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Differential Brain Response to Alcohol Cue Distractors across Stages of Alcohol Dependence

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Abstract

Altered attention to alcohol-related cues is implicated in the craving and relapse cycle characteristic of alcohol dependence (ALC). Prior cue reactivity studies typically invoke explicit attention to alcohol cues, so the neural response underlying incidental cue exposure remains unclear. Here, we embed infrequent, task-irrelevant alcohol and non-alcohol cues in an attention-demanding task, enabling evaluation of brain responses to distracting alcohol cues. Alcohol dependent individuals, across illness phase (n=44), and controls (n=20) performed a cue-reactivity fMRI target detection task. Significant Group-by-Distractor effects were observed in dorsal anterior cingulate cortex (ACC), inferior parietal lobule, and amygdala. Controls and long-term abstainers increased recruitment of attention and cognitive control regions, while recent and long-term abstainers decreased limbic recruitment to alcohol distractors. Across phases of ALC, self-reported craving positively correlated with cue-related activations in ventral ACC, medial prefrontal cortex, and cerebellum. Results indicate that brain responses elicited by incidental alcohol cues differentiate phases of ALC.

Keywords

abstinence; alcoholism; amygdala; anterior cingulate; cognitive control; distraction; inferior parietal lobule

INTRODUCTION

Alcohol dependence (ALC) is a chronic condition, characterized by repeated cycles of anticipation, binge/intoxication, and withdrawal (Koob and Volkow, 2010). Drug craving is a prominent feature of the anticipatory stage of the addictive cycle. Attention to alcohol-

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related environmental cues is associated with heightened craving for alcohol in individuals with ALC (Field and Cox, 2008). Cue-induced craving is thought to be an important mechanism involved in the development and maintenance of ALC, as well as a potential antecedent to relapse in recovering alcoholics (Koob and Volkow, 2010). Accordingly, craving plays a central role in the incentive-sensitization theory of addiction, which holds that with repeated use, drugs of abuse and their associated stimuli (i.e., cues) become imbued with salience, leading to hypersensitizing changes in mesolimbic dopaminergic signaling, which then perpetuate the addictive cycle (Robinson and Berridge, 1993).

Functional magnetic resonance imaging (fMRI) has been helpful in characterizing the neuroanatomical regions that subserve alcohol craving. A widely used cue-reactivity task design presents participants with alcohol-related sensory stimuli during MRI acquisition (Bragulat et al., 2008; Braus et al., 2001; Filbey et al., 2008; George et al., 2001; Grüsser et al., 2004; Heinz et al., 2007; Kareken et al., 2004; Myrick et al., 2004; Schneider et al., 2001; Tapert et al., 2004; Tapert et al., 2003; Vollstadt-Klein et al., 2011; Vollstadt-Klein et al., 2010; Wrase et al., 2002; Wrase et al., 2007). The anterior cingulate (ACC), medial prefrontal (PFC), and orbitofrontal cortices, striatum and amygdala are among the most consistent regions to show increased activation to alcohol cues (vs. control conditions) in individuals with ALC (Heinz et al., 2009), though quantitative meta-analysis of existing cue reactivity studies suggests that mesolimbic and prefrontal response to alcohol cues may not distinguish individuals with ALC from controls (Schacht et al., 2012). Reduced ventral striatal D2 receptor binding observed via PET positively related to ACC and medial PFC cortical fMRI activation to alcohol cues and to self-reported craving in individuals with ALC (Heinz et al., 2004). These findings suggest that alterations in PFC regions along with increased dopaminergic signaling in the striatum, may result in pathological processing of drug cues that is reflected in the subjective experience of craving. Cue reactivity studies examining other substances of abuse have implicated similar neuroanatomy, and many of these brain areas, including PFC (orbitofrontal, medial and cingulate regions), basolateral amygdala, insula and hippocampus, form a circuit thought to subserve the anticipatory stages of drug use (Koob and Volkow, 2010).

Most prior fMRI cue reactivity studies of alcohol have involved blocked task designs with relatively long cue presentation (typically up to several seconds per stimulus) (Bragulat et al., 2008; Braus et al., 2001; Filbey et al., 2008; George et al., 2001; Grüsser et al., 2004; Kareken et al., 2004; Myrick et al., 2004; Schneider et al., 2001; Tapert et al., 2004; Tapert et al., 2003; Vollstadt-Klein et al., 2011; Vollstadt-Klein et al., 2010; Wrase et al., 2002), often with explicit instructions for subjects to attend to alcohol cues. To facilitate craving phenomena, some studies have used a pre-task cue induction strategy such as providing participants with a priming sip of alcohol (George et al., 2001; Myrick et al., 2004). While the prior fMRI cue reactivity literature has been informative, the presence of “demand characteristics,” in which the investigator’s aims are relatively transparent to study participants, may complicate this work. In the context of demand characteristics, study participants may invoke different response strategies, including i) attempting to “crave” in order to comply with perceived investigator expectations, or ii) attempting to suppress craving in order to make a good impression or appear in control of responses to alcohol. Moreover, demand characteristics may interact with clinical stage of ALC. For example, recovering ALC patients, who are maintaining abstinence from alcohol, may have developed strategies to suppress or minimize craving responses, whereas currently drinking alcoholics may not feel ambivalent about allowing themselves to crave. In this study, we sought to minimize the role of demand characteristics by investigating brain responses to infrequent, task-irrelevant alcohol cues that represent distractors in the context of a primary attention-demanding target detection task. Accordingly, we developed a modified cue reactivity paradigm in which low-probability non-target distractors (alcohol and non-alcohol beverage

pictures) were embedded within a visual oddball target detection task, similar to the emotional oddball paradigms developed by McCarthy and colleagues to evaluate brain responses to affective distractors during cognitive performance (Fichtenholtz et al., 2004; Wang et al., 2005; Wang et al., 2008; Yamasaki et al., 2002). This task enabled us to examine brain responses to alcohol cues in the context of cognitive-affective processing interactions.

Because alcohol-related brain alterations may be subject to repair and/or reorganization during periods of abstinence (Crews et al., 2005), functional brain responses to alcohol cues may depend on whether an individual is currently drinking, in early recovery, or in sustained remission. Therefore, in addition to healthy controls, we recruited subjects at three different clinical stages of alcoholism (current drinkers, recent abstainers, and long-term abstainers). Based on previous research suggesting partial reversal of ALC-associated brain damage with abstinence (Crews et al., 2005), our overarching hypothesis was that brain response to task-irrelevant alcohol distractors would differ among the three ALC groups in regions relevant for attentional and affective processing of transient distractors, with the long-term abstinent group most closely resembling healthy control response patterns. However, we also evaluated the alternative possibility that individual subjective craving ratings of alcohol cues would be a determinant of variation in cue-elicited brain activations, by conducting a correlational analysis of self-reported craving and brain response to alcohol cues, collapsed across ALC clinical stage.

MATERIALS AND METHODS

Participants

Four groups of participants (ages 21-60) were included in this study: Current Drinkers (CD, n=16) were non-treatment seeking; Recent Abstainers (RA, n=15) were undergoing treatment for ALC; Long-term Abstainers (LTA; n=13) were maintaining sustained ALC recovery; Healthy Comparisons (HC; n=20) had no history of ALC. CD, RA, and LTA participants met DSM-IV-TR (American Psychiatric Association, 2000) ALC criteria, with the following course specifiers: CD met criteria for continuous ALC (mean last use 1.7 days); RA last used alcohol within 5-30 days (mean last use 20.5 days); and LTA met criteria for sustained full remission, with a minimum of 1 year since last alcohol use (mean last use 1989.0 days). The Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002) was used to confirm a diagnosis of ALC in LTA, RA, and CD groups and to document a negative history of exclusionary psychiatric disorders in all participants. Participants were excluded for meeting lifetime DSM-IV-TR criteria for schizophrenia and other psychotic disorders, post-traumatic stress, obsessive-compulsive, panic, and somatoform disorders. Current or past depressive disorder, substance-induced mood disorder, and past (i.e., not current) drug abuse or dependence were permitted in the ALC groups, based on the high co-morbidity between ALC and these conditions (Hasin et al., 2007). In addition, history of delirium tremens or alcohol withdrawal seizures, neurological disease, head trauma with loss of consciousness, or other serious medical conditions were exclusionary. Patients experiencing acute alcohol withdrawal symptoms, defined by a Clinical Institute of Withdrawal Assessment-Revised (CIWA-Ar) score >8, (Sullivan et al., 1989) were not recruited. Current nicotine use was assessed with the Fagerström Test for Nicotine Dependence (Fagerström et al., 1990) and current depressive symptoms were assessed via the Beck Depression Inventory (BDI) (Beck et al., 1979).

Information related to time course of ALC and quantity/frequency of alcohol use was documented through multi-modal assessment based on participant report, clinical measures, treatment provider evaluation, and breathalyzer samples. In addition to SCID interview, the following assessment measures characterized alcohol dependence in ALC groups: Michigan

Alcohol Screening Test (Selzer, 1971); Alcohol Dependence Scale (ADS) (Skinner and Horn, 1982); and Alcohol Craving Scale (ACS) (Krystal et al., 1994). Family history of ALC was determined by the Family History Assessment Module (Rice et al., 1995). Abstinence monitoring in the LTA group was further achieved by assessing alcohol use biomarkers (e.g., mean corpuscular volume, gamma-glutamyl transferase), which were reviewed by a study physician (D.H.M.). These biomarkers were not reviewed for RA or CD participants, due to their recency of heavy alcohol use. All participants were asked to refrain from alcohol and drug use for 18 hours prior to assessment sessions, and confirmatory breathalyzer samples and urine toxicology screens were collected prior to data collection sessions.

Abstinent participants were recruited from hospital-based (RA) or outpatient (LTA) ALC treatment programs at the West Haven VA Hospital and the Connecticut Mental Health Center. HC and CD participants, and some LTA participants, were recruited from the local community. Written informed consent was obtained from study participants, under protocols approved by the Human Subjects Subcommittee of the VA Connecticut Healthcare System and the Human Investigations Committee of the Yale University School of Medicine.

fMRI Task

Participants performed a visual oddball task that presented 4 trial types in an event-related design: frequents (80% of trials), infrequent targets (10% of trials), non-alcohol distractors (NAD; 5% of trials), and alcohol distractors (AD; 5% of trials). The frequent stimulus was a small blue circle and the target stimulus was a large blue circle. NAD stimuli were color photographs of nonalcoholic beverages (e.g., water, coffee, soda) and AD stimuli were color photographs of alcoholic beverages (e.g., beer, wine, liquor), which were drawn from photograph sets used in prior studies (George et al., 2001; Heinz et al., 2004) supplemented with stimuli developed for the current study. Participants were instructed to respond, via button press, to infrequent target stimuli and to withhold responses to all other stimuli. Trials were presented for 700 ms, with variable inter-stimulus interval (ISI) lengths of 300, 800, 1000, or 1300 ms. Target-to-Target median SOA was 12.5 s (minimum = 4.0 s; maximum = 47.5 s). AD-to-AD median SOA was 22.0 s (minimum = 2.0 s; maximum = 107.0 s). NAD-to-NAD median SOA was 21.8 s (minimum = 4.0 s; maximum = 79.0 s). Median SOA between any two distractor stimuli was 13.0 s (minimum = 2.0 s; maximum = 51.5 s). Task stimuli were inversely projected and viewed through a mirror on the head coil. Behavioral responses were recorded via a fiber-optic response pad. Target accuracy was defined as the percentage of targets that were correctly identified (hits), such that lower accuracy scores reflect omission errors. Commission error rates to both AD and NAD trial types were low across individuals (range: 0-2 errors) and were not subjected to analysis.

Post-Scanner Picture Rating Task

Study participants rated AD and NAD stimuli to assess beverage identification accuracy and elicited craving. For each beverage stimulus, participants were asked to identify the beverage type (possible responses: alcohol, non-alcohol, or unsure). Next, participants answered four questions related to craving for that beverage, each rated on a seven-point Likert scale (see Figure 1). Mean craving ratings were constructed for AD and NAD stimuli, with higher scores reflecting greater craving. Based on accuracy of responses to the post-scan beverage identification task, 6 alcohol and 6 non-alcohol beverage stimuli were declared ambiguous because ≤90% of participants correctly identified them. These ambiguous picture stimuli were excluded from AD and NAD craving summary measures and were modeled separately in the fMRI analysis. FMRI and behavioral data analyses were based on the retained pictures (33 unique AD and 33 unique NAD). For each alcohol and non-alcohol image, means were calculated for red, green and blue intensity (RGB color

space), as well as for luminance (YCbCr color space) using MATLAB's (The MathWorks, Natick, Massachusetts, USA) Image Processing Toolbox. Independent t-tests comparing the two stimulus types on each visual attribute showed no significant differences (two-tailed p-values ranging from .57 to .73).

fMRI Acquisition and Processing

Brain images were acquired at the Yale MRI Center on a Siemens Trio 3 Tesla magnet using a quadrature head coil. Participants completed 3 runs of the visual oddball task, with 260 trials per run. Echoplanar imaging was collected in an axial-oblique plane: TR = 2 sec, TE = 28 msec, flip angle = 85°, NEX = 1, FOV = 22×22cm, 64×64 matrix, 33 4 mm slices with a 0.5 mm gap, and a 3.4375 × 3.4375 mm in-plane voxel size. To mitigate non-equilibrium effects, images corresponding to the first 6 TRs were discarded from analysis, leaving 195 volumes for analysis, per run.

Analysis of Functional NeuroImages (AFNI) software's 3dDespike removed large spike artifacts from the raw time series (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dDespike.html). Subsequent image processing was performed using Statistical Parametric Mapping (SPM5) (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). Preprocessing entailed slice timing correction and motion correction via affine registration of each run's time series to the first image of the run. Mean functional images from each run were then normalized to a standard neuroanatomical space (Montreal Neurological Institute's MNI-152 template), resliced to $2mm^3$ voxel dimensions, and spatially smoothed with a 8mm FWHM Gaussian filter. For individual subject (first-level) analyses, SPM's canonical hemodynamic response function was convolved with temporal event-vectors for the four task conditions (frequents, targets, AD, and NAD), with separate vectors modeling error trials and the 12 ambiguous beverage stimuli. In addition, the 6 motion parameters from realignment, along with their n-1 temporal lags, were included as regressors to remove fluctuations in blood oxygen level-dependent (BOLD) signal attributable to participant head movement. Regressors coding for each run were also included. Beta coefficients representing the fit of each regressor to a voxel's time series were estimated using GLM after applying a high-pass filter (128 s) to remove low-frequency noise. Voxelwise beta estimates for event types were adjusted by their temporal derivative beta images, to reduce amplitude bias arising from spatial non-uniformity of hemodynamic response latency (Calhoun et al., 2004). Group-based (second-level) analyses were then conducted to evaluate brain responses to AD relative to NAD, as described below.

Age-Adjustment Z-scoring Procedure

Although participants were recruited across the same age range and substantially overlapped in their age distributions, the four groups differed by as much as a decade in their mean ages. In order to minimize any potential age-related confounds of our fMRI results, we removed fMRI signal variance attributable to normal aging. However, to accomplish this, we did not implement a standard analysis of covariance (ANCOVA) using age as a covariate, as such an approach fails to distinguish normal aging from pathological aging effects. Pathological aging effects have been described in ALC volumetric brain measurements, whereby older alcoholics have more severe brain alterations, relative to younger alcoholics when controlling for age (Pfefferbaum et al., 2006; Pfefferbaum et al., 1997; Pfefferbaum et al., 1992). These prior findings underscore the importance of separating normal vs. pathological aging effects on brain measurements in this population. Our approach to comparing MRI data across groups that differed in age is based on our prior studies (Mathalon et al., 2003; Pfefferbaum et al., 1992; Pfefferbaum et al., 1997; Sullivan et al., 1998). First, normal aging effects were modeled by conducting a voxelwise regression of each fMRI contrast map on participant age within the HC group. Then, for each contrast image, and for each participant

irrespective of group membership, an age-adjusted z-score was generated for each image voxel, calculated as follows:

$$Age\text{-}\ adjusted\ z\text{-}\ score = (\text{observed contrast value} - \text{contrast value predicted for a healthy individual of a given age}) / \text{standard error of the HC age regression.}$$

Thus, an individual participant's age-adjusted z-score voxelwise map reflects the deviation in brain activity, expressed in standard deviation units, from that expected for a healthy individual of a similar age.

Data Analysis

Target accuracy was analyzed with one-way ANOVA with Group as the between-subjects factor. Post-scan craving ratings of AD and NAD stimuli were analyzed via repeated measures ANOVA (rmANOVA) with Group as the between-subjects factor and Beverage Type (AD, NAD) as the within-subjects factor. Group differences in brain responses to AD vs. NAD were examined using voxelwise rmANOVA with Group as a between-subject factor and Distractor (AD-Frequents, NAD-Frequents) as a within-subject factor. The resulting Group-by-Distractor interaction F-map was thresholded voxelwise (height $p<0.01$; k = 6 voxels, FWE-corrected, $p<.05$). Type 1 error was controlled by only pursuing follow-up analyses on 1) regions meeting criteria FWE-correction ($p<.05$) and 2) an a priori amygdala region of interest (ROI). Amygdala activations were examined via ROI analysis because detection of activity from small volumes is not favored by suprathreshold clustering algorithms which are preferentially sensitive to large regional activations. There were strong a priori indications for examining Group-by-Distractor effects within the amygdala, based on this region's general implication in processing sensory stimuli with affective significance (Anderson and Phelps, 2001; Phelps and LeDoux, 2005) and specific implication in both alcohol cue reactivity (Heinz et al., 2009) and processing of affective distractors during cognitive task performance (Fichtenholtz et al., 2004; Wang et al., 2005; Yamasaki et al., 2002). The bilateral amygdala ROI was defined anatomically using the Talairach-Daemon-based Wake Forest University (WFU) PickAtlas (Maldjian et al., 2003), and was further refined functionally by intersecting it with the thresholded ($p<.01$) Group-by-Distractor interaction F-map. The resulting mask contained mostly (95%) right-sided amygdala voxels. For each participant, mean age-adjusted AD-NAD z-scores were extracted from regional clusters achieving FWE-correction in our whole-brain analysis, as well as from our intersected amygdala ROI. These z-scores were imported into SPSS and subjected to one-way ANOVAs by Group with Tukey-Kramer HSD pairwise post-hoc tests, to determine which groups contributed to observed Group-by-Distractor interactions. Voxelwise correlational analyses evaluated the relationship between AD-NAD fMRI response and subjective craving ratings of the AD stimuli obtained outside the scanner. These correlations were performed in a combined ALC group (CD + RA + LTA; n=44) to evaluate our secondary hypothesis that subjective craving reactions to alcohol cues would be a determinant of variation in brain activation, irrespective of the clinical stage of alcohol dependence. Mean alcohol craving ratings were correlated voxelwise with the age-adjusted AD-NAD contrast z-scores (height $p<0.005$; k = 6 voxels; FWE-corrected, $p<.05$).

RESULTS

Clinical and Behavioral Data

Mean group demographic and clinical variables, as well as statistical tests for group differences are reported in Table 1. A main effect of Group for participant age ($p<.05$) was

observed, reflecting the older age of the LTA and RA groups relative to the HC and CD groups. When following-up the significant omnibus main effect of age, statistical trends (.05<p<.09) were observed between HC vs. LTA, HC vs. RA, CD vs. LTA, and CD vs. RA pairwise comparisons. While pairwise tests only approached statistical significance, mean ages between the groups differed by as much as a decade and consequently we could not rule out the possibility of age confounds to our fMRI group comparisons. Therefore, age differences were addressed by using age-adjusted z-scores as described in the methods section. Across the four participant groups, there were no differences ($p>.05$) in parental SES, as assessed with the Hollingshead Index (Hollingshead, 1957), or gender. Directly after the scan session, the CD group reported significantly more alcohol-related craving on the ACS than both HC and LTA groups ($p<.05$). Comparing the four groups on self-reported depression symptoms, as assessed with the BDI, there was an omnibus main effect of group ($p<.05$), with post-hoc tests showing marginally significant tendencies for greater symptom severity in RA and CD groups, compared to the HC group. 23% of the ALC subjects (41.6% of long-term abstainers, 9.1% of recent abstainers, 16.7% of current drinkers) met criteria for lifetime depressive disorder. However, none of the ALC subjects met criteria for past-month depressive disorder. Moreover, mean BDI scores across the groups were well below the threshold indicative of clinically significant depressive symptoms (Beck et. al., 1988). There was also an omnibus main effect of group for smoking status ($p<.05$), driven by significantly lower Fagerström Test for Nicotine Dependence scores in HC compared to RA, and a trend for lower scores in CD compared to RA. There were no significant differences between any of the ALC groups on Fagerström Test for Nicotine Dependence scores ($p>.05$).

Considering just the three ALC groups (LTA, RA, CD) on clinical characteristics of ALC, there were no differences across ALC groups in family history of alcoholism or age of participant ALC onset. Groups differed in number of alcohol dependency treatment attempts, with both the LTA and RA groups having significantly more prior treatment attempts than the CD group ($p<.05$). There was an omnibus trend for a main effect of ALC group on ADS scores ($p=.06$), a measure of alcohol dependence severity, with the CD tending to have less severe ADS scores than the LTA and RA groups.

Analysis of within-scanner behavioral data revealed no main effect of Group on target accuracy ($p>.05$), indicating similar task engagement by all groups. RmANOVA of post-MRI craving ratings (see Figure 1) revealed significant main effects of Group (F (3, 60) = 4.27, $p=.008$) and Beverage Type (F (1, 60) = 34.91, $p<.001$), in addition to a significant Group by Beverage Type interaction (F (3, 60 = 5.21; $p=.003$). This interaction was followed up via oneway ANOVAs examining the Group effect separately for each Beverage Type (alcohol, non-alcohol). For the alcohol pictures, results revealed a significant main effect of Group on the craving ratings (F (3, 60) = 6.94; $p<.001$), with greater craving endorsed by the CD participants relative to each of the other groups (all $p<.05$), none of which differed significantly from each other. For the non-alcohol pictures, craving ratings did not significantly differentiate the groups ($p>.05$).

Beverage Distractors - Frequents

Prior to identifying brain regions that were differentially responsive to distractor type, activation patterns common to infrequent distractors, irrespective of type, were characterized via a conjunction analysis between the AD-Frequent and NAD-Frequent contrasts (unadjusted for age), each of which were initially averaged across groups. The resulting conjunction map (see Figure 2), thresholded at $p<.01$ (FDR-corrected), revealed prominent activations in ventral stream regions (e.g., extrastriate cortex/BA 18, 19, fusiform gyri), medial temporal regions (hippocampi, parahippocampal gyri), amygdala, thalamus, inferior

and superior parietal lobules (including bilateral BA 7), dorsal cingulate/medial superior frontal cortex (including BA 6, 8, 24, 32), dorsolateral PFC (including BA 9, 46), and inferior frontal cortex (BA 45, 47).

Alcohol vs. Non-Alcohol Distractors (AD vs. NAD)

Before evaluating AD vs. NAD responses across groups, we qualitatively examined the AD-NAD contrast map within the HC group in order to characterize the pattern of healthy brain responses to AD. At a p<.01 uncorrected height threshold, HC showed greater AD than NAD activations in (mostly bilateral, though more extensively right-sided) middle and inferior frontal gyri, inferior parietal lobule, visual cortex, midbrain and putamen, along with very modest amygdala response; at a relaxed height threshold of p<.025 bilateral AD>NAD activations were present in the amygdala. Whole-brain voxelwise rmANOVA (height $p<0.01$; k = 6 voxels, FWE-corrected, p<.05) revealed Group-by-Distractor interaction effects in two clusters that surpassed multiple comparison thresholding: 1) A left inferior parietal lobule (IPL) cluster extending anteriorly through the post- and precentral gyri and 2) a right dorsal ACC cluster. (Of note, a right-sided cluster containing anterior IPL, superior temporal gyrus, and mostly pre- and postcentral gyri did not meet significance thresholding at a $p<.01$ height threshold, but did meet FWE-correction using a relaxed height threshold of $p<.05$; inspection of group cluster means in this right parietal region revealed a similar pattern of AD>NAD patterns to that seen in the left hemisphere. This right-sided parietal region was not analyzed further or interpreted, as the region failed to meet the a priori threshold set for correction of multiple comparisons, but we consider it noteworthy to report that a subthreshold Group-by-Distractor effect was observed in right-sided parietal regions similar to those that met significance thresholding in the left hemisphere). The mean AD-NAD contrast values from the two clusters meeting multiple comparisons correction were extracted for all participants and subjected to follow-up Tukey-Kramer tests to determine which groups differed. Non-significant *p* values from pairwise comparisons that approached $p<.05$ ($.1<p<.05$) were also reported in the interest of identifying which groups contributed to the FWE-corrected cluster interaction effects observed via voxelwise rmANOVA. See Table 2 for neuroanatomical extents and cluster characteristics of Group-by-Distractor interaction effects. Mean raw AD and NAD cluster activations and age-corrected z-scores by Group are shown in Figure 3.

Left Inferior Parietal Cluster—Inspection of the unadjusted activation means in HC revealed an AD > NAD difference involving activation to AD relative to deactivation to NAD stimuli. Between-group post-hoc tests of the age-corrected AD-NAD difference z-scores indicated that relative to this HC pattern, and to the very similar AD > NAD pattern exhibited by the LTA group, the RA group showed a significant pattern reversal (i.e., NAD > AD) involving activation to NAD and deactivation to AD stimuli (RA < HC, $p=.001$; RA < LTA, $p=.001$). In addition, the CD group showed a non-significant ($p=.10$) pattern reversal (NAD > AD) relative to LTA.

Right Dorsal Anterior Cingulate Cluster—Inspection of the cluster means in HC revealed essentially no activation to AD stimuli, compared to deactivation to NAD. Between-group post-hoc tests of the age-corrected AD-NAD difference z-scores indicated that the LTA group AD > NAD response was significantly different from the NAD > AD pattern observed in both RA ($p= .01$) and CD groups ($p=.001$). In addition, the LTA group showed a non-significantly enhanced AD > NAD difference relative to the HC group ($p=.08$).

In the rmANOVA of the a priori amygdala ROI age-adjusted z-scores, there was a significant Group-by-Distractor interaction ($p = .003$). Inspection of the unadjusted

activation means in HC revealed greater activation to AD than to NAD stimuli. Tukey-Kramer follow-up tests of the age-corrected AD-NAD difference z-scores showed a significant reduction from the HC pattern in the LTA group (p =.01) and a non-significant reduction in the RA (p=.07) group, both of which showed an NAD > AD activation pattern. In addition, similar to the HC group, CD showed an AD > NAD activation pattern that differed from the LTA group (*p*=.02). See Figure 4.

Within ALC group correlation between Alcohol Distractor vs. Non-Alcohol Distractor Response and craving

Voxelwise correlation between AD-NAD response and mean alcohol picture craving rating within a combined group of all ALC participants (n=44) revealed a significant positive correlation within two clusters (height $p<0.005$; k = 6 voxels, FWE-corrected, $p<.05$). One region consisted of bilateral (though mostly left hemispheric) medial PFC/ACC and extended inferiorly to subcallosal cortex. The other region consisted of bilateral cerebellum. There were no regions that showed a significant negative association with participant craving ratings that survived FWE-correction. See Table 3 and Figure 5.

DISCUSSION

This study identified brain regions responsive to task-irrelevant alcohol cues embedded in a cognitive task, and examined whether brain activations to these behaviorally salient alcohol distractors differed across stages of ALC. Across the four participant groups, both types of beverage distractors activated ventral stream regions including extrastriate and inferior temporal cortex, as well as lateral PFC. HC activations to alcohol versus non-alcohol distractors (AD-NAD) were observed in visual cortex, middle and inferior frontal gyri, inferior parietal lobule, amygdala, putamen, and midbrain, presumably reflecting normative responses to behaviorally salient stimuli. Many of these regions, including the amygdala and ventral frontal and temporo-occipital cortices show greater activation in healthy adults to affective vs. neutral distractors embedded in a cognitive task (Fichtenholtz et al., 2004; Wang et al., 2005; Yamasaki et al., 2002). Most importantly, AD-NAD activation patterns segregated stages of alcoholism. Inferior parietal and dorsal ACC regions implicated in cognitive control processes (Vincent et al., 2008), showed more AD-NAD activation in HC and LTA groups, in contrast to the pattern exhibited by CD and RA groups. In our ROI analysis, the groups in recovery (LTA and RA) showed smaller AD-NAD amygdala activations relative to HC and CD. Taken together, our results suggest that 1) long-term recovery from ALC, or absence of ALC history, is associated with *increased* recruitment of cognitive control regions in response to alcohol distractors (observed in LTA and HC), and 2) short- and long-term abstinence from alcoholic drinking is associated with *decreased* recruitment of limbic regions associated with affective processing of alcohol distractors (observed in LTA and RA).

Correlation Between Alcohol – Non-alcohol Distractor Activation Differences and Alcohol Cue Craving Ratings

We also considered AD-NAD brain activations in light of post-scan craving ratings. CD participants endorsed greater craving ratings of AD stimuli, relative to each of the other groups, while ratings of NAD stimuli did not distinguish the groups. The correlation analysis, for which all ALC participants were combined into a single group, indicated that individuals who endorsed more craving showed greater AD-NAD activation within two significant clusters: 1) bilateral medial PFC, ventral ACC, and subcallosal cortex and 2) bilateral cerebellum. Medial PFC and ventral ACC regions have been implicated frequently in alcohol cue craving (see Heinz et al, 2009, for review). Indeed, in a recent meta-analysis of alcohol cue reactivity studies (Schacht et al., 2012), ventral ACC was identified as one of

the core regions activated during alcohol cue processing. Brain activity in these regions appears to be modulated by craving behavior, reflected by previous reports of positive correlations between brain responses to alcohol cues and subjective alcohol craving in ventral ACC/subcallosal cortex (Grüsser et al., 2004; Myrick et al., 2004; Tapert et al., 2004). In contrast to the more cognitive dorsal ACC region (Bush et al., 2000) that showed diminished activation to alcohol cues in CD and RA relative to LTA participants, the ACC and subcallosal regions associated with craving are components of the ventral limbic system implicated in affective processing (Bush et al., 2000), and in addiction-related cue-induced craving (Koob and Volkow, 2010). Because ventral ACC AD-NAD activation was associated with craving, but did not differentiate the ALC groups in our Group-by-Distractor analysis, it may be that individual variation in craving is a stronger correlate of activation in this putative reward region than stage of ALC. In addition to ventral ACC, cerebellar activation was positively associated with craving, similar to a prior report (Schneider et al., 2001). While the functional significance of cerebellar activation during alcohol cue processing remains to be elucidated, it may relate to increasingly appreciated cerebellar contributions to affective and executive functions (Stoodley and Schmahmann, 2009). Findings from our correlational analysis show that participant craving ratings of alcohol cues positively related to brain activations elicted in response to brief presentation of these same cues, despite the task-irrelevance of the alcohol cues to the visual oddball task being performed.

Group Differences in Alcohol – Non-alcohol Distractor Activations in Areas Relevant for Attention and Cognitive Control

Voxelwise rmANOVA revealed significant Group-by-Distractor interaction effects in left IPL and right dorsal ACC. The LTA and HC participants generally showed greater AD-NAD IPL activation, whereas the RA and, to a lesser extent the CD, participants showed the opposite pattern (i.e., NAD > AD). Both functional connectivity (Dosenbach et al., 2007; Gao and Lin, 2012; Vincent et al., 2008) and activation-based fMRI studies (Crone et al., 2006; Liston et al., 2006) have linked IPL regions with cognitive control. Cognitive control functions guide goal-directed cognition and behavior, including conflict monitoring and recruitment of top-down control (Miller and Cohen, 2001). In the context of our target-detection task, increased recruitment of cognitive control circuitry in HC and LTA groups may reflect resource allocation to maintain task goals in the face of behaviorally salient alcohol distractors. Consistent with this interpretation, Group-by-Distractor interactions were also identified in dorsal ACC, a cognitive control region implicated in monitoring response conflict (Bush et al., 2000; Carter and van Veen, 2007). Within this dorsal ACC region, LTA participants showed significantly more activation than RA and CD participants, with a similar (though non-significant) pattern evident relative to HCs.

The IPL has also been implicated in the allocation of attention to infrequent salient stimuli, including task-relevant targets and task-irrelevant distractors (Bledowski et al., 2004; Corbetta et al., 2008; Kiehl et al., 2005). From this perspective, our results suggest that alcohol distractors, relative to non-alcohol distractors, were more attention-grabbing to HC and LTA participants than to current and recent drinkers. As noted by Corbetta and colleagues (2008): “Reorienting to new objects may occur reflexively, based on their high sensory saliency…but distinctive objects attract attention more effectively when they are also behaviorally relevant…either because they match our current goals or because of long-term memory associations that signal their importance” (pg. 307). The smaller IPL activation to AD-NAD in RA (and to some extent CD) participants suggests that attentional processing of the alcohol cues was diminished in these groups. This may be a parallel phenomenon to increased deactivation shown in parietal regions by depressed individuals to sad distractors during performance of an emotional oddball task, which has been interpreted

as an indication of emotional distraction (Wang et al., 2008). That is, observed fMRI response reductions in RA and CD groups to alcohol cues may signify decreased processing of these stimuli by parietal attention and/or cognitive control regions, leaving these groups more vulnerable to alcohol cue-induced emotional distraction.

Alcohol Distractor – Non-alcohol Distractor Group Differences in the Amygdala

Examination of AD-NAD amygdala activations revealed more activity in HC compared to both LTA and RA, as well as more activity in CD, compared to LTA. One interpretation of these findings is that amygdala activation was elicited by the appearance of task-irrelevant alcohol distractors in individuals who currently drink alcohol, whether socially (HC) or alcoholically (CD). The amygdala is thought to have a role in saliency detection, achieved through enhancing attentional and perceptual cortical processing of sensory stimuli with affective significance (Anderson and Phelps, 2001; Lim et al., 2009; Phelps and LeDoux, 2005). Research using an emotional oddball task with similar design to the current study revealed that healthy adults engage a ventral brain system including the amygdala in response to task-irrelevant affective distractors (Fichtenholtz et al., 2004; Wang et al., 2005; Yamasaki et al., 2002). Because amygdala activation is reduced during explicit engagement of emotional regulation (Kanske et al., 2011), observed reductions in LTA and RA amygdala activity could reflect an attempt to regulate affective responses to alcohol cues, consistent with the goal of maintaining abstinence from alcohol. Amygdala activity reduction was observed most consistently in the LTA group (which significantly differed from both HC and CD groups), whereas the RA group showed a statistical trend toward reduction from the HC group. This pattern may reflect stronger regulation of limbic responses to alcohol cues with abstinence duration, a speculation that could be directly investigated in future studies employing a longitudinal study design.

Summary

Several brain regions showed differential activation to alcohol cue distractors as a function of ALC phase of illness. First, in response to task-irrelevant alcohol cues, the LTA group, relative to RA and CD groups, showed greater recruitment of regions supporting attention and cognitive control functions. Second, within the amygdala, both LTA and RA groups showed decreased AD-NAD activations. These alterations may represent recovery-associated changes in the brain's response to alcohol distractors via increased engagement of regions that modulate attention and response conflict (observed in LTA) and decreased engagement of limbic regions responsible for processing affectively salient stimuli (observed in LTA and RA). Our results differ from the heightened ALC limbic activation typically reported in the alcohol cue-craving literature (see Heinz et al, 2009, for review). This difference likely relates to the context in which our study presented alcohol cues, as task-irrelevant distractors within an attention-demanding cognitive paradigm. In contrast, extant cue-craving studies typically invoke explicit attention to cues. Also, the ratio of alcohol cues to other task stimuli is low in the current study (probability =.05) compared to previous studies. Accordingly, our task likely captures relatively automatic recruitment of attention, cognitive control, and affective circuitry associated with processing these behaviorally salient, but task-irrelevant, stimuli. These observations beg the question as to how recruitment of these circuits interacts (or perhaps interferes) with neural resource allocations needed to maintain task goals. We did not directly examine the impact of alcohol cue distractors on target detection-related brain activity, as our fMRI task design was not optimized to parse oddball targets by preceding distractor type. In particular, intervals between targets and preceding beverage cues were relatively long and variable, and it seemed unlikely that meaningful influences of the distractors on target processing could be detected. Future work examining the effects of distracting alcohol cue presentation on attention task-related brain activity would be a logical extension of the current study.

Study limitations—Our findings are limited by several factors. Our modest within-group sample sizes may have diminished statistical power to detect relationships with smaller effect sizes than those observed. Selection biases may also arise from study participants self-selecting. We derived our ALC samples via recruitment from the community (CD, LTA) and clinical settings (RA, LTA). Though not uncommon in clinically-focused studies, these recruitment strategies may not yield fully representative samples, which would limit the degree to which our findings generalize to the larger ALC population. While our ALC groups were well-matched on age of onset and family history of alcoholism, there was a tendency for ALC severity to be greater in the RA and LTA groups than in the CD group. The CD group also had significantly fewer prior treatment attempts, compared to both LTA and RA groups, and the modal CD participant was treatment-naïve. Treatment-naïve and treatment-seeking alcoholics may represent distinct sub-populations with different clinical and neurocognitive profiles (Fein and Landman, 2005; Smith and Fein, 2010). Lastly, the possibility of changes in the brain's response to alcohol cues with ALC recovery is intriguing. However, the current cross-sectional study design cannot distinguish between recovery-associated brain changes versus pre-morbid differences among ALC groups, or rule-out other alternative explanations for the differences we observed between ALC clinical stages.

Future studies using a longitudinal design to evaluate changes in brain responses to alcohol cues across phases of alcohol dependence *within* individuals would be helpful in extending our study's findings and overcoming the limitations inherent in our cross-sectional design. Our results suggest that brain response to alcohol cues, presented as task-irrelevant distractors, may be dynamic across the ALC illness course. Although this study does not have direct clinical treatment implications, the association of alcoholic recovery with more cognitive control and less limbic engagement during alcohol cue presentation provides new insights into neural mechanisms underlying recovery from ALC.

Acknowledgments

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References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition, Text Revision. American Psychiatric Association; Washington DC: 2000.

Anderson AK, Phelps EA. Lesions of the human amygdala impair enhanced perception of emotionally salient events. Nature. 2001; 411:305–309. [PubMed: 11357132]

Beck, A.; Rush, A.; Shaw, B.; Emery, G. Cognitive therapy of depression. Guilford Press; New York: 1979.

Beck AT, Steer RA, Garbin MG. Psychometric properties of the beck depression inventory: Twenty-five years of evaluation. Clinical Psychology Review. 1988; 8:77–100.

Bledowski C, Prvulovic D, Goebel R, Zanella FE, Linden DE. Attentional systems in target and distractor processing: a combined ERP and fMRI study. Neuroimage. 2004; 22:530–540. [PubMed: 15193581]

Bragulat V, Dzemidzic M, Talavage T, Davidson D, O'Connor S, Kareken D. Alcohol sensitizes cerebral responses to the odors of alcoholic drinks: an fMRI study. Alcoholism: Clinical and Experimental Research. 2008; 32:1124–1134.

Braus D, Wrase J, Grüsser S, Hermann D, Ruf M, Flor H, Mann K, Heinz A. Alcohol-associated stimuli activate the ventral striatum in abstinent alcoholics. Journal of Neural Transmission. 2001; 108:887–894. [PubMed: 11515754]

Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends in Cognitive Sciences. 2000; 4:215–222. [PubMed: 10827444]

Calhoun V, Stevens M, Pearlson G, Kiehl K. fMRI analysis with the general linear model: removal of latency-induced amplitude bias by incorporation of hemodynamic derivative terms. Neuroimage. 2004; 22:252–257. [PubMed: 15110015]

Carter CS, van Veen V. Anterior cingulate cortex and conflict detection: an update of theory and data. Cognitive, Affective, & Behavioral Neuroscience. 2007; 7:367–379.

Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to theory of mind. Neuron. 2008; 58:306–324. [PubMed: 18466742]

Crews FT, Buckley T, Dodd PR, Ende G, Foley N, Harper C, He J, Innes D, Loh el W, Pfefferbaum A, Zou J, Sullivan EV. Alcoholic neurobiology: changes in dependence and recovery. Alcoholism: Clinical and Experimental Research. 2005; 29:1504–1513.

Crone EA, Wendelken C, Donohue SE, Bunge SA. Neural evidence for dissociable components of task-switching. Cerebral Cortex. 2006; 16:475–486. [PubMed: 16000652]

Dosenbach NU, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RA, Fox MD, Snyder AZ, Vincent JL, Raichle ME, Schlaggar BL, Petersen SE. Distinct brain networks for adaptive and stable task control in humans. Proceedings of the National Academy of Sciences U S A. 2007; 104:11073–11078.

Fagerström KO, Heatherton TF, Kozlowski LT. Nicotine addiction and its assessment. Ear Nose Throat Journal. 1990; 69:763–765.

Fein G, Landman B. Treated and treatment-naive alcoholics come from different populations. Alcohol. 2005; 36:19–26. [PubMed: 16440475]

Fichtenholtz HM, Dean HL, Dillon DG, Yamasaki H, McCarthy G, LaBar KS. Emotion-attention network interactions during a visual oddball task. Brain Research. Cognitive Brain Research. 2004; 20:67–80. [PubMed: 15130591]

Field M, Cox W. Attentional bias in addictive behaviors: A review of its development, causes, and consequences. Drug and Alcohol Dependence. 2008; 97:1–20. [PubMed: 18479844]

Filbey F, Claus E, Audette A, Niculescu M, Banich M, Tanabe J, Du Y, Hutchison K. Exposure to the taste of alcohol elicits activation of the mesocorticolimbic neurocircuitry. Neuropsychopharmacology. 2008; 33:1391–1401. [PubMed: 17653109]

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version. In: B., editor. Research. Patient Edition. New York State Psychiatric Institute; New York: 2002. (SCID-I/P)

Gao W, Lin W. Frontal parietal control network regulates the anti-correlated default and dorsal attention networks. Human Brain Mapping. 2012; 33:192–202. [PubMed: 21391263]

George M, Anton R, Bloomer C, Teneback C, Drobes D, Lorberbaum J, Nahas Z, Vincent D. Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. Archives of General Psychiatry. 2001; 58:345–352. [PubMed: 11296095]

Grüsser S, Wrase J, Klein S, Hermann D, Smolka M, Ruf M, Weber-Fahr W, Flor H, Mann K, Braus D, Heinz A. Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. Psychopharmacology. 2004; 175:296–302. [PubMed: 15127179]

Hasin DS, Stinson FS, Ogburn E, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Archives of General Psychiatry. 2007; 64:830–842. [PubMed: 17606817]

Heinz A, Beck A, Grüsser S, Grace A, Wrase J. Identifying the neural circuitry of alcohol craving and relapse vulnerability. Addiction Biology. 2009; 14:108–118. [PubMed: 18855799]

Heinz A, Siessmeier T, Wrase J, Hermann D, Klein S, Grüsser-Sinopoli S, Flor H, Braus D, Buchholz H, Gründer G, Schreckenberger M, Smolka M, Rösch F, Mann K, Bartenstein P. Correlation between dopamine D(2) receptors in the ventral striatum and central processing of alcohol cues and craving. American Journal of Psychiatry. 2004; 161:1783–1789. [PubMed: 15465974]

Heinz A, Wrase J, Kahnt T, Beck A, Bromand Z, Grüsser S, Kienast T, Smolka M, Flor H, Mann K. Brain activation elicited by affectively positive stimuli is associated with a lower risk of relapse in

detoxified alcoholic subjects. Alcoholism: Clinical and Experimental Research. 2007; 31:1138–1147.

Hollingshead, AB. Two-factor index of social status. Privately Printed; New Haven, CT: 1957.

Kanske P, Heissler J, Schonfelder S, Bongers A, Wessa M. How to regulate emotion? Neural networks for reappraisal and distraction. Cerebral Cortex. 2011; 21:1379–1388. [PubMed: 21041200]

Kareken D, Claus E, Sabri M, Dzemidzic M, Kosobud A, Radnovich A, Hector D, Ramchandani V, O'Connor S, Lowe M, Li T. Alcohol-related olfactory cues activate the nucleus accumbens and ventral tegmental area in high-risk drinkers: preliminary findings. Alcoholism: Clinical and Experimental Research. 2004; 28:550–557.

Kiehl KA, Stevens MC, Laurens KR, Pearlson G, Calhoun VD, Liddle PF. An adaptive reflexive processing model of neurocognitive function: supporting evidence from a large scale (n = 100) fMRI study of an auditory oddball task. Neuroimage. 2005; 25:899–915. [PubMed: 15808990]

Koob G, Volkow N. Neurocircuitry of Addiction. Neuropsychopharmacology. 2010; 35:217–238. [PubMed: 19710631]

Krystal JH, Webb E, Cooney N, Kranzler HR, Charney DS. Specificity of ethanollike effects elicited by serotonergic and noradrenergic mechanisms. Archives of General Psychiatry. 1994; 51:898–911. [PubMed: 7944878]

Lim SL, Padmala S, Pessoa L. Segregating the significant from the mundane on a moment-to-moment basis via direct and indirect amygdala contributions. Proceedings of the National Academy of Sciences U S A. 2009; 106:16841–16846.

Liston C, Matalon S, Hare TA, Davidson MC, Casey BJ. Anterior cingulate and posterior parietal cortices are sensitive to dissociable forms of conflict in a task-switching paradigm. Neuron. 2006; 50:643–653. [PubMed: 16701213]

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage. 2003; 19:1233–1239. [PubMed: 12880848]

Mathalon DH, Pfefferbaum A, Lim KO, Rosenbloom MJ, Sullivan EV. Compounded brain volume deficits in schizophrenia-alcoholism comorbidity. Archives of General Psychiatry. 2003; 60:245–252. [PubMed: 12622657]

Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annual Review Neurosci. 2001; 24:167–202.

Myrick H, Anton R, Li X, Henderson S, Drobes D, Voronin K, George M. Differential brain activity in alcoholics and social drinkers to alcohol cues: relationship to craving. Neuropsychopharmacology. 2004; 29:393–402. [PubMed: 14679386]

Pfefferbaum A, Adalsteinsson E, Sullivan EV. Dysmorphology and microstructural degradation of the corpus callosum: Interaction of age and alcoholism. Neurobiology of Aging. 2006; 27:994–1009. [PubMed: 15964101]

Pfefferbaum A, Lim KO, Zipursky RB, Mathalon DH, Rosenbloom MJ, Lane B, Ha CN, Sullivan EV. Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: a quantitative MRI study. Alcoholism: Clinical and Experimental Research. 1992; 16:1078–1089.

Pfefferbaum A, Sullivan EV, Mathalon DH, Lim KO. Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. Alcoholism: Clinical and Experimental Research. 1997; 21:521–529.

Phelps EA, LeDoux JE. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron. 2005; 48:175–187. [PubMed: 16242399]

Rice JP, Reich T, Bucholz KK, Neuman RJ, Fishman R, Rochberg N, Hesselbrock VM, Nurnberger JI Jr. Schuckit MA, Begleiter H. Comparison of direct interview and family history diagnoses of alcohol dependence. Alcoholism: Clinical and Experimental Research. 1995; 19:1018–1023.

Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Research Reviews. 1993; 18:247–291. [PubMed: 8401595]

Selzer M. The Michigan Alcoholism Screening Test: The quest for a new diagnostic instrument. American Journal of Psychiatry. 1971; 127:1653–1658. [PubMed: 5565851]

Schacht JP, Anton RF, Myrick H. Functional neuroimaging studies of alcohol cue reactivity: a quantitative meta-analysis and systematic review. Addiction Biology. 2012 In Press.

Schneider F, Habel U, Wagner M, Franke P, Salloum J, Shah N, Toni I, Sulzbach C, Hönig K, Maier W, Gaebel W, Zilles K. Subcortical correlates of craving in recently abstinent alcoholic patients. American Journal of Psychiatry. 2001; 158:1075–1083. [PubMed: 11431229]

Skinner H, Horn J. Alcohol dependence syndrome: Measurement and validation. Journal of Abnormal Psychology. 1982; 91:199–209. [PubMed: 7096790]

Smith S, Fein G. Cognitive performance in treatment-naive active alcoholics. Alcoholism: Clinical and Experimental Research. 2010; 34:2097–2105.

Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage. 2009; 44:489–501. [PubMed: 18835452]

Sullivan EV, Mathalon DH, Lim KO, Marsh L, Pfefferbaum A. Patterns of regional cortical dysmorphology distinguishing schizophrenia and chronic alcoholism. Biological Psychiatry. 1998; 43:118–131. [PubMed: 9474444]

Sullivan J, Sykora K, Schneiderman J, Naranjo C, Sellers E. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). British Journal of Addiction. 1989; 84:1353–1357. [PubMed: 2597811]

Tapert S, Brown G, Baratta M, Brown S. fMRI BOLD response to alcohol stimuli in alcohol dependent young woman. Addictive Behaviors. 2004; 29:33–50. [PubMed: 14667419]

Tapert S, Cheung E, Brown G, Frank L, Paulus M, Schweinsburg A, Meloy M, Brown S. Neural response to alcohol stimuli in adolescents with alcohol use disorder. Archives of General Psychiatry. 2003; 60:727–735. [PubMed: 12860777]

Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. Journal of Neurophysiology. 2008; 100:3328–3342. [PubMed: 18799601]

Vollstadt-Klein S, Loeber S, Richter A, Kirsch M, Bach P, von der Goltz C, Hermann D, Mann K, Kiefer F. Validating incentive salience with functional magnetic resonance imaging: association between mesolimbic cue reactivity and attentional bias in alcohol-dependent patients. Addiction Biology. 2011; 17:807–816. [PubMed: 21790907]

Vollstadt-Klein S, Wichert S, Rabinstein J, Buhler M, Klein O, Ende G, Hermann D, Mann K. Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum. Addiction. 2010; 105:1741–1749. [PubMed: 20670348]

Wang L, LaBar KS, Smoski M, Rosenthal MZ, Dolcos F, Lynch TR, Krishnan RR, McCarthy G. Prefrontal mechanisms for executive control over emotional distraction are altered in major depression. Psychiatry Research. 2008; 163:143–155. [PubMed: 18455373]

Wang L, McCarthy G, Song AW, Labar KS. Amygdala activation to sad pictures during high-field (4 tesla) functional magnetic resonance imaging. Emotion. 2005; 5:12–22. [PubMed: 15755216]

Wrase J, Grüsser S, Klein S, Diener C, Hermann D, Flor H, Mann K, Braus D, Heinz A. Development of alcohol-associated cues and cue-induced brain activation in alcoholics. European Psychiatry. 2002; 17:287–291. [PubMed: 12381499]

Wrase J, Schlagenhauf F, Kienast T, Wüstenberg T, Bermpohl F, Kahnt T, Beck A, Ströhle A, Juckel G, Knutson B, Heinz A. Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. Neuroimage. 2007; 35:787–794. [PubMed: 17291784]

Yamasaki H, LaBar KS, McCarthy G. Dissociable prefrontal brain systems for attention and emotion. Proceedings of the National Academy of Sciences U S A. 2002; 99:11447–11451.

Highlights

- We examined brain responses to distracting alcohol cues during an attention task.
- We observe cue-related activation differences between phases of alcohol dependence.
- Alcoholic recovery is associated with more cognitive control and less limbic response.
- Observed differences suggest recovery-associated changes in alcohol cue reactivity.

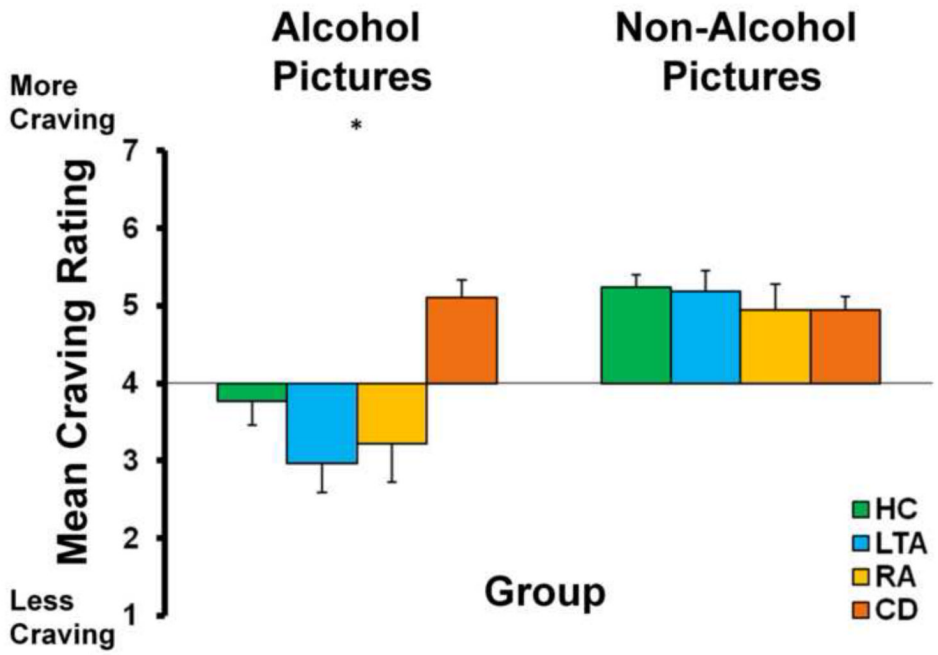

Figure 1.

Mean (± standard error) post-scanner craving ratings by Group (healthy controls = HC; long-term abstainers = LTA; recent abstainers = RA; current drinkers = CD), for alcohol and non-alcohol pictures. For each beverage distractor stimulus, subjects responded to the 4 following statements on a 7-point Likert scale (1= strongly disagree; 7 = strongly agree): 1) I liked looking at this picture, 2) This picture was unpleasant, 3) If I were to drink this, I would enjoy it, 4) I have no desire for this drink. Responses to statements 2 and 4 were inverted, so that for all questions, higher picture rating scores reflect greater endorsement of craving for the beverage stimulus. Results for analyses with craving ratings were as follows (*p< .05):

Main effects of Group by Picture Type

**Alcohol Picture Ratings, Main effect of Group*: (F (3, 60) = 6.94, p<.001); pairwise Tukey HSD corrected follow-ups (CD>HC, p = .03; CD>LTA, p = .001; CD>RA, p = .002)

Non-alcohol Picture Ratings, Main effect of Group: non-significant, p > .7

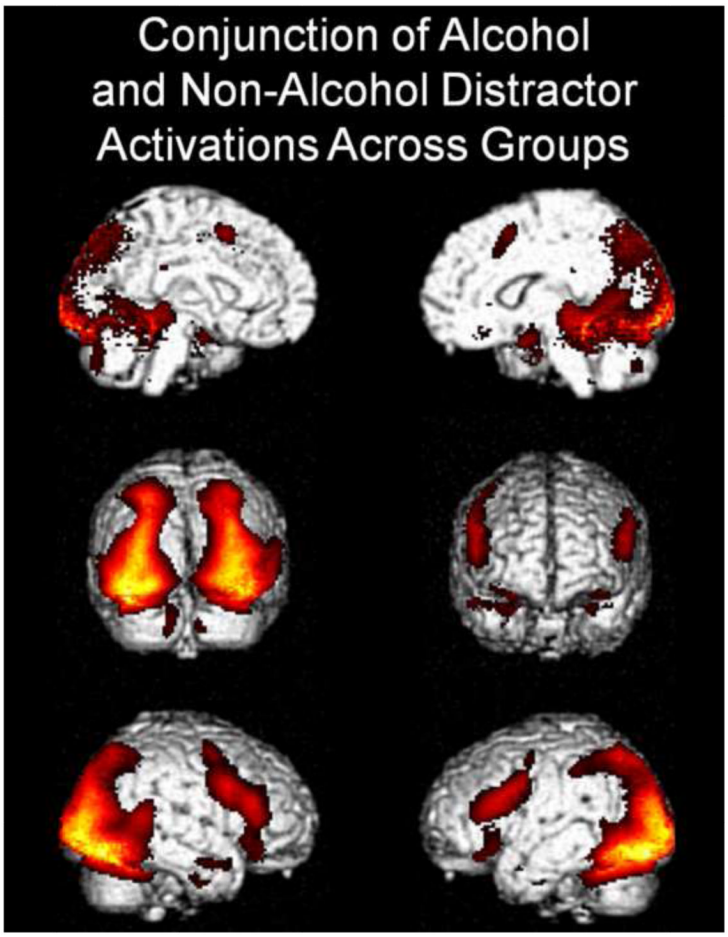

Figure 2.

Conjunction of activations to the Alcohol Distractors – Frequents and Non-alcohol Distractors – Frequents contrasts, averaged across group, revealed activations in ventral stream regions (e.g., extrastriate cortex/Brodmann Areas (BA) 18, 19, fusiform gyri), medial temporal regions (hippocampi, parahippocampal gyri), amygdala, thalamus, inferior and superior parietal lobules (BA 7, 40), dorsal cingulate/medial superior frontal cortex (including BA 6, 8, 24, 32), dorsolateral prefrontal cortex (BA 9, 46), and inferior frontal cortex (BA 45, 47) ($p < .01$, FDR-corrected).

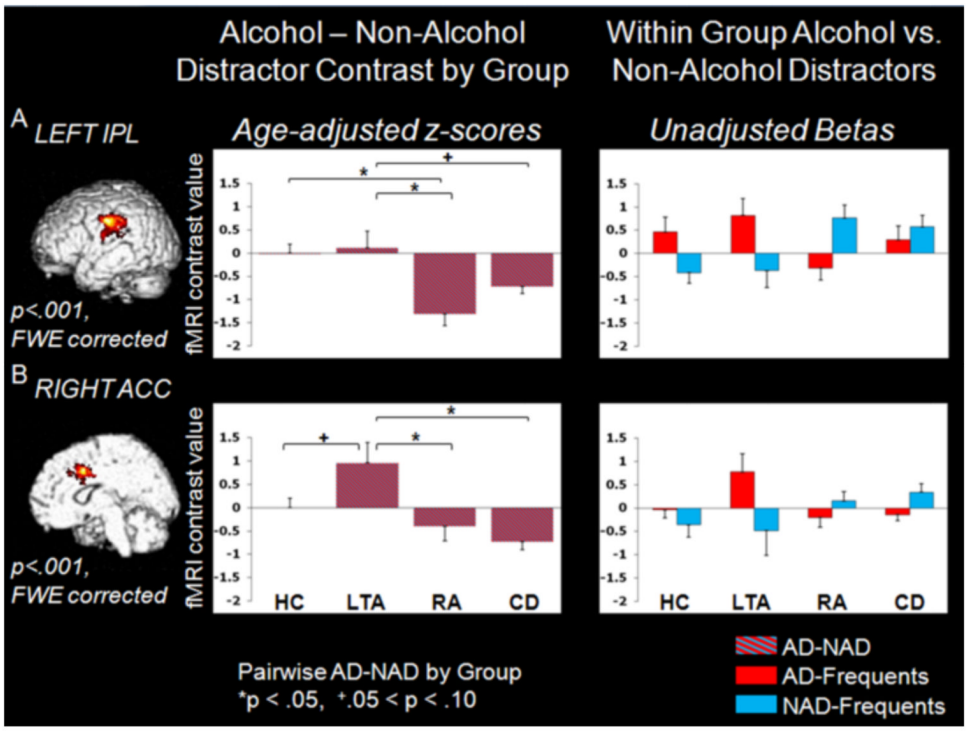

Figure 3.

Group-by-Distractor (Alcohol Distractor (AD), Non-alcohol Distractor (NAD)) interaction effects were observed in two regions: A) a left-hemispheric inferior parietal lobule (IPL) cluster (p<.01, height threshold; p<.05 FWE-corrected) and B) a right-hemispheric dorsal anterior cingulate cortex (ACC) cluster (p<.01, height threshold; p<.05 FWE-corrected). Bar graphs display each region's mean fMRI contrast value (± standard error), by Group (healthy controls = HC; long-term abstainers = LTA; recent abstainers = RA; current drinkers = CD), with each region showing a significant Group-by-Distractor effect depicted in Figure, Left.

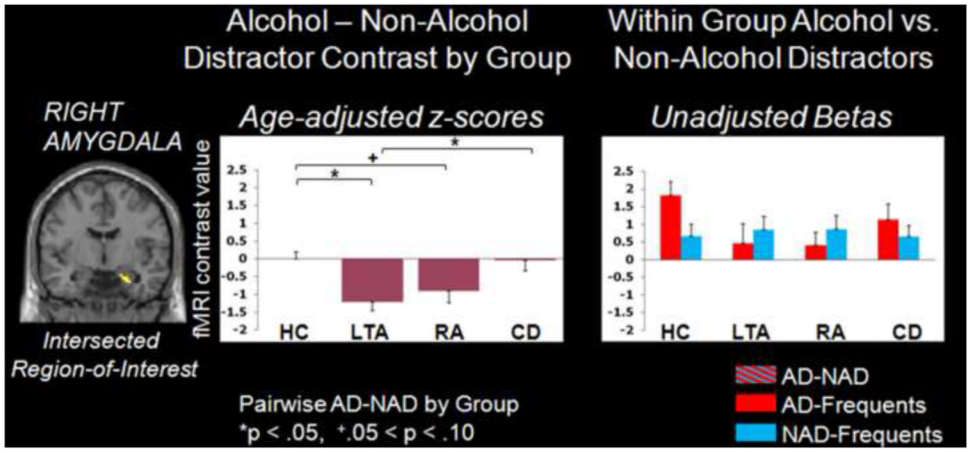

Figure 4.

Group-by-Distractor (Alcohol Distractor (AD), Non-alcohol Distractor (NAD)) interaction effects in the amygdala region-of-interest (ROI) analysis ($p<.003$). Bar graphs display mean fMRI contrast value (± standard error) within the amygdala ROI by Group (healthy controls = HC; long-term abstainers = LTA; recent abstainers = RA; current drinkers = CD). Amygdala voxels surviving Group-by-Distractor F-map intersection are shown in Figure, Left.

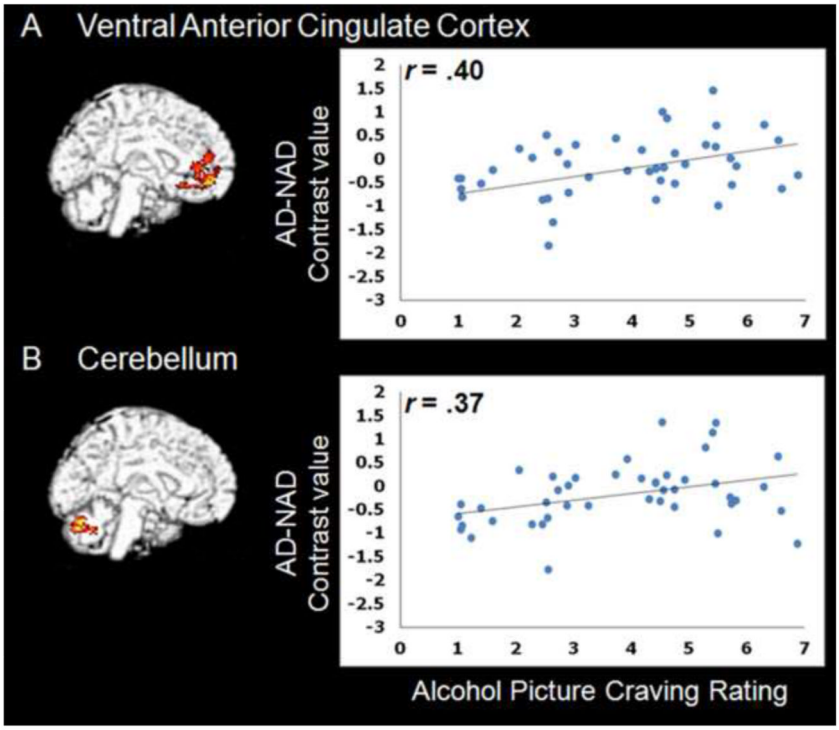

Figure 5.

Alcohol beverage craving ratings were positively correlated with Alcohol Distractor – Non-alcohol Distractor (AD-NAD) fMRI mean cluster contrast values within the combined alcohol dependence (ALC) group. Higher craving scores reflect greater self-reported craving to beverage stimuli. Ventral anterior cingulate cortex is depicted in Figure, Top; bilateral cerebellum is depicted in Figure, Bottom ($p<.005$, height threshold; $p<.05$, FWE-corrected).

Table 1

Demographic and behavioral data by participant group.

	Omnibus Test Statistic	Pairwise Follow-up Tests °	HC Mean ± SD	LTA Mean ± SD	RA Mean ± SD	CD Mean ± SD
Demographic Variables						
N			20	13	15	16
Age (years)	F(3,60) = 4.13 p = .01*	∝LTA>HC ∝LTA>CD ∝RA>HC ∝RA>CD	35.9 ± 10.0	45.3 ± 10.9	44.5 ± 9.6	35.5 ± 10.8
Gender (% male)	X^2(3,N=64)=.15 p = .99	-	75.0	76.9	80.0	75.0
Parental socioeconomic status (SES) §	F(3,56) = 1.83 p = .15	-	29.8 ± 17.4	37.8 ± 14.3	39.6 ± 16.8	40.8 ± 11.6
Visual Oddball Task Performance And Post-Scan Alcohol Craving						
Target Accuracy (% hits)	F(3,60) = 0.25 p = .86	-	97.4	98.4	97.2	97.0
Post-Scan Alcohol Craving Scale (ACS)	F(3,54) = 8.50 p<.001*	*CD>HC *CD>LTA ∝CD>RA	26.7 ± 42.0	64.2 ± 49.3	116.7 ± 116.8	221.3 ± 173.6
Clinical Characteristics						
Family History of Alcoholism (% positive)	X^2(2,N=44)=1.89 p = .39	-	-	69.2	53.3	43.8
Age of ALC Onset (years)	F(2,33) = 0.82 p = .45	-	-	19.4 ± 8.8	22.9 ± 7.1	22.4 ± 4.9
Alcohol Dependence Scale (ADS)	F(2,40) = 2.95 p = .06∝	∝LTA>CD ∝RA>CD	-	15.1 ± 7.0	14.8 ± 5.3	10.6 ± 4.9
Number of Lifetime ALC Treatments*	F(2,40) = 6.13 p = .005*	*LTA>CD *RA>CD	-	1.67 ± 1.1	2.00 ± 2.1	0.31 ± 0.70
Beck Depression Inventory	F(3,55) = 3.10 p = .03*	∝RA>HC ∝CD>HC	1.89 ± 2.73	3.67± 3.60	6.00± 4.98	5.53± 5.63
Fagerström Test for Nicotine Dependence	F(3,58) = 6.02 p <.001*	*RA>HC ∝RA>CD	0.16 ± 0.69	1.75 ± 2.67	3.60 ± 2.90	1.50 ± 2.78

Note, HC= Healthy Controls; LTA = Long-Term Abstainers; RA = Recent Abstainers; CD = Current Drinkers; ALC = Alcohol Dependence

§SES data, measured by the Hollingshead 2-Factor Index, not available from 1 LTA, 1 RA and 2 CD participants; Post-scan ACS, a measure of self-reported craving to alcohol, not available on 5 HC and 1 LTA participant; ALC onset not available from 1 LTA, 1 RA, and 6 CD participants; ADS, a measure of ALC severity, data not available for 1 LTA participant; Number of Lifetime ALC Treatments not available on 1 LTA participant; Beck Depression Inventory not available on 1 HC, 1 LTA, 2 RA, and 1 CD participants; Fagerström Test for Nicotine Dependence not available for 1 HC and 1 LTA participant. For Hollingshead 2-Factor Index, higher scores indicate lower SES. All other assessment measures are scaled such that higher scores reflect greater levels of the measured variable.

*Significant omnibus effects p<.05

∝Nearly significant omnibus effects .05< p<.09

°Tukey-Kramer HSD post-hoc tests, two-tailed

*Pairwise Tukey-Kramer HSD corrected follow-up tests, $p<.05$

∝Pairwise Tukey-Kramer HSD corrected follow-up tests, $.05\leq p\leq .1$

Table 2

Brain regions showing a Group-by-Distractor condition interaction effect ($p<.01$, height threshold; $p<.05$, FWE-corrected cluster).

Neuroanatomical Description	Cluster *p* value, FWE-corrected	Brodmann Area	Peak MNI coordinate			Number of Voxels
			x	y	z	
Left inferior parietal lobule, extending anteriorly through post and precentral gyri	*p* <.001	Left: BA 2, 40	−58	−18	36	1129
Right dorsal anterior cingulate	*p* <.001	Right: BA 24, 32	16	10	40	455

Table 3

Brain regions showing a positive association between participant alcohol craving ratings and alcohol distractor vs. non-alcohol distractor fMRI contrast values, within the ALC group (n = 44; $p<.005$, height threshold; $p<.05$, FWE-corrected cluster).

Neuroanatomical Description	Cluster *p* value, FWE-corrected	Brodmann Area	Peak MNI coordinate			Number of Voxels
			x	y	z	
Bilateral medial prefrontal cluster, largely anterior cingulate gyrus, extending inferiorly through the subcallosal and inferior frontal cortex	*p* =.01	Bilateral: 32 Left: 9, 10, 24	−18	48	−6	487
Bilateral medial cerebellum, extending laterally leftward	*p* =.02		−26	−56	−38	453