimuli. To maintain focus on the task without drawing attention to picture content, instructions consisted of the following: "Press 1 if the picture contains a person; press 2 if there is no person" (30% in each condition contained a person). The task alternated between 30-second blocks of each condition (10 trials per block; 2500-millisecond stimulus presentation and 500-second interstimulus interval), with fixation periods at the beginning, middle, and end (**Figure 1** shows task design and stimulus samples).

## DATA ANALYSIS

Data were processed and analyzed with the Analysis of Functional NeuroImages package.<sup>53</sup> First, we applied to the time series data a 3-dimensional motion-correction algorithm that aligned each volume in the time series to a selected base volume<sup>54</sup> and estimated 3 rotational and 3 displacement parameters for each participant. To determine whether bulk motion differed between groups, each subject's absolute mean for each of the 6 motion parameters across the time series was compared in 1-way analyses of variance (ANOVAs). Controls required significantly more motion correction for 2 parameters (roll, 0.05 vs 0.03 mm [ $P = .02$ ]; left displacement, 0.04 vs 0.02 mm [ $P = .05$ ]) and showed more variability in motion during the time series for 2 parameters (roll SD, 0.05 vs 0.04 [ $P = .04$ ]; yaw SD, 0.08 vs 0.05 [ $P = .02$ ]), although the magnitude of these differences was quite small. To estimate task-correlated motion, the 6 parameters were correlated with the task reference vector across the time series for each subject. The median correlations for the AUD group were -0.069, 0.122, -0.011, -0.006, -0.067, and -0.037; for controls, -0.054, 0.059, 0.003, 0.042, -0.135, and -0.032 for roll, pitch, and yaw rotations and superior, left, and posterior displacements, respectively. Task-correlated values were compared between groups using Spearman correlations ( $P > .18$  for all).



**Table 2. Regions Where Controls and Teens With AUD Showed Significant Differences in BOLD Response While Viewing Alcoholic Beverage Pictures Relative to Neutral Beverage Pictures\***

Anatomic Region	Brodmann Areas	Talairach Coordinates†			Volume, $\mu$ L	Effect Size, Cohen <i>d</i>
		x	y	z		
<b>AUD&gt;Controls</b>						
Left medial frontal and paracentral gyri	6,4	5L	19P	66s	1929	9.21
Left dorsal cingulate and paracentral gyri	6,31,24	2L	22P	52s	815	4.37
Left prefrontal and orbital gyri	11	2L	48A	15i	900	6.83
Left superior and middle frontal gyri	6,8	23L	20A	52s	1158	5.85
Left inferior frontal gyrus	47	26L	13A	15i	557	5.46
Right inferior frontal gyrus‡	47	30R	31A	8i	600	5.55
Left ventral anterior cingulate and subcallosal cortex	24,25,32	9L	31A	8i	600	4.48
Left parahippocampus and amygdala	28,34,35	26L	3A	18i	1072	8.66
Right parahippocampus, amygdala, and uncus	28	19R	5P	25i	900	7.12
Left middle to inferior temporal and fusiform gyri	20,37	58L	40P	11i	1158	4.64
Left middle to superior temporal gyri	22,21	61L	15P	3s	943	6.02
Left hypothalamus	NA	2L	5P	11i	772	9.69
Bilateral posterior cingulate and precuneus	29,31,7	2L	40P	21s	7417	7.27
Left cuneus and angular gyrus	19,39	26L	78P	28s	2572	4.55
Right precuneus and cuneus	7,19	5R	75R	42s	2272	8.61
Right lateral precuneus	19	33R	71P	35s	686	3.67
<b>Controls&gt;AUD</b>						
Right middle frontal gyrus‡	10,46	37R	38A	21s	557	4.64
Right inferior frontal gyrus	46,45	54R	38A	7s	1115	3.72

Abbreviations: A, anterior; AUD, alcohol use disorder; BOLD, blood oxygen level-dependent; i, inferior; L, left; NA, not applicable; P, posterior; R, right; s, superior.

\*N = 30.

†Indicates the maximum signal intensity correlation within the cluster.

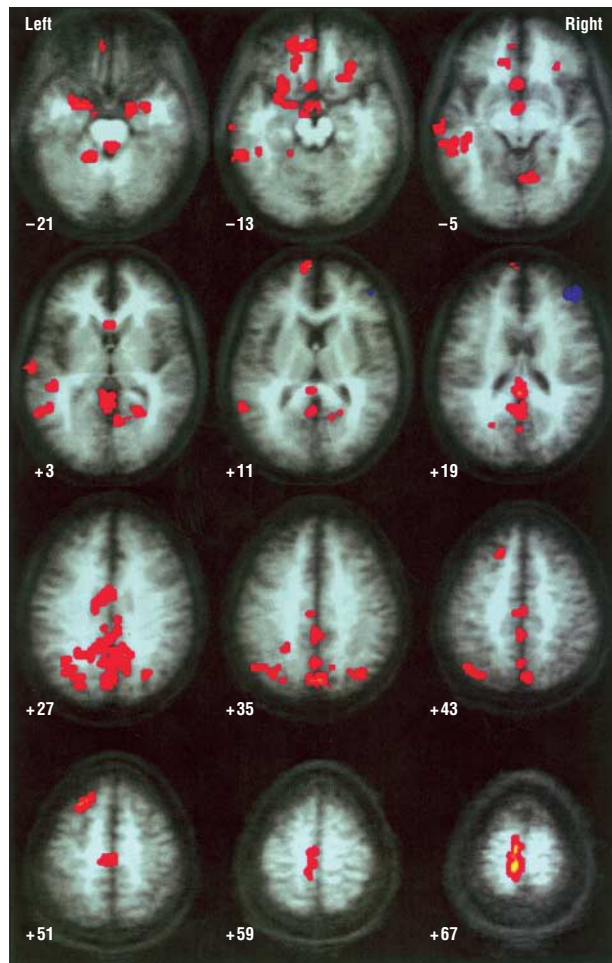
‡Not replicated after the participant with the highest mood symptoms was excluded.

holic beverage pictures in 5 locations, yet more response to neutral pictures relative to alcoholic beverage pictures in 16 regions ( $P < .05$ ). To examine the main effect of group, we contrasted the BOLD response between the alcoholic beverage pictures and fixation conditions. Both groups showed considerably more response to the alcoholic beverage pictures than to the fixation cross, but the AUD group showed a more extensive response contrast. However, this contrast and the contrast between neutral pictures and fixation revealed some BOLD response in the AUD group during fixation blocks, perhaps indicating continued reactivity to alcohol stimuli.

To test the relationship between self-reported desire to drink and brain response, the 3 DAQ factors (reinforcement, strong desires, and mild desires) were examined in regressions to predict the BOLD response contrast between the alcoholic and nonalcoholic beverage pictures for each group. Among those in the AUD group, the reinforcement factor did not predict variability in BOLD response contrast, but the strong desires factor predicted left temporal ( $\beta = 16.15$ ) and right thalamic ( $\beta = -22.88$ ) responses. The mild desires factor significantly and positively predicted 10 regions of enhanced BOLD response to alcoholic beverage pictures relative to neutral pictures in the AUD group (**Table 3**). Among controls, low reinforcement scores predicted more BOLD response contrast in the right posterior cingulate and temporal regions, and the strong and mild desires factors were unrelated to the BOLD response. To confirm these findings, we extracted each participant's signal intensity values from the regions that differed between groups (Table 2) and correlated these values with

drinking and craving scores. For controls, only the following correlations were found: left temporal/fusiform BOLD signal contrast correlated with drinks consumed per month ( $r = 0.56$  [ $P = .03$ ]), and left parahippocampal/amygdalar signal correlated with mild desires to drink ( $r = -0.55$  [ $P = .03$ ]). For the AUD group, 4 regions correlated positively with drinks per month (left inferior frontal,  $r = 0.51$  [ $P = .04$ ]; left paracentral lobule/dorsal cingulate,  $r = 0.59$  [ $P = .02$ ]; right precuneus/cuneus,  $r = 0.64$  [ $P = .01$ ]; and right precuneus/posterior cingulate,  $r = 0.76$  [ $P = .001$ ]) (**Figure 3**), and 2 areas correlated negatively with reinforcement scores (right precuneus/cuneus,  $r = -0.73$  [ $P = .002$ ]; and right inferior frontal,  $r = -0.53$  [ $P = .04$ ]).

Because individuals with family histories of AUD tend to respond abnormally to alcohol and show other neural anomalies,<sup>59-62</sup> we compared brain responses to alcohol pictures between those in the AUD group with family histories that were positive (FHP) and negative (FHN) for AUD. The AUD-group teens with FHP ( $n = 9$ ; 5 [56%] female) showed more BOLD response contrast between the alcoholic and nonalcoholic beverage pictures than the AUD-group teens with FHN ( $n = 6$ ; 1 [17%] female), especially in the left posterior cingulate and prefrontal, orbital, and inferior temporal gyrus. Controls with FHP ( $n = 9$ ; 3 [33%] female) showed more brain response to alcoholic beverage pictures relative to nonalcoholic beverage pictures than controls with FHN ( $n = 6$ ; 3 [50%] female), particularly in the left paracentral, medial frontal, prefrontal, cuneus, and anterior cingulate areas. However, when comparing the 9 AUD-group teens with FHP and the 9 controls with FHP, the AUD group showed sub-



**Figure 2.** Functional magnetic resonance imaging (fMRI) results during alcoholic beverage picture trials relative to nonalcoholic beverage picture trials. Orange indicates where teens with alcohol use disorder ( $n=15$ ) had more response than control subjects ( $n=15$ ) to alcoholic beverage pictures. Blue shows where controls had more response to alcoholic beverage pictures (group  $P<.05$ ; clusters,  $>515 \mu\text{L}$ ). Numbers refer to axial slice positions. The fMRI results are displayed on averaged anatomic brain maps.

stantially more response to alcoholic beverage pictures throughout the brain. Similarly, the 6 AUD-group teens with FHN showed more brain response to alcohol pictures than the 6 controls with FHN, except in the right frontal pole and left dorsolateral prefrontal cortex.

In adolescence, sex differences in neuromaturation<sup>63-65</sup> influence affective response<sup>66</sup> and may relate to cue reactivity. We compared responses with alcohol pictures relative to nonalcohol pictures in boys and girls of the AUD and control groups. In the AUD group, girls ( $n=6$ ) showed more brain response than boys ( $n=9$ ) to alcohol pictures, particularly in the anterior cingulate and left prefrontal regions, whereas boys showed a strong response to alcohol pictures in the left orbital gyrus and bilateral paracentral gyri. No sex differences were apparent among controls.

#### COMMENT

Our results supported the hypothesis that adolescents with AUD produce more brain activity in response to alcohol cues than teens without drinking problems. This was spe-

cifically supported in the ventral anterior cingulate and subcallosal, prefrontal, orbital, and limbic regions, areas previously associated with reward and drug craving. In addition, we found increased response in posterior regions that may be critical to visual association, episodic recall, appetitive functions, and the formation of associations. In teens with alcohol abuse/dependence, mild desires to drink alcohol were associated with enhanced BOLD response in frontal and visual regions and diminished response in the ventral anterior cingulate.

These results are consistent with previous studies on alcohol and other drug cues. Like many neuroimaging studies of craving, we found an anterior cingulate response to substance cues among problem users.<sup>16-18,20-22,25,26,67,68</sup> These findings also support studies that found subcallosal cortex/nucleus accumbens,<sup>16,25,26</sup> orbitofrontal,<sup>17,20-24</sup> left prefrontal,<sup>16-19,22,26,68</sup> amygdala,<sup>17,21</sup> temporal,<sup>17,23,67,69</sup> and posterior cingulate<sup>16,22,23</sup> responses. The most similar design to ours is the 2001 study by George and colleagues.<sup>19</sup> Both studies found increased left prefrontal BOLD response in individuals with AUD during exposure to alcohol relative to nonalcohol pictures. Although our study did not replicate their thalamic activation, the hypothalamus of teens in our AUD group was more responsive to alcohol pictures than to nonalcohol pictures, whereas controls did not show such an effect.

The present study found larger areas of brain activation to alcohol pictures than the study by George et al.<sup>19</sup> Several dissimilarities between projects could account for these differences. First, youth tend to exhibit larger areas of BOLD response relative to adults across tasks<sup>70,71</sup> owing to regional specialization that develops throughout adolescence. Second, our study used personalized stimuli instead of a standard picture series. Many youths have used only certain alcoholic beverage types, and we wanted to ensure previous exposure to beverage pictures to maximize cue reactivity. Third, our study examined the whole brain, demonstrating group differences in posterior regions. Fourth, the current study repeated images, using 40 images, whereas George et al<sup>19</sup> used 56 pictures. This leaves the possibility that recognition might have affected results. Fifth, our pulse sequences collected data spirally in k-space, a technique that is less sensitive to motion artifact.<sup>51,52</sup> Finally, the larger sample size resulted in more statistical power to detect subtler effects.

These results confirm the findings of a recent study from our group<sup>26</sup> in which alcohol-related cues appeared to provoke increased BOLD response in the nucleus accumbens region among college-age women with AUD. However, the magnitude of response in the present study is much larger and involved the visual system, possibly due to the pictorial stimulus modality and younger developmental stage of participants. The role of the visual system in the response of heavy drinkers to pictorial alcohol cues was not predicted, but it merits consideration. Feature-based visual attention may serve as the earliest stage of cortical response to visual stimuli and is linked to substantial BOLD response in visual brain regions.<sup>72</sup> Because of personal experiences and affective responses, adolescents with AUD may have attended to a broader array of features in the alcohol images, involving more visual system neurons than were involved for controls. Future stud-

**Table 3. Relationship Between Mild Desires to Drink and BOLD Response to Alcoholic Beverage Pictures in Adolescents With AUD\***

Anatomic Region	Brodmann Area	Talairach Coordinates†			Volume, $\mu\text{L}$	Coefficient, $\beta$
		x	y	z		
Positive relationship ( $P < .05$ )						
Left superior frontal gyrus	6	9L	5P	66S	1586	12.32
Right precentral gyrus	6	23R	15P	66S	600	7.72
Right postcentral gyrus	5	33R	40P	59S	2272	10.44
Right postcentral gyrus	2	54R	26P	45S	557	7.92
Right paracentral lobule	5	2R	36P	56S	1115	7.61
Right superior parietal lobule	7	16R	61P	59S	686	14.28
Left fusiform gyrus	37	51L	54P	15i	943	8.71
Right fusiform gyrus	37	47R	61P	15i	1029	9.21
Left lingual gyrus	19	12L	54P	1i	600	8.58
Right lingual gyrus	18	16R	82P	11i	2530	13.45
Negative relationship ( $P < .05$ )						
Left ventral anterior cingulate	24	2L	34A	10S	686	-10.73

Abbreviations are explained in the first footnote to Table 2.

\*N = 15.

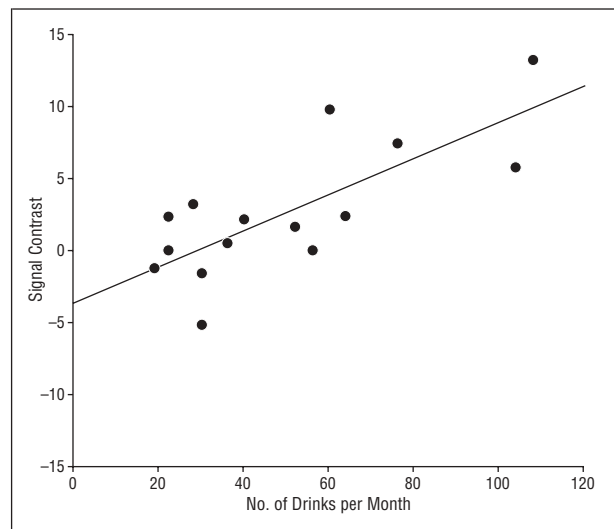
†Indicates the maximum signal intensity group difference within the cluster.

ies could examine this hypothesis using eye-movement measures. The response of the AUD group to alcohol pictures in the ventromedial region (Brodmann area 47) corresponds to findings of decision-making studies<sup>73,74</sup> that showed the importance of this region for making selections based on reward contingencies.

Several limitations of the current study warrant consideration. First, teens did not report increased craving after the alcohol pictures task, whereas the adults in the study by George et al<sup>19</sup> did, suggesting that dynamic craving processes were not captured in the imaging sessions. Teens tend to drink in the absence of adults, so the MRI setting may have been antithetical to typical drinking situations, and youths may be less able to discriminate and report changes in craving than adults. Urge ratings were not collected during scanning, but 5 minutes before and after scanner entry. Second, adolescents with AUD had more extensive histories of other drug and nicotine use than did controls, although sex, ethnicity, and family history were comparable. Third, our use of personalized cues may diminish generalizability and comparability between participants, and it is possible that social aspects of some pictures produced different responses across participants. Within-subject designs are needed to compare the effects of individualized vs standard cues.<sup>75</sup> Fourth, although all participants had some familiarity with the stimuli presented, teens with AUD may have had more experience with the alcohol stimuli, so results may represent differential recall effects.

## CONCLUSIONS

This fMRI study demonstrated that high school youths with alcohol abuse or dependence show widespread and intense brain activation in response to pictures of alcohol advertisements. These results suggest that, not only are liking and remembering alcohol advertisements associated with frequent drinking<sup>76</sup> and expecting to drink more,<sup>77</sup> but alcohol advertisements may have a strong effect on youths with established heavy drinking pat-



**Figure 3.** Blood oxygen level–dependent (BOLD) response signal contrast in the right precuneus/posterior cingulate region during exposure to alcoholic beverage pictures relative to nonalcoholic beverage pictures plotted as a function of drinks consumed per month for adolescents with alcohol use disorder ( $n = 15$ ;  $r = 0.76$  [ $P < .001$ ]).

terns as well as those with family histories of AUD, similar to how media depictions of aggression have detrimental effects on children with preexisting aggressive traits.<sup>78</sup> For young drinkers, this neural response may indicate that advertisement content has been conditioned with drinking experiences, and may reflect increasing salience of alcohol advertisements as drinking escalates. Fortunately, encouraging youths to evaluate advertisements and critique the intentions of advertisers appears to help counter the negative influences.<sup>79,80</sup> For teens in treatment for substance use disorders, research is needed to determine whether cue reactivity can be reduced and whether diminished response to cues predicts treatment success.

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### Correction

**Errors in Text and Table.** In the Original Article by Meltzer et al titled "Clozapine Treatment for Suicidality in Schizophrenia: International Suicide Prevention Trial (InterSePT)," published in the January issue of the ARCHIVES (2003;60:82-91), the following errors occurred in the text and in a table: On page 83, right column, last paragraph, the first sentence should have read as follows: "Every potential type 1 end point (see the 'Outcome Definitions' subsection) was reviewed by all of the members of the SMB, and consensus was obtained." On page 84, right column, last paragraph, the second sentence (continuing to page 85) should have read as follows: "Putative explanatory variables, that is, factors that may have contributed to the primary end point in this model, included treatment, number of previous suicide attempts, active substance or alcohol abuse, pooled country, medical center, sex, and age group (18-32, 33-44, and  $\geq 45$  years) at baseline." On page 86, in Table 4, for the sideheading "Concomitant medications" and the subheading "Antidepressants," the number (percentage) for the clozapine group should have read "221 (46.1)," and for the olanzapine group, "258 (54.1)." In that same table, for the sideheading "Concomitant medications" and the subheading "Anxiolytics/soporifics," the number (percentage) for the clozapine group should have read "301 (62.8)," and the *P* value (95% confidence interval [CI] of the difference) (olanzapine minus clozapine) should have read ".03 (.01 to .13)." On page 87, left column, last paragraph, the third sentence should have read as follows: "On the other hand, when suicide attempts were rated for probability of success by the principal investigator, a 'high probability for success' of a completed suicide was found for 8 events in the clozapine group and 14 events in the olanzapine group." Also on page 87, right column, second paragraph, the third and fourth sentences should have read as follows: "The time in days to observe the first 70 patients with type 1 events was 185 days for the clozapine-treated patients and 126 days for the olanzapine-treated patients. A significant reduction in the 2-year event rate at the end of the study (olanzapine, 32.2% vs clozapine, 24.0%; 95% CI of the difference, 0.02-0.14; number needed to treat, 13) and a delay in time to event were demonstrated for clozapine-treated patients." The last sentence in that same paragraph should have read as follows: "The overall annualized rate for attempted suicides (including suicide deaths) was 7.2%, with a rate of 8.7% for olanzapine-treated patients and 5.8% for clozapine-treated patients." On page 88, left column, second paragraph, the first and second sentences should have read as follows: "Comparison of the overall use of concomitant medications for any reason, not only suicidality, shows that antidepressants were used more frequently in patients treated with olanzapine (54.1%) than in those treated with clozapine (46.1%) (*P* = .01) (Table 4). Anxiolytics and soporifics were also used more frequently in patients treated with olanzapine (69.4%) than in those treated with clozapine (62.8%) (*P* = .03)." Also on page 88, right column, in the "Comment" section, second paragraph, the first sentence should have read as follows: "Although the total number of suicide-related deaths was greater in the clozapine-treated group, this was not significant and, as indicated already, the study was not powered to evaluate this as an end point." Finally, on page 90, right column, second paragraph, the third sentence should have read as follows: "The InterSePT indicates that, on average, treatment of only 13 patients with clozapine rather than olanzapine will show benefit for clozapine to reduce suicidal behavior."