

# Subjective Responses to Alcohol in the Lab Predict Neural Responses to Alcohol Cues

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**ABSTRACT. Objective:** Subjective responses to alcohol represent a biologically based, genetically moderated, and clinically informative marker of alcoholism risk; however, the physiology underlying this phenotype remains unclear. This study tested whether subjective responses during alcohol administration predict neural responses to alcohol cues in the scanner and whether these neural responses differ between *OPRM1* genotypes. **Method:** Twenty alcohol-dependent individuals were recruited (10 G-allele carriers; 6 women;  $M_{\text{age}} = 29.4$ ) for a within-subjects alcohol administration in the laboratory and a functional magnetic resonance imaging session consisting of an alcohol taste cues task. Laboratory assessments of alcohol high, liking, craving, and positive and negative reinforcement during alcohol administration were entered as predictors of neural response to the presentation of alcohol cues versus water cues in the scanner and further tested for *OPRM1* genotype

moderation (whole-brain cluster-corrected at  $Z > 1.96, p < .05$ ). **Results:** Alcohol craving during alcohol administration predicted less neural activity, whereas alcohol reinforcement predicted greater neural activity to alcohol cues versus water cues in regions including the precuneus, posterior cingulate gyrus, and lingual gyrus. Alcohol high predicted greater neural activity to alcohol cues in regions including the precuneus and anterior cingulate cortex. *OPRM1* genotype was found to moderate these relationships. No results were observed for alcohol liking. **Conclusions:** This study provides initial evidence that subjective responses to alcohol, namely craving, high, and the reinforcing properties of alcohol, predict neural markers of alcohol cue reactivity. These results support the validity of laboratory and neuroimaging measures of subjective responses to alcohol and offer an integration of these methods in a sample of alcohol-dependent individuals. (*J. Stud. Alcohol Drugs*, 75, 124–135, 2014)

**S**UBJECTIVE RESPONSES TO ALCOHOL have been proposed to represent a biologically based and clinically informative marker of alcoholism risk (e.g., Ray et al., 2010a). Controlled alcohol administration studies followed by longitudinal assessments revealed that lower sensitivity to the aversive effects of alcohol, or “low level of response” to alcohol, confers a higher risk for the development of alcoholism at follow-up (Schuckit and Smith, 1996; Schuckit et al., 2004); and individuals who are more sensitive to the stimulant and rewarding effects of alcohol in the laboratory are more likely to develop an alcohol use disorder at follow-up (King et al., 2011). Further, medications that can attenuate the subjective reinforcing effects of alcohol, such as naltrexone, are clinically useful in the treatment of alcoholism (Anton et al., 2006; King et al., 1997). Together, these studies have advanced subjective response to alcohol as a translational phenotype for alcoholism.

To that end, recent studies have combined alcohol administration with neuroimaging methods to elucidate the biological bases of subjective responses to alcohol. Specifically, low levels of response to alcohol have been consistently

associated with greater activation of the right prefrontal cortex under placebo, but not under alcohol, during memory tasks (Paulus et al., 2006; Tapert et al., 2004; Trim et al., 2010). Differential brain activation between low-level and high-level responders to alcohol has also been observed during a response inhibition task (Schuckit et al., 2012) and in response to emotional stimuli (Paulus et al., 2012) as a function of alcohol condition, whereby low-level responders typically exhibit more brain activity under placebo conditions but less activity after a moderate dose of alcohol as compared with matched high-level responders. A study combining intravenous (IV) alcohol administration with functional magnetic resonance imaging (fMRI) found that social drinkers displayed greater activation of the nucleus accumbens and greater subjective ratings of intoxication than heavy drinkers, thereby suggesting that heavy drinking may be associated with a blunted response to alcohol in the brain’s reward circuitry (Gilman et al., 2012a). Subjective ratings of alcohol stimulation were associated with risk taking, and striatal activation in response to risky choices was potentiated by alcohol administration compared with placebo (Gilman et al., 2012b).

Although these studies help triangulate across alcohol administration, subjective responses to alcohol, and neural responses to alcohol, they are limited by the fact that alcohol administration occurred in the scanning environment, which may not generalize to alcohol administration in the laboratory (e.g., full scales of subjective responses were not administered, and the entire slope of the ascending limb of intoxication was not captured in the scanner). To address this

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limitation, the present study examined a sample of alcohol-dependent individuals during controlled IV alcohol administration in the human laboratory followed by alcohol cues administration during fMRI. The primary aim of this study was to integrate human laboratory methods with neuroimaging by testing whether subjective responses to alcohol during alcohol administration predict neural responses to alcohol cues in the scanner.

Subjective responses to alcohol appear to be, at least in part, genetically determined, as retrospective self-report and alcohol administration methods investigating low-level responses to alcohol have identified heritabilities of 40%–60% (Heath et al., 1999; Schuckit et al., 2001). As such, a secondary aim of the study was to investigate whether the *OPRM1* gene, which encodes the  $\mu$ -opioid receptor, moderates the relationship between subjective response to alcohol and neural response to alcohol cues. The  $\mu$ -opioid receptor has been identified as the primary site of action for opiates with high potential for dependence (Pasternak, 1993). Non-opioid drugs such as cocaine and alcohol may also exert some of their effects through the activation of these receptors (Herz, 1997). The +118A/G polymorphism (located on the +118 position in exon 1 of the *OPRM1* gene, which codes for the Asn40Asp substitution) has been shown to affect receptor activity for the endogenous ligand  $\beta$ -endorphin, such that the Asp40 (i.e., G-allele) variant binds  $\beta$ -endorphin three times more strongly than the Asn40 allele (i.e., A-allele). Individuals with the G-allele have been shown to experience greater subjective reinforcing effects after alcohol consumption (Ray and Hutchison, 2004; Ray et al., 2010b) and exhibit greater dopamine release in the striatum during IV alcohol administration, although no associations between subjective ratings of alcohol effects and dopamine release measured using positron emission tomography imaging were observed (Ramchandani et al., 2011). Further, the G-allele of the *OPRM1* gene has been shown to moderate the strong effects of parental rule-setting on adolescent alcohol use (Pieters et al., 2012), although the mechanism of action underlying this relationship remains unknown. Together, these studies advance *OPRM1* as a plausible candidate gene that may moderate the relationship between subjective response to alcohol in the laboratory and neural response to alcohol cues.

To promote consistency between the alcohol administration and neuroimaging literatures, a set of reliable and neuroscience-informative dimensions of subjective responses to alcohol was selected for this study. Specifically, the incentive salience model of dependence emphasizes “liking” and “wanting” (i.e., craving) as dissociable entities that are, in turn, central to the development (liking) and maintenance (wanting) of dependence (Berridge et al., 2009; Robinson and Berridge, 1993, 2001). Conversely, the allostatic model highlights the transition from drinking for positive to negative reinforcement as a marker of the progression of alcohol-

ism from heavy episodic use to the withdrawal and negative affect stage of the disorder (Koob, 2003; Koob and Le Moal, 1997, 2005, 2008). The distinction between dimensions of positive and negative reinforcement from alcohol administration has been supported in a recent factor-analytic study by our laboratory examining multiple measures of subjective responses to alcohol (Ray et al., 2009). Thus, measures of craving (i.e., wanting), liking of the alcohol exposure, and the positive and negative reinforcement experienced from the alcohol exposure, represent the chosen predictors of neural response as they capture important theoretical constructs and have high translational value. A measure of the magnitude of the alcohol “high” experienced is also included in the model to partial out variance associated with acute intoxication (i.e., feelings of drunkenness) from the alcohol administration.

In the present study, a sample of alcohol-dependent participants balanced on *OPRM1* genotype completed a controlled IV alcohol administration in the laboratory (Ray et al., 2013a) followed by a functional neuroimaging task consisting of exposure to alcohol taste cues (Filbey et al., 2008a, 2008b). Alcohol cue exposure is the most widely used paradigm in fMRI studies of alcoholism (Schacht et al., 2013) and has been shown to elicit activation in the ventral striatum that correlated with self-reported craving (Wrase et al., 2007). Hence, it represents the ideal task to validate the association between subjective responses to alcohol in the laboratory and neural response to alcohol in the scanner. Given that this is the first study examining subjective responses to alcohol along with neural responses to alcohol cues in individuals with alcohol dependence, no specific regions of interest were advanced, and instead a whole-brain approach was selected for data analyses. This study builds on the growing literature suggesting that subjective responses to alcohol represent a biologically based and clinically informative marker of alcoholism risk and recovery (Heilig et al., 2010; Ray and Heilig, 2013).

## Method

### *Sample characteristics*

A community sample of non-treatment-seeking individuals reporting alcohol problems ( $N = 295$ ) was evaluated in the laboratory to investigate the effect of the *OPRM1* gene on subjective responses to alcohol. Recruitment occurred through community flyers and online advertisements. The protocol was approved by the UCLA Institutional Review Board. After written informed consent, participants provided a saliva sample for DNA analyses, completed individual differences measures, and attended a physical examination. From those screened, 48 participants were invited to participate in the experimental portion of the study based on *OPRM1* genotype and alcohol dependence status. Of those,

45 were medically eligible, and 43 individuals were randomized. These 43 participants completed two randomized infusion sessions in the laboratory—one alcohol infusion and one saline control infusion.

Twenty of the 43 individuals then went on to the neuroimaging portion of the study approximately 1 week following the last infusion. These individuals were selected to ensure equal numbers of male and female participants with and without the G allele of the *OPRM1* gene (for genotyping methods, see Ray et al., 2013a). The order of the infusion sessions for the individuals who completed the fMRI component was roughly balanced (64% received alcohol first), and the mean time between infusion sessions was 7.6 days. The mean length of abstinence from alcohol before scanning was 1.6 days.

Inclusion criteria for the neuroimaging portion of the study were the following: (a) ages 21–55 years; (b) met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV; American Psychiatric Association, 1994), criteria for current alcohol dependence; (c) non-treatment seeking for alcohol problems; (d) Clinical Institute Withdrawal Assessment for Alcohol (Sullivan et al., 1989) score <10; (e) no serious medical illness within the past 6 months, use of psychotropic medications, or lifetime history of psychotic disorders, bipolar disorder, or major depression with suicidal ideation; (f) no current use of illicit substances (other than marijuana), verified by a toxicology screen; (g) no DSM-IV abuse or dependence on any illicit substance (including marijuana) in the past year; (h) predominantly right-handed, assessed via self-report; and (i) no MRI contraindications (i.e., metallic fragments, clips, or devices in the brain, eye, spinal canal, etc.). Participants were instructed to abstain from alcohol consumption for 24 hours and were required to produce a breath alcohol concentration (BrAC) reading equal to 0.00 g/dl on an Alcotest 6510 breath alcohol analyzer (Dräger, Telford PA) to ensure acute alcohol abstinence, and a negative pregnancy test (if female) before all testing visits.

#### Individual difference measures

Demographic information for the neuroimaging sample is presented in Table 1. Alcohol use and acute abstinence before the neuroimaging session were assessed using the 30-day Timeline Followback (Sobell and Sobell, 1980). Alcohol dependence and the exclusionary diagnoses were assessed using the Structured Clinical Interview for DSM-IV (First et al., 1995). No *OPRM1* genotype group differences were found for any of the demographic variables measured.

#### Laboratory infusion procedures and measures

Alcohol administration was conducted using a single-blinded, randomized, crossover design as described in Ray et

TABLE 1. Neuroimaging sample demographics ( $n = 20$ )

Variable	Frequency or $M$ ( $SD$ )
Age (range: 21–51)	29.40 (9.01)
Sex, male/female	14/6
Ethnicity	
White	18
African American	2
Drinks per drinking day	6.42 (2.24)
Percentage drinking days, past 30 days	61.83% (2.1%)
Withdrawal symptoms, total CIWA-Ar score	2.25 (1.65)
Alcohol abuse/dependence symptom count	6.20 (2.12)
ADS total score	17.10 (5.28)
Education, years	15.00 (2.29)
Shipley IQ, standard score ( $n = 19$ )	109.84 (19.43)
Working memory, Digit Span, scaled score ( $n = 15$ )	11.6 (2.72)
Marijuana use, none/moderate	14/6
Cigarettes per day	
0	6
$1 \leq 10$	12
$>10$	2

Notes: No variables were found to differ based on *OPRM1* genotype. CIWA-Ar = Clinical Institute Withdrawal Assessment for Alcohol; ADS = Alcohol Dependence Scale.

al. (2013a). Alcohol was administered intravenously using an established nomogram that takes into account participants' sex and weight (Ray and Hutchison, 2004; Ray et al., 2007). Target BrACs were .02, .04, and .06 g/dl. Participants were required to have a BrAC  $\leq$  .02 g/dl before leaving the laboratory (or a BrAC = .00 g/dl if driving).

At baseline and each target BrAC, participants completed the following: (a) the Alcohol Urge Questionnaire (AUQ), an eight-item assessment of urge/craving to drink (Bohn et al., 1995; MacKillop, 2006); (b) the Alcohol Rating Scale (ARS), a seven-item assessment of participants' responses to the hedonic properties of alcohol, from which two subscales were extracted indexing "liking" of the alcohol ( $\alpha = .98$ ) and alcohol-induced feelings of "high" ( $\alpha = .89$ ) (Ray and Hutchison, 2007); (c) the Biphasic Alcohol Effects Scale (BAES), which captures feelings of alcohol-induced stimulation and sedation across 14 items (Erblich and Earleywine, 1995; Martin et al., 1993); and (d) the vigor, tension, positive mood, and negative mood subscales, each composed of 10 items from the Profile of Mood States (POMS; McNair et al., 1971).

A principal components analysis as described by Ray et al. (2009) was conducted on the baseline-corrected items from the BAES and POMS subscales across the sample of imaging participants to produce the two factors of interest, namely positive reinforcement (i.e., the stimulating and rewarding effects of the alcohol) and negative reinforcement (i.e., the alcohol-induced alleviation of tension and negative mood). The principal factor method (promax oblique rota-

tion) confirmed two meaningful factors (first Eigenvalue = 2.922, second Eigenvalue = 2.488, third Eigenvalue = 0.418) representing positive reinforcement (BAES-stimulation = .971, POMS-vigor = .968, POMS-happiness = .978, BAES-sedation = .103, POMS-tension = -.134, POMS-depression = .154) and negative reinforcement (BAES-stimulation = .174, POMS-vigor = .035, POMS-happiness = -.070, BAES-sedation = .846, POMS-tension = -.923, POMS-depression = .964). Together, the two factors accounted for 90% of the total variance. Thus, the primary subjective responses of interest in this study were the baseline-corrected average scores (across BrAC) from the following: (a) craving (AUQ), (b) liking of alcohol (ARS), (c) alcohol high (ARS), (d) positive reinforcement (BAES, POMS), and (e) negative reinforcement (POMS, BAES).

### *Alcohol cues task*

While in the scanner, participants underwent an alcohol taste-cue paradigm previously reported to elicit blood oxygen level-dependent response in mesocorticolimbic areas (Filbey et al., 2008a, 2008b). Alcohol and water taste stimuli were delivered via Teflon tubing using a computer-controlled delivery system (Infinity Controller) as described by Filbey and colleagues (Filbey et al., 2008b). The paradigm consisted of six alcohol and six water trials in which 1 ml of liquid was delivered. Each trial consisted of a 24-second taste delivery period followed by a 6-second rest period, a 12-second craving rating period, and a 2-second delay before the initiation of the next trial. The words *Alcohol Taste* or *Control Taste* were visually presented during cue delivery. During the craving rating period, participants were instructed to rate their current subjective urge to drink alcohol using a scale of 1 (*no urge at all*) to 4 (*very high urge*) using a four-button response box placed in their right hand. White wine was used for the alcohol taste cue and distilled water for the control cue. The presentation of visual stimuli and response collection were programmed using E-Prime (Psychology Software Tools, Inc., Sharpsburg, PA). Visual stimuli were presented using MRI-compatible goggles (Resonance Technologies, Van Nuys, CA).

### *MRI data acquisition*

Neuroimaging was conducted using a 3 Tesla Siemens Trio MRI scanner, at the UCLA Ahmanson-Lovelace Brain Mapping Center. The protocol began with initial structural scans followed by a series of four functional runs: the alcohol-cue exposure task, a stop signal task, a delay-discounting task, and a risky decision-making task (results from the latter three tasks will be reported elsewhere). A T2-weighted, high-resolution, matched-bandwidth, anatomical scan and a magnetization-prepared rapid-acquisition gradient echo (MPRAGE) were acquired for each subject to enable regis-

tration (TR, 1.9s; TE, 2.26 ms; FOV, 250 mm; matrix, 256 × 256; sagittal plane; slice thickness, 1 mm; 176 slices). The alcohol taste cues scan included 184 functional T2\*-weighted EPIs (TR, 2s; TE, 30ms; flip angle, 90°; FOV, 192 mm; matrix, 64 × 64; voxel size, 3 × 3 × 4mm<sup>3</sup>; slice thickness, 4 mm; 34 slices). The first six volumes collected were discarded to allow for T1 equilibrium effects.

### *Imaging preprocessing and registration*

FSL 4.1 (FMRIB's Software Library, [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)) was used for the imaging analyses. Motion correction was carried out using the Motion Correction Linear Image Registration Tool (McFLIRT, Version 5.0) with the estimated motion parameters entered as covariates in the general linear model. Non-brain tissue/skull removal was conducted with the Brain Extraction Tool. The images were smoothed using a FWHM Gaussian kernel (5 mm) and high-pass filtered (100s cutoff) in the temporal domain using a Gaussian weighted straight line using the FMRI Expert Analysis Tool (FEAT, Version 5.63). The EPI images were first registered to the matched-bandwidth, anatomical scan, then to the MPRAGE using affine linear transformations, and finally into standard (Montreal Neurological Institute [MNI] avg152 template) space for between-subject analyses refined by FSL's FNIRT nonlinear registration (Andersson et al., 2007). Three subjects (two G-allele carriers and one A-allele homozygote) were excluded from further analyses because of excessive motion (exceeding 3 mm of translation), resulting in a final sample of 17 participants (9 A-allele homozygotes, 8 G-allele carriers) for all imaging analyses reported.

### *Statistical analyses*

Whole-brain statistical analysis was performed in FSL using a multistage approach to implement a mixed-effects model treating participants as a random-effects variable. Explanatory variables for the alcohol-taste cues task were created by convolving delta functions representing the onset of the taste period for each trial type with a double-gamma hemodynamic response function in FSL's FEAT. Alcohol and water cue exposure were modeled as separate event types. The onset for each event was set at the first instruction to swallow (10s after the initial taste cue) with duration of 20s plus the response time for the urge-to-drink rating. Temporal derivatives were included as covariates of no interest to improve statistical sensitivity. Null events, consisting of the post-response rating period, rest period, and first cue delivery, were not explicitly modeled and therefore constituted an implicit baseline. The alcohol- versus water-cues contrast was computed, as it was the primary contrast of interest.

The subjective response correlation analyses (i.e., alcohol craving, liking, high, and positive and negative reinforcement) were conducted on the alcohol- versus water-cues

TABLE 2. Means, standard deviations, and Spearman's rho correlations between craving ratings during the functional magnetic resonance imaging alcohol cues task and subjective response to alcohol in the laboratory

Variables	<i>M</i>	<i>SD</i>	1.	2.	3.	4.	5.	6.
1. Craving after alcohol cues <sup>a</sup>	2.36	0.870	–					
2. Craving after water cues <sup>a</sup>	2.02	0.740	.774**	–				
3. AUQ–craving	1.06	1.860	.497*	.419	–			
4. ARS–liking	0.001	0.929	.347	.623**	.314	–		
5. ARS–high	0.001	0.861	.109	.084	.166	.024	–	
6. Positive reinforcement <sup>b,c</sup>	-0.167	1.210	.484*	-.216	.347	.335	.313	–
7. Negative reinforcement <sup>b</sup>	-0.117	1.210	-.152	-.231	.153	-.392	-.230	-.408

Notes: All laboratory variables were baseline corrected and averaged across breath alcohol concentration. Higher scores represent greater endorsement of the criteria for all measures. AUQ = Alcohol Urge Questionnaire (range: 1–7); ARS = Alcohol Rating Scale (range: 0–10). <sup>a</sup>Craving ratings acquired within the functional magnetic resonance imaging alcohol cues task (range: 1–4); <sup>b</sup>factor scores derived from a principal components analysis; <sup>c</sup>mean ratings differed ( $p < .05$ ) as a function of *OPRM1* genotype.

\* $p < .05$ ; \*\* $p < .01$ .

contrast images transformed into standard space. Z-statistic images were thresholded with cluster-based corrections for multiple comparisons based on the theory of Gaussian Random Fields with a cluster-forming threshold of  $Z > 1.96$  and a probability threshold of  $p < .05$  (Worsley, 2001). Participant scores on the subjective response measures from the laboratory were modeled as covariates of interest in a single analysis on the whole-brain contrast maps. Subjective responses were averaged across BrAC to limit the number of statistical analyses conducted. Follow-up *OPRM1* genotype (AA versus AG/GG) analyses were conducted in separate models for each of the significant subjective response relationships identified. Anatomical localization within each cluster (maximum Z statistics and MNI coordinates) was obtained by searching within maximum likelihood regions from the FSL Harvard-Oxford probabilistic atlas.

## Results

Means, standard deviations, and Spearman's rho correlations between craving and subjective responses to alcohol during the laboratory infusion, and craving ratings during the fMRI alcohol cues task, are presented in Table 2. Craving ratings following the presentation of alcohol cues were found to significantly correlate with craving ratings following the water cues presentation (ratings acquired during the alcohol taste cues task in the scanner), as well as reported craving and positive reinforcement elicited during the alcohol infusion ( $ps < .05$ ). As would be expected given the literature on *OPRM1* and reward (Ray and Hutchison, 2004; Ray et al., 2010b), and consistent with the full sample ( $n = 43$ ) results on the individual subscales (Ray et al., 2013a), the laboratory measure indexing the positive reinforcing properties of

TABLE 3. Locations of significant activation from the alcohol- versus water-cue contrast across all subjects. The results are from an analysis using an increased cluster-correction threshold (whole-brain cluster-corrected at  $Z > 3.7$ ,  $p < .05$ ) to enhance the separation of clusters.

Clusters/brain regions	Alcohol cue vs. water cue					
	Hemi-sphere	Cluster voxels	Max. Z	X	Y	Z
Postcentral gyrus	L	38,161	6.06	-54	6	-2
Middle temporal gyrus	L		6.04	-48	-12	10
Insular cortex	R/L		5.87/4.55	36/-38	-10/10	4/2
Superior parietal lobule	R/L		4.42/5.66	30/-24	-58/-32	50/54
Caudal anterior cingulate gyrus	R		4.98	2	18	38
Supplementary motor cortex	R		4.53	2	-2	58
Thalamus	R/L		4.51/4.93	16/-14	-14/-16	14/6
Putamen	L		4.72	16	12	-6
Cerebellum	L		4.81	-12	-58	-28
Occipital pole	R/L		4.47/4.03	30/-28	-90/-88	10/8
Middle frontal gyrus	R/L	339/332	4.86/4.80	38/-30	48/50	24/28
Posterior cingulate/precuneus	R/L	80/279	4.40/4.99	10/-8	-40/-52	20/16
Caudate/putamen (ventral)	R	257	5.37	14	16	-4
Rostral anterior cingulate/medial prefrontal cortex	R/L	190/91	4.57/4.08	6/-6	4/40	-42/20
Lateral occipital cortex	L	47	4.40	-54	-70	28

Notes: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. Max. = maximum; L = left; R = right.

TABLE 4. Locations of significant activation from the alcohol cues vs. water cues contrast that negatively correlated with alcohol craving (Alcohol Urge Questionnaire score) averaged across breath alcohol concentration (whole-brain cluster corrected at  $Z > 1.96$ ,  $p < .05$ ). No positive correlation was found.

Clusters/brain regions	Alcohol cue vs. water cue negative correlation with craving					
	Hemi- sphere	Cluster voxels	Max. Z	X	Y	Z
Postcentral gyrus	R	1,405	3.13	50	-22	52
Posterior cingulate gyrus/precuneus	R		3.05	22	-46	6
Lingual gyrus	R		2.82	28	-46	4

Notes: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. Max. = maximum; R = right.

alcohol during alcohol infusion was found to differ based on *OPRM1* genotype,  $t(18) = 2.294$ ,  $p = .034$ , whereby the G-allele carriers expressed higher reward from the alcohol ( $M = 0.395$ ) than the A-allele homozygotes ( $M = -0.728$ ). No other measures of subjective response were found to differ by genotype.

#### *fMRI predictions from laboratory measures*

Consistent with the previous studies of the alcohol cues task, and as reported by Ray and colleagues (2013b), the alcohol- versus water-cues contrast activated a broad set of regions including mesocorticolimbic areas, limbic cortex (insula, posterior cingulate gyrus), parietal lobe (precuneus), thalamus, and occipital areas (Table 3). All subsequent analyses were conducted on the alcohol- versus water-cues contrast images.

*Wanting (i.e., craving).* The baseline-corrected average craving scores across BrAC were found to negatively correlate with the neural response to alcohol cues in the postcentral gyrus, precuneus, posterior cingulate gyrus, and lingual gyrus regions (Table 4, Figure 1).

*Liking and high.* There was a positive correlation between average alcohol high reported across BrAC and neural response to alcohol cues in the pre- and postcentral gyri, precuneus, anterior cingulate cortex, and supplementary motor cortex (Table 5). No significant correlation between alcohol liking and neural response to alcohol cues was observed.

*Positive and negative reinforcement.* A positive correlation was observed between scores on the positive reinforcement factor and neural responses to alcohol cues in three large clusters of regions: the posterior cingulate and precuneus, parietal operculum cortex, and brainstem (Table 6, Figure 2). Further, a positive correlation was observed between scores on the negative reinforcement factor (where more negative scores reflect greater reductions in tension and negative mood compared with baseline) and some of these same regions (the precuneus, posterior cingulate, and lingual gyrus) (Table 7, Figure 3).

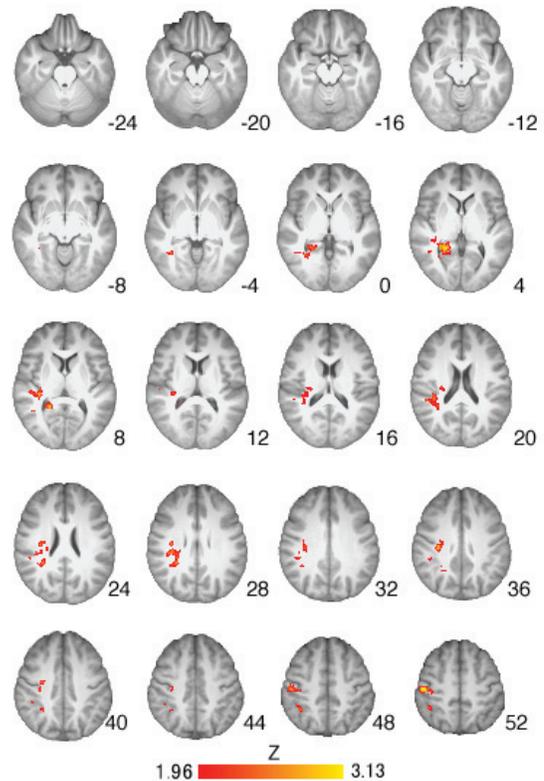


FIGURE 1. Brain activation within the alcohol cue vs. water cues contrast that negatively correlated with alcohol craving (Alcohol Urge Questionnaire score) averaged across breath alcohol concentration (see Table 4 for full list of regions). Z-statistic maps are whole-brain cluster corrected,  $Z > 1.96$ ,  $p = .05$ . Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

Overlapping regions of activation from all significant laboratory measure correlations are shown in Figure 4.

*OPRM1 moderation.* As a secondary aim of investigation, *OPRM1* genotype was found to moderate the significant relationships observed between neural responses to alcohol versus water cues and alcohol high, positive reinforcement, and negative reinforcement (Table 8). Consistent with the analyses across genotype, A-allele homozygotes exhibited a stronger positive correlation between the laboratory measure of alcohol high and neural activation to alcohol cues in such regions as the right precuneus and right lingual gyrus. Within the positive reinforcement and alcohol cues neural activity relationship, the A-allele homozygotes exhibited a stronger positive correlation in the right superior frontal gyrus and right caudate, as compared with the G-allele carriers. Within the negative reinforcement and alcohol cues neural activity relationship, the G-allele carriers exhibited a stronger positive correlation (i.e., less tension and negative mood reduction from the alcohol as compared with baseline) in regions again including the right precuneus and right lingual gyrus, as compared with the A-allele homozygotes.

TABLE 5. Locations of significant activation from the alcohol cues vs. water cues contrast that positively correlated with alcohol high (Alcohol Rating Scale subscale score) averaged across breath alcohol concentration (whole-brain cluster corrected at  $Z > 1.96, p < .05$ ). No negative correlation was found.

Clusters/brain regions	Alcohol cue vs. water cue positive correlation with high					
	Hemi- sphere	Cluster voxels	Max. Z	X	Y	Z
Postcentral gyrus/precuneus	L	710	2.86	-6	-40	62
Anterior cingulate cortex	L		2.85	-12	18	28
Supplementary motor cortex	L		2.77	-2	6	58
Precentral gyrus	L		2.73	-10	-24	62

Notes: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. Max. = maximum; L = left.

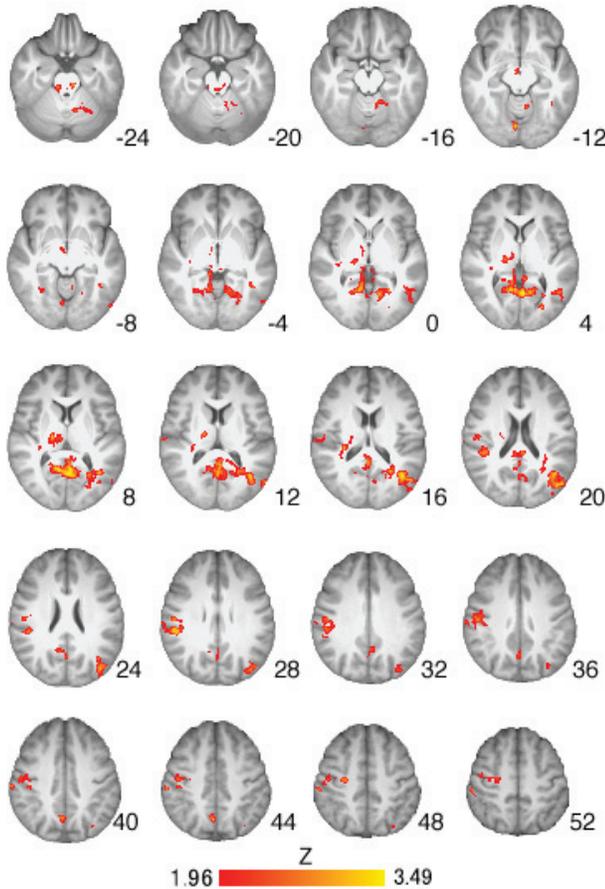


FIGURE 2. Brain activation within the alcohol cue vs. water cues contrast that positively correlated with positive reinforcement factor scores averaged across breath alcohol concentration (see Table 5 for full list of regions). Z-statistic maps are whole-brain cluster corrected,  $Z > 1.96, p = .05$ . Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

**Discussion**

This study examined whether subjective responses to alcohol in the laboratory predict neural response to alcohol cues in the scanner. The results suggest that, indeed, subjec-

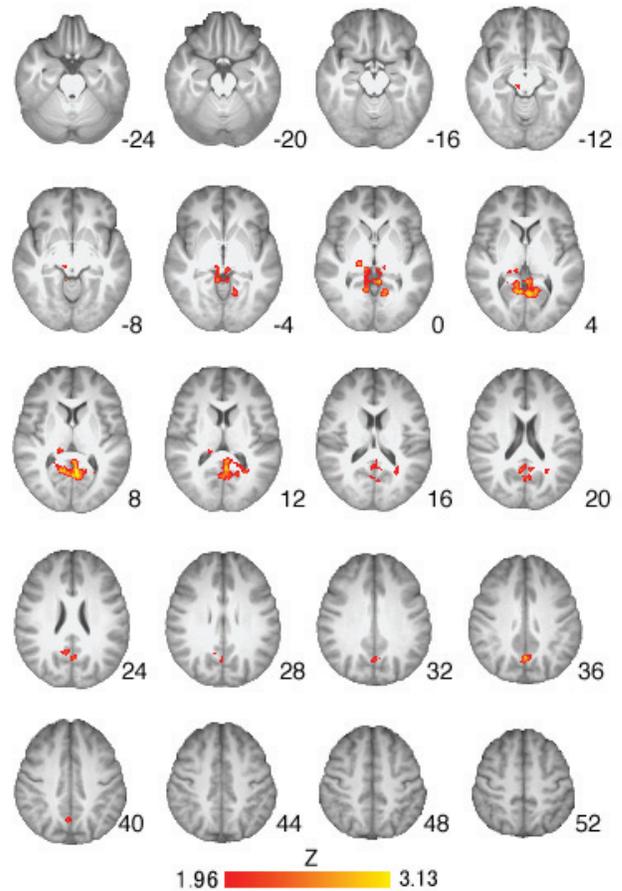


FIGURE 3. Brain activation within the alcohol cues vs. water cues contrast that positively correlated with negative reinforcement factor scores averaged across breath alcohol concentration (see Table 6 for full list of regions). Z-statistic maps are whole-brain cluster corrected,  $Z > 1.96, p = .05$ . Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

tive reports of craving, alcohol high, and the experience of the reinforcing properties of alcohol during alcohol administration predict specific patterns of brain activation at time of alcohol cue exposure. Importantly, two of the regions consistently identified by these analyses, namely the precuneus and the posterior cingulate cortex (depicted in Figure 4), have emerged in a recent meta-analysis as being selectively affected by alcohol (vs. control) cue presentation in samples of alcohol-dependent individuals as compared with healthy controls (Schacht et al., 2013).

The precuneus has been purported to be involved in self-centered mental imagery strategies and successful episodic memory retrieval (Cavanna and Trimble, 2006), both of which are likely to play a role in the subjective experience of craving (e.g., remembering and imagining the experience of the substance) as well as the reinforcing value of alcohol via provoking conditioned responses (e.g., through the engagement of alcohol expectancies, which involve retrieval of past experiences; Sell et al., 2000). Consistent with these

TABLE 6. Locations of significant activation from the alcohol cues vs. water cues contrast that positively correlated with positive reinforcement factor scores averaged across breath alcohol concentration (whole-brain cluster corrected at  $Z > 1.96, p < .05$ ). No negative correlation was found.

Clusters/brain regions	Alcohol cue vs. water cue positive correlation with positive reinforcement					
	Hemi- sphere	Cluster voxels	Max. Z	X	Y	Z
Superior lateral occipital cortex/angular gyrus/posterior cingulate	L	3,212	3.49	-40	-62	18
Lingual gyrus	L		3.48	-4	-60	6
Precuneus	L		3.3	-2	-54	10
Precuneus/lingual gyrus	R		3.25	12	-56	6
Middle temporal gyrus	L		3.13	-38	-60	8
Parietal operculum cortex	R	1,339	3.18	50	-34	28
Thalamus	R		2.95	18	-16	8
Postcentral gyrus	R		2.89	50	-20	34
Brainstem	L	698	2.92	-4	-24	-38
Cerebellum	L/R		2.65/2.61	-24/12	-48/-48	-36/-38

Notes: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. Max. = maximum; L = left; R = right.

interpretations, correlations between alcohol cue-elicited activation of the precuneus and alcohol craving (Park et al., 2007; Tapert et al., 2003), as well as a variety of measures of alcohol use disorder severity, including Alcohol Use Disorders Identification Test score and years of heavy drinking (Claus et al., 2011), have been reported. A recent study investigating the relationship of genome-wide copy number variations with alcohol cue-elicited activation in participants with alcohol use disorders found that the precuneus mediated the association between the homozygous deletions at copy number variation region 22q13.1 and alcohol dependence severity. This suggests that the homozygous deletion at 22q13.1 may play a role in precuneus functioning, which in turn appears to relate to the development of alcohol dependence (Liu et al., 2013).

Activation of the posterior cingulate cortex, another region found to consistently differ between individuals with and without alcohol dependence during alcohol cues presentation (Schacht et al., 2013), was predicted by craving and the subjective reinforcement value of the alcohol in the present study. The posterior cingulate cortex has been

consistently associated with aspects of risky decision making (Hayden et al., 2008; Kable and Glimcher, 2007) and may represent updating of decision-making strategies when reward contingencies change as a function of the alcohol-induced reward or alleviation of tension and negative mood (McCoy and Platt, 2005). Furthermore, the consistency of observed activation of the lingual gyrus across analyses of craving and reinforcement suggests this region may be important for the global processing of responses to alcohol cues. Others have also implicated activation of this region during the pictorial presentation of alcohol (Gilman and Hommer, 2008) and smoking (David et al., 2005) cues, suggesting that the lingual gyrus may play an important role in responses to drug cues in general.

As a secondary aim, this study investigated whether the *OPRM1* genotype moderates the relationship between subjective responses to alcohol in the laboratory and neural responses to alcohol cues in the scanner. Specifically, *OPRM1* genotype was found to moderate the relationships observed between neural responses to alcohol cues in the scanner and laboratory measures of alcohol high, positive

TABLE 7. Locations of significant activation from the alcohol cues vs. water cues contrast that positively correlated with negative reinforcement factor scores averaged across breath alcohol concentration (whole-brain cluster corrected at  $Z > 1.96, p < .05$ ). No positive correlation was found.

Clusters/brain regions	Alcohol cue vs. water cue negative correlation with negative reinforcement					
	Hemi- sphere	Cluster voxels	Max. Z	X	Y	Z
Lingual gyrus/precuneus	L	1,579	3.31	-4	-60	6
Posterior cingulate cortex	L		3.14	-4	-50	10
Precuneus	R		3.06	10	-56	6
Lingual gyrus	R		3.00	6	-58	6

Notes: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. Max. = maximum; L = left; R = right.

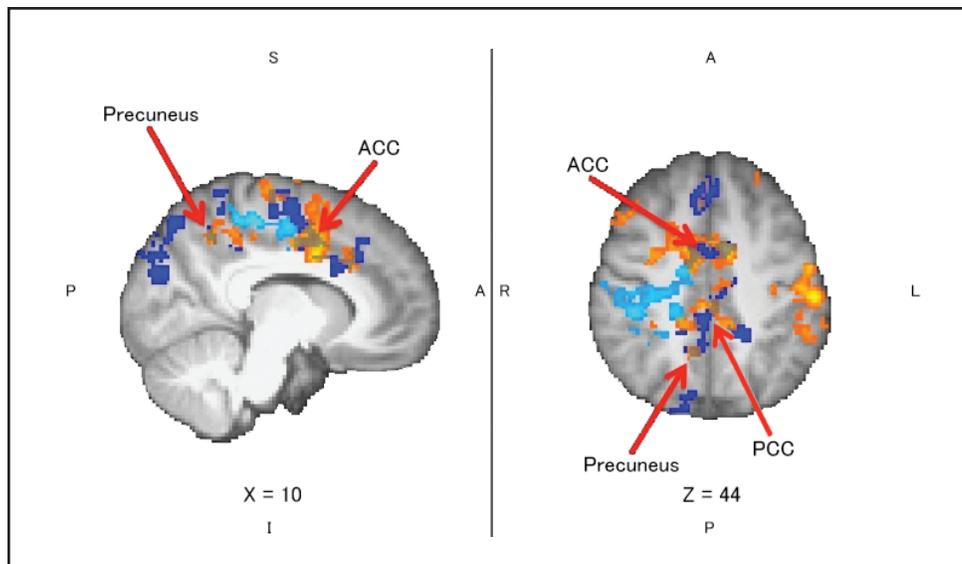


FIGURE 4. Brain activation within the alcohol cues vs. water cues contrast that positively correlated with alcohol high (yellow), positive reinforcement factor scores (red/orange), negative reinforcement factor scores (dark blue), and that negatively correlated with alcohol craving (light blue). Overlap in activation is presented in brown. All lab measures of subjective responses to alcohol were averaged across breath alcohol concentration. Z-statistic maps are whole-brain cluster corrected,  $Z > 1.96$ ,  $p = .05$ . Coordinates are in MNI space. ACC = anterior cingulate cortex. PCC = posterior cingulate cortex.

TABLE 8. Locations of significant *OPRM1* moderated activation (AA vs. AG/GG) from the alcohol cues vs. water cues contrast that positively correlated with (A) alcohol high (Alcohol Rating Scale subscale score), (B) positive reinforcement factor scores, and (C) negative reinforcement factor scores (whole-brain cluster corrected at  $Z > 1.96$ ,  $p < .05$ ). All laboratory measures were averaged across breath alcohol concentration. No negative correlations were found.

(A) <i>OPRM1</i> moderated (AA vs. AG/GG) alcohol cue vs. water cue positive correlation with alcohol high						
Clusters/brain regions	Hemi-sphere	Cluster voxels	Max. Z	X	Y	Z
Parietal operculum cortex/precuneus	R	1,006	2.71	42	-30	24
Lingual gyrus	R		2.65	32	-58	2
Middle temporal gyrus	R		2.61	50	-50	4
Angular gyrus	R		2.57	38	-50	28
(B) <i>OPRM1</i> moderated (AA vs. AG/GG) alcohol cue vs. water cue positive correlation with positive reinforcement						
Superior frontal gyrus	R	1,579	3.00	16	10	50
Caudate	R		2.72	20	2	34
(C) <i>OPRM1</i> moderated (AA vs. AG/GG) alcohol cue vs. water cue positive correlation with negative reinforcement						
Posterior cingulated cortex/precuneus	R	2,367	2.86	20	-44	14
Lingual gyrus	R		2.83	34	-56	-2
Temporal occipital fusiform cortex	R		2.79	38	-46	-6
Planum temporale	R		2.75	30	-30	12
Central opercular cortex	R		2.68	48	-10	18

Notes: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. Max. = maximum; R = right.

reinforcement, and negative reinforcement. Regions including the precuneus and lingual gyrus were found to differ as a function of genotype such that, compared with G-allele carriers, A-allele homozygotes exhibited a stronger correlation between these regions and the feeling of alcohol high but a weaker correlation between these regions and subjective negative reinforcement of the alcohol administration. In other words, for the A-allele homozygotes, the feeling of alcohol high more strongly predicted activation in these regions as compared with the G-allele carriers; but for the G-allele carriers, greater tension and negative mood reduction from the alcohol was more strongly predictive of less activation in these regions as compared with the A-allele homozygotes. The de-coupling of behavioral to neural responses by *OPRM1* genotype may indicate that G-allele carriers are more sensitive to the pharmacological effects of alcohol experienced during acute alcohol administration, as compared with cue-exposure paradigms performed under sober states.

The observed correlations between laboratory and behavioral measures during scanning address a significant question in the imaging and dependence literature: Should self-reported craving levels in the scanner correlate with observed brain activation during drug cue presentation? These results suggest the restricted measurement capability imposed by the scanning environment may be a constraining factor. Consistent with many previous studies (e.g., Due et al., 2002; Filbey et al., 2008a; Heinz et al., 2004), we failed to find a significant relationship between self-reported craving in the scanner and brain activity during alcohol cue presentation. We did, however, find a correlation between self-reported craving level in the scanner and self-reported craving during alcohol administration in the laboratory, which in turn was found to correlate with brain activity during alcohol cue presentation in the scanner. This triangular finding suggests that the expanded item set and the use of the full Likert rating scale to assess craving in the laboratory, as opposed to the single item and 4-point scale used in the scanner, allowed for the acquisition of more meaningful variance from which the association with brain activity could be detected. Thus, this finding highlights the utility of expanding our measures in the scanner, possibly by asking multiple items or through the programming of larger scale rating systems. Further, it is possible that although moment-to-moment craving assessments do not track well with brain activation, composite scales of craving that are more “trait-like” may be able to detect between-subject variance in subjective craving that, in turn, predicts neural response to cues.

Of note, the directions of the observed predictions are consistent with the state of alcohol intoxication at the time of subjective response acquisition in the laboratory. Since the subjective ratings were acquired while alcohol was on board, we would expect to see less craving and greater alcohol high, thus resulting in the observed negative and positive

associations, respectively, during alcohol cue presentation at sober state. Furthermore, the lack of neural association with the alcohol liking subscale supports the validity of the laboratory paradigm in dissociating craving from liking in alcohol dependence. This is consistent with the hypothesized transition of our dependent sample from the heavy drinking (liking) stage to the maintenance (wanting) stage of the disorder (Berridge et al., 2009).

These results should be interpreted in the context of the study's strengths and limitations. Strengths include the well-validated laboratory and neuroimaging methods and the well-ascertained sample of individuals with alcohol dependence. The use of factor scores for alcohol reinforcement (positive and negative), alcohol liking, and alcohol high variables represents another significant strength and is consistent with previous recommendations (Ray et al., 2009). These factors allowed for the examination of constructs consistent with the neurobiological theories of alcoholism development in a clinical sample. Study limitations include the lack of control group and the relatively small sample size for correlational analyses, which is mitigated by the within-subject design presumably increasing the power to detect true associations. In addition, the use of a common alcoholic beverage (white wine) as opposed to the participants' preferred (Filbey et al., 2008a), or most commonly consumed (Filbey et al., 2008b), alcoholic beverage represents a limitation; however, as demonstrated in the article by Ray and colleagues (2013b), the participants exhibited a significant increase in self-reported alcohol craving across alcohol taste cue trials as compared with water taste cue trials. It should also be noted that the results obtained from the prospective genotyping groups may be different in a genetically unselected sample, and the exclusion of treatment seekers and individuals endorsing significant alcohol withdrawal symptoms likely resulted in a sample with mild to moderate levels of alcohol dependence. Future research is needed to validate these findings in larger, genetically unselected, and more severe samples of alcohol dependence.

In conclusion, this study provides initial evidence that subjective responses to alcohol, namely craving, alcohol high, and the reinforcing properties of alcohol, predict neural activation during cue reactivity. These results cross-validate laboratory and neuroimaging measures while suggesting that in-depth assessment of subjective ratings in fMRI protocols is warranted.

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