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Negative urgency and ventromedial prefrontal cortex responses to alcohol cues: fMRI evidence of emotion-based impulsivity

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Abstract

Background—Recent research has highlighted the role of emotion-based impulsivity (negative and positive urgency personality traits) for alcohol use and abuse, but has yet to examine how these personality traits interact with the brain’s motivational systems. Using functional magnetic resonance imaging (fMRI), we tested if urgency traits and mood induction affected medial prefrontal responses to alcohol odors (AcO).

Methods—Twenty seven social drinkers (mean age = 25.2, 14 males) had six fMRI scans while viewing negative, neutral, or positive mood images (3 mood conditions) during intermittent exposure to AcO and appetitive control (AppCo) aromas.

Results—Voxel-wise analyses ($p < 0.001$) confirmed [AcO > AppCo] activation throughout medial (mPFC) and ventromedial prefrontal regions (vmPFC). Extracted from *a priori* mPFC and vmPFC regions, and analyzed in Odor (AcO, AppCo) × Mood factorial models, AcO activation was greater than AppCo in left vmPFC ($p < 0.001$), left mPFC ($p = 0.002$), and right vmPFC ($p = 0.01$) regions. Mood did not interact significantly with activation but the covariate of trait negative urgency accounted for significant variance in left vmPFC ($p = 0.01$) and right vmPFC ($p = 0.01$) [AcO > AppCo] activation. Negative urgency also mediated the relationship between vmPFC activation and both (1) subjective craving and (2) problematic drinking.

Conclusion—The trait of negative urgency is associated with neural responses to alcohol cues in the vmPFC, a region involved in reward value and emotion-guided decision-making. This suggests that negative urgency might alter subjective craving and brain regions involved in coding reward value.

Keywords

fMRI imaging; alcohol; olfaction; emotion; impulsivity

Introduction

Recent research has highlighted the role of emotion-based impulsivity for alcohol use and abuse (see Cyders & Smith, 2008). Urgency, which refers to rash action in response to extreme negative (negative urgency) and positive (positive urgency) emotional states, has

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been shown to be the most important and consistent trait predictor of alcohol problems in cross-sectional (e.g., Cyders et al., 2007), longitudinal (e.g., Cyders et al., 2009; Settles et al., 2010), and experimental (e.g., Cyders et al., 2010, Coskunpinar et al., in press) designs (see a review and meta-analysis by Coskunpinar et al., 2013). However, research has yet to elucidate how these personality traits interact with the brain's motivational systems. Thus, the current study sought to determine how neural responses to alcohol cues are related to mood states and urgency, and how neural responses and urgency relate to alcohol craving and use.

Urgency traits, emotions, and mood states might increase the salience and subjective value of alcohol (e.g., Field and Powell, 2007; Niaura et al., 1988). Cyders and colleagues (2009) found that positive urgency predicted increased alcohol consumption following positive mood induction, whereas negative urgency predicted lower consumption in the positive mood condition. A recent meta-analysis found a small but significant relationship between impulsivity and substance-related attentional biases although the specific relationship between urgency and attentional biases could not be examined because of the paucity of such studies (Coskunpinar & Cyders, in press). More specifically, Coskunpinar and colleagues (in press) found that negative (but not positive) urgency predicted increased attentional biases to alcohol in response to alcohol aroma cues, after controlling for demographics, previous drinking history, current emotional state, and other impulsivity-related traits. Two recent studies have also supported a role of urgency in increasing craving for alcohol following alcohol cue exposure (Karyadi & Cyders, under review; Pavlick, 2007).

Alcohol cues (e.g. sight or smell of alcohol) can trigger alcohol craving (e.g., Carter & Tiffany, 1999), attentional biases (e.g., Field & Eastwood, 2005), and consumption (e.g., Perkins et al., 1994). The brain's medial prefrontal cortex region is likely to play a key role in these effects (Engleman et al., 2006). The aromas of both alcohol and food provoke significant medial prefrontal activity (Bragulat et al., 2010; Eiler, et al., 2011; Kareken et al., 2010b), where the extent of BOLD activation is associated with the subjective reward value of stimuli (Hare et al., 2009). Negative and positive urgency traits, particularly in conditions of extreme mood, might then bias attention to alcohol cues (Coskunpinar et al., in press), which, in turn, induce craving (Pavlick, 2007) and subsequent alcohol consumption (Cyders et al., 2010). Activity in the ventromedial prefrontal cortex (vmPFC) is a particular candidate mechanism for such mood-cue reactivity, given its theorized role in affect-guided planning (Bechara et al., 2000; Naqvi et al., 2006) and subjective reward value (Bragulat et al., 2010; Eiler et al., 2011; Kareken et al., 2010b), and the significant reciprocal influences between the amygdala and medial prefrontal cortex (Barbas & Zikopoulos, 2007; Bechara et al., 2000; Ghashghaei & Barbas, 2002; LeDoux, 2000).

As a first step in determining the neurobiological underpinning of urgency (Cyders & Smith, 2008), the goals of the current study are to examine how: (1) medial frontal responses to alcohol olfactory cues are modified by mood induction, (2) negative and positive urgency traits are associated with medial frontal activation induced from alcohol olfactory cues and mood induction, and (3) urgency and neural responses to alcohol olfactory cues relate to subjective craving and self-reported alcohol use.

Materials and Methods

Participants

Thirty-eight right-handed healthy social drinkers between the ages of 21 and 35 were recruited. They endorsed drinking at least one to three drinks per week and reported at least one incidence of drunkenness over the previous month. No participants were alcohol

dependent or had a maternal history of alcoholism. They had to be in good health, without medications (licit or illicit), and have a normal sense of smell. Smokers enrolled if they could abstain from tobacco smoking for four hours without nicotine withdrawal. All participants voluntarily signed informed consent statements approved by the Indiana University institutional review board and received \$150 for completion of study. Of the recruited sample, 30 completed the study. Participants who completed the study did not differ from non-completers on any demographic variables (p -values = 0.19-0.86), drinking-related problems (AUDIT total score, $p = 0.57$), or family histories of alcohol problems ($p = 0.53$). Three subjects whose head motion during functional imaging exceeded peak-to-peak translations of 2 mm and rotations of 2 deg were excluded from further analyses, resulting in a final sample of $n = 27$ (Table 1).

Self-Report Measures

The Alcohol Craving Questionnaire (ACQ; Singleton et al., 2000). Alcohol cravings were assessed using three ACQ items (*Nothing would be better than having a drink right now*, *Having a drink right now would make things seem just perfect*, and *I crave a drink right now*). Items were rated on a visual analog scale (VAS; 1=strongly disagree, 7=strongly agree).

The Affect Grid (Russell et al., 1989) is a 9×9 grid with affect descriptors in each corner. Participants check the appropriate cell of the grid that represents current emotions. The affect grid results in separate valence (pleasantness vs. unpleasantness) and arousal (high arousal vs. low arousal) ratings, and has good inter-rater reliability (0.98 for valence and 0.97 for arousal) and convergent validity (with the Positive and Negative Affect Scale; PANAS; Russell et al., 1989).

The UPPS Impulsive Behavior Scale (UPPS-P; Lynam et al., 2007) is a 59-item self-report scale, with responses ranging from 1 (agree strongly) to 4 (disagree strongly). The UPPS-P is designed to measure five separate dispositions to rash action (see Lynam et al., 2007). However, only the positive urgency (14 items; $\alpha = 0.91$, $M (SD) = 1.68 (0.44)$) and the negative urgency (11 items; $\alpha = 0.85$; $M (SD) = 1.94 (0.42)$) subscales were utilized in the present study. Items were recoded so that higher mean scores on the subscales represent higher levels of impulsive action.

The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994) is a polydiagnostic interview emphasizing substance use and comorbid diagnoses. Research has supported the validity and reliability of the SSAGA (Bucholz et al., 1994; Hesselbrock et al., 1999; Schuckit et al., 1995).

The Alcohol Use Disorders Identification Test – Self Report Version (AUDIT; Babor et al., 2001) is a 10-item test that assesses problematic alcohol use.

Scales for intensity, pleasantness, and representativeness of odorants were used to rate the characteristics of the individual odorants used in the study. Intensity was rated using Green's labeled magnitude scale from 1 (barely detectable) to 100 (strongest imaginable; Green et al., 1996), whereas pleasantness and representativeness were rated from 1 (very unpleasant or very unrepresentative) to 9 (very pleasant to very representative).

Procedure

Study sessions—Participants completed two sessions: a screening session and an imaging session. Screening sessions were held at a private research lab, where participants completed a series of self-report questionnaires (listed above) and the *Pocket Smell Test* (to assess for normal sense of smell; Sensonics, Inc.). Participants were scheduled for imaging

if they met inclusion criteria (average of 32 days between screening session and scan day). They were asked to refrain from alcohol consumption for 3 days prior to the study. On the imaging day, participants reported to the Indiana University Clinical Research Center between 8 and 10 a.m. and were provided with a light, standardized breakfast. Vitals were checked, and repeat drug and pregnancy urine screens were conducted. Participants were then escorted to the imaging suite, where they rated current alcohol craving by responding to a subset of items on the Alcohol Craving Questionnaire (ACQ; Singleton et al., 2000) and current mood using the Affect Grid (Russell et al., 1989). As a comparison, subjects were also asked to rate their craving for grape juice (used as an appetitive control; AppCo) by responding to the same ACQ items (but rephrased for grape juice).

Participants were then exposed to the odorants and sample images they would encounter during the imaging session. Odorants were delivered with a computer-controlled air-dilution olfactometer as described elsewhere (e.g., Bragulat et al., 2008; Kareken et al., 2004). The three presented odorant stimuli were: (1) Each subject's most frequently consumed alcoholic drink (AcO; see Table 1), (2) Grape juice (Appetitive control odor; AppCo), and (3) a sham odorant (SO) created by shunting the continuous airstream through an alternate valved pathway). Participants smelled each odor through the olfactometer while simultaneously seeing representative pictures on a computer monitor. They then rated each odorant on intensity, representativeness, and pleasantness using scales described above.

Mood images from the International Affective Picture System (IAPS; Lang et al., 1999) were chosen based on developmental ratings of valence and arousal provided by Lang and colleagues (1999). Participants then viewed three sample images (one from each mood condition) that were similar to those that they would see during imaging. Three image groups were formed (mean values taken from developmental ratings): neutral images (mean valence = 5.11, mean arousal = 3.28), negative images (mean valence = 2.55, mean arousal = 5.55), and positive images (mean valence = 6.94, mean arousal = 5.78).

Scan characteristics—A total of six functional imaging scans of combined olfactory/visual stimulation were performed (24 2-second odor events in each of the 3 stimulus classes of AcO, AppCo, and SO were intermixed with 32 2-second IAPS image presentations), with two scans completed for each mood (2 positive image scans, 2 negative image scans, and 2 neutral image scans). Scan order was randomly assigned, with a break after the first three scans, although randomization was restricted so that all three moods were experienced prior to and again following the break (see Figure 1). Participants reported the presence (left click) or absence (right click) of an odorant on an MRI-compatible trackball (Current Designs, Philadelphia, PA) while exhaling, but were not asked to identify the odorants. Between scans, participants again rated their current mood using the Affect Grid, and their current craving for any drink, grape juice, and alcohol.

Image acquisition—Blood oxygenation level dependent (BOLD) contrast sensitive functional imaging was conducted with a 12-channel head coil array on a Siemens 3T Magnetom Trio-Tim scanner (Erlangen, Germany). A whole-brain high-resolution anatomic image volume ($1.0 \times 1.0 \times 1.2$ mm³ voxels) was first collected using a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence for anatomic registration of the functional images. For each functional scan, 189 BOLD volumes were acquired in 6:54 min using an echo-planar imaging pulse sequence (gradient echo; 2250/29 ms repetition/echo time, 78° flip angle, 88×88 matrix, $2.5 \times 2.5 \times 3.0$ mm³ voxels, 39 slices, GRAPPA acceleration factor 2) that incorporated a 3D prospective acquisition correction to minimize effects of the head motion (Thesen et al., 2000).

Data analysis—Data were analyzed using SPM8 (Wellcome Department of Imaging Neuroscience, University College, London) and PASW Statistics v. 20.0 (SPSS, Inc.). Functional volumes were corrected for differences in slice acquisition timing and rigid-body realigned to the initial volume of the first functional imaging scan to account for residual movement after prospective motion correction (Thesen et al., 2000). Each subject's high-resolution anatomic image was co-registered to the reference functional volume and segmented into tissue classes. Nonlinear spatial transformation parameters from this segmentation were utilized to convert BOLD volumes to the Montreal Neurological Institute (MNI) space, with the resulting volumes re-sampled to isotropic (2 mm per side) voxels and smoothed by a 6 mm full-width at half-maximum isotropic Gaussian Kernel.

Discrete 2-second periods of odorant (or sham) presentations were modeled in a within-subjects general linear model, using SPM's canonical hemodynamic response function (HRF). HRF onset was delayed one second after the sniff instruction based on prior empirical evidence that this optimizes the response of the piriform and orbital olfactory association areas (Kareken et al., 2010a). Time and dispersion derivatives of the HRF accounted for slight variations in response onset and duration. Movement parameters from realignment were included as regressors, while a high-pass filter with a cutoff of 1/128 Hz was applied to each voxel's time series to remove low frequency noise. This within-subject model yielded contrast images of activation within a mood condition (Positive, Negative, Neutral), and with one odorant (e.g., AcO) compared to another odorant (e.g., AppCo) and the SO.

We targeted our search to four *a priori* defined medial prefrontal cortex (PFC) regions of interest (ROIs), as previously derived (see Kareken et al., 2010b; Figure 3). These comprised right and left medial prefrontal (mPFC), and right and left ventromedial prefrontal (vmPFC) areas. All PFC ROIs have rostral-caudal extents spanning +56 mm to +36 mm in MNI space. The mPFC has a superior extent of +14 mm and an inferior extent of -6 mm, while vmPFC spans -6 mm to -22 mm. The MarsBar utility (Brett et al., 2002; <http://marsbar.sourceforge.net/>) was used to extract each subject's mean AcO and AppCo activation value as contrasted with the odorless control for each ROI. We hypothesized that (1) there would be increased activation to AcO in these ROIs, (2) mood condition would interact with the activation, (3) self-reported negative and positive urgency would be positively associated with this AcO-induced activation, and (4) urgency and AcO activation would be associated with self-reported subjective craving and problematic alcohol use.

Results

Preliminary Analyses

Odorant Characteristics—Across the range of alcoholic drinks chosen as participants' most frequently consumed beverage, a multivariate analysis of variance found no significant differences in intensity ($F = 0.57$, $df = 3$, $p = 0.64$), pleasantness ($F = 0.63$, $df = 3$, $p = 0.60$), or representativeness ($F = .047$, $df = 3$, $p = 0.71$) across subjects' preferred alcohol aromas (beer, white wine, red wine, and other beverage).

We next compared the characteristic ratings for AcO and AppCo odors in an Odor (2; AcO and AppCo) \times Rating (3; intensity, pleasantness, representativeness) linear mixed-effects model, which showed a main effect of Odor ($p = 0.003$) and Rating Type ($p < 0.001$), but no interaction ($p = 0.73$). Follow-up paired *t*-tests indicated that the alcohol aromas were significantly more pleasant ($t = 2.80$, $p = 0.01$) and representative ($t = 2.55$, $p = 0.02$) than the grape juice aromas, although the magnitude of these differences was small (mean alcohol pleasantness = 6.54 vs. mean grape pleasantness = 5.65 on a scale of 1-9; mean alcohol representativeness = 7.90 vs. mean grape representativeness = 7.22 on a scale of

1-9). There was no significant difference between alcohol and grape aromas in intensity ($t = 1.67, p = 0.11$; mean alcohol intensity = 24.60 vs. mean grape intensity = 22.40 on a scale of 1-100).

Mood and Craving—Self-reported mood (on the affect grid) and craving (from the ACQ) ratings did not differ following the first and second scans for each condition (e.g., between “Positive 1” and “Positive 2” scans); therefore, we averaged across these two separate scans to create variables that represented mood valence, mood arousal, grape juice (AppCo) craving, and alcohol (AcO) craving following positive, negative, and neutral mood conditions.

A Mood Condition (3: positive, negative, neutral) \times Mood Rating (2: valence and arousal) linear mixed-effects model showed a significant main effect for Mood Condition ($p < 0.001$) and Mood Rating ($p = 0.03$), as well as a significant interaction between these two factors ($p < 0.001$). Planned follow-up paired t -tests indicated that, as expected, valence ratings following the negative mood condition were significantly lower than the neutral mood valence ratings ($t = -7.14, p < 0.001$) and the positive mood valence ratings ($t = -7.46, p < 0.001$), with positive mood valence ratings also significantly higher than the neutral mood valence ratings ($t = 2.53, p = 0.02$). Both negative and positive arousal ratings were higher than those for the neutral mood condition ($t = 2.85, p = 0.01$ and $t = 6.44, p < 0.001$, respectively). Contrary to expectations, positive mood arousal was significantly higher than negative mood arousal ($t = 2.60, p = 0.02$).

Craving for either alcohol or grape juice on the ACQ was analyzed in a Mood Condition (3 levels; positive, negative, and neutral) \times Craving Type (2 levels; alcohol vs. grape juice) linear mixed-effects model, with urgency as a covariate. This showed a significant main effect of craving type ($p < 0.001$), and an interaction between mood and craving type ($p = 0.028$) (See Figure 2), such that the difference in craving between alcohol and grape juice was accentuated in the negative and positive mood conditions. Overall, participants reported higher cravings to alcohol than to grape juice across conditions (mean alcohol craving = 2.30 vs. mean grape juice craving = 1.71 on a scale of 1-7). Alcohol and grape cravings were, however, weakly correlated ($r = 0.21, p = 0.05$).

fMRI Results

Stimulus effects—A whole-brain voxel-wise analysis of odor effects was first conducted to confirm mPFC and vmPFC ROI activation in response to [AcO > SO] and [AcO > AppCo]. This analysis indeed shows activation in the *a priori* ROIs, particularly in the mPFC (see Figure 3): Medial frontal response to alcohol aromas, regardless of the control condition, reaches cluster level significance, $p_{FDR} < 0.05$, after correcting for false discovery rate (FDR) for the whole brain volume (voxel-wise height threshold, $p < 0.001$, see Table 2 for details). Both [AcO > AppCo] and [AcO > SO] contrasts elicited peak activity in the left vmPFC (Table 2) that extended dorsally into left mPFC and laterally into right vmPFC.

To better understand the nature of the activation, we extracted average BOLD contrast values (without applying a threshold) from each *a priori* medial frontal ROI (left and right mPFC, vmPFC) and tested in a Mood (3) \times Odor (AcO vs. AppCo) linear mixed-effects model. The Left vmPFC ROI showed a significant effect of Odor ($p < 0.001$), and an interaction between odor and mood that fell short of significance ($p = 0.08$), in which [AcO > AppCo] contrast activation was greatest under negative mood (see Figure 4); contrary to our hypothesis, there was no main effect of Mood ($p = 0.51$). The left mPFC and right vmPFC ROIs had significant odor effects only ($p = 0.002$ and $p = 0.01$, respectively). There were no significant effects in the right mPFC ROI.

Urgency traits—To test our hypothesis that urgency traits would be related to ROI activation, we entered negative urgency as a covariate in the previously conducted Mood (3) × Odor (2) linear mixed-effects model. Adding the covariate significantly improved model fit in the left vmPFC (X^2 difference = 7.87, $p = 0.025$) and the right vmPFC (X^2 difference = 9.20, $p = 0.01$), as indicated by log likelihood difference tests, with negative urgency being a significant predictor of BOLD in left ($p = 0.03$) and right vmPFC ($p = 0.03$). There was no improvement of fit in the left or right mPFC. In addition, when negative urgency was added to the models, the main effects of odor were no longer significant ($p = 0.51$ in the left vmPFC and $p = 0.91$ in the right vmPFC). Thus, after accounting for urgency, there were no longer any differences in the magnitude of responses between AcO and AppCo. Positive urgency was not a significant variance covariate in any of the ROIs.

When examining the simple correlations between urgency and activation to the stimuli, there was a significant correlation between the [AcO > SO] BOLD response and negative urgency in the left ($r = 0.45$, $p = 0.01$) and right vmPFC ($r = 0.47$, $p = 0.01$; see Figure 5), but not the right ($p = 0.36$) or left mPFC ($p = 0.16$). Negative urgency did not correlate with the [AppCo > SO] response (p 's ranged from 0.58 in the right mPFC to 0.16 in the left vmPFC).¹

Relationships to Craving and Alcohol use—To examine our hypothesis that negative urgency would be related to self-reported craving, we conducted a Mood Condition (3 levels; positive, negative, and neutral) × Craving type (2 levels; Alcohol drink craving vs. Grape juice drink craving) linear mixed-effects model analyses, with negative urgency as a covariate. There was no main effect of mood ($p = 0.79$), odor ($p = 0.08$), or negative urgency ($p = 0.35$). However, there was a significant negative urgency × craving type interaction ($p = 0.01$): as negative urgency increases, alcohol cravings became stronger ($\beta = 0.35$, $p = 0.04$), but grape juice cravings became weaker ($\beta = -0.20$, $p = 0.16$) (See Figure 6). This pattern did not differ across the mood conditions.

To examine how vmPFC activation and negative urgency relate to alcohol craving and problematic alcohol use, we conducted a series of mediation analyses using the INDIRECT SPSS macro provided by Preacher and Hayes (2008). This analysis uses the product of coefficients approach and bootstrapping to examine indirect effects; confidence intervals (90%) that do not contain zero are considered significant indirect effects. Negative urgency significantly mediated the effects of L vmPFC [AcO > SO] responses ($b = 0.18$, $SE = 0.14$, 90% CI [0.04, 0.55]) and R vmPFC [AcO > SO] responses ($b = 0.23$, $SE = 0.13$, 90% CI [0.05, 0.48]) on subjective alcohol craving. The reverse mediation (vmPFC activation mediating the effects of negative urgency on subjective alcohol craving) was not significant. Negative urgency also significantly mediated the effects of L vmPFC [AcO > SO] activation ($b = 0.40$, $SE = 0.39$, 90% CI [0.06, 1.37]) and R vmPFC [AcO > SO] activation ($b = 0.54$, $SE = 0.32$, 90% CI [0.17, 1.21]) on problematic alcohol use (AUDIT total score). The reverse mediations (vmPFC activation mediating the effects of negative urgency on AUDIT) were not significant. Figure 7 depicts these mediational analyses.

Discussion

The goals of the current study were to examine how medial frontal responses to alcohol cues are modified by mood, how negative and positive urgency traits are related to neural

¹We also examined the relationship between negative urgency and posterior cingulate activation using both functional clusters (AcO > SO, extracted at voxel-wise $p < 0.001$) and structural clusters from the MarsBar utility (Left and Right Posterior Cingulate Cortex) as a supplemental region of interest given previous findings relating activation in this region to alcohol cue-reactivity (see Bragulat et al., 2008). Negative urgency was unrelated to this activation ($r = 0.17$ for the functional cluster, $r = 0.18$ for the left posterior cingulate structural cluster, and $r = 0.14$ for the right posterior cingulate structural cluster).

responses to alcohol cues and mood, and how urgency and neural responses to alcohol's olfactory cues are related to alcohol craving and problematic alcohol use. Although mood did not affect neural responses to alcohol's olfactory cues, the data suggest that neural responses to these cues in the vmPFC, a region thought to both encode subjective reward value (Hare et al., 2008, 2009; Kable & Glimcher, 2007), are related to negative urgency. Additionally, neural responses to alcohol's olfactory cues in this region relate to subjective alcohol craving and problematic alcohol use through, in part, the trait of negative urgency.

Mood induction did not, in and of itself, significantly alter medial prefrontal responses to the alcohol cues, although some trends in the data suggest that negative mood might have enhanced the contrast between the AcO and AppCo stimuli in the left vmPFC. Interestingly, mood did alter subjective reports of craving for alcohol and grape juice, in that the contrast between alcohol and grape juice cravings was largest in the positive and negative mood conditions. Therefore, although mood did not largely alter neural responses, it did appear to alter subjective craving.

Negative urgency was related to subjective craving for alcohol, and AcO BOLD activation in left and right vmPFC, which sends axonal projections to the ventral striatum and nucleus accumbens (Chiba et al., 2001; Haber et al., 2006; Williams & Goldman-Rakic, 1998), and which responds to both alcohol cues (e.g., Bragulat et al., 2010; Filbey et al., 2008; Kareken et al., 2010a, 2010b; Myrick et al., 2008) and food aromas during fasting (Bragulat et al., 2008; Eiler et al., 2011). The current data suggest that vmPFC neural responses and negative urgency have much shared variance, and that vmPFC responses to alcohol olfactory cues might exert the effect on alcohol craving and problematic alcohol consumption by increasing the likelihood of negative emotion-based rash action. This suggests a potential underlying neurobiological mechanism for the development and maintenance of the trait of negative urgency, and suggests that general negative emotion-based rash action might be a means through which increased reactivity towards alcohol cues might facilitate subsequent alcohol craving and consumption. Negative urgency also interacted with craving type, such that negative urgency was positively associated with alcohol cravings and not associated with appetitive control cravings.

The lack of any positive mood or positive urgency effects on medial frontal neural responses to alcohol aromas could suggest that positive emotion-based rash action is less robust or perhaps somewhat more multi-factorial. For instance, much anecdotal evidence for positive urgency is rooted in social contexts, such as group "riots" after sports wins (e.g., Kornefel, 2002). Additionally, emotional intensity can also be hard to match across valences, with negative emotions also being inherently more intense than those of positive emotions (see Cyders & Coskunpinar, 2011). Somewhat contrary to that assertion, however, was our unanticipated finding of slightly greater self-reported arousal in the positive mood induction than in the negative mood induction. Additionally, positive mood did increase subjective craving for alcohol, even though it did not alter neural responses to alcohol cues. The sample size and lack of power may be a consideration in the absence of findings related to positive mood induction. It is also possible that positive urgency and positive mood might be related to different brain regions than those investigated in the current study.

Future research should consider how negative urgency might be related to genetic risk for alcoholism, which would better inform theories that posit urgency as a general risk factor for a wide range of risk-taking and externalizing behavioral disorders (e.g., Cyders & Smith, 2008; Verdejo-Garcia et al., 2008). In that regard, subsequent studies could also examine how vmPFC responses to multiple addictive stimuli (e.g., alcohol, cigarettes, drugs, food) are related to negative urgency, which would in turn validate the importance of negative urgency's role in multiple risk domains. Additionally, considering that the current sample

was comprised of social drinkers, the findings might not generalize to heavier drinkers or those with alcohol dependence; thus, the extent to which urgency traits relate to putative ventromedial frontal value signals in those who drink abusively remains to be determined.

In conclusion, this study is the first to show that responses in ventromedial prefrontal brain reward regions may vary as a function of negative emotion-based rash action, and that responses to alcohol cues in this region relate to alcohol craving and problematic use through negative urgency. However, future research is needed to replicate this finding in larger samples and in groups at higher risk for alcohol dependence.

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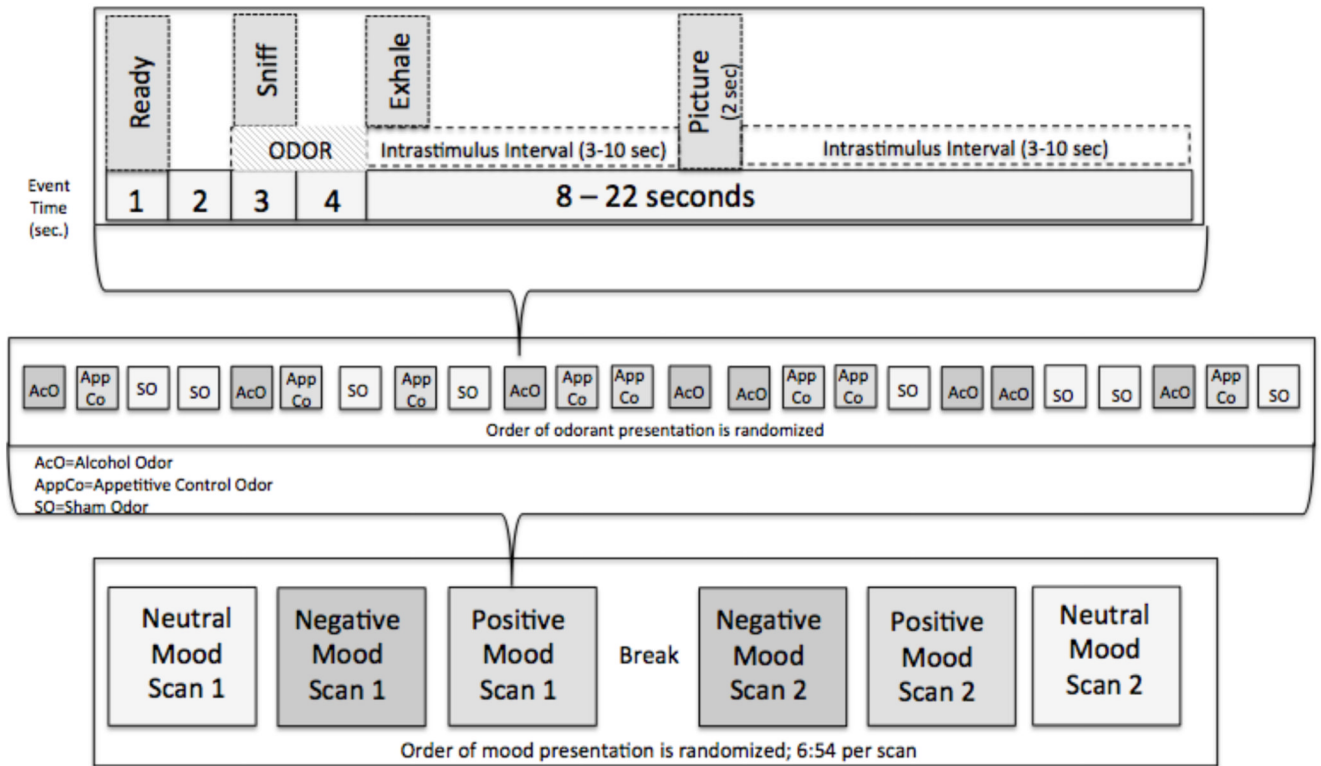


Figure 1. Outline of the imaging session. A total of six functional imaging scans of combined olfactory/visual stimulation were performed (24 2-second odor events in each of the 3 stimulus classes of AcO, AppCo, and SO were intermixed with 32 2-second IAPS image presentations), with two scans completed for each mood (2 positive image scans, 2 negative image scans, and 2 neutral image scans). Scan order was randomly assigned, with a break after the first three scans, although randomization was restricted so that all three moods were experienced prior to and again following the break.

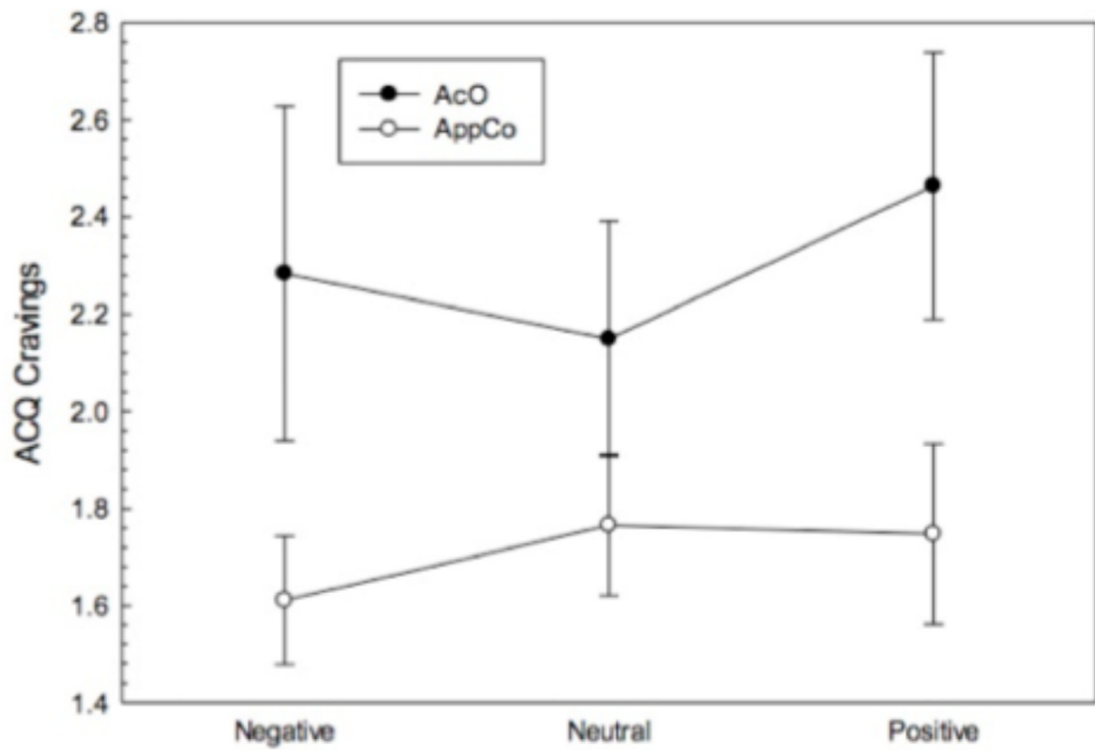


Figure 2. Significant interaction between drink type (AcO = alcohol, AppCo = grape juice) for self-reported craving levels ($p = 0.028$), such that the difference in craving between alcohol and grape juice was accentuated in the negative and positive mood conditions.

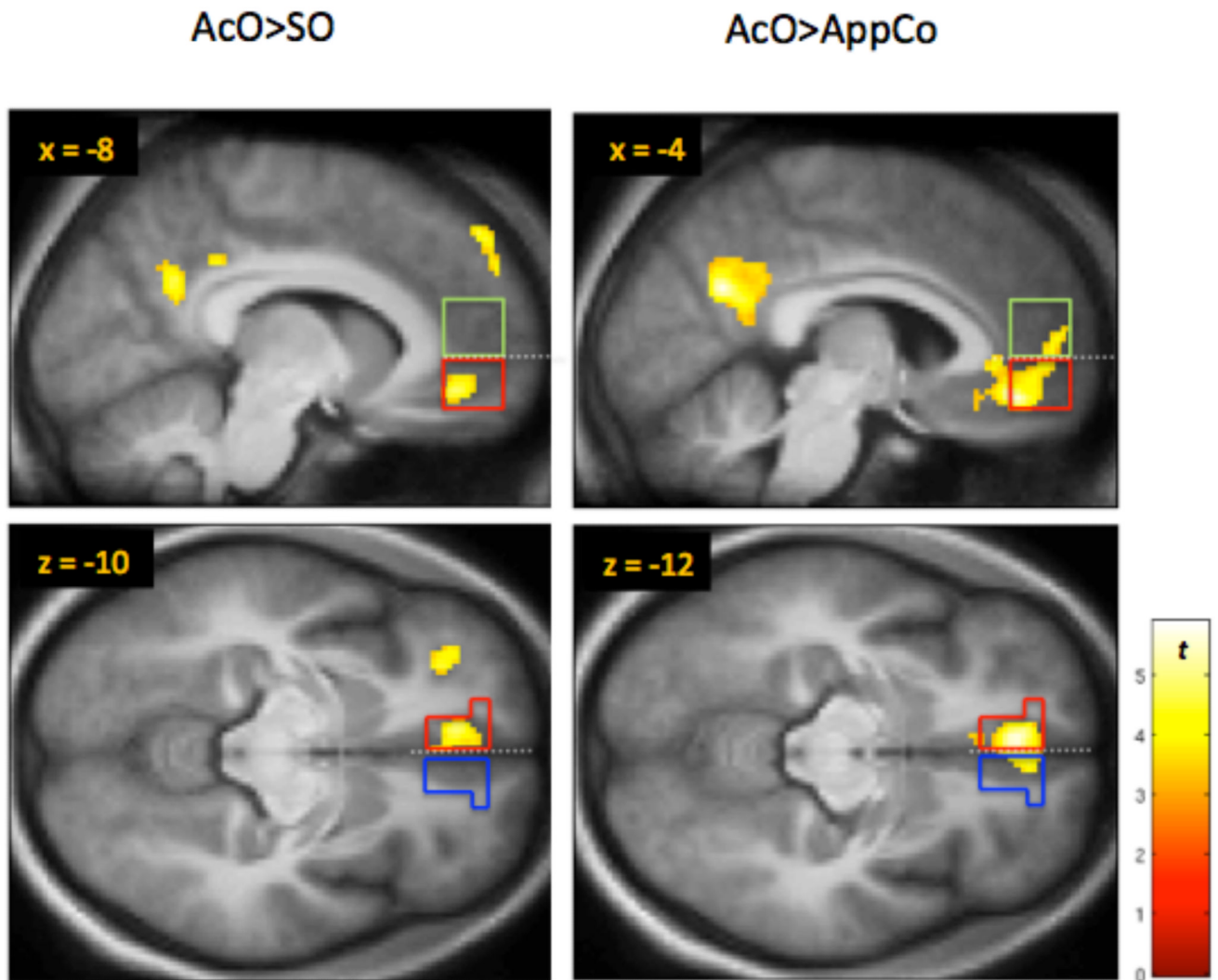


Figure 3. Main Effect of olfactory cues. Brain regions showing [AcO > SO; left panel] and [AcO > AppCo; right panel] BOLD activation pooling over Mood Condition, cluster-level significance, $p_{FDR} < 0.05$, display height $p = 0.001$. Four ROIs were identified: left ventromedial prefrontal cortex (red box), right ventromedial prefrontal cortex (blue box), left medial prefrontal cortex (green box) and right medial prefrontal cortex (not shown). The dashed line indicates the boundaries between the medial and prefrontal ROIs ($z = -6$ on sagittal views; top panel), and between the right and left vmPFC boundaries ($x = 0$ on axial views; bottom panel). For more details see Table 2. Color bar represents the t-statistic value.

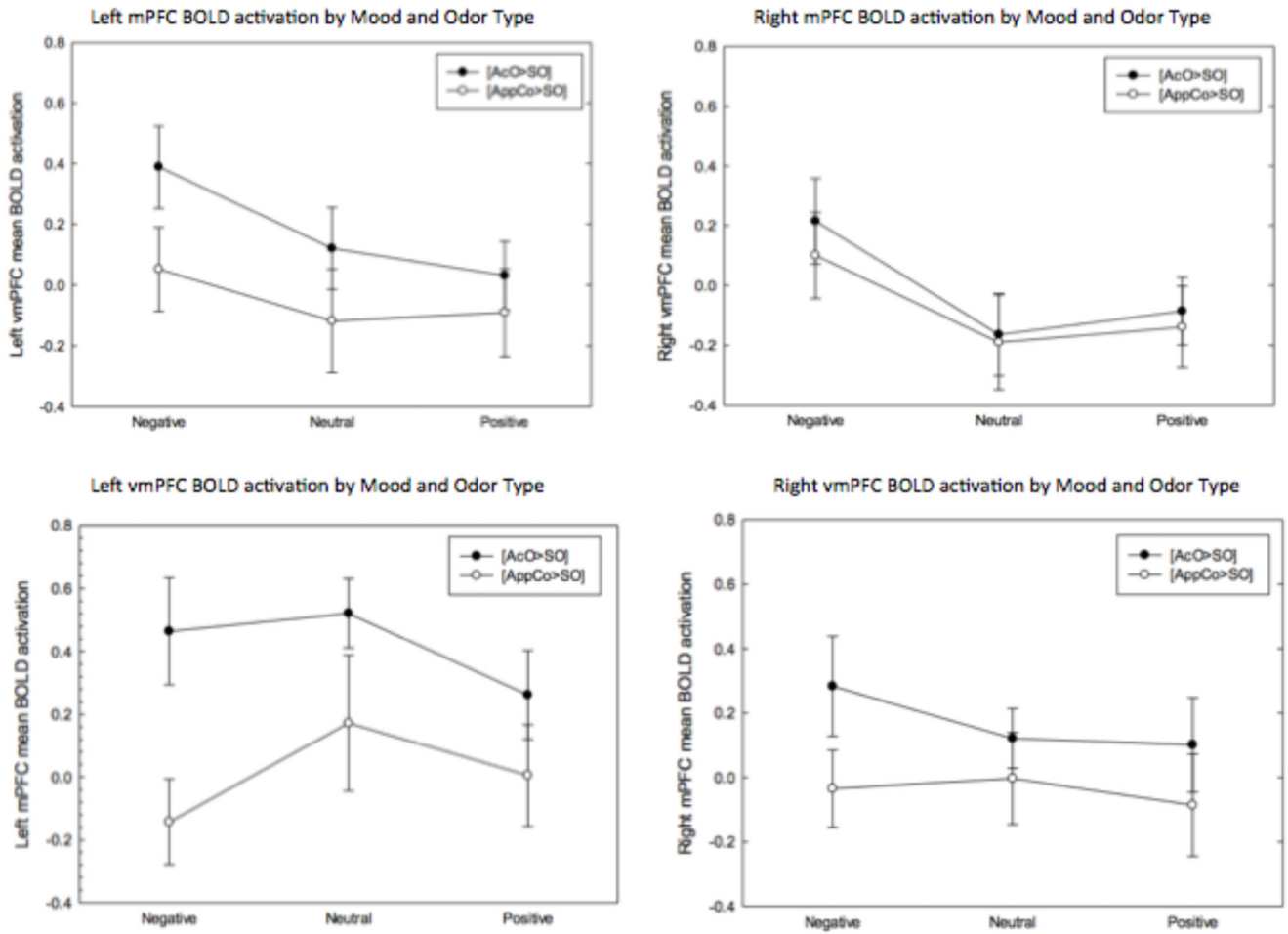


Figure 4. Mood (3: Negative, Neutral, Positive) × Odor (2: [AcO > SO] and [AppCo > SO]) Linear Mixed-Effects Model Results in four medial frontal regions of interest.

AcO>SO BOLD Response correlated with Negative Urgency

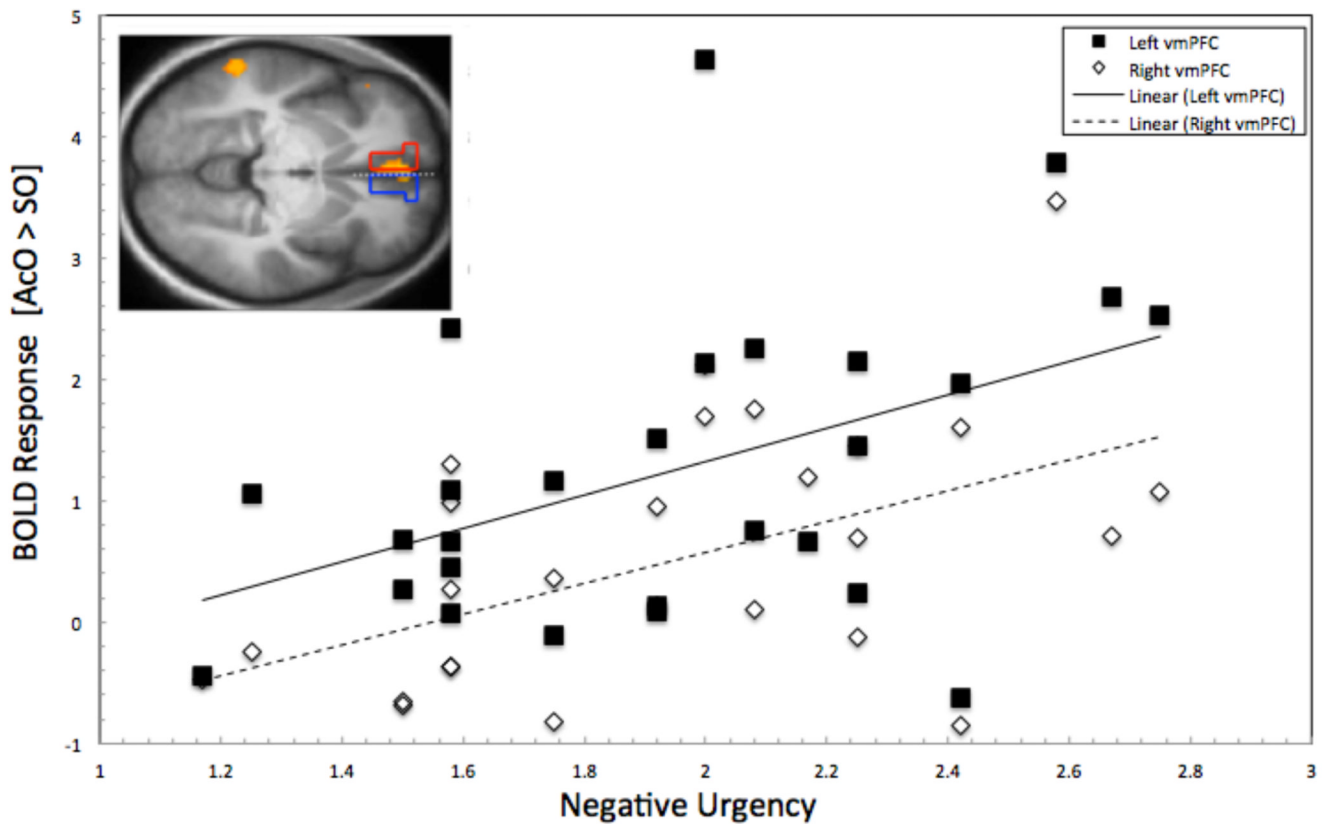


Figure 5. Positive correlation between negative urgency and [AcO>SO] BOLD activation in Left and Right vmPFC. Positive correlation between mean [AcO > SO] BOLD activity as extracted (height threshold $p < 0.001$) from the left vmPFC (red box) and right vmPFC (blue box) with negative urgency (NUR). For reference, the inset shows a voxel-wise map of the correlation between [AcO > SO] and NUR in voxel-wise analysis (display threshold, $p < 0.05$; masked for [AcO > SO] activation).

Interaction between Negative Urgency and Craving Type

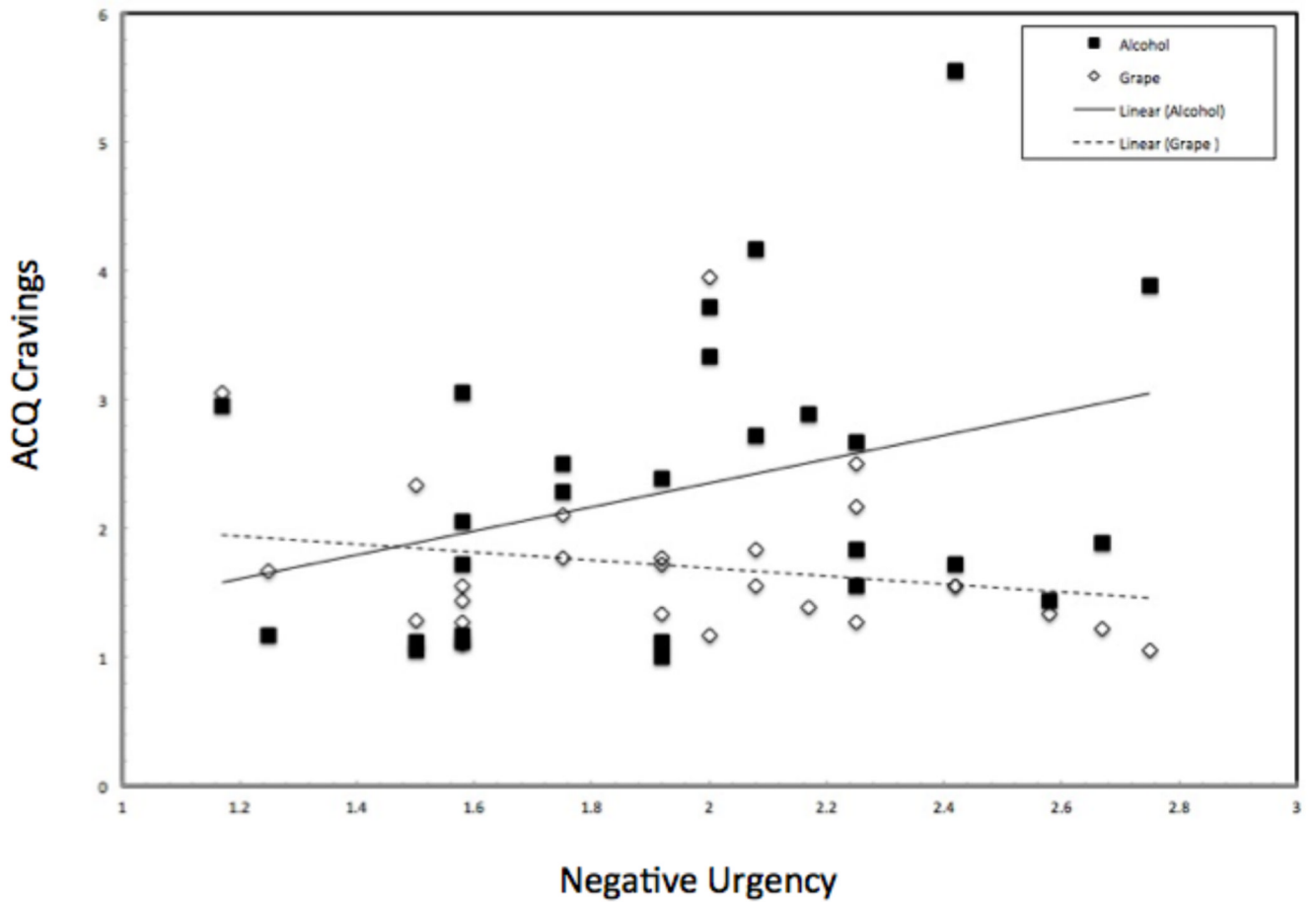


Figure 6. Interaction between Negative Urgency and Craving Type (Alcohol, Grape) for self-reported craving levels.

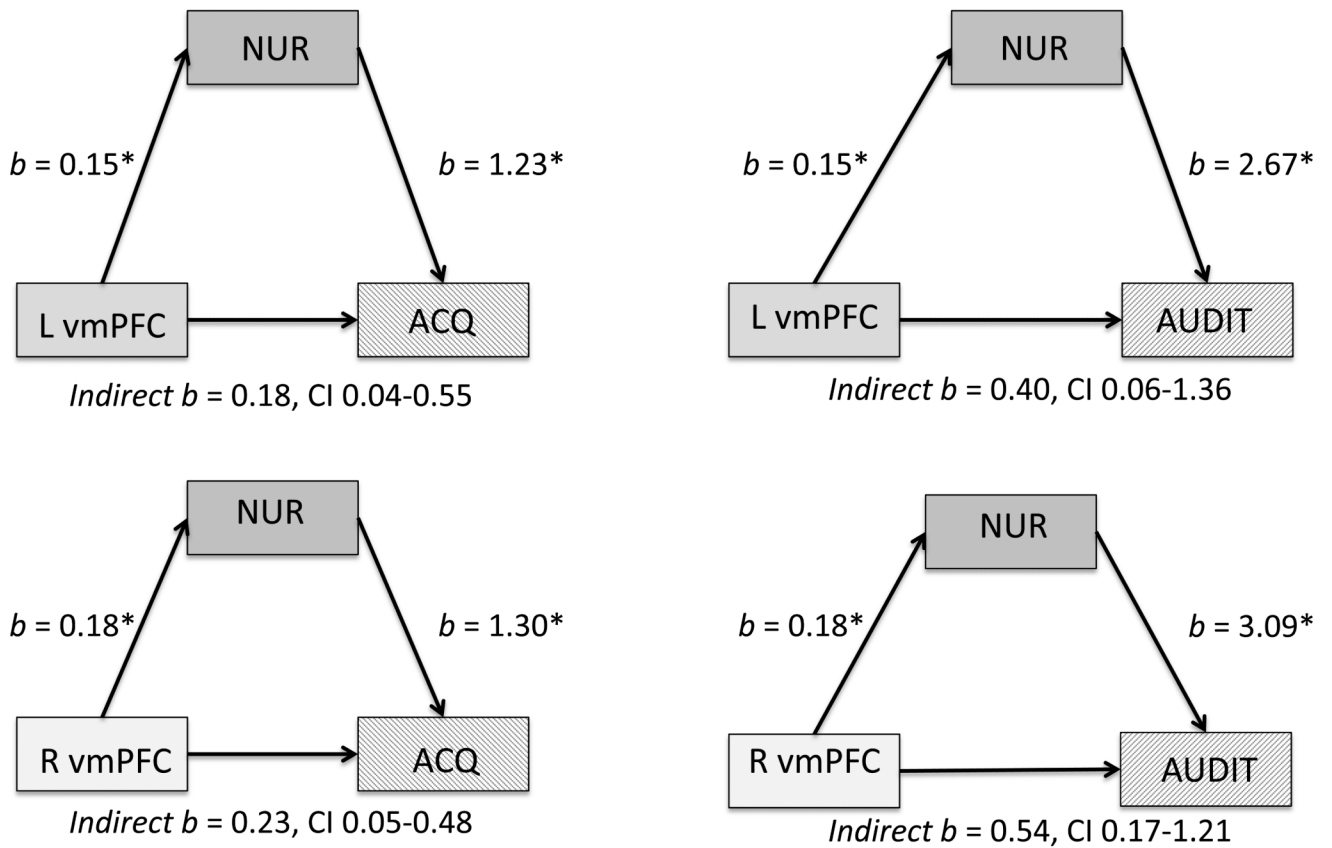


Figure 7. Negative Urgency (NUR) as a mediator between mean [AcO > SO] BOLD activation in the left and right ventromedial prefrontal cortex mean BOLD activation and (a) Subjective Alcohol Craving (ACQ; left panel) and (b) Problematic Alcohol Use (AUDIT; right panel).

Table 1
Subject Characteristics

	Mean (SD)	n (%)
Age	25.19 (3.62)	
Sex		14 (51.9) Male 13 (48.1) Female
Race		2 (7.4) African-American 23 (85.2) European-American 2 (7.4) Asian-American
Mother's Education/ Father's Education		10/9 (37.0/34.6) High School Graduate or GED 5/5 (18.5/18.5) Some College 8/5 (29.6/18.5) College Graduate 3/7 (11.1/25.9) Post-College Education 1/1 (3.7/3.7) Missing
Education		9 (33.3) Some College 9 (33.3) College Graduate 5 (18.5) Post-College Education 4 (14.8) Missing
Estimated household income		4 (14.8) Under \$10,000 a year 5 (18.5) \$10,000-24,000 a year 3 (11.1) \$25,000-39,000 a year 3 (11.1) \$40,000-59,000 a year 4 (14.8) \$60,000-79,000 a year 2 (7.4) \$80,000-99,000 a year 5 (18.5) over \$100,000 a year 1 (3.7) Missing
Frequency of drinking days		5 (18.5) 2-4 times per month 16 (59.3) 2-3 times a week 6 (22.2) 4 or more times per week
Number of drinks during drinking days		14 (51.9) 1 or 2 6 (22.2) 3 or 4 4 (14.8) 5 or 6 2 (7.4) 7 or 9 1 (3.7) 10 or more
AUDIT	7.74 (3.38)	
Current Smoking		27 (100.0) No
Most Frequently consumed alcoholic beverage		10 (37.0) Beer 3 (11.1) Red Wine 3 (11.1) White Wine 11 (40.7) Mixed drinks/hard liquor
Endorsement of Family History of alcohol problems		14 (51.9) Yes, some endorsement 13 (48.1) No, no endorsement

Table 2

Voxel-wise activation to AcO > SO and AcO > AppCo for all Mood Conditions.

AcO > SO

Region	MNI coordinate x,y,z (mm)	Cluster significance p_{FDR}	Cluster size k	Peak voxel Z
L IPL	-42 -70 48	<0.001	553	5.15
L SFG	-12 48 44	0.000	481	4.60
R Amygdala	26 0 -18	0.043	65	4.41
L vmPFC	-8 42 -10	0.004	139	4.31
PCC/Precuneus	-4 -56 22	<0.001	314	4.30
L OFC	-30 36 -10	0.040	70	4.02
L MFG	-40 16 48	0.017	94	3.94

AcO > AppCo

Region	MNI coordinate x,y,z (mm)	Cluster significance p_{FDR}	Cluster size k	Peak voxel Z
PCC/Precuneus	-6 -60 26	<0.001	463	5.33
L vmPFC	-4 42 -12	<0.001	460	5.07
L SFG	-16 36 42	<0.001	254	4.79

Note. Brain regions that show [AcO > SO] and [AcO > AppCo] BOLD activation pooled over Mood Condition (cluster-level significance, $p_{FDR} < 0.05$, voxel-wise height threshold, $p = 0.001$). No significant clusters were observed in the [AppCo > SO] contrast. FDR = False Discovery Rate, MNI = Montreal Neurological Institute, L = Left; R = Right; IPL = Inferior Parietal Lobule, SFG = Superior Frontal Gyrus, PCC = Posterior Cingulate Cortex, OFC = Orbitofrontal Cortex, MFG = Middle Frontal Gyrus.