



Alcohol Cues Elicit Differences in Brain Activation Patterns of Abstinent Men and Women with Alcohol Use Disorders

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Introduction: Cognitive, emotional, and behavioral abnormalities have been associated with alcohol use disorders (AUD). Because of their reward salience, photographs of alcoholic beverages can influence brain activation in individuals with AUD.

Methods: We employed fMRI to measure gender differences in brain activation elicited by alcohol cues in 84 men and women with and without a history of alcohol use disorders (ALC and NC, respectively). Brain activity was measured during performance on a delayed matching-to-sample (DMTS) working memory task; emotional faces served as the sample and match cues. During the delay period, intervening distractors were either reward-salient cues (alcoholic beverages) or neutral cues (nonalcoholic beverages or scrambled pictures).

Results: Region of interest analyses showed that the ALC group had significantly higher levels of activation throughout reward-related circuitry during alcohol distractor interference than during scrambled picture interference. Significant Group-by-Gender interactions were also observed: Compared to NC men (NCm), ALC men (ALCm) evidenced lower activation contrast between reward-salient cues and neutral cues in *default mode network* regions (including superior prefrontal and precuneus areas), while ALC women (ALCw) had more activation than NC women (NCw). Similar significant interactions were observed for *task-regions* (including superior parietal, lateral occipital, and prefrontal areas). Additionally, ALCw had higher DMTS accuracy scores than ALCm.

Discussion: The findings suggest that abstinent ALCm and ALCw differ in processing reward-salient cues, which can impact treatment and recovery.

Plain Language Summary: Brain reward regions activate highly when individuals with a history of alcohol use disorder view alcoholic beverages.

The brain regions identified subserve vision, memory, and judgment.

Opposite abnormalities in activation patterns appeared for men and women.

Keywords: alcoholism, reward, fMRI, gender, memory, emotion

Introduction

Alcohol use disorders (AUD) have been associated with deficits in cognitive and emotional functions.¹ Because of their reward salience, alcohol cues such as pictures of alcoholic beverages elicit attentional bias and brain activation in individuals with AUD.²⁻⁴ Alcohol cues induce a hyperattentive state with attention drawn to the rewarding stimuli.⁵⁻⁸ Therefore, the cues selectively interfere with other cognitive abilities such as memory. Importantly, attentional bias toward alcohol-related stimuli also has been associated with level of craving, consumption, dependence, and physiological arousal.⁹⁻¹⁸

Functional magnetic resonance imaging (fMRI) studies of attentional biasing, and specifically cue reactivity, have often included either only men with and without a history of AUD, or groups of men and women with sample sizes too small to examine gender effects.^{4,19} However, gender impacts the ways in which alcohol affects the brain and behavior,^{20–29} due to interactions with physiological and social factors.^{30,31} In the present study with a cohort of men and women with and without AUD (ALCm, ALCw, NCM, and NCw), we examined gender differences using a delayed matching-to-sample (DMTS) task,³² which requires an attention-demanding kind of memory called *working memory*. The participants were required to remember photographs of emotional faces (the sample) while distracting pictures of alcoholic beverages, nonalcoholic beverages, or scrambled images intervened during the delay period. We chose faces as the sample stimuli, because in a prior study,³³ we found that men with AUD had abnormally low brain activity in temporal limbic regions when viewing emotional face stimuli. Further, it has been shown that alcoholism is associated with impaired emotional perception, and specifically impaired emotional face decoding.^{22,34–37}

It is important to note that two aspects of our DMTS task are relevant for differentiating cognitive and brain deficits in AUD, and these were analyzed separately: (1) attentional biasing, as indicated by brain responses to distractor cues, along with behavioral responses to probe faces, and (2) affective processing, as indicated by brain responses to the encoded faces.^{38,39} Therefore, we divided the results of the present project into two separate reports. One report⁴⁰ described abnormalities in AUD-related brain activation to the encoded faces, and identified gender-related differences. For the present report, the data derived from the delay and match (the probe face) portions of the task allowed us to test the attentional biasing effect,^{41,42} wherein we expected alcohol cues, more than other cue types, to impair performance on memory for face identity. Thus, the present report contains the results pertaining only to the distractor and the probe face.

Functional MRI task contrasts reveal activation of multiple brain networks, and abnormalities in the default mode network (DMN) have been implicated in AUD and in psychiatric disorders.^{43,44} The DMN has been observed to be more active during storytelling, reading and memory tasks, imagining future scenarios, self-reference, rumination, and when the mind wanders while staring at a fixation cross during fMRI scanning.^{45–48} We refer to the DMN regions as *fixation-regions* because they are more active during the idle delay intervals when the fixation stimulus is presented between DMTS trials than during stimulus presentations. Cortical fixation-regions include: (1) an “anterior hub,” consisting of portions of the rostral anterior cingulate cortex (ACC), ventromedial prefrontal cortex, and medial superior frontal cortex; (2) a “posterior hub,” which includes portions of the posterior cingulate and precuneus, (3) the temporoparietal junction, which covers parts of the angular gyrus and inferior parietal lobule; and (4) the superior and middle temporal gyrus region.^{47,49} With functional connectivity analyses, these regions, as well as subcortical structures, including ventral tegmental area, nucleus accumbens, and caudate nucleus, also have been identified as part of the DMN.⁵⁰

In addition to the fixation-regions, we examined *task-regions*, which are more engaged during the DMTS task than while looking at unengaging fixation crosses. Literature on distractor interference during working memory has suggested that task-regions involve a distributed network including prefrontal cortex, along with dorsal and ventral visual association cortex, which are necessary for attentional functioning⁵¹ and for inhibiting distracting visual stimuli.^{52,53} Additional task-regions involved in attention, working memory, and emotional processing, include the dorsal ACC and lateral prefrontal areas. The dorsal ACC in particular has been implicated in craving and attentional biasing.⁵⁴

In advance of any analyses, we used prior literature to select ten a priori anatomically defined regions of interest (ROI) involved in cue exposure, distractor interference, craving, reward processing, salience, working memory, or emotional faces. The first nine ROI are the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), orbitofrontal cortex (OFC), insular cortex, parahippocampal gyrus, hippocampus, amygdala, fusiform, and ACC. Previous studies provide support for each of those nine a priori ROI and are detailed in the [Appendix \(Table A1\)](#).^{4,54–63} The tenth ROI is the “extended reward and oversight system” (EROS) as described and named in our previous papers.^{25,64} The EROS ROI is a single large but discontinuous composite ROI that had been created by combining 11 regions (seven of the ROI noted above, all but the VLPFC and fusiform), plus an additional four: nucleus accumbens, ventral diencephalon, subcallosal cortex, and temporal pole. Selection of these regions was based upon extant literature, and updated regionally-specific insight can be obtained from more recent reviews.^{65–68} For each of the ten ROI, we intended to confirm findings from each of the aforementioned studies that had identified abnormal activation by alcohol cues in AUD, and additionally to investigate

differences between men and women. We expected lower brain activation in the ALC group in regions involved in facial identity and inhibition of distractor interference, but higher in regions responsible for reward salience.

In summary, we investigated brain activation for ten ROI, and for vertex-wise cortical analyses of fixation-regions and task-regions. We examined the accuracy of the participants' memory for the face identities after exposure to attentionally salient pictures to test our hypothesis that alcohol cues would distract the ALC group more than the NC group. We determined how brain regions were activated by the distractor contrasts, how the contrasts differed for ALC and NC groups, and how those abnormalities varied by gender. We hypothesized that attentional biasing would be evident for the ALC group in the form of stronger brain activity contrasts (alcoholic beverage cues compared to nonalcoholic and scrambled stimuli). We conceptualize attentional biasing as the cognitive manifestation of cue reactivity; the diversion of working memory resources toward reward-salient distractors (alcoholic beverages) and away from maintaining task-relevant face identity. Thus, stronger brain activity contrasts for alcohol cues relative to neutral cues reflect both cue reactivity and attentional biasing within the task context.

Regarding gender differences, we made predictions based upon previously published work from our laboratory wherein we found that brain regions of ALCw (compared to NCw) were overactive in response to highly charged emotional stimuli.²⁴ We hypothesized that the ALCw would evidence hyperactivation to alcohol stimuli (because they would be emotionally salient to the ALC group), whereas the activation contrasts for ALCm would be weaker. The emotional salience of alcoholic beverage stimuli is well established.^{55,69} We also expected to reinforce prior results^{24,33} showing diminished responses in ALCm than NCm during the processing of salient imagery, specifically for alcohol-related cues in regions making up the EROS ROI.

Methods

Participants

Participants in this study included 42 abstinent long-term ALC individuals (21 ALCw) and 42 NC controls (21 NCw), with comparable age, education, and IQ (see Table 1 in the Results). Participants were recruited through flyers placed in treatment and after-care facilities, the Boston VA Healthcare System facility, Massachusetts General Hospital, the Boston University School of Medicine, and in public places (eg, churches, stores), as well as through newspaper and internet

Table 1 Participant Characteristics

	ALC n = 42	ALCw n = 21	ALCm n = 21	NC n = 42	NCw n = 21	NCm n = 21
Age^a (years)						
Mean	53.9	53.4	54.4	53.9	57.7	50.2
Standard deviation	11.0	11.4	10.8	12.4	13.6	10.1
Range	26.5–76.7	26.5–73.0	26.6–76.7	25.8–76.9	25.8–76.9	29.0–69.6
Education^b (years)						
Mean	14.7	15.3	14.1	15.5	15.6	15.4
Standard deviation	2.0	2.0	1.9	2.0	2.3	1.6
Range	12–19	12–19	12–18	12–19	12–20	12–18
WAIS-III Full Scale IQ						
Mean	110.3	110.1	110.5	111.6	111.2	112.0
Standard deviation	15.0	14.2	16.0	16.3	19.3	13.1
Range	72–140	72–137	81–140	79–152	79–142	90–152
WMS-III IMI						
Mean	109.7	114.4	104.7	111.9	114.8	109.0
Standard deviation	16.6	18.3	13.4	16.9	16.4	17.4
Range	63–144	63–144	82–130	80–146	84–138	80–146

(Continued)

Table 1 (Continued).

	ALC n = 42	ALCw n = 21	ALCm n = 21	NC n = 42	NCw n = 21	NCm n = 21
WMS-III DMI						
Mean	112.6	116.7	108.3	111.8	113.5	110.1
Standard deviation	17.3	20.4	12.5	16.0	14.9	17.2
Range	52–140	52–140	86–132	83–150	83–140	84–150
Duration of Heavy Drinking^{cdef} (years)						
Mean	17.4	14.3	20.5	0.0	0.0	0.0
Standard deviation	7.7	5.2	8.5	0.0	0.0	0.0
Range	5.0–35.0	6.0–25.0	5.0–35.0	0.0–0.0	0.0–0.0	0.0–0.0
Quantity Frequency Index^{cde} (ounces ethanol/day; ~drinks/day)						
Mean	11.2	8.7	13.7	0.3	0.2	0.4
Standard deviation	8.8	5.8	10.5	0.6	0.5	0.7
Range	2.7–38.4	2.7–28.1	4.5–38.4	0.0–2.6	0.0–2.4	0.0–2.6
Length of Sobriety^{cde} (years)						
Mean	8.3	10.6	5.9	NA	NA	NA
Standard deviation	10.3	11.1	8.8	NA	NA	NA
Range	0.1–32.3	0.1–32.1	0.1–32.3	NA	NA	NA
Penn Alcohol Craving Scale^{cde}						
Mean	3.8	3.8	3.9	1.2	1.1	1.3
Standard deviation	4.4	5.1	3.8	2.0	2.2	1.8
Range	0–19	0–19	0–12	0–9	0–9	0–5
Hamilton Rating Scale for Depression^g						
Mean	3.5	4.9	2.2	2.4	3.1	1.8
Standard deviation	4.2	4.1	4.0	2.8	3.3	2.1
Range	0–18	0–17	0–18	0–12	0–12	0–8

Notes: Participants Characteristics ($p < 0.05$): ^aControl Women > Control Men; ^bControl Men > Alcoholic Men; ^cAlcoholics > Controls; ^dAlcoholic Men > Control Men; ^eAlcoholic Women > Control Women; ^fAlcoholic Men > Alcoholic Women; ^gAlcoholic Women > Alcoholic Men. See Results for additional details on number of participants.

Abbreviations: NA, Not Applicable; WAIS-III, Wechsler Adult Intelligence Scale, 3rd edition; WMS-III, Wechsler Memory Scale-3rd edition; IMI, Immediate Memory Index; DMI, Delayed Memory Index.

advertisements This research was approved by the Boston University Chobanian & Avedisian School of Medicine Institutional Review Board (#H24686), VA Boston Healthcare System Institutional Review Board (#1017 and #1018), and the Partners Healthcare System Human Research Institutional Review Board (#2000P001891), and conforms with the principles of the Declaration of Helsinki. All participants gave written informed consent prior to participation, and they were compensated for their time.

Selection procedures began with a telephone interview to obtain age, education, health, alcohol and drug use history, including prescription drugs. Participants were right-handed, had normal or corrected-to-normal vision, and spoke English as their first language (or had acquired English as a second language by age five). Current drug use excepting nicotine was cause for exclusion, as were history of alcohol-related liver disease, epilepsy, head trauma resulting in loss of consciousness for 15 minutes or more, HIV, schizophrenia, or metal implants. Selection procedures were followed by self-reported psychological and behavioral assessments of participant characteristics.

Neuropsychological Assessment

Neuropsychological testing was conducted at the Department of Veterans Affairs (VA) Boston Healthcare System facility prior to scanning. Participants completed a medical history interview, vision test, handedness questionnaire,⁷⁰ and a battery of tests as described below. All subjects were screened using the Hamilton Rating Scale for Depression⁷¹ and the Diagnostic Interview Schedule for the DSM-IV.⁷² The majority of participants also were administered the

Wechsler Adult Intelligence Scale (WAIS-III) and the Wechsler Memory Scale (WMS-III).⁷³ Four participants (two ALCw and two ALCm) received the WAIS-IV and WMS-IV,⁷⁴ and WMS-III scores were not obtained from one ALCm. The scores for these participants were adjusted to account for differences in scoring outcomes relative to the earlier versions of the scales. Because craving for the rewarding effects of alcohol is known to serve as a trigger for relapse in those recovering from AUD,⁷⁵ and alcohol cue exposure in particular is known to be related to relapse,⁷⁶ all participants were administered the Penn Alcohol Craving Scale⁷⁷ immediately before and approximately two weeks following the scan to assess any changes in alcohol craving patterns.

Alcohol Screening

The ALC participants met criteria for alcohol abuse or dependence, and consumed 21 or more alcoholic drinks per week for five or more years. Extent of alcohol use was assessed by calculating Quantity Frequency Index scores.⁷⁸ The scores approximate the number of drinks consumed per day, and take into consideration the amount, type, and frequency of alcohol consumption either over the last six months (NC participants), or over the six months preceding cessation of drinking (ALC participants), and yields an estimate of ounces of ethanol per day. To remove the influence of current alcohol abuse, ALC participants must have been abstinent for at least four weeks before the scan date to be included. The ALC participants did not display symptoms of Korsakoff's Syndrome nor dementia.⁷⁹ Potential NC participants who had consumed 15–20 drinks per week for any length of time or who engaged in binge drinking were disqualified.

Functional Imaging Task

All participants were given a delayed matching-to-sample memory task³² in a magnetic resonance imaging (MRI) scanner, whereby they were asked to encode two faces that both had one of three emotional valences: positive, neutral, or negative (Figure 1). The face stimuli were shown in grayscale and were taken from a set of faces used in a previous study.³³ These faces were displayed simultaneously for three seconds, followed by an asterisk (*) for one second. Subjects were asked to maintain these faces in memory while a colored distractor stimulus was shown. On different trials, the distractor stimulus was either a picture of an alcoholic beverage (*alcbbev*; beer, wine, liquor, or mixed drink), a picture of a nonalcoholic beverage (*nonalcbbev*; water, juice, milk, soda, coffee, tea, etc), or a scrambled nonsense picture (*scrambled*). Alcoholic and nonalcoholic beverage pictures were a combination of images used with permission from the Normative Appetitive Picture System (NAPS),⁸⁰ and other previously published works on alcohol cues.^{60,61,81} Additional distractor images were modified from digital photographs taken at bars, liquor stores, and convenience stores. The scrambled images were created by inverting half the alcoholic and half the nonalcoholic beverage images and distorting them until they were not recognizable as any particular object, while preserving a match of primary visual characteristics. Each distractor picture was shown for three seconds, followed by an asterisk (*) for one second. Following the distractor picture, a single probe face was shown for two seconds, and the participants were instructed to report whether this face was one of the two faces they had just seen.

Each trial was 10 seconds in length, and was followed by a variable delay period (with a mean duration of 10 seconds, ranging from 2 to 22 seconds) during which the subject saw a set of crosshairs (+++) serving as a visual fixation. The task was divided into nine runs, each of which contained 18 trials. There were nine trial types made up of each combination of face valence and distractor type (eg, positive faces followed by alcohol distractor). Each emotion–distractor combination appeared twice per run. The stimulus order and variable inter-trial intervals were determined using *optseq2* (<http://surfer.nmr.mgh.harvard.edu/optseq>), which optimizes statistical efficiency and hemodynamic response estimate accuracy for event-related experimental designs.⁸² In total, there were 54 trials for each distractor type (combined across facial expressions) and each face valence (combined across distractor types), for a total of 162 trials across the entire scan. The stimulus faces were balanced to contain 50% male and 50% female faces. Within a trial, the two encoded faces and probe face were matched on emotional expression and gender. This way, on match trials the probe facial image was identical to one of the encoded images, and on mismatch trials the facial identity changed but the emotional expression and gender did not.

The probe face matched one of the encoded faces on 50% of the trials, and match/mismatch trials appeared in a randomized order within each run. Responses were made by pressing one of two buttons with the index finger (match)

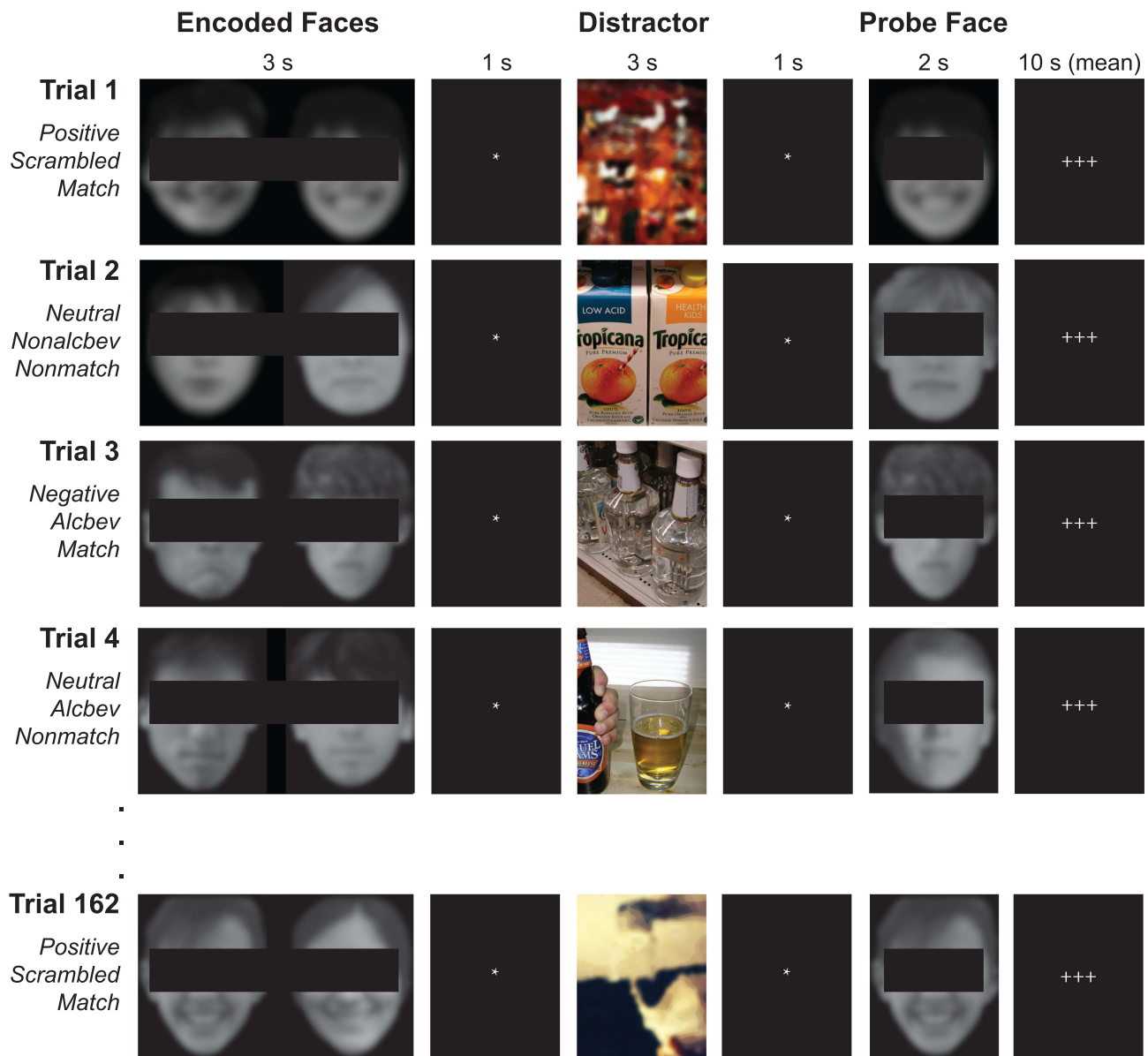


Figure 1 Task presented during functional neuroimaging. The participants were shown two faces simultaneously for three seconds, followed by an asterisk (*) for one second. Next, a distractor was presented for three seconds. The probe face immediately followed, during which the participants had been trained to respond with a button press with either their index or middle finger to indicate whether the probe face matched the encoded face. During the inter-trial fixation interval, three crosses (+++) were shown on the screen for 2 to 30 seconds (mean 10 seconds). A total of 162 trials were presented. While the faces in this figure have been blurred and obscured in this publication to protect the identities of the individuals, the research participants saw the original unblurred and unobscured photographs.

or middle finger (mismatch) of the right hand. Participants were instructed to respond as quickly as possible without sacrificing accuracy. Additionally, participants could immediately correct a response by pressing the opposite button. To ensure the distractor images were viewed by all participants, they were told that it was necessary to pay attention to the pictures shown in between the faces on each trial, as they would be questioned about those images following the scan.

Behavioral Task Analyses

Responses to the face memory task were analyzed on the first level (individual subjects) using custom Excel templates. Trials were organized by Distractor type, facial Emotion, and Face Gender. Each trial was scored as correct, incorrect, or miss (*ie*, no response) When more than one response was made to a trial, the last response type (*ie*, yes/match or no/nonmatch) was accepted as the final answer, provided that the final response was at least 200 ms after the preceding

response and no more than 10 s following the preceding response. When a single response was recorded and the reaction time was less than 200 ms, the trial was scored as a miss. For each participant, a mean overall reaction time (regardless of trial type) was calculated. Reaction times that exceeded three standard deviations from this mean were excluded from reaction time calculations by trial type. Participants' patterns of responses were analyzed for consecutive misses to assure that they remained awake throughout the task. Three separate runs were identified, each in a different participant, wherein greater than five consecutive trials were missed; these runs were excluded from behavioral analyses.

Second level (group) effects on percent correct and reaction time (correct trials) were investigated using SPSS Version 17.0 (IBM, Chicago, IL, USA). Repeated-measures analyses of variance (ANOVA) were carried out with between-subjects factors of Group (ALC or NC) and Gender (female participant or male participant) and within-subjects factors of Distractor (albev, nonalbev, or scrambled), Emotion (positive, negative, or neutral), and Face Gender (female face or male face). Repeated-measures ANOVA was selected for behavioral analyses given its robustness to moderate violations of normality assumptions with balanced sample sizes and continuous dependent variables such as percent correct and reaction times.

Image Acquisition

Imaging was conducted at the Massachusetts General Hospital's Athinoula A. Martinos Center for Biomedical Imaging in Charlestown, MA. Data were acquired on a 3 Tesla Siemens (Erlangen, Germany) MAGNETOM Trio Tim MRI scanner with a 12-channel head coil. Sagittal T1-weighted MP-RAGE scans (TR = 2530 ms, TE = 3.39 ms, flip angle = 7°, FOV = 256 mm, slice thickness = 1.33 mm, slices = 128, matrix = 256 × 192) were collected for all subjects. For most participants, two such volumes were collected and averaged to aid in motion correction. An auto-align localizer was employed to adjust the acquired slices such that they ran parallel to an imaginary plane between the anterior and posterior commissures. Echo planar functional MRI blood oxygen level dependent (BOLD) scans were collected axially with 5 mm slice thickness and 3.125 × 3.125 mm in-plane resolution (64 × 64 matrix), allowing for whole brain coverage (32 interleaved slices, TR = 2 s, TE = 30 ms, flip angle = 90°). The event-related design included 18 trials per run with a total of nine runs. Within each six-minute run, 180 T₂*-weighted volumes were collected. Functional volumes were auto-aligned to the anterior/posterior commissure line to ensure a similar slice prescription was employed across participants. Prospective Acquisition Correction (3D-PACE) was applied during collection of the functional volumes to minimize the influence of participants' body motion.⁸³ An IBM ThinkPad (Windows XP) running Presentation version 11.2 (NeuroBehavioral Systems, Albany, CA) software was used for visual presentation of the experimental stimuli and collection of participants' responses. Stimuli were back projected onto a screen at the back of the scanner bore and were viewed by the participants through a mirror mounted to the head coil. All participants wore earplugs to attenuate scanner noise.

Structural Image Processing

Structural MPRAGE image analyses were performed for all participant data using the FreeSurfer (version 4.5.0) image analysis suite (<http://surfer.nmr.mgh.harvard.edu>). A multi-stage cortical surface reconstruction process was run on the two collected T1-weighted MP-RAGE scans,⁸⁴ starting with motion correction, intensity normalization,⁸⁵ Talairach registration,⁸⁶ skull stripping,⁸⁷ and segmentation⁸⁸ of white matter, gray matter, and ventricles. Subsequently, boundaries were calculated delineating where gray and white matter meet, and where gray matter adjoins cerebrospinal fluid ("pial surfaces") based on maximal shifts in image intensity between tissue types. These boundaries, as well as the subcortical segmentations, were visually inspected on each coronal slice for every subject, and manual interventions (eg, white matter volume corrections) were made when needed. The surface boundaries were used to generate computationally inflated two-dimensional cortical surface models, which allowed individual subjects to be registered to a spherical atlas by utilizing each subject's cortical folding patterns. This registration was used to align the cortical geometry of all subjects within a group. Creation of these cortical surface models allowed improved data visualization as well as improved accuracy of within-group co-registration relative to an affine morph procedure.⁸⁹ The cortical surface models were employed in an automated parcellation procedure that divides the surface into subregions based on gyral and sulcal anatomy. The Destrieux atlas parcellation for FreeSurfer⁹⁰ was used to define anatomical ROI in the functional analyses for cortical areas, and the Desikan-Killiany FreeSurfer segmentation was used for subcortical areas.⁹¹

Functional Image Processing and Statistical Analyses

Effects of Group, Gender, Distractor, and Emotion on the BOLD signal were evaluated using both a whole-brain cluster analysis as well as ROI analyses. Processing of the functional data was performed using the FreeSurfer Functional Analysis Stream (FS-FAST), SPSS Version 17.0, and Matlab 7.4.0.

First-Level Functional Analyses

Preprocessing of the functional images for first level (individual subject) FS-FAST analysis included motion correction, intensity normalization,⁸⁵ and spatial smoothing with a 5-mm Gaussian convolution kernel at full-width half-maximum. Trials were first combined across runs by distractor-emotional face valence pairs (*ie*, alcbv-positive, alcbv-negative, alcbv-neutral, nonalcbv-positive, nonalcbv-negative, nonalcbv-neutral, scrambled-positive, scrambled-negative, scrambled-neutral) and then collapsed across emotional valence. The BOLD response was estimated using a Finite Impulse Response (FIR) model, which allows for estimation of the time course of activity (percent signal change for a given condition) within a vertex or ROI for the entire trial period. For each condition, estimates of signal intensity were calculated for 2 pre-trial and 10 post-trial onset TRs, for a total analysis window of 24 seconds. Motion correction parameters calculated during alignment of the functional images were entered into the analysis as external regressors. Alignment of the T2*-weighted functional images with T1-weighted structural volumes was accomplished through an automated boundary-based registration procedure.⁹² These automated alignments were manually inspected to ensure accuracy.

Statistical maps were generated for each of the 84 individual subjects for contrasts between experimental conditions. Three contrasts were used to identify fixation-regions; they were made between distractor types and fixation: (1) alcbv vs. fixation, (2) nonalcbv vs. fixation, and (3) scrambled vs. fixation. Another three contrasts were used to assess cue responsivity: (1) alcbv vs. nonalcbv, (2) alcbv vs. scrambled, (3) nonalcbv vs. scrambled. Analyses of each of these contrasts included removal of prestimulus differences between the contrasted conditions by averaging the first three time points (two pre-trial onset and one post-trial onset) for each condition and subtracting this mean from each time point for that condition. Time points summed for inclusion in each contrast were chosen to reflect peak stimulus-related activity: Finite Impulse Response estimates of hemodynamic responses to the distractors were analyzed using a mean of the five TRs collected during the time period of 2–12 seconds post-distractor onset. Since the distractor is shown 4 seconds after the trial onset, the analysis window is 6–16 seconds following trial onset (time points 3 through 8).

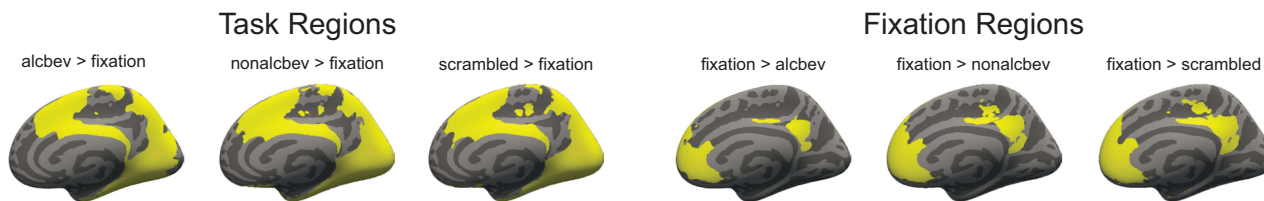
Cortical Surface Cluster Analyses

We investigated cue-related brain activation in two separate cortical brain networks: (1) cue reactivity in fixation-regions, and (2) cue reactivity in task-regions. The brain network that was more active during presentation of the fixation cue than during the distractor images was used as our measure of fixation-regions. The network that was more active during the presentation of distractor images than during presentation of the fixation stimulus was used as our measure of the task-regions. In what follows, we first describe masking procedures and analyses we used to separate the networks.

The *t*-statistic maps for each condition vs. fixation were thresholded at $p < 0.05$ vertex-wise and were used to generate binary masks (Figure 2) separating fixation-regions and task-regions, thereby forming the six masks: alcbv greater than (or less than) fixation, nonalcbv greater than (or less than) fixation, scrambled greater than (or less than) fixation. These masks were used to separate the between-distractor analyses (described below).

Second-level (group) analyses on cortical regions were accomplished using FS-FAST version 5.3, a surface-based morphing procedure for intersubject alignment and statistics.⁸⁹ Group-averaged signal intensities during each experimental condition (alcbv, nonalcbv, scrambled) relative to fixation were calculated using the general linear model in spherical space for cortical regions, and were mapped onto the canonical cortical surface *fsaverage*, generating group-level weighted random-effects *t*-statistic maps masked to include only the cortex. Weighted random effects models were employed to reduce noise by considering individual subject variance. A 5 mm smoothing kernel (full-width half-maximum) was employed for all group and intergroup maps. Cluster correction on maps showing activity for each distractor condition vs. fixation was applied using FS-FAST Monte Carlo simulation with a clusterwise threshold of $p < 0.05$ corrected for two spaces (left hemisphere cortical and right hemisphere cortical), and additionally permutation testing with a vertex-wise threshold of $p < 0.001$ and a cluster-wise threshold of $p < 0.05$ corrected for two spaces (left

A. Fixation Masking



B. Distractor Masking

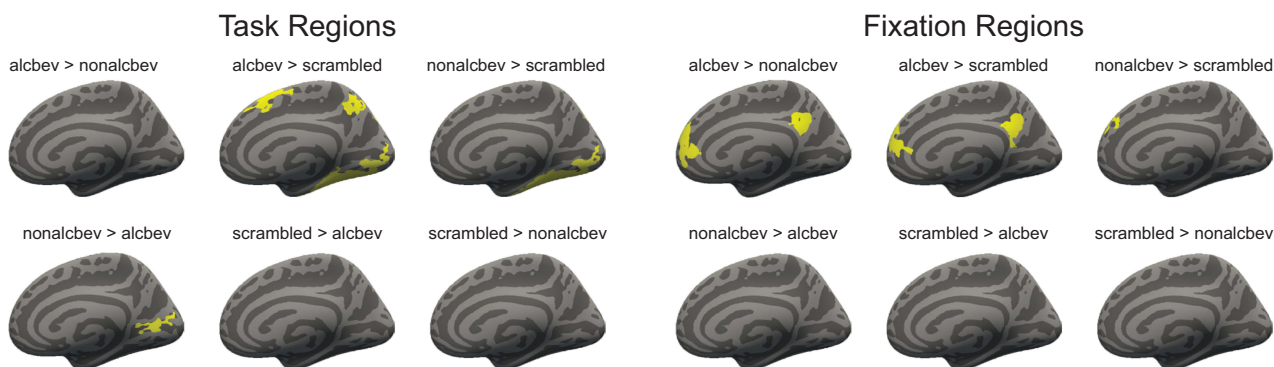


Figure 2 Analyses conducted with masked fMRI data for cortex. **(A)** The top set of brains represents analyses conducted for cortical regions in which network masking (for task and fixation-regions) were performed. **(B)** The bottom set of brains represents analyses conducted for cortical regions in which distractor masking (for task and fixation-regions) were performed.

hemisphere cortical and right hemisphere cortical). Cortical surface cluster regions were identified by the location of each cluster's peak vertex on the cortical surface according to the Desikan-Killiany atlas.⁹¹

When we examined brain activation differences between the distractor types, we used three contrasts: alcbv vs. nonalcbv, alcbv vs. scrambled, and nonalcbv vs. scrambled. We investigated each direction of these contrasts separately. For example, brain regions with higher activation for alcbv than nonalcbv would be analyzed separately from those regions with higher activation for nonalcbv than alcbv.

Intergroup comparison *t*-statistic maps were generated using FS-FAST by comparing activation levels of all of the ALC participants with levels of all of the NC participants. Additionally, Group-by-Gender interaction maps for each contrast were calculated.

Region of Interest Analyses

The anatomically defined ROI for the distractor analyses included areas hypothesized a priori to be implicated in alcohol craving, distractor interference, and working memory for emotional faces, as described in the Introduction. Details, including atlas index numbers from the Destrieux⁹⁰ parcellation (for cortical regions) and Desikan-Killiany⁹¹ segmentation (for subcortical regions), are provided in [Table A1](#). The ROI were DLPFC, VLPFC, OFC, insular cortex, parahippocampal gyrus, hippocampus, amygdala, fusiform, ACC, and the multi-regional EROS.^{25,64} While not examined as a separate ROI, the PCC was included in the whole-brain cluster analysis, although recent research suggests the PCC is relevant to addictions.⁶⁵ Left and right hemisphere regions were analyzed as separate ROI.

Statistical preprocessing and time course visualization of ROI data were performed using scripts written for Matlab version 7.4.0. Signal intensity for each region was averaged across all vertices (for surface-based ROI) or voxels (for volume-based ROI) included in the region for each condition on the individual participant level. To compute percent signal change for each participant within an ROI, signal estimate per condition and time point was divided by the average baseline activity for that participant. Time courses were normalized at the individual subject level for each condition by taking the mean of the first three time points (two pre-trial and one post-trial onset) and subtracting this mean from each time point. Group and Group-by-Gender averages of the normalized time courses were computed for each condition, and were visualized by plotting the percent signal change for each condition at each time point (*ie*, TR) of the trial.

For the distractor ROI analyses, percent signal changes of the BOLD signal within each ROI for the time window from 2 to 12 sec after distractor onset were entered as dependent variables into repeated-measures ANOVA models with between-group factors of Group (ALC or NC) and Gender (men or women) and within-subjects factor of distractor type (alcbv, nonalcbv, or scrambled).

Results

Research Participant Characteristics

Table 1 summarizes means, standard deviations, and ranges of participant demographics, drinking variables, and IQ and memory test scores.

The ALC and NC groups did not differ significantly by age. Although the NCw were older than the NCm, controls did not differ significantly from their respective ALC counterparts by age. ALCm had on average one year less education relative to NCm. Groups did not differ significantly on WAIS-III Full Scale IQ scores. While ALCw had higher Hamilton Rating Scale for Depression scores than ALCm, the average scores for all four subgroups (ALCm, ALCw, NCm, and NCw) were low. The mean scores for all subgroups were under 5, below the threshold for mild depression, which is 8. Therefore, depression likely contributed little to our observed gender differences.

By definition, the ALC group had longer durations of heavy drinking than the NC group. The ALCm on average drank heavily for six years more than did the ALCw. Five NCm and two NCw reported being lifetime abstainers. The ALC group reported higher levels of craving for alcohol than the NC group on the Penn Alcohol Craving Scale administered immediately prior to the scan; ALCm and ALCw did not differ on reported level of pre-scan alcohol craving. Eighty-one of the 84 participants were reached approximately two weeks after their scan date to be reassessed on alcohol craving level. One ALCw, one ALCm, and one NCw could not be reached for follow-up assessment on craving scores. Neither the ALC group nor the NC group displayed an increase in alcohol craving (*ie*, a significant change in craving scores) from the assessment on their scan date to their follow-up assessment.

Behavioral Results

Measures of participant performance on the face memory task were calculated for overall performance and for performance by each distractor type and facial emotion. Means, standard deviations, and ranges are reported for percent correct responses and reaction times in Tables A2 and A3, respectively.

A significant Group-by-Gender interaction was found for overall accuracy ($F_{1,80} = 6.880, p = 0.01$, Figure A1 and Table A2): ALCw had significantly higher accuracy scores than ALCm (mean 85.3% vs. 77.4%), and this gender difference was larger than that observed in the NC group. Accuracy and reaction times (Figure A2 and Table A3) did not vary significantly as a function of the Distractor, nor were there any significant interactions of Distractor with Group or Gender (all $p > 0.05$). The main effect of Emotion was significant for percent correct responses, wherein ALC and NC participants alike performed better on both positive and negative faces relative to neutral faces. Performance on positive and negative faces did not differ significantly. The effect of Emotion on percent correct responses did not vary as a function of Group or Gender (all $p > 0.05$). Regarding reaction time and Emotion, participants responded more quickly to positive face trials relative to neutral face trials; this effect did not vary by Group or by Gender. The main effect of Face Gender on percent correct responses was also significant ($F_{1,80} = 6.80, p = 0.01$), with the overall performance being better for male faces than for female faces. The effects of Group and Gender on percent correct responses and reaction times for Face Gender were not significant (all $p > 0.05$).

fMRI BOLD Effects

Effects of the distractors on the BOLD signal were assessed using group and intergroup cluster analyses for cerebral cortex, along with a-priori analyses of anatomical ROI that had been implicated by the literature. Below, we report group analyses of fixation contrasts and between-distractor conditions, followed by intergroup analyses of the same contrasts.

Cortical Cluster Analyses of Distractor Effects

Analyses of task contrasts revealed broadly similar activation patterns for the ALC_w, ALC_m, NC_w, and NC_m groups. During fixation, regions involved in the DMN were significantly more active than during the presentation of distractor images. As detailed in the Methods, these fixation-regions were masked and examined separately for subsequent analyses of contrasts between distractor types. Identical analyses were then performed for the task-regions. Significant clusters for between-distractor contrasts can be seen for fixation-regions first (Figures 3 and A3), and then for task-regions (Figures 4 and A4).

All four groups had more brain activity (Table A4) in response to albebv than scrambled distractors in the four main fixation-regions (the anterior and posterior medial hub regions, the temporal parietal junction, and the middle temporal gyrus), while the nonalbebv vs. scrambled contrast was less consistent. The albebv vs. nonalbebv contrast generally indicated higher activation for the albebv than nonalbebv. For task-regions, albebv and nonalbebv elicited higher activation than scrambled in the occipital lobe and adjoining visual areas in temporal and parietal cortex (Table A4 and Figure A4).

Distractor Intergroup Cluster Analyses

The pattern of results indicated that ALC_w and NC_m had strong activation contrasts (beverages > scrambled) in visual areas and the medial fixation-regions, especially the posterior hub. The ALC_w had greater activation contrast than NC_w, while ALC_m had lower activation contrast than NC_m. Table 2 summarizes the regions where significant Group-by-Gender interactions were found for the distractor contrasts, *ie*, for albebv vs nonalbebv, albebv vs. scrambled, and nonalbebv vs. scrambled. Table A5 provides all significant Group-by-Gender interactions, and Figures 3, 4, A3, A4 illustrate albebv vs. scrambled contrasts. In total, we observed 22 clusters where the Group-by-Gender interaction was statistically significant: Seven in fixation-regions and 15 in task-regions.

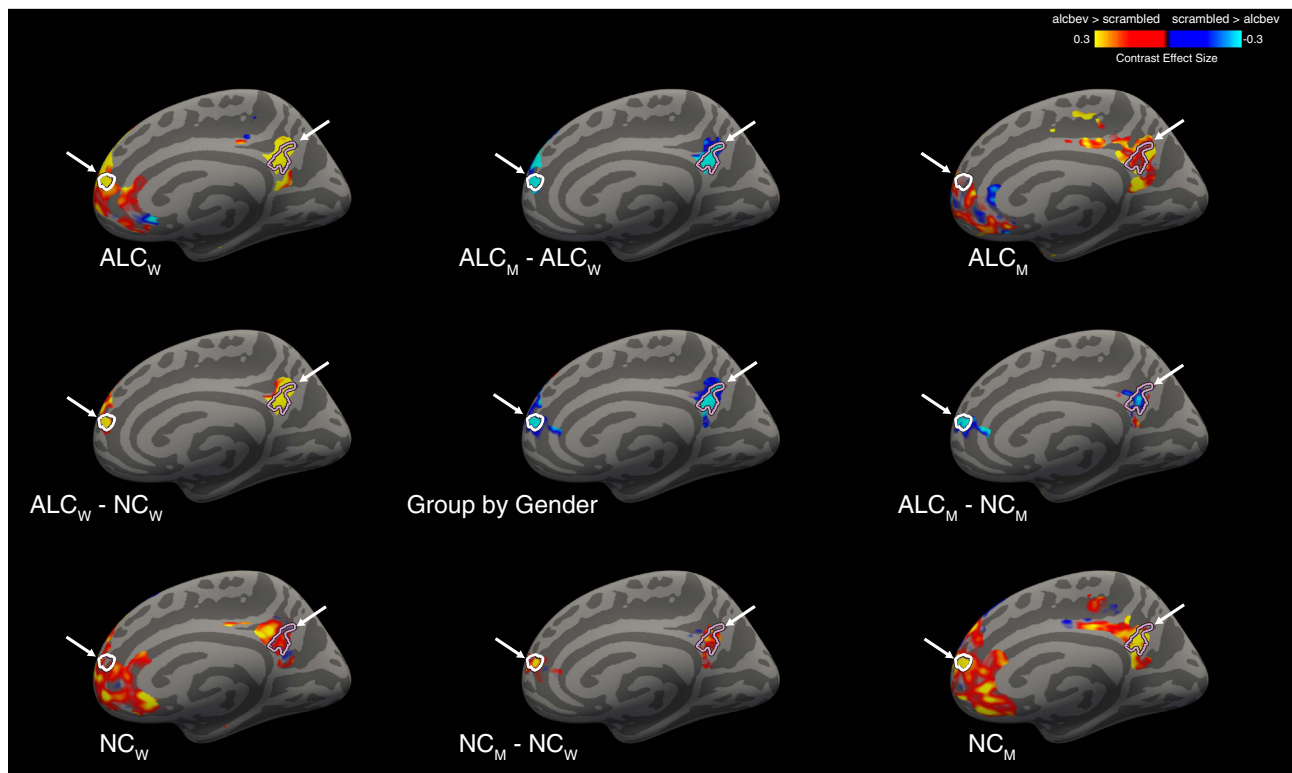


Figure 3 Cortical clusters significant for Group-by-Gender interactions for the albebv vs. scrambled contrast within fixation-regions (right medial view). A significant Group-by-Gender interaction revealed several clusters (see Table A5), two of which are indicated by arrows on the medial surface of the right hemisphere, with cluster outlines overlaid on contrast values between albebv and scrambled distractors. Group mean contrast values (for albebv vs. scrambled within fixation-regions) are displayed in the four brain images located in the corners of the figure, and group comparisons are indicated by minus signs.

Abbreviations: ALC_m, Alcoholic men; ALC_w, Alcoholic women; NC_m, Nonalcoholic men; NC_w, Nonalcoholic women.

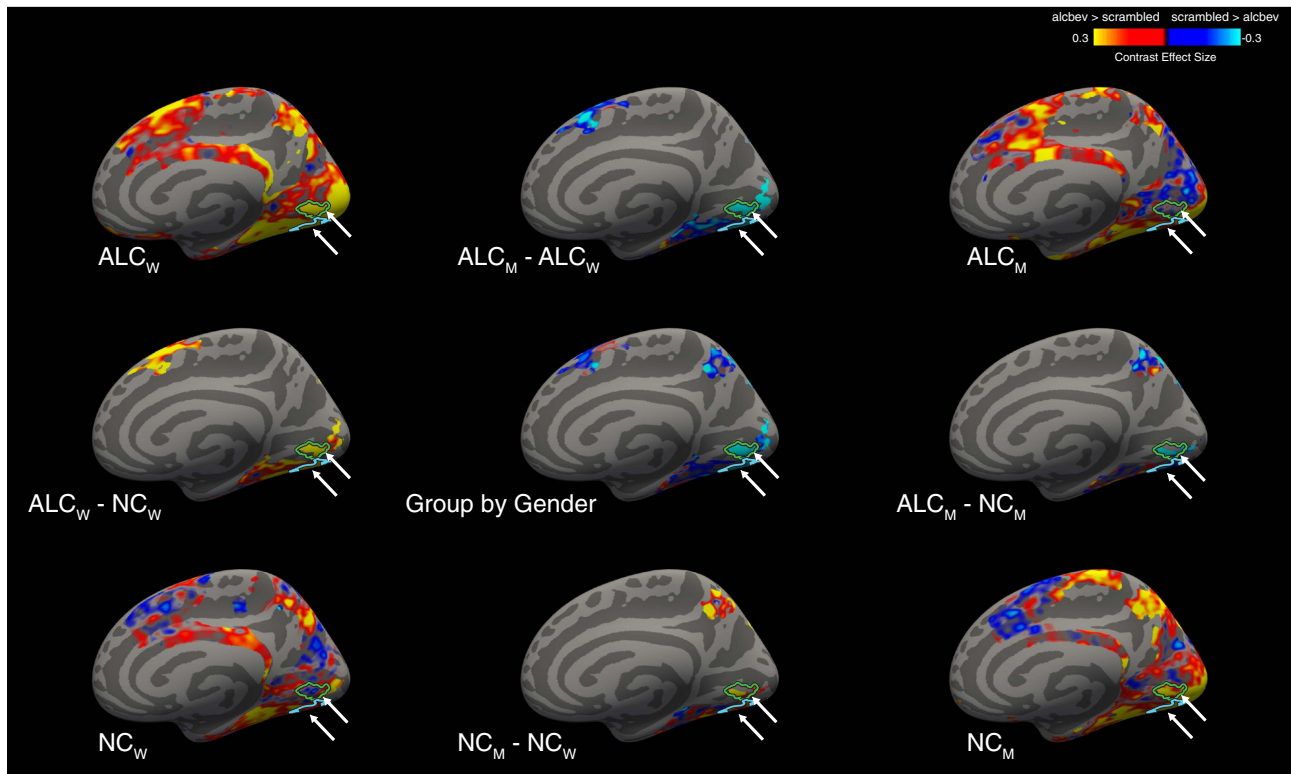


Figure 4 Cortical clusters significant for Group-by-Gender interactions, for the alcbev vs. scrambled contrast within task-regions (right medial view). A significant Group-by-Gender interaction revealed several clusters (see [Table A5](#)), two of which are indicated by arrows on the medial surface of the right hemisphere, with cluster outlines overlaid on contrast values between alcbev and scrambled distractors. Group mean contrast values (for alcbev vs. scrambled within task-regions) are displayed in the four brain images located in the corners of the figure, and group comparisons are indicated by minus signs.

Abbreviations: ALC_M, Alcoholic men; ALC_w, Alcoholic women; NC_M, Nonalcoholic men; NC_w, Nonalcoholic women.

For the seven clusters in fixation-regions, six were in the anterior hub and one was in the posterior hub. For alcbev > scrambled, we observed one cluster in the posterior hub and three in the anterior hub. For three of these four clusters, ALC_w and NC_M had the strongest contrasts; in the fourth cluster, ALC_w had the strongest contrast, whereas ALC_M had the weakest. The remaining three clusters were found for nonalcbev > scrambled. As with the alcbev contrasts, ALC_w and NC_M had the strongest contrasts. All three clusters were in the right hemisphere of the anterior hub. Thus, the overall pattern consistent among the seven clusters was as follows: NC_M had stronger contrast (beverage > scrambled) than ALC_M, while muted or opposite direction comparison was observed for the women.

Table 2 Group-by-Gender Cortical Cluster Summary

Fixation Masking	Distractor Contrast	Clusters	Annotation (Hemisphere: Number of Clusters)
Fixation-regions	alcbev > scrambled	4	Superior frontal (L: 1, R: 2), precuneus (R: 1)
Fixation-regions	nonalcbev > scrambled	3	Superior frontal (R: 2), caudal middle frontal (R: 1)
Task-regions	alcbev > scrambled	5	Superior parietal (L: 1, R: 2), fusiform (R: 1), lingual (R: 1)
Task-regions	nonalcbev > scrambled	4	Superior parietal (L: 1, R: 1), lateral occipital (R: 2)
Task-regions	scrambled > nonalcbev	4	Superior frontal (L: 2), rostral middle frontal (L: 2)
Task-regions	nonalcbev > alcbev	2	Superior frontal (L: 2)

Notes: Annotations (using the Desikan-Killiany atlas) are shown for each of the 22 clusters with significant Group-by-Gender interactions in distractor contrasts. The Fixation Masking column refers to the separate analyses conducted for fixation-regions and task-regions as shown in [Figure 2](#). The clusters reported can be understood to span multiple functional regions.⁷² That is, they are not limited to a single region, as reported by the maximal vertex or voxel. See [Table A5](#) for detailed cluster information. For the fixation-regions, superior frontal and caudal middle frontal are part of the anterior hub; and precuneus is part of the posterior hub.

Abbreviations: alcbev, alcoholic beverages; nonalcbev, nonalcoholic beverages; L, left hemisphere; R, right hemisphere.

Of the 15 task-regions clusters, two were found for nonalcbv > alcbv (left superior frontal cortex). In both clusters, NCw had higher activation to nonalcoholic beverages, while NCm had higher activation to alcoholic beverages. In the other 13 clusters, the strongest contrasts were found for NCm and ALCw. Of those, the significant interactions were found in visual regions where nonalcbv > scrambled, while significant interactions in frontal regions were found for scrambled > nonalcbv.

Setting aside gender, analyses of activation levels comparing ALC and NC groups revealed 15 cortical clusters with significantly greater contrast levels for the ALC group than for the NC group (Table A6). Two of the clusters were in fixation-regions: one alcbv-region (temporoparietal junction), and one nonalcbv-region (posterior hub). The other 13, all alcbv-regions, were in task-regions located throughout the cortex: 7 frontal, 3 temporal, 2 parietal, and 1 occipital.

Distractor Region of Interest Analyses

Results of ANOVAs examining between-subjects effects of Group and Gender and within-subjects effects of Distractor type on BOLD percent signal change within each ROI are summarized in Table 3. Reported means and standard deviations represent the percent signal change across each ROI (unmasked) for the time period of 2 to 12 seconds post-distractor stimulus onset. These anatomically defined ROI included regions in EROS areas,^{25,64} as well as in regions associated with face memory maintenance and distractor interference, as described in the Introduction and Methods.

Results from the ROI analyses of distractor effects indicated strong effects of distractor type on neural activation patterns. Specifically, among all participants, significantly higher responses were observed in several regions (EROS, left DLPFC, left VLPFC, right OFC, bilateral parahippocampal gyrus, bilateral hippocampus, bilateral amygdala, and bilateral fusiform) to both alcbv and nonalcbv relative to scrambled stimuli. The effect was significantly larger for the ALC group than the NC group in the left EROS and left fusiform regions, and in four prefrontal brain areas (left DLPFC, left VLPFC, left OFC, and right OFC). Additionally, in the alcbv vs. nonalcbv contrast, the ALC group showed significantly higher responses than the NC group in the left OFC ROI. Figure 5 shows percent signal change over time for the OFC, VLPFC, fusiform, and ACC activation, to demonstrate representative activity patterns. The left OFC shows the heightened activation for alcbv for the ALC group, the fusiform and VLPFC show higher activation in both groups to both beverage types, and the ACC demonstrates how activation is lower during distractor presentation than during fixation (for both groups and for all three distractor types).

Applying a Bonferroni correction accounting for all 25 tests would set a critical value for statistical significance of main effects and Distractor, Group, and Gender interactions at $p < 0.002$. Using this threshold, main effects of Distractor would remain significant in left OFC, bilateral parahippocampal gyrus, bilateral hippocampus, right amygdala, and bilateral fusiform gyrus. All main effects of Group and Gender, as well as all interaction effects were $p > 0.002$.

Discussion

Behavioral Responses to Probe Face and Distractor Cues

In this study, ALC and NC participants alike were able to use emotional information to improve memory as assessed by a DMTS task, as has been previously reported in NC participants.^{32,93,94} This was evidenced by better memory performance (*ie*, higher accuracy) on positive and negative faces, and faster reaction times to positive faces, than neutral faces.

We had postulated that, compared to the NC group, the ALC group would make more recognition errors after alcohol distractors (relative to other distractor types). However, we found that regardless of the group, the distractor type did not substantially influence accuracy or reaction time. Although we also had expected performance by the ALC group to be impaired by alcoholic beverage cues, a significant interaction between group and distractor type was not evident. We did not find a behavioral attentional bias effect: The alcoholic beverage distractors (relative to nonalcoholic beverage or scrambled picture distractors) did not disproportionately decrease the number of correctly recalled faces among either the ALC or the NC group. As suggested in a review by Field and Cox,⁵ the strength of a bias effect among ALC groups may depend upon their drinking histories. Interestingly, Loeber et al⁵¹ found that reduced attentional biasing to alcohol cues was associated with longer durations of heavy drinking, and our sample also had long durations. Further, participants with short vs. long lengths of abstinence might use different cognitive strategies, which could be reflected in both behavioral performance and brain activity. While the results were consistent with findings by Loeber and colleagues⁵¹

Table 3 Percent Signal Change for Each Distractor Type by Group, for a-Priori Regions

	ALC				NC				Distractor by Group
	Alcoholic Beverage	Nonalcoholic Beverage	Scrambled Picture	Distractor Main Effect	Alcoholic Beverage	Nonalcoholic Beverage	Scrambled Picture	Distractor Main Effect	
	Percent Signal Change: Mean ± SD			$F_{1,41}$	Percent Signal Change: Mean ± SD			$F_{1,41}$	
EROS	0.073 ±.093	0.059 ±.072	0.030 ±.068	8.795*ab	0.047 ±.089	0.051 ±.085	0.040 ±.063	0.407	3.650 ⁺
EROS LH	0.071 ±.097	0.058 ±.079	0.024 ±.071	10.567*ab	0.049 ±.093	0.055 ±.093	0.040 ±.066	0.580	4.217*
EROS RH	0.075 ±.093	0.061 ±.071	0.037 ±.069	7.003*a	0.047 ±.089	0.048 ±.081	0.041 ±.067	0.247	3.034 ⁺
DLPFC LH	0.060 ±.111	0.049 ±.103	0.017 ±.085	7.529*ab	0.041 ±.098	0.047 ±.096	0.040 ±.073	0.032	4.481*
DLPFC RH	0.069 ±.111	0.060 ±.094	0.039 ±.077	3.953 ⁺	0.034 ±.097	0.035 ±.093	0.039 ±.077	0.169	3.382 ⁺
VLPFC LH	0.198 ±.132	0.181 ±.147	0.145 ±.111	11.680*ab	0.157 ±.115	0.182 ±.129	0.154 ±.097	0.062	5.820*
VLPFC RH	0.210 ±.122	0.195 ±.134	0.173 ±.124	5.387*a	0.157 ±.114	0.174 ±.134	0.155 ±.104	0.039	2.925 ⁺
OFC LH	0.125 ±.130	0.090 ±.135	0.057 ±.107	16.019*ac	0.071 ±.164	0.085 ±.193	0.058 ±.157	0.399	6.105*
OFC RH	0.256 ±.179	0.234 ±.203	0.178 ±.210	10.130*ab	0.184 ±.224	0.195 ±.249	0.177 ±.199	0.176	5.608*
Insula LH	0.104 ±.105	0.096 ±.091	0.069 ±.077	5.920*a	0.067 ±.088	0.082 ±.080	0.066 ±.061	0.001	3.275 ⁺
Insula RH	0.098 ±.097	0.082 ±.091	0.068 ±.073	4.084*a	0.061 ±.088	0.068 ±.075	0.059 ±.066	0.025	2.109
Parahippocampal LH	0.126 ±.149	0.125 ±.098	0.052 ±.101	12.216*ab	0.130 ±.136	0.136 ±.141	0.083 ±.100	4.915*ab	0.894
Parahippocampal RH	0.156 ±.140	0.136 ±.093	0.083 ±.090	12.220*ab	0.160 ±.119	0.167 ±.126	0.109 ±.090	9.013*ab	0.743
Hippocampus LH	0.085 ±.131	0.077 ±.096	0.021 ±.094	13.908*ab	0.050 ±.108	0.054 ±.105	0.012 ±.090	7.179*ab	1.394
Hippocampus RH	0.088 ±.120	0.066 ±.083	0.024 ±.088	11.669*ab	0.077 ±.106	0.074 ±.088	0.038 ±.085	7.955*ab	1.134
Amygdala LH	0.093 ±.188	0.098 ±.154	0.041 ±.154	6.019*ab	0.094 ±.194	0.095 ±.203	0.064 ±.137	2.207	0.581
Amygdala RH	0.105 ±.140	0.089 ±.126	0.027 ±.134	14.976*ab	0.121 ±.175	0.118 ±.160	0.085 ±.130	4.389*a	2.519
ACC LH	-0.059 ±.119	-0.080 ±.094	-0.095 ±.106	5.019*a	-0.092 ±.109	-0.088 ±.116	-0.089 ±.105	0.036	3.195 ⁺
ACC RH	-0.056 ±.119	-0.068 ±.102	-0.080 ±.111	2.026	-0.085 ±.107	-0.089 ±.100	-0.085 ±.097	0.000	1.179
Fusiform LH	0.758 ±.258	0.743 ±.207	0.553 ±.120	65.492*ab	0.705 ±.285	0.724 ±.294	0.579 ±.259	22.579*ab	4.803*
Fusiform RH	0.855 ±.303	0.851 ±.234	0.669 ±.229	49.514*ab	0.823 ±.292	0.845 ±.301	0.694 ±.253	49.438*ab	3.322 ⁺

Notes: Distractor by Group F-values are reported from a full factorial ANOVA model with between-groups factors of Group and Gender and within-groups factors of Distractor type. Distractor main effect F-values within each group are reported from ANOVA model including within-subjects factor of Distractor type. a. Alcoholic Beverage > Scrambled Picture, $p < 0.05$. b. Nonalcoholic Beverage > Scrambled Picture, $p < 0.05$. c. Alcoholic Beverage > Nonalcoholic Beverage, $p < 0.05$. * $p < 0.05$ (bold). $+0.05 < p < 0.10$.

Abbreviations: EROS, Extended Reward and Oversight System; DLPFC, Dorsolateral Prefrontal Cortex; VLPFC, Ventrolateral Prefrontal Cortex; OFC, Orbitofrontal Cortex; ACC, Anterior Cingulate Cortex; LH, Left Hemisphere; RH, Right Hemisphere.

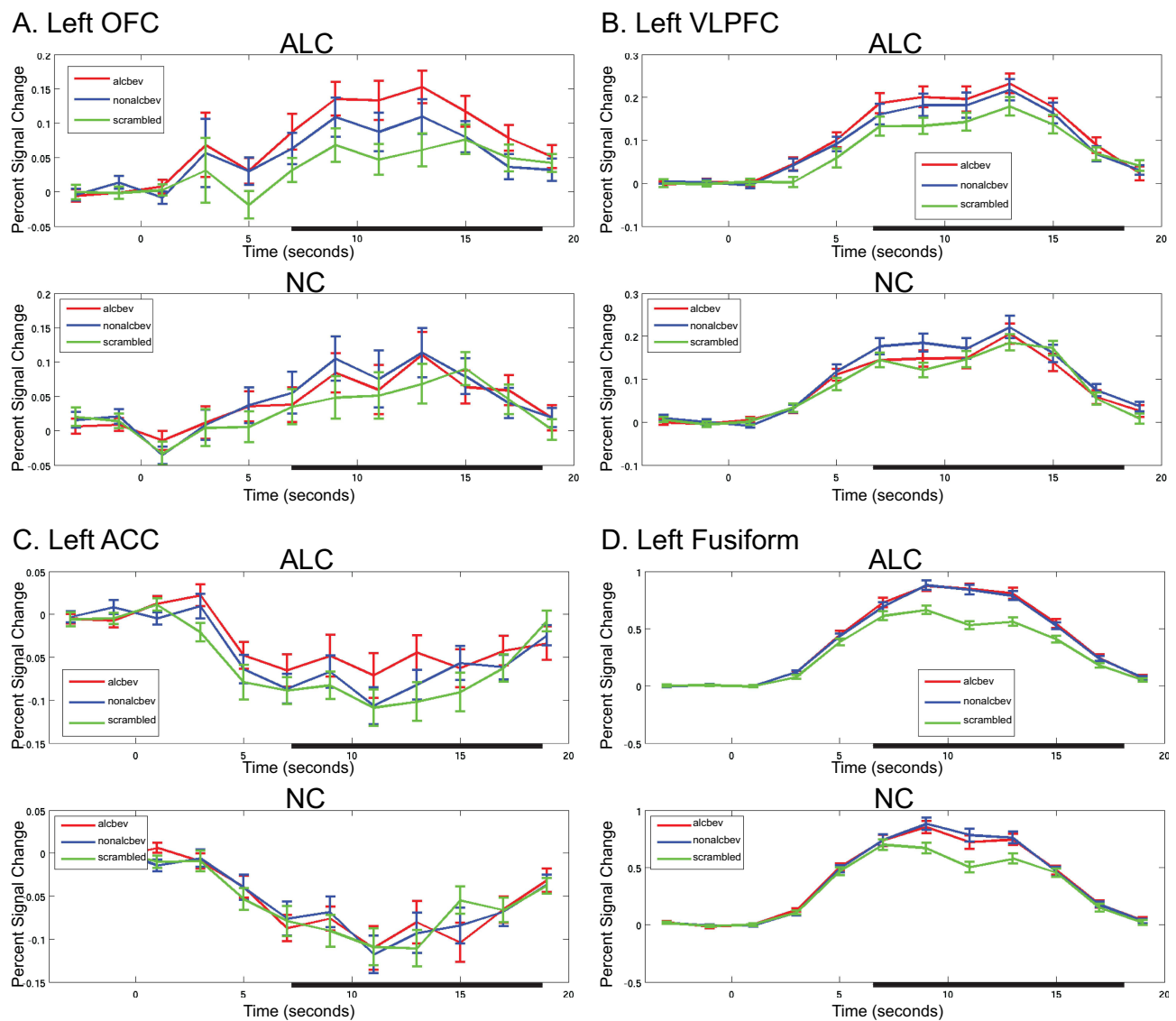


Figure 5 ROI - Percent signal changes in regions of interest for ALC and NC participants by distractor type. The regions of interest are: (A) Left OFC; (B) Left VLPFC; (C) Left ACC; and (D) Left Fusiform. The percent signal change represents brain activity during presentation of fixation and the task stimuli. Error bars represent the standard error of the mean. Time zero was set to the onset of the encoded faces, and signal zero was set to the average signal for the three initial time points (two pre-trial and one post-trial onset). The analysis window used to examine the distractor was 6 to 16 seconds following trial onset (2 to 12 seconds after distractor onset), as indicated by the thick line on the x axis. The ACC (C) is part of the anterior hub within the fixation-regions. The remaining areas are primarily task-regions.

Abbreviations: OFC, orbitofrontal cortex; VLPFC, ventrolateral prefrontal cortex; ACC, anterior cingulate cortex.

regarding chronicity, direct correlational analyses between drinking duration and attentional bias effects were not conducted in the present study, and findings would benefit from research with larger samples. Although combining participants with variable drinking histories might have masked the attentional biasing effect, measures of neural activity were more sensitive than behavioral measures. That is, the activation levels reflected attentional bias to beverage cues even when combining participants with differing patterns of drinking and abstinence.

Distractor fMRI Contrasts

The fMRI contrasts revealed broadly similar patterns of brain activity among the four subgroups, for both fixation-regions and task-regions. In both brain networks, the beverages (alcbbev and nonalcbbev) elicited higher activation than the scrambled distractors. This amounts to internal replications of our present fMRI results, with four independent samples (ALCm, ALCw, NCm, and NCw) revealing the same fixation-regions, same task-regions, and with mostly the same

direction of effects for task contrasts within those regions. The results reflect the existence, location, and extent of the DMN,^{47,49} and also indicate that beverage pictures elicit higher activation than scrambled pictures in the DMN. Moreover, our results indicate that DMN regions are sensitive to the informational content of visual stimuli. In task-regions, the occipital lobe, along with adjoining visual areas in temporal and parietal cortex, were clearly more activated by beverage stimuli than by scrambled images. The results further suggest that content processing is not solely performed by those visual regions, because activation to beverage cues was identified in middle to posterior cingulate regions, which are involved in a multitude of cognitive functions.^{95,96}

Gender Differences

The present research provides further evidence for the importance of considering gender when exploring effects of alcoholism on the brain.^{97,98} Many factors contribute to the observed differences in function for abnormalities identified comparing ALCm with NCm vs. ALCw with NCw.

Cortical group-level cluster analyses revealed significant Group-by-Gender interaction effects in 22 clusters. The general pattern of those findings indicated that ALCm had lower activation contrasts than NCm, while ALCw had higher activation contrasts than NCw. This pattern was observed primarily in contrasts between beverage and scrambled distractor conditions, and they were found in the two core medial DMN regions, as well as in visual association cortices. A similar pattern of results was found in a previous report²⁴ in which emotional vs. neutral image contrasts were lower in ALCm than NCm, and stronger in ALCw than NCw. The lower brain reactivity for ALCm, and higher for ALCw, highlighted gender effects, suggesting possible differences in underlying bases for development of AUD. Of note, the results from other modalities also have indicated similar directions of the fMRI effects, with ALCw having larger reward regions than NCw, and higher fractional anisotropy than NCw, as compared to the smaller regions and lower fractional anisotropy found for ALCm than NCm.^{25,27}

The gender-divergent abnormalities in the anterior and posterior hub regions of the DMN could be reflective of other gender differences observed in conjunction with AUD. The role of these regions in internal monitoring could relate to differences in pre-existing risk factors,^{30,31,99} or could represent differential consequences of alcohol abuse.¹⁰⁰ The pattern of higher activation contrasts in ALCw versus ALCm localized to posterior DMN regions (precuneus) aligns with findings by Tschuempelin and colleagues,¹⁰¹ who reported stronger implicit association-related activation localized to PCC and precuneus in female compared to male AUD patients. This convergence suggests that gender-divergent DMN responses to alcohol-related stimuli may reflect differential engagement of self-referential or memory-related processes during cue exposure. A similar pattern of group differences was identified in cortical regions associated with visual processing. That is, the results could represent a more fundamental impact that is not regionally specific. In the present study, effects of both increased activation in reward regions and decreased deactivation in DMN regions in response to alcohol pictures were strongest among ALCw in particular. One reason stronger alcohol cue-specific responses were observed among ALCw could be related to gender-based differences in physiological responses to alcohol cues,¹⁰² and with respect to gender-divergent responses to stress and craving.¹⁸ Aligned with this, larger responses to alcohol cues by female social drinkers relative to male social drinkers have been reported in superior and middle frontal gyri.¹⁰³

Group Differences

In addition to significant gender interactions, we identified regions with differences between the ALC and NC groups. Cluster analyses showed that the ALC group had higher activation in two fixation-regions and 13 task-regions ([Table A6](#)). Differences in the posterior hub were identified in regions with stronger activation to nonalcoholic beverages than to scrambled images, while the other clusters had stronger activation to alcoholic beverages. The higher contrasts observed for the ALC group indicate a processing bias toward beverage cues across fixation- and task-regions. However, the stronger activation observed in the ALC group during alcohol distractors also may reflect engagement of executive control processes necessary to overcome attentional capture and maintain task performance.^{104,105} The absence of behavioral impairment despite elevated neural activation could indicate successful compensatory control processes, consistent with models suggesting enhanced executive control activation in addiction contexts to maintain behavioral regulation.^{65,68,106,107}

Brain Responsivity in the Default Mode Network

Compared to the NC group, cluster analyses showed that the ALC group, and the ALCw in particular, had stronger contrasts in the anterior and posterior hubs, along with the temporoparietal junction. The results for ROI that include DMN regions also support the finding of contrast dampening in response to alcohol cues. Abnormal DMN functioning has been observed in other addictions and neuropsychiatric conditions.^{108–110} In AUD, abnormal functional connectivity among DMN regions has been reported.^{111,112} ALCw in particular had stronger contrasts for both the anterior and posterior hubs, an abnormality which could indicate a limitation in the level of detail processed, or the way in which it is integrated.¹¹³ Lower activation of the anterior hub specifically has been associated with dynamic attention allocation during task executions.¹¹⁴ This suggests that reduced deactivation of this region in AUD individuals when viewing alcohol pictures could be associated with failure to reallocate attention back to the task. That is, the ALC group could have decreased attention to the alcohol distractor cues. While the ALCw group's abnormal DMN activation in conjunction with strong task performance may seem counter-intuitive, another explanation involves an interaction between task demands and DMN functions.¹¹⁵ In other words, in conjunction with equivalent or superior memory performance, our results suggest that, for ALCw especially, parts of the DMN might disengage, and show higher connectivity with control networks during highly demanding working memory tasks.

Brain Responsivity in Regions of Interest

The ROI analysis of the OFC provides evidence for reward-specific processing in the ALC group. In particular, reward-specific processing refers to their higher activation from the contrast between alcbev and nonalcbev. Several studies have reported enhanced OFC activation to alcohol cues,^{58,61,116,117} and research has established the role of the OFC in alcohol and drug addiction more generally.³ We had initially hypothesized lower activation for the ALC group in regions subserving facial identity maintenance and distractor inhibition. However, an alternative hypothesis also could be supported by our ROI findings in the OFC and EROS. That is, higher activation to alcoholic beverages in reward-salient regions may override or compete with task-related processes, thereby disrupting working memory maintenance via attentional capture rather than by diminished reward responsivity. The OFC activity may be particularly important for preoccupation and anticipation stages of the addiction cycle.¹¹⁸ Additionally, activity in this region has been shown to correlate with subjective craving ratings of viewed alcohol cues,⁶⁰ and further correlated with relapse risk.¹¹⁹

In the regions where significant interactions of Group and Distractor type were identified, the distractor effect was found to be significant among the ALC group, but not among controls. In the EROS, DLPFC, VLPFC, OFC, and fusiform, the differences in activation levels among beverage distractor conditions (alcoholic and nonalcoholic) were larger relative to scrambled pictures in the ALC group than in the NC group. The higher responsivity of the ALC group to alcoholic beverages supports our hypothesis of greater attentional bias in the form of stronger alcbev vs. nonalcbev activity contrasts, but we did not expect the ALC group to have greater activation than the NC group to nonalcoholic beverages relative to scrambled cues. One explanation for this result is that many of the nonalcoholic beverages contain caffeine or sugar (*eg*, coffee, tea, soda), which, like alcoholic beverages, also stimulate reward-network activity.¹²⁰ As was suggested in an earlier meta-analysis,¹²¹ the attentional bias for caffeine-related cues may correlate more strongly with subjective craving than for alcohol-related cues. Moreover, craving for both caffeine and alcohol utilize similar neural circuits as are used for processing alcohol reward,¹²² as do the effects of sugar-related reward.^{123,124}

Limitations

Although we observed a significant Group-by-Gender interaction in overall accuracy, we did not observe significant attentional bias (Distractor type) on behavior, despite significant findings of the bias effects in brain activation. This may reflect differences in sensitivity of the two types of measures, in the abstinence characteristics of our cohort, or in sample sizes too small to detect complex Group-by-Gender-by-Distractor interactions. Furthermore, behavioral measures may not be normally distributed, and violation of parametric assumptions may limit the interpretability of the repeated-measures ANOVA conducted. Those with long sobriety may have developed different cognitive strategies than AUD participants at an early stage of abstinence, especially strategies to deal with alcohol stimuli and to overcome craving. In

that case, combining AUD participants with long and short LOS may have masked behavioral measures of attentional bias of accuracy and reaction time, while preserving the more sensitive and robust brain activation measures. Moreover, gender differences within the AUD group could be probed with sobriety as a covariate, or a subgroup analysis with narrow range could be conducted, although these analyses were beyond the scope of this report. Likewise, the variability in other participant characteristics such as IQ and age may diminish disclosure of AUD-related differences that additional research with larger samples could remedy.

It is not clear to what degree the abnormalities we observed result from, or predate, heavy drinking. In any case, our AUD cohort had drinking history values representative of the national population,¹²⁵ thereby improving the generalizability of our results. The mean abstinence period for the ALC group was 8.3 years (range 4 weeks to 32 years). These values represent cross-sectional data, limiting conclusions regarding the trajectory of changes in brain activation or behavioral responses over the course of abstinence. Importantly, however, the processing deficits in AUD populations may vary by gender, and short- and long-term abstinence may have different paths of recovery for men and women.²⁸

In conjunction with the multiple-comparison cluster correction procedures employed, the significance level we used ($p < 0.05$) has been shown to have higher false-positive rates than expected.¹²⁶ Therefore, we conducted additional analyses to control false-positive errors with strict permutation testing (with a vertex-wise threshold of $p < 0.001$ and a cluster-wise threshold of $p < 0.05$), which has been shown to avoid the unexpectedly high false-positive rates identified for Gaussian field theory-based cluster-correction.^{126,127} However, the use of strict thresholds increases the chance of false-negative errors, and the stricter significance level may have resulted in us missing real gender effects; therefore, we reported the entirety of the group comparisons (with [Tables A5](#) and [A6](#) reflecting the main results, and [Tables A7](#) and [A8](#) reflecting the results using strict permutation testing). Although we report cluster labels by the location of the peak voxel or vertex, the clusters reported can be understood to span multiple functional regions.¹²⁸ That is, they are not limited to a single region, as reported by the maximal vertex or voxel.

In the present study, there were 21 participants in each of the four subgroups. These cohort sizes may be considered as underpowered for examining sex differences. This is a persistent limitation faced by alcohol researchers studying sex differences, and we acknowledged that larger samples of male and female participants would strengthen our conclusions about sex differences.

Finally, our analyses did not include factors such as cigarette smoking, body mass index, and hormone therapy,^{1,129} which could possibly influence alcohol cue processing, reward, and DMN activity.

Conclusion

Compared to the NC group, the ALC group had stronger activation for the DMN, and overactivated reward regions during alcohol cue distraction. This suggests that attentional capture is not limited to reward regions, but also includes the DMN. If so, the DMN has a role in processing salient aspects of addictive substances.

The present study showed that alcohol cue distractors have powerful effects on reward-related regions of the brain, even in the absence of impaired performance when alcohol cues are employed as distracting stimuli. We also demonstrated that the increased responses in reward regions are accompanied by dampened DMN activity during the presentation of alcohol cues. Our results suggest that these effects are strongest among ALCw, and provide evidence for dimorphic patterns of responses to alcohol cues between ALCm and ALCw.

Abbreviations

ACC, anterior cingulate cortex; ALC, individuals with alcohol use disorders; ALCm, men with a history of alcohol use disorders; ALCw, women with a history of alcohol use disorders; ANOVAs, analyses of variance; AUD, alcohol use disorders; BOLD, blood oxygen level dependent; DIS, Diagnostic Interview Schedule; DMN, default mode network; DMTS, delayed matching-to-sample; DLPFC, dorsolateral prefrontal cortex; DMI, Delayed Memory Index; DSM-IV, Diagnostic Interview Schedule- 4th edition; EROS, extended reward and oversight system; fMRI, functional magnetic resonance imaging; FS-FAST, FreeSurfer Functional Analysis Stream; IMI, Immediate Memory Index; MRI, magnetic resonance imaging; NC, control participants without alcohol use disorders; NCm, women without a history of alcohol use disorders; NCw, men without a history of alcohol use disorders; OFC, orbitofrontal cortex; ROI, regions of interest; TR,

repetition time; duration for collecting an entire fMRI volume; VLPFC, ventrolateral prefrontal cortex; WAIS-III, Wechsler Adult Intelligence Scale 3rd edition; WMS-III, Wechsler Memory Scale-3rd edition.

Data Sharing Statement

The original data contain protected health information and cannot be shared directly. Upon request to the corresponding author, specified portions may be able to be shared, depending upon institutional review board review.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Primary contributors to study conception and design were MOB, SMR, KSS, KM, and GJH. The methodology, data curation, analyses, and figure creation were conducted primarily by SMR and KSS. Day-to-day operations were performed primarily by SMR, MMV, and KSS. The manuscript was written primarily by SMR, KSS, and MOB, and reviewed by all of the authors.

Disclosure

The authors report no conflicts of interest in this work.

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