Regulation of Craving and Negative Emotion in Alcohol Use Disorder

Shosuke Suzuki, Maggie Mae Mell, Stephanie S. O’Malley, John H. Krystal, Alan Anticevic, and Hedy Kober

ABSTRACT

BACKGROUND: Alcohol use disorder (AUD) is a chronic, relapsing condition with poor treatment outcomes. Both alcohol craving and negative affect increase alcohol drinking, and—in healthy adults—can be attenuated using cognitive strategies, which rely on the prefrontal cortex (PFC). However, AUD is associated with cognitive impairments and PFC disruptions. Thus, we tested whether individuals with AUD can successfully recruit the PFC to effectively regulate craving and negative emotions, whether neural mechanisms are shared between the two types of regulation, and whether individual differences influence regulation success.

METHODS: During functional magnetic resonance imaging, participants with AUD completed the regulation of craving task (n = 17) that compares a cue-induced craving condition with an instructed regulation condition. They also completed the emotion regulation task (n = 15) that compares a negative affect condition with an instructed regulation condition. Regulation strategies were drawn from cognitive behavioral therapy treatments for AUD. Self-reported craving and negative affect were collected on each trial.

RESULTS: Individuals with AUD effectively regulated their craving and negative affect when instructed to do so using cognitive behavioral therapy–based strategies. Regulation was associated with recruitment of both common and distinct PFC regions across tasks, as well as with reduced activity in regions associated with craving and negative affect (e.g., ventral striatum, amygdala). Effective regulation of craving was associated with negative alcohol expectancies.

CONCLUSIONS: Both common and distinct regulatory systems underlie regulation of craving and negative emotions in AUD, with notable individual differences. This has important implications for AUD treatment.

Keywords: Alcohol use disorder, Craving, Emotion regulation, fMRI, Negative affect, Regulation of craving

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Craving and Its Regulation in AUD

One factor that contributes to drug and alcohol use is craving, defined as “a strong desire or urge” (12). Craving has been linked to drug and alcohol use across retrospective reports (13–15), prospective clinical studies (16–21), and ecological momentary assessments (22–25). Such studies have found that craving is cross-sectionally and prospectively associated with increased drug use. Thus, craving was added as a diagnostic criterion for SUDs in the DSM-5 (12).

Importantly, craving can be triggered by stimuli that have previously been associated with the substance (26). Such cue-induced craving has been directly linked to drug and alcohol use (27–31). Additionally, intensity of cue-induced craving predicts relapse to drugs (20,32) and alcohol (33–36), and increases in cue-induced responses are reported months into abstinence (37). As such, cue-induced craving contributes to high rates of relapse, and thereby to the chronicity of SUDs and difficulty of treatment.

Given the role of cue-induced craving in relapse and SUD maintenance, regulation of craving (ROC) has become an important clinical target. In fact, cognitive behavioral therapy (CBT) for SUDs focuses on situations in which individuals may be exposed to drug cues or crave or seek the substance (38). To cope with such “high-risk situations,” CBT teaches cognitive strategies, such as orienting individuals to focus on the negative consequences of drug use [vs. pleasurable consequences (38)]. Importantly, recent experiments have demonstrated that cognitive strategies can reduce cue-induced craving for cigarettes (39–41), stimulants (42,43), and food...
(39,40,44–46). Clinically, implementation of such strategies has been associated with reduced smoking (47), and acquisition of such skills mediates CBT treatment success for drug and/or alcohol use (48). These data suggest that cognitive strategies are an active component of CBT, at least in part owing to their effects on reducing craving.

However, only one study, to our knowledge, has experimentally investigated ROC in AUD (49). In this previous study, we taught participants to focus on the negative consequences of drinking during cue-induced alcohol craving (38–40). We observed that—compared with social drinkers—individuals with AUD were less able to regulate craving using this CBT-based cognitive strategy (49). This is consistent with abundant evidence linking alcohol drinking to deficits in cognitive control [for a review, see Day et al. (50)] and studies that further link deficits to subsequent alcohol use [e.g., (51)].

Despite the clinical importance of the ability to regulate craving, its underlying neural mechanisms have not been investigated in AUD. Using functional magnetic resonance imaging (fMRI), we previously showed that ROC in cigarette smokers depends on recruitment of prefrontal brain regions, such as the dorsolateral prefrontal cortex (dPFC), ventrolateral PFC (vPFC), and dorsomedial PFC (dmPFC) (40). This was accompanied by relative deactivations in reward-related regions, including the ventral striatum (VS) and ventromedial PFC (vmPFC) (40). Similar findings have been reported in cocaine use disorder (43) and with regulation of food craving (52–54).

Alcohol Expectancies

Regulation strategies require individuals to focus on the negative effects of alcohol; thus, individual differences in expectancies about alcohol may affect ROC. For example, individuals who drink the most report higher expectations for the positive effect of alcohol (55) and may disregard the negative consequences of excessive drinking. However, it is unknown whether individuals who have higher negative expectations are better at regulating craving. Importantly, identification of individual differences that modulate regulation processes may help optimize and individualize treatments.

Negative Affect and Its Regulation in AUD

Negative affect is also thought to contribute to drug and alcohol use (56–58). Indeed, many theories of SUDs and AUD focus on reduction of negative affect as motives for consumption (57,59–61). In turn, the reduction of negative affect is considered negatively reinforcing, increasing the likelihood of continued use (62). Consistently, several lines of work link negative affect, drug use, and SUDs. First, SUDs (including AUD) frequently co-occur with mood and anxiety disorders (6,56,63–65), and major depression predicts AUD (66). Second, levels of self-reported negative affect have been linked to drug use. For example, negative affect predicts relapse in cigarette smokers (16) and correlates with drinking problems in adult drinkers (67). Third, negative affective states trigger craving across drug types. Specifically, acute induction of negative affect has been shown to increase craving for cigarettes (68), cocaine (69), opiates (70), and alcohol (33,71,72). Fourth, negative affect and stress have been directly linked to drug use and relapse after treatment (72).

Given the relationship between negative affect and drug use, regulation of negative affect has important implications for SUD treatment (along with ROC) (56). A rich literature has demonstrated that healthy adults can use cognitive strategies to regulate affective responses to aversive stimuli (73). A recent meta-analysis demonstrated that regulation is associated with recruitment of the dPFC, vPFC, and dmPFC (similar to ROC) and with reduced activation in the amygdala (74). However, cognitive emotion regulation (ER) has been poorly investigated in SUDs, with only 2 published studies to date (to our knowledge). In these studies, cognitive strategies reduced negative emotional responses toward negative images in nicotine-dependent cigarette smokers (75) and patients with cocaine use disorder (76).

Shared Neural Systems Supporting ROC and Negative Emotion

An important remaining question is whether shared neural mechanisms underlie the implementation of cognitive strategies to regulate craving and negative affect. Prior studies suggest that neural activation during different types of self-control may converge in the PFC (77,78). One study in cigarette smokers found that the dPFC, vPFC, and dmPFC in anterior cingulate cortex (ACC) during relaxing imagery (71), hypoactivity in the medial PFC (mPFC) and ACC during threat processing (63), and disruptions in the PFC during negative emotional processing (64–66). Investigating whether individuals with AUD can effectively recruit PFC mechanisms during regulation will inform treatment approaches that utilize cognitive strategies (46).

The Current Study

To address these questions, we used fMRI to scan individuals with AUD while they completed the ROC and ER tasks. These tasks are specifically designed to examine the neural mechanisms underlying cognitive ROC and negative affect—invoked using alcohol-related and negatively valenced pictures, respectively—given the importance of these processes to AUD. In addition, we tested whether there are shared prefrontal mechanisms across these forms of cognitive regulation. Further, we used self-report to assess regulation success across tasks, and whether regulation success for alcohol craving is modulated by individual differences in negative alcohol expectancies.
METHODS AND MATERIALS

Participants

Twenty-six individuals with AUD (Table 1) participated in this 2-visit outpatient study. Recruitment was conducted via advertisements in the New Haven community. Participants were eligible if they 1) met diagnostic criteria for alcohol abuse or dependence (assessed via the Structured Clinical Interview for DSM-IV Axis I Disorders); 2) did not meet criteria for any other Axis I disorder, except nicotine dependence; 3) consumed ≥20 drinks/week for men and ≥20 drinks/week for women; 4) consumed alcohol on ≥4 days/week; and 5) could understand and consent to study procedures. Participants were excluded if they 1) had contraindications for MRI (e.g., pregnancy, metallic implants); 2) reported currently taking centrally active medications; 3) tested positive for psychoactive drugs (cocaine, opiates, methamphetamine, amphetamine, PCP, or benzodiazepines) as indicated by urinalysis; or 4) provided false information during screening. All participants provided informed consent during the initial screening visit and returned for fMRI scanning at Yale University’s Magnetic Resonance Research Center.

A priori sample size and data collection stopping targets were based on sample and effect sizes reported at the time in the extant ER literature [i.e., commonly around 16–20 participants; for a meta-analysis, see Buhle et al. (74)], on our prior study with the ROC task (n = 21) (40), and on availability of funding. Four participants could not complete the MRI session owing to unanticipated claustrophobia. One participant provided false information during screening, which was discovered following completion of the study. This participant’s data were removed prior to analysis (specifically, we discovered that the participant was previously enrolled in another study in our lab and had provided conflicting information regarding his or her substance use). Data from another participant were excluded due to noncompliance (e.g., no responses in some runs). All but the first 2 participants were scanned in the afternoon (~4 PM) to minimize any diurnal variations in alcohol craving; therefore, the 2 participants scanned in the morning were excluded from ROC analysis. In addition, ROC data from 1 participant and ER data from 3 participants were excluded for excessive motion or technical errors. Thus, the final sample included 17 participants for the ROC task and 15 participants for the ER task. All procedures were approved by Yale University’s Institutional Review Board.

Procedures

Participants were instructed to abstain from alcohol on scanning day and from eating for 2 hours prior to their visit. Alcohol abstinence was confirmed using a breathalyzer (BACtrack, San Francisco, CA). Psychoactive substance use was tested via urinalysis (Redwood Toxicology Laboratory, Santa Rosa, CA).

Negative Alcohol Expectancy Questionnaire

The Negative Alcohol Expectancy Questionnaire (87) assessed participants’ expectations about the negative consequences of alcohol (3 subscales: same day, next day, long term). The long-term subscale is known to predict abstinence 3 months later (88).

ROC Task

The ROC task assesses craving and ROC (39,40,42,45,49,89) using an event-related design. On each trial, participants were presented with a unique picture of alcohol or food shown to induce craving in prior studies (Figure 1A) (39,40,49). Prior to the picture, an instruction cue appeared in the center of the screen, orienting participants to view the picture in one of two ways: 1) craving condition: “think about the immediate effects of consuming the item,” indicated by the word NOW; or 2) regulation condition (based on CBT): “think about the long-term effects of regularly consuming the item,” indicated by the word LATER. Importantly, to minimize demand characteristics, participants were not explicitly told to reduce craving. Then, following an exponentially jittered interstimulus interval (~2.73 seconds) (90), participants rated the intensity of their craving on a scale from 1 (not at all) to 5 (very much). Trials were separated by exponentially jittered intertrial intervals (~3.43 seconds) (90). Participants completed 4 runs (20 trials/run).

ER Task

The ER task assesses the regulation of negative affect (73,74,91,92) in response to negative images using an event-related design. On each trial, participants were shown an instruction cue orienting them to view a subsequent picture in one of two ways: 1) look condition: “simply look at the picture,” indicated by the word LOOK, for neutral and negative pictures; or 2) regulation condition: “think about the image in a less negative way,” indicated by the word REAPPRAISE, for negative pictures only (Figure 1B). Unique negative and neutral pictures were drawn from the International Affective Picture System (93). Following exponentially jittered interstimulus intervals (~2.8 seconds) (90), participants rated the intensity of their negative affect on a scale from 1 (not at all) to 5 (very negative). Trials were separated by exponentially jittered intertrial intervals (~3.5 seconds) (90). Participants completed 4 runs (15 trials/run).

Table 1. Participant Demographics for Each Task

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>ROC Task (n = 17)</th>
<th>ER Task (n = 15)</th>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>%</td>
</tr>
<tr>
<td>Age, Years</td>
<td>33.35 ± 10.97</td>
<td>20</td>
</tr>
<tr>
<td>Education, Years</td>
<td>14.29 ± 1.21</td>
<td>14.07 ± 1.22</td>
</tr>
<tr>
<td>Female</td>
<td>41.2</td>
<td>6</td>
</tr>
<tr>
<td>Hispanic</td>
<td>17.6</td>
<td>20</td>
</tr>
<tr>
<td>White</td>
<td>47.1</td>
<td>40.0</td>
</tr>
<tr>
<td>African American</td>
<td>47.1</td>
<td>46.7</td>
</tr>
<tr>
<td>More than 1 race</td>
<td>5.9</td>
<td>6.7</td>
</tr>
<tr>
<td>NA</td>
<td>0.0</td>
<td>6.7</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependence</td>
<td>76.5</td>
<td>73.3</td>
</tr>
<tr>
<td>Abuse</td>
<td>23.5</td>
<td>26.7</td>
</tr>
<tr>
<td>Time Since Last Drink, Hours</td>
<td>18.60 ± 14.35</td>
<td>19.79 ± 15.42</td>
</tr>
<tr>
<td>Average Drinks/Day During Past Month</td>
<td>8.22 ± 5.02</td>
<td>7.63 ± 4.76</td>
</tr>
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</table>

ER, emotion regulation; NA, not available; ROC, regulation of craving.
Behavioral Data Acquisition and Analysis

The tasks were programmed in E-Prime version 2.0 (Psychology Software Tools, Sharpsburg, PA) and presented using a back-projection mirror. Participants provided ratings using an MRI-compatible 5-button box. Order of tasks was counterbalanced. Analyses of behavioral data were conducted in SPSS, version 22 (IBM Corp., Armonk, NY). For the ROC task, we conducted a 2 instruction (NOW/LATER) x 2 image type (alcohol/food) repeated-measures analysis of variance. For the ER task, we conducted a 1-way analysis of variance with condition as a within-subjects factor with 3 levels (REAPPRAISE-Negative/LOOK-Negative/LOOK-Neutral). Significant effects were followed up using post hoc pairwise comparisons. Finally, following prior studies using the ROC and ER tasks [e.g., (40,49,89,92,94)], we calculated a “regulation success” score for each participant, for each task. Specifically, for the ROC task, the mean self-reported craving during the regulation condition was subtracted from that during the craving condition, and for the ER task, the mean self-reported negative affect during the REAPPRAISE-Negative condition was subtracted from that during the LOOK-Negative condition. Thus, for each task, positive regulation success scores indicated successful reduction in craving or negative affect, whereas negative scores indicated an increase in craving or negative affect during the regulation condition. We then assessed whether negative alcohol expectancies correlated with regulation success in the ROC task, and whether ROC regulation success correlated with regulation success in the ER task. A missing value on the subsequent presented picture in particular ways. Then, a picture was presented for 6300 ms (alcohol or food in the ROC task; negative or neutral image in the ER task). A jittered interstimulus interval (1400–8400 ms) followed the image presentation. Participants were then asked to make a rating of their craving (ROC) or negative affect (ER) on a 5-point scale (2800 ms). The intertrial interval was jittered at 2100–9100 ms. IAPS, International Affective Picture System.

fMRI Data Acquisition and Analysis

Participants were scanned in a 3T Siemens TIM Trio scanner (Siemens AG, Munich, Germany). One participant was scanned in a 3T Siemens Prisma (Siemens AG) due to scanner upgrade during the study period (between-scanner differences are minimal and do not compare with physiological noise) (97). Importantly, excluding this participant did not change the main findings; thus, we included these data in analyses. Scan parameters followed Human Connectome Project recommendations (98). Functional images were acquired with T2*-weighted echo-planar pulse sequences with a multiband acceleration factor of 6 (repetition time/echo time = 700 ms/31 ms; flip angle = 55°; field of view = 210 × 210 mm; 54 × 2.50 mm slices). High-resolution structural images were acquired using a single-shot, magnetization prepared rapid acquisition gradient-echo sequence (repetition time/echo time = 2400 ms/2.01 ms; flip angle = 8°; field of view = 256 × 256 mm; 224 × 0.80 mm slices).

Functional images were preprocessed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom) following our prior work [e.g., (99)]. Specifically, functional images were co-registered to the structural image, motion-corrected, warped to the Montreal Neurological Institute template, and smoothed using a Gaussian filter (5-mm full width at half maximum). Both before and after preprocessing, data were subjected to multiple tests for quality assurance and inspected for signal spiking and motion. Volumes were discarded if the root mean square of motion parameters exceeded half of a single voxel size (100). First-level modeling of trial events was conducted using robust regression to reduce the influence of strong outliers (99,101,102). Following prior work [e.g., (40,92)], for both tasks, the instruction cue and picture
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**Figure 2.** Behavioral ratings (y-axis) from the (A) regulation of craving and (B) emotion regulation tasks, separated by condition (x-axis). Significance is noted: *p < .05, **p < .01, ***p < .005, and ****p < .001.

Results were familywise error corrected at a combined voxelwise and cluster threshold (k) of p < .05, with a voxelwise threshold of p < .001 (105) (see Supplement for analyses corrected with p < .005 voxelwise threshold). The estimated spatial smoothness of the residual was used to determine the k threshold for each second-level map: ROC task LATER>NOW (k = 27), ROC task effect of craving as parametric regressor (k = 56), ER task REAPPRAISE-NEGATIVE>LOOK-Negative (k = 27), ER task effect of negative affect as parametric regressor (k = 68), and ROC task and ER task conjunction map (k = 2). The VS/subgenual ACC (sgACC) and vmPFC/orbitofrontal cortex (OFC) in the ROC task and the amygdala in the ER task were selected as a priori regions of interest (ROIs), given the evidence implicating these areas in craving and affective processing, respectively. To do this, the amygdala ROI was defined using an anatomical mask, while the VS/sgACC and vmPFC/OF C ROIs were defined using spherical ROIs (radius = 6 mm) centered around peaks previously observed during ROC in cigarette smokers (VS/sgACC: −3, 11, −2; vmPFC/OF C: 0, 56, −2) (40). These regions were considered significant at a familywise error rate of p < .05 using a voxelwise threshold of p < .005 and small volume correction.

**RESULTS**

**Self-reported Craving in the ROC Task**

We found a main effect of instruction ($F_{1,16} = 13.04, p = .002$), such that participants reported lower craving in LATER than in NOW, as expected ($t_{16} = −3.58, p = .003$) (Figure 2A, Supplemental Figure S1). We also found a main effect of image type ($F_{1,16} = 5.50, p = .03$), such that alcohol images induced significantly greater craving than food ($t_{16} = 2.48, p = .02$). We did not find a significant interaction ($p = .24$). Regulation success did not significantly differ between image types ($p = .24$).

**Self-reported Negative Affect in the ER Task**

We found a main effect of condition ($F_{1,14} = 57.70, p < .001$), such that participants reported greater negative affect when looking at negative images than at neutral images ($t_{14} = 10.59, p < .001$), and reported lower negative affect when instructed to reappraise negative images compared with looking at them ($t_{14} = −3.40, p = .004$), consistent with prior work (Figure 2B, Supplemental Figure S1). Regulation success in the ER and ROC tasks was not significantly correlated ($p = .41$).
Correlation With Negative Alcohol Expectancy

Regulation success during alcohol trials of the ROC task was significantly and positively correlated with long-term negative alcohol expectancies ($r_{19} = .54, p = .03$), such that participants with greater expectancies about the long-term negative effects of alcohol were better able to regulate their craving. Regulation success did not correlate significantly with the same-day or next-day subscales ($p$s $.12$).

Neural Activity During ROC

We observed greater recruitment of the dlPFC and vlPFC during cognitive ROC (LATER→NOW) (Figure 3A, Table 2). We also observed relative deactivations in the VS/sgACC and vmPFC/OFC (a priori ROIs). We did not find significant modulation of activity in the amygdala.

Neural Activity During ER

We observed increased activations in the dlPFC, vlPFC, and dmPFC during ER (REAPPRAISE-Negative→LOOK-Negative) (Figure 3B, Table 2). We also observed a relative deactivation in the amygdala (a priori ROI). We did not find significant modulation of activity in the VS/sgACC or vmPFC/OFC.

Parametric Modulation

We observed a significant positive association between trial-by-trial brain activity and craving in the vmPFC/OFC and VS/sgACC (Figure 4, Table 2). We did not observe any parametric associations between brain activity and negative affect during the ER task.

Conjunction Between Regulation of Craving and Emotion

We observed significant coactivation in the left vlPFC between ROC (LATER→NOW) and negative affect (ER; REAPPRAISE-Negative→LOOK-Negative) (Figure 5, Table 2) (see Supplement for dlPFC in analysis using a $p < .005$ threshold). As a result, this analysis revealed that subregions of the right dlPFC and left vlPFC were uniquely active during ROC but not during ER (Table 2). When the conjunction analysis was masked with regions previously observed in smokers during various forms of cognitive control, we observed significant overlap in the left vlPFC.

DISCUSSION

The results indicate that individuals with AUD can regulate craving as well as negative affect using cognitive strategies. Further, those who reported greater long-term negative alcohol
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Table 2. Peak Coordinates of Regions Identified in Whole-Brain Analyses

<table>
<thead>
<tr>
<th>Region of Activation</th>
<th>Hemisphere</th>
<th>Peak MNI Coordinates</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
<td>k</td>
<td>Maximum</td>
<td>Mean</td>
</tr>
<tr>
<td>ROC (LATER−NOW)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dlPFC/middle frontal gyrus</td>
<td>Right</td>
<td>45</td>
<td>12</td>
<td>51</td>
<td>39</td>
<td>5.47</td>
<td>4.37</td>
</tr>
<tr>
<td>viPFC/inferior frontal gyrus</td>
<td>Left</td>
<td>-42</td>
<td>21</td>
<td>-3</td>
<td>63</td>
<td>4.87</td>
<td>4.33</td>
</tr>
<tr>
<td>VS and subgenual anterior cingulate*</td>
<td>Left</td>
<td>0</td>
<td>15</td>
<td>-12</td>
<td>6</td>
<td>3.63</td>
<td>3.30</td>
</tr>
<tr>
<td>vmPFC/medial frontal gyrus*</td>
<td>Left</td>
<td>-3</td>
<td>57</td>
<td>-6</td>
<td>45</td>
<td>3.18</td>
<td>3.03</td>
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<tr>
<td>ER (REAPPRAISE-Negative−LOOK-Negative)</td>
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<td></td>
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<tr>
<td>Middle temporal gyrus</td>
<td>Left</td>
<td>-48</td>
<td>-18</td>
<td>-27</td>
<td>97</td>
<td>7.08</td>
<td>4.87</td>
</tr>
<tr>
<td>dlPFC/middle frontal gyrus</td>
<td>Left</td>
<td>-45</td>
<td>6</td>
<td>54</td>
<td>38</td>
<td>6.47</td>
<td>4.85</td>
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<td>dmPFC/superior frontal gyrus</td>
<td>Left</td>
<td>-15</td>
<td>9</td>
<td>72</td>
<td>111</td>
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<td>4.82</td>
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<tr>
<td>viPFC/inferior frontal gyrus</td>
<td>Left</td>
<td>-39</td>
<td>21</td>
<td>-6</td>
<td>61</td>
<td>3.94</td>
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<tr>
<td>Amygdala*</td>
<td>Left</td>
<td>-30</td>
<td>3</td>
<td>-21</td>
<td>5</td>
<td>-4.66</td>
<td>-3.88</td>
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<tr>
<td>ROC Parametric Analysis</td>
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<tr>
<td>vmPFC/dmPFC/medial frontal gyrus*</td>
<td>Left</td>
<td>3</td>
<td>51</td>
<td>3</td>
<td>40</td>
<td>5.30</td>
<td>3.97</td>
</tr>
<tr>
<td>VS*</td>
<td>Left</td>
<td>-6</td>
<td>6</td>
<td>-3</td>
<td>15</td>
<td>3.98</td>
<td>3.50</td>
</tr>
<tr>
<td>Conjunction: ROC (LATER−NOW) and ER (REAPPRAISE-Negative−LOOK-Negative)</td>
<td></td>
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</tr>
<tr>
<td>Inferior frontal gyrus*</td>
<td>Left</td>
<td>-42</td>
<td>21</td>
<td>-6</td>
<td>20</td>
<td>5.01</td>
<td>4.50</td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>Left</td>
<td>-48</td>
<td>21</td>
<td>12</td>
<td>3</td>
<td>4.42</td>
<td>4.27</td>
</tr>
</tbody>
</table>

Results are $p < .05$ (familywise error corrected), with applied voxelwise threshold of $p < .001$. k indicates number of 2.5-mm isometric voxels. Maximum indicates the maximum $t$ statistic in region; mean indicates the average $t$ statistic.

dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; ER, emotion regulation; MNI, Montreal Neurological Institute; ROC, regulation of craving; viPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; VS, ventral striatum.

*Region of interest small volume familywise error corrected at $p < .05$ with a voxelwise threshold of $p < .005$.

Figure 4. Regions that parametrically covaried with levels of craving in the regulation of craving task trial by trial. The ventral striatum (VS) and ventromedial prefrontal cortex (vmPFC) were regions of interest (shown uncorrected; $p < .005$).

expectancies were more successful at regulating their craving. Importantly, regulation was accompanied by increased activity in the dlPFC, viPFC, and dmPFC, and relative deactivations in regulation targets, namely the VS/sgACC and vmPFC/OFC for craving and the amygdala for negative affect. Furthermore, the VS/sgACC and mPFC/medial OFC activity parametrically varied with moment-to-moment craving. Finally, formal conjunction analysis showed that activations during both types of regulation spatially converged in viPFC (and dlPFC at a more relaxed threshold; see Supplement). These findings have important implications for our understanding of AUD, CBT, and SUD treatment more broadly.

Our results demonstrate that individuals with AUD can use cognitive strategies to reduce cue-induced craving for both alcohol and food, consistent with our prior behavioral findings (49). This is an important replication given the wealth of research linking alcohol use and AUD to cognitive impairments (106). In addition, we provide novel evidence suggesting that individuals with AUD can successfully regulate negative affective responses toward negative stimuli. As such, these findings provide experimental validation of cognitive strategies that are used in psychological AUD treatments.

Interestingly, although results suggest that individuals with AUD are able to use cognitive strategies to regulate craving and negative emotion in a laboratory setting, they may not spontaneously do so in everyday life. Indeed, AUD is clinically characterized by impaired control of emotion (12,56). This seeming contradiction—whereby individuals with AUD can use regulatory strategies in the lab despite apparent deficits in everyday life—parallels findings in depression. Specifically, studies have demonstrated that individuals with depression can use cognitive reappraisal to reduce negative affect in
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Importantly, along with PFC recruitment, we observed relative deactivations in the VS/sgACC and vmPFC/OFC during ROC. Parametric modeling demonstrated that VS/sgACC and mPFC/OFC activity tracked with moment-to-moment changes in craving across image types and instructions. These results are consistent with meta-analyses showing that craving for drugs and food is associated with VS/sgACC and mPFC/OFC activations [115–118] and with the broader role proposed for these regions in value computation [119–122]. Taken together, these results provide further evidence for the role of a prefrontal-striatal pathway in the ROC [40].

Across both tasks, conjunction revealed coactivation of the vIPFC during regulation (and dIPFC at a more relaxed threshold; see Supplement). Interestingly, this region overlapped with a region previously identified across 3 domains of cognitive control in cigarette smokers [78]. We also observed nonoverlapping activations in PFC subregions during ROC and negative emotion. These spatial differences may be partially attributable to differences in strategy implementation between the ROC and ER tasks: the strategy used for alcohol cues involved focusing on the negative consequences of consumption, whereas the strategy used for negative stimuli involved generating positive reinterpretations. Thus, differential engagement of prefrontal regions associated with autobiographical memory [e.g., (123)], prospective thinking [e.g., (124)], self-referential processing [e.g., (125)], and affective processing [e.g., (126)] is likely.

In addition, given that domain-specific subcortical targets were modulated during ROC and negative emotion, different cortical mechanisms may be engaged during each type of regulation, forming distinct regulatory pathways. That is, although PFC activation during both types of regulation largely overlap, different cortical circuits are likely engaged in the modulation of distinct subcortical targets. Importantly, these neural differences may account for the absence of correlation between regulation success for craving and regulation success for negative emotion. In other words, behavioral differences between the two tasks may be due to the domain-specificity of pathways that underlie these two types of regulation.

Importantly, the sample size was relatively small. Although this is often the case with fMRI studies in AUD [127–130] and in clinical populations more generally [for meta-analysis, see Picó-Pérez et al. (131)], this is a limitation that reduces the likelihood of detecting small effects and may limit generalizability of the findings. We hope that future studies will expand on this work with larger samples. Such studies could also include healthy control participants and social drinkers to examine whether regulation success relates to drinking severity. Such studies could also test whether AUD affects prefrontal-subcortical pathways within and across domains of regulation (e.g., selecting appropriate regulatory outputs). Additionally, longitudinal designs could test the relationships between negative alcohol expectancy, ROC, and clinical outcomes. Finally, given that individuals with AUD are capable of regulating craving when instructed to do so, the next important step may be to identify ways to train them to increase their tendency to use such strategies in their daily lives.
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