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Influence of Alcohol Use and Family History of Alcoholism on Neural Response to Alcohol Cues in College Drinkers

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Abstract

Background—Heavy drinkers show altered functional magnetic resonance imaging (fMRI) response to alcohol cues. Little is known about alcohol cue reactivity among college age drinkers, who show the greatest rates of alcohol use disorders. Family history of alcoholism (FHP) is a risk factor for problematic drinking, but the impact on alcohol cue reactivity is unclear. We investigated the influence of heavy drinking and family history of alcoholism on alcohol cue-related fMRI response among college students.

Method—Participants were 19 family history negative (FHN) light drinkers, 11 FHP light drinkers, 25 FHN heavy drinkers, and 10 FHP heavy drinkers, ages 18–21. During fMRI scanning, participants viewed alcohol images, non-alcohol beverage images, and degraded control images, with each beverage image presented twice. We characterized blood oxygen level-dependent (BOLD) contrast for alcohol vs. non-alcohol images, and examined BOLD response to repeated alcohol images to understand exposure effects.

Results—Heavy drinkers exhibited greater BOLD response than light drinkers in posterior visual association regions, anterior cingulate, medial frontal cortex, hippocampus, amygdala, and dorsal striatum, and hyperactivation to repeated alcohol images in temporo-parietal, frontal, and insular regions (clusters > 8127 μ l, $p < .05$). FHP individuals showed increased activation to repeated alcohol images in temporo-parietal regions, fusiform and hippocampus. There were no interactions between family history and drinking group.

Conclusions—Our results parallel findings of hyperactivation to alcohol cues among heavy drinkers in regions subserving visual attention, memory, motivation, and habit. Heavy drinkers

demonstrated heightened activation to repeated alcohol images, which could influence continued drinking. Family history of alcoholism was associated with greater response to repeated alcohol images in regions underlying visual attention, recognition, and encoding, which could suggest aspects of alcohol cue reactivity that are independent of personal drinking. Heavy drinking and family history of alcoholism may have differential impacts on neural circuitry involved in cue reactivity.

Keywords

fMRI; alcohol; adolescence; cue reactivity; brain

Adolescence is a high-risk period for initiating alcohol use and for developing problem drinking. The majority of drinkers begin alcohol use in their teenage years, and the greatest rates of alcohol abuse and dependence are between the ages of 18 and 25 (SAMHSA, 2011). The biological mechanisms underlying the transition from occasional use to problem drinking remain unclear. Family history of alcohol use disorders (AUD) is a significant predictor of future alcohol dysfunction (e.g., Cloninger et al., 1981; Kendler et al., 2003; Schuckit, 1985). This increased risk may be subserved, in part, by altered processing of alcohol-specific cues by reward-related neural systems (Tapert et al., 2003).

Cue reactivity studies demonstrate that alcohol dependent adults, compared to moderate drinkers, show altered neural responses to alcohol-related stimuli in multiple brain regions, including amygdala, anterior cingulate and medial prefrontal cortex, ventral striatum/nucleus accumbens (NAcc), dorsal striatum, and orbitofrontal cortex, and that greater activation of these regions predicts relapse risk (for review, see Heinz et al., 2009). To date, most alcohol cue reactivity studies have focused on adult populations with extensive drinking histories. It is important to understand how cue reactivity might contribute to the transition from initiation to regular use in younger individuals who are at the greatest risk for developing AUD, as this may provide insight into early interventions. Initial work has suggested that teenagers with AUD demonstrate similar functional magnetic resonance imaging (fMRI) response patterns as adults when viewing alcohol-related images, despite relatively short drinking histories (Tapert et al., 2003). Alcohol-dependent young adult women, who had been in alcohol treatment programs as teenagers, exhibited ventral striatal response to alcohol-related words (Tapert et al., 2004). Heavy drinking college students showed greater fMRI response to alcohol images compared to neutral images in the insula, anterior cingulate, caudate, and prefrontal cortex (Ray et al., 2010a). Cue reactivity has not yet been explored within a community sample of male and female young adults who are in the primary age for developing AUD.

There is extensive literature demonstrating that individuals with a family history of AUD (FHP) are at increased risk for developing AUD. One possible mechanism for this vulnerability is increased sensitivity to the rewarding effects of alcohol (Pollock, 1992), which may be manifested, in part, through increased alcohol cue reactivity. In an fMRI study of cue reactivity in adolescents with AUD, the possible influence of FH was examined in follow-up exploratory analyses (Tapert et al., 2003). Among adolescents with AUD, FHP youths showed greater alcohol-cue related neural response than family history negative (FHN) teens in posterior cingulate, prefrontal, orbitofrontal, and inferior temporal cortices. FHP nondrinking teens also showed more response to alcohol cues than FHN nondrinkers, particularly in medial frontal, anterior cingulate, prefrontal, and occipital regions. In another study of heavy drinkers, medial prefrontal cue reactivity to alcohol odors was more pronounced in FHP than in FHN (Kareken et al., 2010). FHP young adult female social drinkers also showed greater salivary response to alcohol cues than FHN women (Lundahl and Lukas, 2001), providing further evidence of increased cue reactivity among FHP non-

abusers. FH has also been related to monetary reward sensitivity among adults without AUD. Compared to FHN participants, FHP individuals showed greater caudate response to the prospect of reward and reduced NAcc, insula, and orbitofrontal response during reward anticipation (Andrews et al., 2011).

Thus, there is some evidence of greater alcohol cue reactivity and reward sensitivity in FHP individuals, which may be a pre-existing risk factor for the development of AUD. It is possible that this FH-related effect becomes diminished after heavy alcohol involvement is initiated (Tapert et al., 2003) and personal alcohol use becomes a better predictor of cue reactivity. The influence of FH on alcohol cue reactivity has been examined separately in heavy drinkers and non-abusers; therefore, the interactive nature of FH and personal drinking remains unclear. The impact of FH on alcohol cue reactivity needs further clarification, particularly during the age range of greatest risk for AUD.

The current study characterized blood oxygen level dependent (BOLD) fMRI response to alcohol-related images among young adult heavy and light drinkers, both with and without a family history of AUD. We predicted that 1) heavy drinkers would show greater BOLD response than light drinkers to alcohol images, relative to non-alcohol images, in reward-related regions including NAcc and medial frontal cortex, 2) FHP would show greater response than FHN individuals in these reward-related regions, and 3) there would be an interaction between family history of AUD and personal drinking on BOLD response to alcohol-related cues, such that enhanced cue reactivity among FHP would be more apparent in light drinkers than in heavy drinkers.

Method

Participants

Participants were 65 young adults, ages 18–21, who were recruited as part of an ongoing study of alcohol and neurocognitive function in first-year college students, the Brain and Alcohol Research in College Students (BARCS) study. A subset of individuals from the larger 2000-person BARCS study participated in neuroimaging. Each participant provided written informed consent, approved by the institutional review boards at Yale University, Hartford Hospital, Trinity College, and Central Connecticut State University. Exclusion criteria included current psychotic or bipolar disorders based on the MINI interview (Sheehan et al., 1998), history of seizures, head injury with loss of consciousness >10 minutes, left handedness, positive urine toxicology screen for illicit substances, and MRI contraindications. Eligible participants were evaluated for family history of alcoholism and personal drinking history. Family history negative (FHN) participants had no first or second degree relatives with AUD, and family history positive (FHP) participants had at least one first degree relative with AUD. Heavy drinking was defined using a combination of AUD diagnosis and quantity/frequency of current alcohol consumption (e.g., Cahalan et al., 1969; Squeglia et al., 2009). Participants were considered light drinkers if they 1) did not meet current or past criteria for AUD, and 2) drank during fewer than half of the weeks during the preceding six months. Participants were considered heavy drinkers if they either 1) met criteria for current AUD, or 2) drank more than half of the weeks in the preceding six months *and* reported that they typically binge drank when drinking (4 drinks/occasion for females or 5 drinks/occasion for males; (e.g., Courtney and Polich, 2009; Schweinsburg et al., 2010)). The final sample consisted of 19 FHN light drinkers, 11 FHP light drinkers, 25 FHN heavy drinkers, and 10 FHP heavy drinkers (see Table 1 for demographics).

Measures

Family history of alcohol use disorders was ascertained using the Family History Assessment Module (FHAM) (Rice et al., 1995). Detailed alcohol use history was obtained using the alcohol use module of the SCID (First et al., 2002). Current and past DSM-IV diagnoses of anxiety, psychotic, mood and substance use disorders were ascertained using the MINI (Sheehan et al., 1998) and information on cigarette smoking was obtained using the Fagerstrom Test of Nicotine Dependence (Heatherton et al., 1991). At the time of scanning, participants were free of alcohol and illicit substances as verified by breathalyzer and urine toxicology, and females provided negative pregnancy screens.

Alcohol Pictures Task

The Alcohol Cue Reactivity task was modified from a design of Pulido (Pulido et al., 2010) and consisted of 44 beverage pictures (22 alcohol and 22 matched soft drink/bottled water) derived from advertising images matched on valence, arousal, image complexity, brightness, and hue, and 44 degraded stimuli (see Figure 1). To improve signal in the primary task condition and contrast of interest, alcohol and non-alcohol stimuli were presented two times each (44 trials per condition), while degraded stimuli were each presented once (44 trials per condition). Each picture was presented for 1750 ms with intermittent fixation periods (screen with a centered fixation cross, 250 – 4250 ms). The degraded stimuli condition provides the opportunity to contrast functional brain activation to alcohol and/or non-alcohol pictures to a visual baseline. The alcohol cue reactivity task was 5 minutes and 54 seconds in duration, and included an initial 9 second fixation period to allow T1 effects to stabilize (not included in analyses). Ratings and reaction times were logged via fiber-optic response box. Task instructions were to press a key within 2000 ms of stimuli presentation in response to whether participants liked (left button), disliked (middle button) or felt neutral about (right button) seeing the beverage picture. A task with non-beverage pictures was created for practice purposes. Participants were instructed to use the left, down, and right arrows on a computer keyboard while practicing the task outside the scanner.

Image Acquisition

Structural imaging consisted of a sagittally-collected T1 MPRAGE with the following parameters: TR/TE/TI=2300/2.74/900 msec, flip angle=8°, slab thickness =176 mm, FOV=176 × 256 mm, matrix =176×256×176, voxel size=1 mm³, pixel band-width=190 Hz, total scan time =10:09 min). Functional images were collected in the axial plane with a Siemens 3T Allegra high performance head-dedicated system optimized for functional imaging using an echoplanar image (EPI) gradient-echo pulse sequence covering the whole brain (TR/TE 1500/28 ms, flip angle 65 degrees, FOV 24 cm × 24 cm, 64 × 64 matrix, 3.4 mm × 3.4 mm in plane resolution, 5 mm effective slice thickness, 30 slices).

Data Analyses

Functional images from the Alcohol Cue Task were analyzed in SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>). Event-related responses were modeled using a synthetic hemodynamic response function composed of 2 gamma functions (Friston et al., 1995; Worsley and Friston, 1995). Functional images were realigned, spatially normalized to Montreal Neurological Institute (MNI) standardized space, resampled to 3 mm³ voxels, and smoothed with an 8 mm full-width, half-maximum Gaussian filter. Realignment parameters were examined for excessive motion, and participants with movement >4.5 mm or >3 degrees were not included in analyses. BOLD response was modeled for alcohol images, non-alcohol beverage images, and degraded images while covarying for the degree of motion and linear baseline trends.

In addition, there is interest in understanding the neurobiological mechanism by which repeated alcohol cue exposure might be associated with drinking trajectories. There is preliminary evidence that binge drinking college students demonstrated a repetition suppression effect for repeated alcohol images, wherein fMRI response was reduced for images that had been previously viewed (Ray et al., 2010b). Therefore, we also conducted exploratory analyses investigating the effect on BOLD response of repeated exposure to alcohol stimuli over the course of the task by contrasting second presentation vs. first presentation of stimuli. To clarify, greater repetition BOLD response represented more response to the second presentation of images relative to the first presentation.

Group level analysis of BOLD response contrast to alcohol vs. non-alcohol beverage images was conducted using a two-factor ANOVA, coding for drinking status, family history, and their interaction. We also conducted similar exploratory analyses contrasting repeated alcohol images and repeated non-alcohol images. We performed a whole-brain correction for multiple comparisons using a combination of cluster volume and individual voxel threshold (e.g., Forman et al., 1995) as determined *a priori* through a Monte Carlo simulation (Ward, 2000). Clusters were considered significant if they were comprised of 301 contiguous activated voxels ($p < .05$, cluster volume 8127 μl), yielding a whole-brain $\alpha = .05$.

The NAcc plays a critical role in reward processing and cue reactivity in alcoholism (Heinz et al., 2009); however, this structure may be too small to encompass activations that surpass our stringent whole-brain corrections. Therefore, we examined BOLD response within the NAcc separately using an anatomic mask that was previously delineated in our lab (Andrews et al., 2011) based on stereotactic coordinates and other published work. BOLD response for each participant was then averaged across this region and examined between groups.

Results

Demographic Results

Demographic variables were compared among all four groups using ANOVA or χ^2 as appropriate (see Table 1). There were no differences among groups on sex, ethnicity, age, or presence of an Axis-I disorder other than substance use disorder (all $p > .10$). Approximately 17% of participants met criteria for a current depressive or anxiety disorder. Heavy drinkers showed higher rates of substance use disorders other than AUD as compared to light drinkers ($\chi^2(1) = 7.82$, $p = .005$). Among heavy drinkers, six (four FHP, two FHN) met criteria for current marijuana use disorder, one (FHN) for Ecstasy abuse, and one (FHP) for cocaine dependence. Alcohol use variables were compared between groups using 2×2 ANOVA or nonparametric tests as appropriate. Compared to light drinkers, heavy drinkers reported greater levels of lifetime alcohol consumption ($U(65) = 38$, $p < .001$); and number of weeks ($U(65) = 44$, $p < .001$), number of days per week ($U(65) = 61.5$, $p < .001$), and amount ($U(65) = 118$, $p < .001$) of drinking during the past six months. There were no main effects of family history on alcohol use variables. FHP heavy drinkers showed higher lifetime number of alcohol drinks than FHN heavy drinkers ($U(35) = 68$, $p = .035$), although FHP heavy drinkers and FHN heavy drinkers did not differ on current drinking frequency or quantity.

Behavioral Results

Behavioral data were unavailable for one participant (FHP light drinker). Responses to task stimuli were investigated with repeated measures ANOVA with picture type (alcohol, non-alcohol, degraded) and picture rating (like, dislike, neutral) as repeated factors, and family history and drinking groups as between-groups factors (see Table 2 for behavioral

responses). There was a picture type $\times$ rating $\times$ drinking group interaction [$F(4, 240) = 7.00$, $p < .001$]. Follow-up tests of the three-way interaction (Bonferroni corrected at a family-wise $\alpha = .05$) indicated that heavy drinkers were more likely to “like” alcohol images than light drinkers [$t(62) = 6.10$, $p < .001$], and less likely to “dislike” alcohol images as compared to light drinkers [$t(62) = 5.95$, $p < .001$], whereas groups did not differ on their responses to non-alcohol beverage pictures or degraded images. Family history was not related to image ratings.

Reaction times were analyzed with repeated measures ANOVA modeling picture type as a repeated factor, and family history and drinking groups as between groups factors. Greenhouse-Geisser corrections were used due to violation of sphericity for picture type ($\chi^2(2) = 14.46$, $p = .001$). There was a main effect of picture type [$F(1.64, 98.58) = 53.50$, $p < .001$], such that reaction times were faster for degraded images than for alcohol [$F(1,60) = 61.61$, $p < .001$] or non-alcohol beverage pictures [$F(1,60) = 67.92$, $p < .001$]. There were no differences in reaction times associated with drinking group or family history. In addition, we examined the difference in reaction time to first vs. second presentation of each alcohol and non-alcohol image; this test yielded no significant results.

There were no significant group differences on average movement during fMRI scanning. Displacement ranged from 0.08 to 1.50 mm in the X direction, 0.12 to 2.47 mm in the Y direction, and 0.33 to 4.20 mm in the Z direction. Rotational movement ranged from 0 to 0.05 degrees for pitch, 0 to 0.04 for roll, and 0 to 0.02 degrees for yaw; group differences in rotational movement were not examined due to the limited range of movement.

Alcohol vs. Non-alcohol Beverage Images

Main Effect of Task—Participants showed greater BOLD response to alcohol pictures relative to non-alcohol beverage pictures in the following regions: medial precuneus/posterior cingulate, bilateral supramarginal gyrus, and right lingual gyrus (clusters $> 8127 \mu\text{l}$, $p < .05$). Participants demonstrated greater BOLD response to non-alcohol beverage pictures relative to alcohol pictures in bilateral fusiform, right anterior insula, bilateral middle frontal gyrus, and superior medial frontal cortex (clusters $> 8127 \mu\text{l}$, $p < .05$). Participants showed activation to degraded images in occipital, posterior parietal, and superior and medial frontal regions; there were no differences in response to degraded images related to drinking group, family history, or their interaction.

Main Effect of Drinking—Heavy drinkers showed significantly more BOLD response than light drinkers to alcohol pictures relative to non-alcohol beverage images within three clusters (see Table 3 and Figure 2; clusters $> 8127 \mu\text{l}$, $p < .05$). The first very large cluster encompassed widespread brain areas, including bilateral superior occipital, posterior parietal, cingulate and medial superior frontal cortices, caudate, thalamus, left hippocampus and amygdala. Heavy drinkers also demonstrated greater response to alcohol pictures than light drinkers in right precentral and inferior frontal gyri, and right inferior temporal cortex. There were no regions in which light drinkers showed greater response than heavy drinkers to alcohol pictures compared to non-alcohol beverage images. Similar results were obtained when examining the contrast of alcohol pictures vs. implicit baseline and alcohol pictures vs. degraded images, indicating that the group difference was not accounted for by differential response to control images. Follow-up analyses of BOLD response contrasts of control images (i.e., non-alcohol beverage images vs. baseline, degraded images vs. baseline, and non-alcohol beverage images vs. degraded images) revealed no significant group differences. Thus, the greater BOLD response among drinkers was specific to alcohol-related stimuli.

Nine light drinkers reported occasional binge drinking; group differences between heavy and light drinkers were diminished, particularly in superior frontal and posterior regions, when these individuals were removed from analyses. We also reran analyses after excluding participants with current SUD (6 FHN heavy drinkers, 3 FHP heavy drinkers). Results remained similar with the exception of less prominent differences between heavy and light drinkers in occipital response.

Main Effect of Family History—Collapsing across drinking group, FHN individuals showed more BOLD response than FHP individuals when viewing alcohol beverage pictures compared to non-alcohol beverage images in one cluster, comprising left fusiform gyrus, lingual gyrus, superior portions of the cerebellum and thalamus (see Table 3 and Figure 3, clusters > 8127 μ l, $p < .05$). There were no regions in which FHP demonstrated more BOLD response to alcohol pictures than FHN. Because lifetime alcohol consumption was greater among FHP drinkers as compared to FHN drinkers, we determined whether the observed FH-related BOLD effects were related to lifetime alcohol use. Group differences remained after controlling for lifetime alcohol consumption.

Family History x Drinking Interaction—There were no regions in which there was an interaction between family history and drinking group for alcohol vs. non-alcohol beverage images.

Alcohol Image Repetition Effect

Main Effect of Drinking—Heavy drinkers demonstrated greater BOLD response contrast to alcohol picture repetition (i.e., greater response to second presentation than to first presentation) than light drinkers in right superior medial frontal, dorsolateral prefrontal, and inferior frontal cortices, right anterior insula, right middle temporal cortex, right lateral posterior parietal cortex, left inferior occipital gyrus, and left middle temporal gyrus (see Table 4 and Figure 4, clusters > 8127 μ l, $p < .05$). In these regions, light drinkers showed the opposite pattern, with less response during second presentation than during first presentation. There were no regions in which light drinkers showed greater alcohol repetition BOLD response than heavy drinkers. In addition, there were no regions in which heavy and light drinkers differed in response to non-alcohol beverage images.

Main Effect of Family History—Regardless of drinking status, FHP individuals showed widespread increased activation during repeated alcohol pictures compared to FHN individuals (see Table 4 and Figure 5, clusters > 8127 μ l, $p < .05$). Greater alcohol repetition-related BOLD response was observed among FHP in bilateral occipital cortex, posterior parietal cortex, parahippocampal gyrus and hippocampus, and bilateral cerebellum. Although these effects were largely bilateral, activations were more apparent on the right for occipital and parietal cortices as well as the hippocampus. Follow-up analyses revealed that family history-related differences were due to an increase in activation to repeated alcohol images among FHP individuals, rather than a repetition-related decrease among FHN individuals. There were no regions in which FHN displayed greater alcohol picture repetition-related BOLD response than FHP. There were also no regions in which family history was associated with repetition response for non-alcohol beverage images. In addition, FH-related differences remained after controlling for lifetime alcohol consumption.

Family History x Drinking Interaction—There were no regions demonstrating a family history x drinking interaction effect for repeated alcohol images or for repeated non-alcohol beverage images.

NAcc

Heavy drinkers and light drinkers showed significantly different BOLD response to alcohol vs. non-alcohol images ($t(63) = 2.17, p = .034$) in the right NAcc. More specifically, light drinkers demonstrated greater BOLD response to non-alcohol beverage images than alcohol images ($t(29) = 2.4, p = .023$), whereas drinkers demonstrated similar levels of BOLD response to both alcohol and non-alcohol images ($t(34) = 0.42, p = .69$). Within the left NAcc, light drinkers showed somewhat greater activation to non-alcohol beverage images than alcohol images ($t(29) = 1.72, p = .10$), whereas heavy drinkers showed similar activation to both alcohol and non-alcohol beverage images ($t(34) = 0.24, p = .81$). In addition, heavy drinkers showed significant alcohol picture repetition-related response (i.e., second presentation > first presentation) in both left ($t(34) = 2.93, p = .006$) and right ($t(34) = 2.11, p = .042$) NAcc. Light drinkers showed no such repetition-related response. There were no drinking group differences on response to non-alcohol images. There were no differences in NAcc activation related to family history.

Discussion

The current study characterized neural response to alcohol cues associated with heavy drinking and family history of alcoholism among first-year college students. Our results parallel existing literature on cue reactivity in AUD, and extend these findings by identifying family history-related patterns. In particular, FHP individuals demonstrated neural alterations to repeated alcohol images that were distinct from drinking-related activations.

Consistent with previous work among teenagers (Tapert et al., 2003), heavy drinkers in the current study demonstrated increased BOLD response to alcohol pictures in occipital and posterior parietal cortices, indicative of greater visual processing and visuospatial attention for alcohol-related stimuli (Heinz et al., 2009; Tapert et al., 2003). Thus, the alcohol images may have been more visually salient than non-alcohol images for heavy drinkers, despite the fact that these images were matched on valence, arousal, image complexity, brightness, and hue (Pulido et al., 2010).

The current study also replicates findings of increased activation of limbic structures, including anterior cingulate and adjacent medial prefrontal cortex, hippocampus, and amygdala, among heavy drinkers (Grusser et al., 2004; Heinz et al., 2009; Ray et al., 2010a; Tapert et al., 2003). The anterior cingulate has been implicated in attention and motivation related to alcohol cue reactivity (Grusser et al., 2004; Heinz et al., 2009; Myrick et al., 2004). Previous work also suggests that medial prefrontal cortical alcohol cue-related hyperactivity is associated with greater future alcohol consumption (Grusser et al., 2004). Increased medial prefrontal response among heavy drinking college students may subserve greater attention and motivational incentive for alcohol, which may contribute to escalation of drinking. Heightened hippocampal and amygdala response could represent greater episodic encoding and emotional significance of alcohol-related stimuli for heavy drinkers (Schneider et al., 2001; Tapert et al., 2003). These heightened neural responses also coincided with greater self-reported liking of alcohol images among heavy drinkers as compared to light drinkers.

The addiction literature indicates that the ventral striatum, including NAcc, subserves reward response to novel stimuli, while the dorsal striatum, encompassing dorsal caudate and putamen, supports habit formation and compulsive drug seeking (Everitt and Robbins, 2005; Schacht et al., 2011; Vollstadt-Klein et al., 2010). In the current study, heavy drinkers did not show greater BOLD response to alcohol images relative to non-alcohol images in NAcc, suggesting that both alcohol and non-alcohol images elicited similar incentive

salience and reward-related response. Moreover, heavy drinkers exhibited increased dorsal striatal alcohol cue-related activation, which has been linked to AUD severity in older samples with more chronic use (Claus et al., 2011) and could indicate greater habit formation among heavy drinkers (Claus et al., 2011; Everitt and Robbins, 2005; Vollstadt-Klein et al., 2011; Vollstadt-Klein et al., 2010). Heavy drinkers and light drinkers showed comparable responses to non-alcohol images, indicating that heavy drinkers were not more sensitive to appetitive stimuli in general, but that the observed effect was specific to alcohol-related cues.

In addition to overall hyperactivation to alcohol cues, heavy drinkers also showed increased response to repeated alcohol images, although light drinkers demonstrated a BOLD response reduction to repeated cues. This repetition effect was observed in several frontal, temporo-parietal, dorsal striatal, and insular regions and may have implications for future drinking. In contrast to our findings, others have demonstrated a repetition suppression effect among binge drinking college students, in which repeated exposure to alcohol pictures led to decreased BOLD response in occipital, frontal, and insular cortices (Ray et al., 2010b). However, others have suggested that lower fMRI cue reactivity is related to diminished future drinking (Grusser et al., 2004), and that suppression of cue-related response may be relevant for addiction treatment (Kosten et al., 2006; Vollstadt-Klein et al., 2011). When viewing repeated alcohol picture cues, alcohol-dependent patients who received cue-exposure based extinction training exhibited reduced fMRI response, while those who received treatment as usual showed an increase in frontal and insular activation (Vollstadt-Klein et al., 2011). Altered cue reactivity may be mediated by NMDA receptor abnormalities, and enhancing glutamatergic functioning may contribute to reducing drinking by facilitating extinction of cue reactivity (Cleva et al., 2010). In contrast, greater repetition-related cue response among heavy drinkers in the current study may contribute to the maintenance and amplification of problematic drinking.

Individuals with a family history of alcoholism showed an enhanced response during repetition of previously viewed alcohol images throughout the brain. This increased repetition effect was observed in bilateral fusiform, hippocampus, amygdala, and temporo-parietal regions, and may subserve greater recognition and encoding, emotional reactions, and visuospatial attention and working memory for alcohol-related stimuli (Heinz et al., 2009; Tapert et al., 2003). This effect of family history on repetition-related response has not been examined in previous studies, and could suggest greater sensitivity to recognizing and encoding alcohol-related information among individuals with a family history of alcoholism. Similarly, both among AUD and nondrinking teenagers, FHP youths showed greater BOLD response to alcohol images than FHN teens (Tapert et al., 2003). FHP young adult female social drinkers showed larger salivary responses when holding an alcohol drink compared to FHN women (Lundahl and Lukas, 2001). Our results are consistent with these previous studies identifying augmented cue reactivity in FHP individuals, and in particular, sensitization to previously observed cues. As mentioned previously, failure to extinguish alcohol cue-related response may be a risk factor for continued heavy drinking (Grusser et al., 2004; Vollstadt-Klein et al., 2011) or escalation of use among those who have not yet manifested symptoms. Longitudinal follow-ups of these individuals will help clarify these relationships.

Although FHP individuals did show altered response patterns compared to FHN, we did not find the hypothesized interaction between family history and personal drinking on BOLD response to alcohol cues. Family history and personal drinking may differentially influence brain functioning (Andrews et al., 2011), and heavy drinking may not further impact pre-existing family history-related cue-elicited activation. Similarly, family history and personal drinking were associated with different neural response patterns during inhibitory processing

(Heitzeg et al., 2010). To our knowledge, this is the first study to attempt to differentiate cue reactivity circuitry associated with family history and problem drinking.

It is not surprising that heavy drinkers provided more positive ratings of alcohol images than the light drinkers. It is difficult to disentangle BOLD response differences related to “liking” and alcohol consumption in the current study, as these variables were highly correlated in our sample. Similarly, previous work using these picture stimuli in college students has shown a positive relationship between current alcohol involvement and valence ratings of alcohol images (Pulido et al., 2009). Indeed, “liking” may be a conditioned response to alcohol cues among heavy drinkers (e.g., Heinz et al., 2009). Additionally, Robinson and Berridge (1993) have theorized distinct processes of “liking” and “wanting” an addictive substance, cautioning that humans may have little insight into recognizing these subjective experiences. Cue reactivity may therefore be a more sensitive measure of addictive processes than subjective report. Future studies equating groups on ratings of alcohol images might help differentiate brain response patterns related to “wanting” and “liking” during the transition to AUD.

Limitations of the current study should be considered. First, we examined a relatively small sample of FHP individuals. Despite our limited sample, we did observe large effect sizes for significant activations. Yet we may not have had sufficient power to detect interaction effects. We did not assess self-reported craving, which has been associated with fMRI response and cue reactivity (Myrick et al., 2004; Tapert et al., 2003). However, others have suggested that fMRI of cue reactivity better differentiates groups and predicts future use than subjective reports of craving (Grusser et al., 2004; Vollstadt-Klein et al., 2011). To this end, this study will provide the foundation for longitudinal work characterizing neural endophenotypes of cue reactivity that predict future drinking trajectories. In addition, we did not examine the role of personality characteristics, yet traits such as impulsivity or sensation seeking may be associated with both alcohol use and family history, and have been shown to contribute to neural reward processing among FHP individuals (Andrews et al., 2011). Finally, we did not exclude participants with current or past psychiatric disorders, including abuse of other substances, as we wanted to study a representative sample of college students and of drinkers. It is possible that these co-occurring conditions may have influenced our results, although we did not have sufficient power to examine this further.

Together, these findings indicate altered neural activations associated with both heavy drinking and family history of alcoholism among college students, although no significant interaction between the two. Heavy drinkers demonstrated evidence of increased processing associated with visual attention, memory, motivation, and habitual responding for alcohol cues, as well as greater sensitivity to repeated alcohol images, which could underlie vulnerability for intensified future drinking. Regardless of drinking status, individuals with a family history of alcoholism exhibited amplified response to repeated alcohol images, particularly in attention and memory-related regions. Together, these results could indicate that personal drinking and family history of alcoholism represent different risk pathways contributing to alcohol cue-reactivity.

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Figure 1.
Sample task stimuli.

Heavy Drinkers > Light Drinkers

Figure 2. Regions demonstrating significant difference between heavy drinkers and light drinkers for fMRI response to alcohol pictures compared to non-alcohol beverage pictures (clusters $>8127 \mu\text{l}$, $p < .05$).

Figure 3.
Regions demonstrating significant difference between FHN and FHP for fMRI response to alcohol pictures compared to non-alcohol beverage pictures (clusters $>8127 \mu\text{l}$, $p < .05$).

Heavy Drinkers > Light Drinkers

Figure 4. Regions showing significant difference between heavy drinkers and light drinkers for fMRI response to repeated alcohol pictures (clusters $>8127 \mu\text{l}$, $p < .05$).

FHP > FHN

Figure 5. Regions showing significant differences between FHP and FHN for fMRI response to repeated alcohol pictures (clusters $>8127 \mu\text{l}$, $p < .05$).

Table 1

Demographic and Substance Use Characteristics of Study Participants

	Heavy Drinkers (n=35)		Light Drinkers (n=30)	
	FHP (n=10)	FHN (n=25)	FHP (n=11)	FHN (n=19)
	M (SD) or %	M (SD) or %	M (SD) or %	M (SD) or %
Age	19.30 (0.82)	19.20 (0.71)	18.91 (1.04)	19.42 (0.61)
Race (% Caucasian)	80.0%	72.0%	72.7%	52.6%
Sex (% Male)	70.0%	44.0%	18.2%	52.6%
Current depressive or anxiety disorder	10.0%	20.0%	18.2%	15.8%
Current SUD other than AUD ^b	30.0%	20.0%	0%	0%
Lifetime drinks ^{a, b}	527.00 (487.12)	213.00 (259.85)	21.36 (32.18)	14.05 (23.42)
# weeks of drinking, past 6 months ^b	15.90 (8.90)	13.10 (7.51)	1.91 (3.98)	1.26 (1.97)
Drinking days/week, past 6 months ^b	4.30 (2.63)	3.24 (1.54)	0.64 (1.03)	0.63 (0.76)
Drinks/day, past 6 months ^b	8.65 (4.31)	7.52 (3.84)	1.36 (2.66)	2.32 (3.25)
Current alcohol dependence	50.0%	24.0%	-	-
Current alcohol abuse	90.0%	92.0%	-	-
Fagerstrom Test of Nicotine Dependence Total	0.80 (1.75)	0.20 (0.51)	0.09 (0.30)	0.00 (0.00)

^aFHP heavy drinkers FHN heavy drinkers, $p < .05$

^bHeavy drinkers light drinkers, $p < .05$

Table 2

Alcohol Cue Task Responses

	Heavy Drinkers (n=35)	Light Drinkers (n=29)
	M (SD)	M (SD)
Alcohol picture responses (number)		
Like *	25.26 (12.88)	7.00 (10.64)
Dislike *	6.51 (7.01)	23.41 (14.97)
Neutral	8.94 (10.24)	10.00 (12.07)
Non-alcohol picture responses (number)		
Like	27.77 (9.54)	23.24 (9.09)
Dislike	6.42 (7.25)	9.59 (7.64)
Neutral	6.74 (5.68)	7.00 (6.53)
Degraded image responses (number)		
Like	2.54 (6.77)	3.03 (8.33)
Dislike	23.60 (18.61)	19.69 (18.36)
Neutral	15.89 (17.15)	18.24 (17.87)
Alcohol picture reaction time (ms)	900.72 (115.80)	872.90 (71.36)
Non-alcohol picture reaction time (ms)	887.79 (111.26)	902.84 (70.13)
Degraded image reaction time (ms)	731.75 (135.89)	743.76 (116.73)

* Heavy drinkers – light drinkers, $p < .005$

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Table 3

Regions Showing Significant Main Effects for Heavy Drinking and Family History of Alcoholism on BOLD Response to Alcohol vs. Non-alcohol Images (clusters > 8127 μl , $p < .05$)

Anatomic Region	Brodmann Areas		MNI Coordinates			Effect Size Cohen's d	t value
	x	y	z				
Heavy Drinkers > Light Drinkers							
Cluster 1 (266,085 μl)							
Bilateral middle occipital, cuneus	18, 19	30	-78	12	1.14		4.44
Bilateral inferior parietal, precuneus	7	-9	-45	9	1.10		4.28
Bilateral cingulate, anterior cingulate	24, 31	-15	-21	42	1.10		4.31
Bilateral medial superior frontal gyrus	10	3	54	0	0.87		3.40
Bilateral caudate, left putamen		-15	9	18	0.83		3.25
Bilateral thalamus		15	-12	3	0.93		3.65
Left hippocampus, amygdala		-21	-27	-6	0.71		2.78
Cluster 2 (28,053 μl)							
Right precentral gyrus	6	42	-9	48	0.94		3.69
Right inferior frontal gyrus	46	33	27	-21	0.94		3.67
Cluster 3 (10,449 μl)							
Right inferior temporal gyrus	20	42	-3	-27	0.85		3.33
FHN > FHP							
Cluster 1 (14,958 μl)							
Left fusiform, lingual gyrus	6, 24	-36	-36	-21	0.93		3.63
Left cerebellum		-15	-42	-15	0.88		3.45

Note: Coordinates, effect size, and t value refer to extrema within each cluster.

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Regions Showing Significant Main Effects for Heavy Drinking and Family History of Alcoholism on BOLD Response to Repeated Alcohol Images (clusters > 8127 μ l, $p < .05$)

Table 4

Anatomic Region	Brodmann Areas			MNI Coordinates			Effect Size Cohen's d	t value
	x	y	z					
Heavy Drinkers > Light Drinkers								
Cluster 1 (148,392 μ l)								
Right superior frontal gyrus	6	9	15	60		1.06		4.13
Right middle frontal gyrus	8	45	12	42		1.01		3.96
Right inferior frontal gyrus	11, 44, 45	57	18	9		1.03		4.05
Right anterior insula	44	48	15	12		0.92		3.59
Right inferior parietal, supramarginal	40	60	-45	36		0.93		3.64
Right middle temporal gyrus	21	66	-39	-6		0.95		3.72
Bilateral cerebellum		51	-63	-21		1.05		4.11
Right putamen, caudate, thalamus		15	15	12		0.91		3.57
Cluster 2 (10,341 μ l)								
Left middle occipital gyrus	19	-48	-78	-12		0.92		3.59
Left middle temporal gyrus	21	-48	-18	-15		0.89		3.47
FHP > FHN								
Cluster 1 (178,146 μ l)								
Left fusiform	37	-30	-57	-6		1.10		4.30
Right fusiform	37	36	-39	-21		0.94		3.69
Right parahippocampal gyrus, hippocampus, amygdala		30	-15	-15		0.78		3.06
Left superior temporal gyrus, hippocampus, amygdala	22	-45	-15	-12		1.02		4.02
Right superior temporal gyrus	38	51	-3	-12		0.88		3.42
Right superior/inferior parietal	7, 40	39	-42	42		0.94		3.66
Bilateral cerebellum		-9	-48	-18		0.99		3.87
Cluster 2 (10,719 μ l)								
Right precentral gyrus	6	39	-18	33		0.88		3.44

Note: Coordinates, effect sizes, and t-values refer to extrema within each cluster.